# Routine data collection and evaluations of onasemnogene abeparvovec in Germany

## Study Protocol

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## Signature Page

The signatories agree to the content of the final study protocol as presented.

## Responsibilities

[redacted]

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**Index of abbreviations and definition of terms**

| Abbreviation | Term/Definition |
|---|---|
| AAV | Adeno-associated virus serotype |
| AbD | Routine Data Collection and Evaluations (Anwendungsbegleitende Datenerhebung) |
| Abs | absolute |
| ACT | Appropriate Comparative Therapy |
| ASO | Antisense oligonucleotide |
| ATE | Average Treatment Effect |
| ATT | Average Treatment Effect among Treated |
| AWMF | Working Group of the Scientific Medical Societies e.V. (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.) |
| BO-Ä | Professional Code for Physicians in Germany (Berufsordnung Ärzte) |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CMA Infobase: (CPGs) | Canadian Medical Association Infobase: Clinical Practice Guidelines |
| CMAP | Compound muscle action potential |
| COV | Close-Out Visit |
| CRF | Case report form |
| CUP | Compassionate use program |
| DMD | Disease modifying drug |
| DNA | Deoxyribonucleic acid |
| EAP | Expanded access program |
| EFS | Event free survival |
| EMA | European Medicines Agency |
| G-BA | Federal Joint Committee (Gemeinsamer Bundesausschuss) |

| Abbreviation | Term/Definition |
|---|---|
| GLMM | Generalized linear mixed model |
| HFMSE | Hammersmith Functional Motor Scale Expanded |
| HINE | Hammersmith Infant Neurological Examination |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HSP | Healthcare service provider |
| ICD | International Statistical Classification of Diseases and Related Health Problems |
| IPCW | Inverse-probability-of-censoring weighting |
| IPTW | Inverse probability of treatment weighting |
| IQWiG | Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) |
| ISS | Intronic splice silencing site |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| LTFU | Loss-to-follow-up |
| MAH | Marketing authorization holder |
| MAP | Managed access program |
| MedDRA | Medical Dictionary for Regulatory Affairs |
| mRNA | Messenger ribonucleic acid |
| n.a. | Not applicable |
| NGT | Novartis Gene Therapies |
| NPP | Named patient program |
| OS | Overall survival |
| PICO | Patient-Intervention-Comparator-Outcome |
| PS | Propensity Score |

| Abbreviation | Term/Definition |
|---|---|
| PT | Preferred term (MedDRA) |
| RMV | Routine Monitoring Visit |
| RPSFT | Rank Preserving Structural Failure Time Model |
| RULM | Revised Upper Limb Module |
| RWE | Real World Evidence |
| SAP | Statistical analysis plan |
| SGB V | Social Code Book V (Sozialgesetzbuch V) |
| SLR | Systematic literature review |
| SMA | Spinal muscular atrophy |
| SMD | Standardized mean difference |
| SMN | Survival motor neuron |
| SMN1 | Survival motor neuron 1 gene |
| SMN2 | Survival motor neuron 2 gene |
| SmPC | Summary of Product Characteristics |
| SMRW | Standardized mortality ratio weights |
| SOC | System Organ Class (MedDRA) |
| SPI | Single Patient Investigational New Drug |
| Treat-NMD Neuromuscular Network | Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease Neuromuscular Network |
| TRIP Database | Turning Research Into Practice Database |
| TTE | Time to event |
| WHO | World Health Organization |

# Revision History

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| 0.1 | Jul 02, 2021 | Fabian Berkemeier (IGES) | Set up protocol |
| 0.2 | Jul 16, 2021 | Fabian Berkemeier (IGES) | Implementation of feedback from NGT project team |
| 0.3 | Jul 21, 2021 | Fabian Berkemeier (IGES) | Implementation of feedback from NGT project team |
| 1.0 | Aug 04, 2021 | Fabian Berkemeier (IGES) | Implementation of feedback from ISRC review |
| 1.01 | Aug 05, 2021 | Fabian Berkemeier (IGES) | Changed role of Omar Dabbous from Project Management to Project Lead |
| 2.0 | Nov 05, 2021 | Fabian Berkemeier (IGES) | Implementation of G-BA requests from letter dated 9/28/2021:<br>▪ Updated synopsis according to changes in protocol<br>▪ Updated milestones according to G-BA change requests<br>▪ Added section 1.2 and 1.3 to cover procedural background information<br>▪ Updated section 1.3.5 to cover the two analysis approaches implemented as a consequence of G-BA change requests<br>▪ Updated section 4 to include safety endpoints requested by G-BA<br>▪ Updated section 5 to address G-BA change requests on endpoints with a focus on motor function endpoints depicted in section 5.1.2 and safety endpoints depicted in section 5.2<br>▪ Updated section 6 and added section 0 covering G-BA's change request on a utilization of the RESTORE registry<br>▪ Updated section 6.3 to address G-BA's change request of not applying G-BA quality criteria and dropping restriction to German sites administering both interventions of this study<br>▪ Updated section 7.1 to eliminate treatment center inclusion criterion<br>▪ Updated section 7.3 to depict G-BA's change request of utilizing historic data and non-parallel data for nusinersen as well as requiring information on all baseline confounders<br>▪ Updated section 8.1 to depict NGT and G-BA approach in order to include analysis populations |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | | requested by G-BA<br>▪ Updated section 8.2 to include sample size calculations for G-BA analysis populations with different methodologies as requested by G-BA in section 8.2.2<br>▪ Updated section 8.2.3 to provide details on sample size recalculations and specifically refer to the methodology defined in the SAP<br>▪ Updated section 8.3 to include historic data as well as expected patient numbers for G-BA analysis populations<br>▪ Updated section 8.4 according to G-BA's change requests on utilization of historic and non-parallel data, interim analysis times, and sample size calculations<br>▪ Updated section 8.5 according to G-BA change request on analysis times and reporting content<br>▪ Updated section 8.6 to include G-BA analysis populations and definitions of applications per confounder per analysis population<br>▪ Updated section 8.7 to define subgroup analysis per analysis population and performance of subgroup analysis irrespective of statistically significant interaction per G-BA change requests<br>▪ Updated section 12 to depict changes made in protocol |
| 2.01 | Nov 15, 2021 | Fabian Berkemeier (IGES) | Implementation of feedback from NGT project team |
| 2.02 | Nov 18, 2021 | Fabian Berkemeier (IGES) | Implementation of feedback from ISRC review |
| 3.00 | Jul 1, 2022 | Fabian Berkemeier (IGES) | Implementation of G-BA requests and recommendations from resolution on 1/20/2022<br>▪ Updated synopsis according to changes in protocol<br>▪ Updated milestones according to G-BA change requests<br>▪ Updated section 1.3 to cover background information on procedural developments after submission of study protocol and SAP version 2.02<br>▪ Updated section 2.1 to depict changes in analysis approach implementing change requests from G-BA<br>▪ Updated section 4 to discuss G-BA's recommendation of adding a formal hypothesis<br>▪ Updated section 5.2.2 to depict G-BA's change request on SAE analysis in SMArtCARE |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | | ▪ Updated section 6 to include RESTORE registry as secondary data source along with all subsequent adaptions other protocol sections<br>▪ Updated section 7.1 to clarify that inclusion criterion for pre-symptomatic patients applies to reference date, i.e. time of treatment initiation<br>▪ Updated sections 8.1 to also include populations defined for sensitivity analysis defined in SAP<br>▪ Updated section 8.2.2 to implement G-BA's recommendation of performing an orienting sample size calculation with shifted null-hypothesis and power of 0.8<br>▪ Updated section 8.2.3 to depict changes in submission schedule from G-BA<br>▪ Updated section 8.3 to include information on patient enrollment from first status report<br>▪ Updated section 8.4 to clarify study feasibility is given if at least one endpoint is likely to enroll required patient numbers and also clarify that no action on population termination will be taken without explicit alignment with G-BA<br>▪ Updated section 8.5 to depict changes in submission schedule per G-BA resolution and list content of reports in more detail per G-BA request<br>▪ Updated section 8.6.1 to clarify that categorization of confounders as "very important" vs. "less important" is merely a documentation of assessment from clinical experts and has no influence on study analyses to address G-BA request. In addition, SMN2 copy number was added as a confounder for populations GBA-B and GBA-D. Sensitivity analysis populations were added in allocation of confounders to analysis populations.<br>▪ Updated section 8.6.2 to depict changes to confounder adjustment methods performed in SAP per G-BA's change requests |
| 3.01 | Jul 13, 2022 | Fabian Berkemeier (IGES) | Implementation of feedback from ISRC review |
| 3.1 | Jan 8, 2024 | Fabian Berkemeier (IGES) | Due to resolution on October 20, 2022 the G-BA did mandate the following changes leading to technical adaptations of the study protocol:<br><br>RESTORE related sections were transferred into a separate addendum (Addendum 1), including the |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | | following sections:<br>▪ Synopsis and milestones<br>▪ Section 2.1: Pre-specification of study population<br>▪ Section 5: Endpoints (deleting RESTORE as a column in tables and sections about RESTORE in general)<br>▪ Section 6: Data sources and specifically 6.2 and 6.3<br>▪ Section 7: Population selection (deleting RESTORE as a column in tables)<br>▪ Section 8.1: Analysis populations<br>▪ Section 8.3: Expected patient numbers<br>▪ Section 8.5: Planned analyses<br>▪ Section 8.6: Prognostic factors (deleting RESTORE as a column in tables)<br>▪ Section 8.7: Subgroups<br>▪ Section 10.1: Data management<br>▪ Section 10.2: SDV<br>▪ Section 11.2: Informed consent<br><br>The G-BA requested to reverse the sections of protocol 3.01 that were not depicted in previous protocol version 2.02. These include:<br>▪ Deleting annex A3 and all respective references throughout the protocol. Tables from A3 were placed in the main section of the protocol: section 5, section 7, section 8.6 and section 8.7<br>▪ Tables in section 5, 7, 8.6 and 8.7 that addressed the depictability in SMArtCARE registry were deleted and depicted in the second addendum (Addendum 2) of the study protocol<br>▪ Sections regarding updated results from status report in section 8.3; updates were depicted in Addendum 4.<br><br>Additionally, changes were addressed that were forgotten to include in the previous revision history in protocol version 3.01.<br>▪ Updates throughout the protocol were made, regarding corrections of spelling, re-phrasing to improve clarity and addition of previously forgotten sources, version numbers and dates. However, these changes are not related to the actual change of study content.<br>▪ Update table in section 1.2<br>▪ Elimination of discrepancies regarding endpoints ventilatory support (at least 16 hours) in synopsis and section 5.<br>▪ Update table in 6.1 regarding SDV in |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | | SMArtCARE<br>▪ Update of operationalization in section 7.1 regarding inclusion criteria. Misunderstanding regarding inclusion of historic Zolgensma patients<br>▪ Update of section 7.3 regarding historical data (not only nusinersen)<br>▪ Deletion of Ulnar CMAP in section 8.6 and 8.7 due to insights from first status report<br>▪ Section 8.6.1: explanation of inclusion of previous forgotten SMN2 copy number and reasoning for categorization of confounders<br>▪ Section 8.6.2: update of figures regarding decision tree for statistical analyses (overlap and SMD criteria)<br>▪ Inclusion of SMN2 copy number as confounder in section 8.6 and 8.7<br>▪ Update of section 8.7.2 due to feasibility reasons of subgroup analyses<br>▪ Section 10.2, 10.3, 11.2 and 12: Update to reflect developments regarding study implementation after previous submission of study document<br><br>New changes made in this protocol (due to mandates in resolution of October 2022) and additional mandates from IQWiG:<br>▪ Elimination of discrepancies within study protocol regarding time period of study centers in SMArtCARE<br>▪ Update of table in section 1.3.1 to reflect new October 2022 change request<br>▪ Inclusion of new section 1.3.5 reflecting change requests of October 2022 resolution<br>▪ Addition of sensitivity analysis for parallel patients in NGT and G-BA population in section 8.1<br>▪ Change of confounder categorization in section 8.6.1 for age at symptom onset<br>▪ References made to RESTORE addendum (Addendum 1) as well as addendum reflecting additional non mandated changes in the study protocol version 3.01 (Addendum 2)<br>▪ Safety endpoints were renamed to be in line with standard terminology of safety reporting in section 5.2 as well as in all addenda of this study protocol (Addendum 1, Addendum 2, Addendum 3)<br>▪ Addition of Addendum 4 reflecting sample size re-calculation and feasibility assessment |
| 4.00 | | Fabian | Inclusion of risdiplam in the following sections: |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | Berkemeier (IGES) | ▪ Section 1.3.1: G-BA resolution and procedures as well as change of the PICO scheme<br>▪ Section 1.3.6: New section reflecting the G-BA resolution of September 21, 2023<br>▪ Section 2 regarding treatment switching<br>▪ Section 3.3: Information on risdiplam regarding mechanisms of acting and method administration and dosage<br>▪ Section 4: Objectives of this study<br>▪ Section 5: Operationalization of endpoints<br>▪ Section 7 regarding operationalization of inclusion and exclusion criteria<br>▪ Section 8.1: Sensitivity analyses<br>▪ Section 8.4: Feasibility assessment<br>▪ Section 8.5: Planned analyses<br>▪ Section 8.6: Prognostic factors<br>▪ Section 8.7: Subgroup analysis<br>▪ 10.2: Source data verification<br>▪ Annex A2: Relevant variables in SMArtCARE registry |
| 4.01 | Jan 26, 2024 | Fabian Berkemeier (IGES) | Implementation of feedback from ISRC review |
| 5.0 | Jun 9, 2025 | Fabian Berkemeier (IGES) | Implementation of G-BA mandated changes from resolution date June 6, 2024:<br>• Synopsis and Milestones: Added final sample size estimation and futility assessment for the second interim analysis; updated the PS-Scoring methodology from ATT to ATE.<br>• Section 8.1: To ensure consistency on sensitivity analyses between study protocol and SAP, list of sensitivity analysis populations was eliminated from study protocol and reference to SAP is made.:<br>• Sections 8.2.3, 8.4, 8.5.3: Added final sample size estimation and futility assessment for the second interim analysis.<br>• Section 8.5.4: Added clarification that interpretation of results will be in light of shifted null-hypothesis and including the elimination of a sensitivity analysis incl. ulnar CMAP due to lack of data<br>• Section 8.6.1: "n.a." was removed as a category for CHOP-INTEND, the addition with version 4 of the study documents was unintentional. N.a. was never used as a category and missing values in CHOP-INTEND and missing values in CHOP-INTEND are subject to confounder imputation.<br>• Section 8.6.2: Revised the propensity score |

| Version | Date | Revised by | Change made – Reason for the change |
|---|---|---|---|
| | | | (PS) methodology from ATT to ATE.<br>• Addendum 5: Added sample size update and futility assessment |
| 5.01 | Aug 1, 2025 | Fabian Berkemeier (IGES) | Implementation of feedback from Novartis project team |

# Synopsis and Milestones

Table 1: Synopsis

| | |
|---|---|
| Title | Routine Data Collection and Evaluations of onasemnogene abeparvovec in Germany |
| Study responsibilities | Marketing authorization holder (MAH) sponsored non-interventional study carried out based on resolution (February 4, 2021) of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). SMArtCARE, which will be used as the primary data source is responsible for patient data collection. Statistical analysis will be performed by IGES Institut GmbH. Source data verification will be performed by CSG (Clinische Studiengesellschaft mbH). Information on RESTORE registry as the secondary data source was depicted in a separate addendum (Addendum 1) to the actual study protocol. |
| Principal Investigator | Prof. Dr. Janbernd Kirschner<br>Universitätsklinikum Freiburg<br>Breisacher Straße 153<br>79110 Freiburg, Germany |
| Rationale and background | Federal Joint Committee (G-BA) demanded Routine Data Collection and Evaluations for Zolgensma® (onasemnogene abeparvovec) compared to therapy as determined by a physician, taking into account Spinraza® (nusinersen) and Evrysdi® (risdiplam) with its resolutions from February 2021 and September 2023. The present study is conducted to fulfill the requirements specified therein as well as requirements from the resolution of January 20, 2022.<br><br>Following an assessment of the study protocol and SAP by IQWiG and G-BA, unresolved differences on major aspects of the study design and analysis methods with regard to their appropriateness in German routine SMA care and feasibility remain. The study thus depicts two design and methodology approaches referred to as "NGT approach" and "G-BA approach". |
| Study objective and related endpoints | The objective of this study is to evaluate the overall effectiveness and safety in patients with spinal muscular atrophy (SMA) treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to therapy as determined by a physician, taking into account Spinraza® (nusinersen) and Evrysdi® (risdiplam). As such, the comparator consists of the other two therapies authorized for the treatment of SMA.<br><br>The following endpoints are subject to investigation in this study:<br>▪ **Effectiveness**<br>○ Survival<br>▪ Overall survival<br>▪ Event free survival<br>○ Motor function<br>▪ Achievement of motor milestones according to age (NGT approach only)<br>▪ Head control at the age of 8 months (NGT approach only)<br>▪ Crawl on hands and knees at the age of 18 months |

(NGT approach only)
- Sitting without support at the age of 18 months (NGT approach only)
- Standing without support at the age of 24 months (NGT approach only)
- Walking without support at the age of 24 months (NGT approach only)
- Sustainability of motor milestones
  - Loss of ability to sit without support
  - Loss of ability to stand without support
  - Loss of ability to walk without support
- CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)
  - Change from baseline after 6 months
  - Change from baseline after 12 months
- HINE (Hammersmith Infant Neurological Examination)
  - Change from baseline after 12 months
  - Change from baseline after 24 months
- Time to sitting without support
- Time to standing without support
- Time to walking without support

- Nutrition
  - Difficulties in swallowing
  - Difficulties in chewing
  - Gastric or nasal feeding tube
    - Any type of tube feeding (supplementary or exclusively)
    - Supplementary (e.g. for fluids)
    - Exclusively
- Orthopedic complications
  - Scoliosis or orthopedic surgery
  - Scoliosis
  - Orthopedic surgery
- Respiratory function
  - Time of ventilator use
    - Any ventilator support
    - Ventilator support at night (during sleep)
    - Intermittent ventilator support at day time and continuous at night
    - Permanent ventilator support (≥16 hours per day)
    - Intermittent ventilator support with acute illnesses
  - Type of ventilator use
    - Non-invasive ventilation
    - Invasive ventilation
  - Improvement in time of ventilator support from baseline
- Planned hospitalizations

- Safety

| | |
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| | ○ Adverse events<br>▪ Any Adverse events with or without hospitalization<br>▪ Any Adverse events with or without hospitalization related to treatment<br>▪ Adverse events without hospitalization<br>▪ Adverse events without hospitalization related to treatment<br>○ Serious adverse events<br>▪ Serious adverse events with hospitalization<br>▪ Serious adverse events with hospitalization related to treatment<br>▪ Serious adverse events with hospitalization or death<br>▪ Serious adverse events with hospitalization or death related to treatment<br>▪ Serious adverse events (RESTORE only)<br>▪ Serious adverse events related to treatment (RESTORE only)<br>○ Adverse events of special interest<br>▪ Hydrocephalus<br>▪ Hepatotoxicity<br>▪ Thrombocytopenia<br>▪ Cardiac events<br>▪ Dorsal root ganglia cell inflammation<br>▪ Renal toxicity<br>▪ Respiratory tract infection<br>▪ Epileptic seizure<br>▪ Post lumbar puncture syndrome |
| Population | Treatment-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the survival motor neuron 2 (SMN2) gene as well as symptomatic patients with 5q-associated SMA type I treated with onasemnogene abeparvovec or nusinersen/risdiplam.<br><br>Patients will be stratified into two analysis populations for NGT approach and into four analysis populations for G-BA approach:<br>▪ NGT approach<br>○ Population NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene<br>○ Population NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene<br>▪ G-BA approach<br>○ Population GBA-A: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene<br>○ Population GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br>○ Population GBA-C: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene |

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| | and 3 copies of the SMN2 gene<br>o Population GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene |
| Inclusion criteria | ▪ Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene or<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA or<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene<br>▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to body weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per summary of product characteristics (SmPC))<br>▪ Body weight at treatment initiation ≤ 21 kg<br>▪ Appropriate consent/assent has been obtained for participation in the study |
| Exclusion criteria | ▪ Pretreatment with an approved disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam)<br>▪ Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea<br>▪ Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA |
| Study design and data sources | Non-interventional, non-randomized data collection using secondary data from the SMArtCARE registry as primary data source<br><br>Information on RESTORE registry as the secondary data source will be depicted in a separate addendum (Addendum 1) to the actual study protocol<br>*In case of participation of a treatment center in both SMArtCARE and other registries as secondary data source, only data documented in SMArtCARE will be used to avoid duplication of patient records.* |
| Expected patient numbers | All patients fulfilling inclusion/exclusion criteria during study duration will be included in the study. As the study is conducted in a standard of care setting, the actual numbers of subjects per study population cannot be controlled. Also, as SMA is a rare disease, there is a finite number of patients that can be enrolled. An additional restriction is that included patients need to be stratified into two analysis populations for NGT approach and into four analysis populations for G-BA approach.<br><br>Based on SMA incidence information derived from the results of pilot newborn screening in Germany, the study is anticipated to enroll up to 599 |

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| | patients in its primary data source SMArtCARE, which will be included both retrospectively and prospectively from the initiation of the SMArtCARE registry in July 2018 to the time of data cut for final analysis on December 31, 2026. Due to required stratification into analysis populations, patient numbers relevant for achieving sufficient power per analysis population are significantly lower:<br>▪ NGT approach<br>o Population NGT-A: Up to 377 patients<br>o Population NGT-B: Up to 222 patients<br>▪ G-BA approach<br>o Population GBA-A: Up to 157 patients<br>o Population GBA-B: Up to 220 patients<br>o Population GBA-C: Up to 161 patients<br>o Population GBA-D: Up to 61 patients<br><br>In an effort to increase patient numbers for the study, all retrospective and prospective patients registered in the secondary data source RESTORE that fulfill inclusion and exclusion criteria of this study will also be enrolled. Data will be sourced from all de-novo sites worldwide (currently 113) unless they participate in SMArtCARE to avoid duplicate records.<br>Expected patient numbers cannot be reasonably estimated at current, because substantial structural changes are being implemented in RESTORE to fulfill the data source requirements from G-BA. These changes will lead to more patients treated with both nusinersen/risdiplam and onasemnogene abeparvovec eligible for inclusion in the Routine Data Collection and Evaluations.<br>Information on RESTORE registry as the secondary data source will be depicted in a separate addendum (Addendum 1) to the actual study protocol |
| Sample Size | Sample size calculations were performed separately for NGT and G-BA approaches due to differences in study populations and methodology.<br>▪ For NGT approach, a standard null hypothesis ($RR_0$=1), alpha = 0.05 (two-sided), and beta= 0.1 was used. Since regression-based confounder adjustment may be performed in this analysis approach, sample size ranges for different degrees of association between treatment and confounders are illustrated.<br>▪ For G-BA approach, a shifted null hypothesis ($RR_0$/$HR_0$=0,5), alpha= 0.05 (two-sided), and beta = 0.2 was used. Sample size calculations for G-BA approach were performed in an orienting character for variable time to event (TTE) effectiveness endpoints, effect sizes |

and event rates at 36 months.

The following sample sizes result:

- NGT approach
  - Population NGT-A
    - EFS: 48-68 patients
    - Sitting: 189-270 patients
  - Population NGT-B
    - Standing: 155-221 patients
- G-BA approach (all populations)
  - HR = 0.2
    - Event rate = 20%: 432 patients
    - Event rate = 50%: 142 patients
    - Event rate = 80%: 68 patients
  - HR = 0.4
    - Event rate = 20%: 4,718 patients
    - Event rate = 50%: 1,488 patients
    - Event rate = 80%: 672 patients

Based on current estimates of patient enrollment the study will be powered for EFS and sitting in study population NGT-A and for standing in population NGT-B. Due to application of a shifted null-hypothesis in G-BA approach, only populations GBA-A, GBA-B, and GBA-C seem to potentially be sufficiently powered and only in case of very substantial effect sizes (e.g. HR=0.2) and high event rates (around 50%). For all other endpoints and populations that were included in sample size calculations, expected patient numbers are expected to be insufficient to ensure adequate power.

Assumptions for sample size calculation will be re-evaluated at first interim analysis 36 months after the initial G-BA resolution date using actual observed event rates and effect sizes. A futility check and a final sample size estimation will be performed for the 2nd interim analysis.

Re-calculation of sample size as well as feasibility assessment is provided in Addendum 4 for the first interim analysis and in Addendum 5 for the second interim analysis.

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| Statistical methods | NGT approach<br>All endpoints will be evaluated using a treatment episode design to address the possibility of treatment changes between study interventions in this non-interventional study. For TTE endpoints, treatment episodes and their durations are considered in the context of a Cox regression with time-dependent covariates. For binary endpoints, scores and count data, weighting with the length of treatment episodes is appropriate within the generalized linear mixed model framework.<br><br>The comparison of both interventions is carried out descriptively with appropriate statistical methods. Inhomogeneity between treatment episodes with regard to the following baseline confounders will be addressed via an improvement of the structural comparability by propensity score weighting methods (ATE fine stratification weights or inverse probability of treatment weights depending on best overall confounder |

balance after weighting):

- Symptom status at treatment initiation
- Age at treatment initiation
- Nutrition support
- Ventilation support
- Contractures
- Motoric function: Highest motor milestone
- Motoric function: CHOP-INTEND

If overlap pre-weighting or balance post-weighting (using both ATE fine stratification weights or inverse probability of treatment weights) is not sufficient for applying propensity score methods (i.e. <50% overlap pre-weighting or abs(SMD) > 0.25 for any confounder post-weighting), confounder adjustment will be attempted in the framework of regression models (generalized linear model, Cox-regression).

G-BA approach

All endpoints will be evaluated based on an allocation to the patient's initial treatment ("new user design"). Per G-BA request, treatment changes will be ignored for main analysis, i.e. no censoring is performed.

The comparison of both interventions is carried out descriptively with appropriate statistical methods. Inhomogeneity between treatment episodes with regard to the following baseline confounders will be addressed via an improvement of the structural comparability by propensity score methods (ATE fine stratification weights or inverse probability of treatment weights depending on best overall confounder balance after weighting):

- SMN2 copy number
- Age at symptom onset
- Age at treatment initiation
- Nutrition support
- Ventilation support
- Contractures
- Motoric function: Highest motor milestone
- Motoric function: CHOP-INTEND

In case patient numbers are too small to allow for interpretable calculation of propensity scores or in case overlap pre-weighting or balance post-weighting (using both ATE fine stratification weights or inverse probability of treatment weights) is not sufficient for applying propensity score methods (i.e. <50% overlap pre-weighting or abs(SMD) > 0.25 for any confounder post-weighting), confounder adjustment will not be attempted and a naïve comparison will be performed.

Both approaches

Potential confounders and patient characteristics are evaluated descriptively and SMDs are reported for all variables. If adjustment of covariates is performed via propensity score methods, patient characteristics and SMDs for patients included in the analyses will be reported both weighted and unweighted. Patient characteristics and SMDs will be reported unweighted for patients trimmed from adjusted analyses.

- Continuous characteristics: Measures of position and dispersion (arithmetic mean with 95% confidence interval, standard deviation,

| | |
|---|---|
| | minimum, maximum and quartiles)<br>▪ Categorical characteristics: absolute and relative frequencies.<br><br>TTE endpoints are estimated in the context of a Cox regression. For binary endpoints and count data, a generalized linear model is used. Scores will be analyzed using a mixed model for repeated measurement.<br><br>Survival curves and median survival time as well as hazard ratios are used for the representation of the TTE endpoints. Binary endpoints are analyzed using Risk Ratio as effect measure. Scores will be evaluated using mean differences and Hedges' g. Count endpoints will be evaluated using Rate Ratio as effect measure.<br><br>For all effect measures 95% confidence interval limits are presented. Adverse events are summarized by SOC/PT in terms of absolute and relative frequencies as well as time to first event by treatment episode. |
| Duration of study | The duration of the study is 59 months prospectively from study start in February 2022 to data cut for final analysis in December 2026. In addition, 43 months of retrospective data is available from the primary data source SMArtCARE registry, which started enrolling patients in July 2018. Collectively, there is a timeframe of 102 months (8.5 years) for patient enrollment results.<br>Information on RESTORE registry will be depicted in a separate addendum (Addendum 1) to the actual study protocol. |

Table 2: Milestones

| Study milestones | (Planned) Date |
|---|---|
| G-BA resolution mandating the study | 4 February 2021 |
| Submission of study protocol and SAP to G-BA | 13 August 2021 |
| Written results of assessment of study protocol and SAP by G-BA and IQWiG | 28 September 2021 |
| Re-submission of study protocol and SAP | 24 November 2021 |
| Approval by G-BA under the condition of additional changes to study protocol and SAP | 20 January 2022 |
| Study start | 1 February 2022 |
| First status report and submission of updated protocol and SAP | Data cut: 28 February 2022<br>Submission: 4 August 2022 |
| Second status report and interim analysis and submission of updated protocol and SAP | Data cut: August 2023<br>Submission: 4 February 2024 |
| Third status report and interim analysis | Data cut: January 2025<br>Submission: 4 August 2025 |
| Final analysis for benefit assessment | Data cut: 31 December 2026<br>Submission: 1 July 2027 |

# 1. Background

## 1.1 Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular disease associated with progressive, irreversible motor neuron loss that results in muscle atrophy leading to progressive muscle weakness and paralysis, impairment of swallowing and breathing, and premature death in its more severe forms (1, 2). SMA is caused by a homozygous absence of the survival motor neuron gene 1 (SMN1), resulting in a lack of survival motor neuron (SMN) protein (1, 2). The SMN protein is also encoded by the survival motor neuron 2 (SMN2) back-up gene that is closely homologous to SMN1; however, only 10–15% of the protein produced by SMN2 is a full-length, functional SMN protein (3–6). SMA is historically classified into five clinical types (0 through 4) based on the age at symptom onset and highest motor milestone achievement. SMN2 copy number is inversely associated with disease severity and is correlated with SMA type; 97% of infants with two SMN2 copies will develop type 1, and infants with three copies of SMN2 have a 7% chance of developing SMA type 1 and 83% chance of developing SMA type 2 (7–9).

Although infants with SMA type 1 are alert and aware, they lose the ability to swallow and safely feed by mouth, never gain developmental milestones after initial presentation and develop progressive skeletal muscle weakness and atrophy, and suffer from chronic ventilatory failure (10–15). SMA type 2 is defined by the maximum motor ability to be able to sit unsupported, which is achieved at the average age of 1 year (16–20). SMA type 3 is distinguished from SMA type 2 by the ability to walk independently (20). While infants with a later age of onset have better functional ability initially, their condition deteriorates over time and often results in severe disability, regardless of SMA type.

The main cause of mortality is respiratory failure (21, 22). Infants experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow and ultimate death, typically following a severe respiratory illness (11). Without intensive respiratory and nutritional intervention and disease modifying treatment, the life expectancy of infants with SMA type 1 is typically <2 years (23). The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods (24–26).

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, modulation of splicing, motor neuron protection and muscle enhancement are continually changing the management and prognosis of these patients.

## 1.2 Benefit assessments for onasemnogene abeparvovec

Onasemnogene abeparvovec (Zolgensma®) is a gene therapy medicinal product that expresses the human SMN protein. It is delivered by a one-time intravenous infusion.

Onasemnogene abeparvovec was approved by the European Commission on 18 May 2020 for the following indication:

- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

According to § 35a of the German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) evaluates the additional benefit of reimbursable medicinal products with new active ingredients, and pharmaceutical companies are obliged to submit a dossier on product benefit when a new product is launched on the German market or authorized for new indications. The purpose of early benefit assessment in Germany is to compare newly authorized drugs to an appropriate comparative therapy (ACT) in order to establish a ruling on their additional benefit, which serves as the basis for price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

Novartis Gene Therapies EU Ltd. initially submitted a dossier for the benefit assessment on 1 July 2020 and submitted for a renewed benefit assessment according to § 35a section 1 sentence 12 on 15 May 2021 as per the requirement of G-BA.[1] G-BA determined nusinersen as ACT for the renewed benefit assessment and ruled on 4 November 2021 that an additional benefit is not demonstrated (27).

## 1.3 Routine Data Collection and Evaluations for onasemnogene abeparvovec

### 1.3.1 G-BA resolutions and procedures

On 4 February 2021 G-BA requested the first-ever Routine Data Collection and Evaluations according to § 35a paragraph 3b SGB V for onasemnogene abeparvovec (28). The resolution was preceded by a G-BA resolution of 16 July 2020 (29), which initiated the procedure as well as a concept development by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) of 1 October 2020 (30).

Along with the resolution mandating the Routine Data Collection and Evaluations, G-BA passed a resolution restricting reimbursement of onasemnogene abeparvovec to physicians participating in the Routine Data Collection and Evaluations on 4 February 2021 (31). G-BA also passed a resolution on quality criteria for the application of onasemnogene abeparvovec on 20 November 2020 (32). This resolution includes quality aspects specifically aimed at ensuring a high validity and comparability of the data collected for the Routine Data Collection and Evaluations (e.g. experience and training of physicians and physical therapists).

[1] Operational responsibility for the study was transferred to Novartis Pharma GmbH in 2024.

Prior to the initiation of the specific procedures mandating the Routine Data Collection and Evaluations for onasemnogene abeparvovec, IQWiG was commissioned to develop methodological guidance for this new form of evidence generation, which was published as a rapid report in January 2020 (33).

As required by the G-BA code of procedure, four out of six G-BA resolutions on onasemnogene abeparvovec included a public consultation procedure allowing for participation of stakeholders, including clinical SMA experts. Table 3 summarizes the relevant G-BA procedures as well as their public consultations.

Table 3: Relevant G-BA procedures concerning the Routine Data Collection and Evaluations for onasemnogene abeparvovec

| G-BA procedure | Resolution date | Public consultation |
|---|---|---|
| Initiation of a procedure to request Routine Data Collection and Evaluations for onasemnogene abeparvovec | 16 July 2020 | None |
| Quality criteria for onasemnogene abeparvovec | 20 November 2020 | 11 August 2020: Consultation on the written statements<br>22 September 2020: Oral hearing |
| Requirement of Routine Data Collection and Evaluations | 4 February 2021 | Written statements on IQWiG concept development: 30 October 2020<br>Exchange of expertise on IQWiG concept development: 23 November 2020 |
| Restriction of the Authority to Supply Care | 4 February 2021 | 6 January 2021: Consultation on the written statements<br>11 January 2021: Oral hearing |
| Start of study, change requests for protocol and SAP, change of submission requirements | 20 January 2022 | None |
| Change requests for protocol and SAP | 20 October 2022 | None |
| Change of comparator: inclusion of risdiplam besides nusinersen | 21 September 2023 | 24 August 2023: Consultation on the written statements; no oral hearing |

Source: (34), (35), (36), (37), (38), (39), (40), (41)

The G-BA resolution from 4 February 2021 (28) defined a number of aspects for the Routine Data Collection and Evaluations for onasemnogene abeparvovec. The population to be included in the study as well as intervention, comparator, and outcomes are defined by a PICO scheme depicted in Table 4.

Table 4: PICO scheme for Routine Data Collection and Evaluations for onasemnogene abeparvovec

| | |
|---|---|
| **Population** | ▪ Pre-symptomatic patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br>▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1<br>▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 2 and up to 3 copies of the SMN2 gene<br><br>The survey should also include patients in the above patient population who are older than 6 months or 6 weeks at the time of gene therapy with onasemnogene abeparvovec. |
| **Intervention** | ▪ Onasemnogene abeparvovec<br><br>The marketing authorization and the dosage information in the product information of the active ingredients must be taken into account. |
| **Comparator** | ▪ Therapy as determined by a physician, taking into account nusinersen and risdiplam<br><br>*Note:*<br>▪ *As such, the comparator consists of the other two therapies authorized for the treatment of SMA.*<br>▪ *The marketing authorization and the dosage information in the product information of the active ingredients must be taken into account.* |
| **Outcome** | Mortality<br>▪ Deaths<br><br>Morbidity<br>▪ Motor functioning (surveyed with age-appropriate instruments) and<br>▪ Achievement of motor development milestones of the WHO and<br>▪ Respiratory functioning (need for [continuous] ventilation) and<br>▪ Bulbar functioning (ability to swallow and speak, need for non-oral nutritional support) and<br>▪ Further complications of the disease (e.g. pain, orthopedic complications)<br><br>Side effects<br>▪ Serious adverse events (SAE)<br>▪ Adverse events leading to hospitalization<br>▪ Serious specific adverse events: Hepatotoxicity, thrombocytopenia, cardiac events, inflammation of spinal ganglion cells, renal toxicity, hydrocephalus |

Source: (28)

In addition to the PICO scheme, G-BA defined that the SMArtCARE registry is to be used as the primary data source provided that the quality criteria mentioned in Table 5 are fulfilled. G-BA also defined that "it is also possible to integrate other registries, taking into consideration all the data source requirements" depicted in Table 5.

The G-BA resolution of 4 February 2021 (28) further required Novartis Gene Therapies to submit a study protocol and SAP to G-BA by 15 August 2021, in which information on a number of aspects depicted in Table 5 is to be provided.

Table 5: Requirements on data source, study protocol, and SAP per G-BA resolution

| Aspect | Requirements of G-BA resolution |
|---|---|
| Data Source | Use of indication registries as a data source that meet the requirements for the routine data collection and fulfill at least the following quality criteria:<br>▪ Detailed registry description (protocol)<br>▪ Exact definition or operationalization of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints, and confounders<br>▪ Use of standard classifications and terminologies<br>▪ Use of validated standard survey instruments (questionnaires, scales, tests)<br>▪ Training on data collection and recording<br>▪ Implementation of an approved disease-specific core data set<br>▪ Use of exact dates for the patient, the disease, important examinations, and treatments/interventions<br>▪ Clearly defined inclusion and exclusion criteria for registry patients<br>▪ Strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness<br>▪ Specifications to ensure completeness of data per survey date and completeness of survey dates<br>▪ Source data verification for 100% of patients per survey center for the primary endpoint and for at least 10% of randomly selected patients per survey center for all other endpoints over the period since the start of data collection<br>▪ Assurance of scientific independence and transparency of the registry<br><br>Use of an indication registry in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany. |
| Protocol & SAP | The pharmaceutical company shall prepare a study protocol and a SAP before carrying out the Routine Data Collection and Evaluations. In this context, it shall, in particular, provide the following information in advance with regard to the evaluation of the data:<br>▪ Information on the statistical methods and models used as well as naming of the procedures and the criteria used in model selection and fitting Information on the expected scope and |

| Aspect | Requirements of G-BA resolution |
|---|---|
| | reasons for missing data as well as measures to avoid missing data and evaluation strategies to deal with missing data<br>▪ Information on dealing with implausible data and outliers<br>▪ Information on planned sensitivity analyses<br>▪ Information on the identification and adequate pre-specified adjustment for confounders<br>▪ Information on the investigation of potential effect modifiers<br>▪ Information on subgroup analyses based on the copy number of the SMN2 gene for pre-symptomatic patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene for the purpose of verifying whether a joint evaluation is appropriate<br>▪ Information on the extent to which the data on nusinersen/risdiplam collected in parallel and not collected in parallel are suitable for a pooled analysis<br>▪ Information on the extent to which data, if any, comparing onasemnogene abeparvovec and nusinersen/risdiplam from different data sources are suitable for a pooled analysis<br>▪ Information on dealing with patients who change their medicinal therapy or receive combination therapy<br>▪ Information on interim analyses taking into account the requirements defined in the G-BA resolution<br>▪ Information on discontinuation criteria because of futility |

Source: (28)

### 1.3.2 Written change requests from G-BA based on IQWiG assessment of study protocol and SAP

In accordance with the G-BA resolution from 4 February 2021, Novartis Gene Therapies submitted a study protocol and SAP to G-BA on 13 August 2021 (protocol version 1.01, SAP version 1.01). The G-BA justification (Tragende Gründe) of the 4 February 2021 resolution defined that "G-BA, with the involvement of the IQWiG, will review the study protocol and the statistical analysis plan and send the pharmaceutical company the result in writing within 4 to 6 weeks. If, after review by the Subcommittee on Medicinal Products of the G-BA, there is no need to adapt the study protocol and the statistical analysis plan submitted by the pharmaceutical company, the pharmaceutical company shall be informed of the result in writing. If, after examination by the Subcommittee on Medicinal Products of the G-BA, there is a need for adjustments, the G-BA will pass a resolution regarding the adjustments deemed necessary" (37).

With a letter dated 28 September 2021, G-BA's Subcommittee on Medicinal Products informed Novartis Gene Therapies of 22 change requests (42) based on an assessment of the submitted study protocol and SAP by IQWiG (43). In contrast to the provisions of the justification of the 4 February 2021 resolution (37), no G-BA resolution was passed on these change requests. Accordingly, no public

consultation took place and the change requests match the content and order of the IQWiG assessment of protocol and SAP. The 22 change requests are depicted in Table 6.

Seven change requests concerned study design aspects, for which Novartis Gene Therapies deviated from the provisions of the G-BA resolution of 4 February 2021 (No. 1, 3-5, 15, 16, 22, Table 6). Novartis Gene Therapies had provided rationales for these deviations, of which many were performed on the explicit recommendation of six advising German clinical SMA experts named in the protocol.

Three change requests (No. 6-8, Table 6) concerned the data sources. In its 4 February resolution (28) and its justification (37), G-BA defined SMArtCARE as the primary data source and required the "use of an indication register in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany". The integration of other registries was defined as "possible" – not mandatory – if the quality criteria depicted in Table 5 were fulfilled. It was also explained that "if there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present Routine Data Collection and Evaluations". As part of the change request depicted in the 28 September 2021 letter, G-BA has requested to include the RESTORE registry (change request No. 6, Table 6), study sites outside of Germany (change request No. 7, Table 6), and study sites within Germany not fulfilling G-BA quality criteria and thus not able to offer both interventions of this study (change request No. 8, Table 6).

The remaining 12 change requests (No. 2, 9-15, 17-21, Table 6) concerned details on the methods of statistical analysis. None of these aspects were depicted in the 4 February 2021 ruling (28), as Novartis Gene Therapies was mandated by G-BA to develop methodological approaches for aspects depicted in Table 5 without guidance as to which methods should be used.

Table 6: G-BA change requests from 28 September 2021

| No. | Topic | G-BA Request | Depicted in 4 February 2021 resolution |
|---|---|---|---|
| 1 | Question according to PICO: patient population | The definition of the patient population and the evaluation of the data should be carried out separately for pre-symptomatic and symptomatic patients according to the specifications of the G-BA. | Yes |
| 2 | Question according to PICO: Outcome (morbidity) | The multiplicity created by the number of endpoints describing motor function should be reduced by selecting the relevant endpoints and hierarchizing the endpoints overall. These decisions must be prespecified in the study protocol. Primarily, endpoints covering the entire | No |

| No. | Topic | G-BA Request | Depicted in 4 February 2021 resolution |
|---|---|---|---|
| | | relevant observation period should be used. | |
| 3 | Question according to PICO: Outcome (side effects) | The thresholds for the collection of the specific AEs referred to in the decision should be defined and prespecified before the start of the study.<br><br>As an approach to collecting SAEs, a combined endpoint of AEs leading to death and AEs leading to hospitalization should be evaluated. | Yes |
| 4 | Study design: prospective / retrospective data collection | The use of already collected data on nusinersen and onasemnogene abeparvovec (from the SMArtCARE registry and possibly other registries) should be planned for the registry study, provided that they meet the stated data quality requirements in the AbD (Routine Data Collection and Evaluations) decision on onasemnogene abeparvovec. | Yes |
| 5 | Study design: selection of confounders | The list of confounders should be adapted to the patient populations mentioned in the decision and to the data sources used for the registry study. | Yes |
| 6 | Data source | The pharmaceutical company should make the necessary adjustments to the self-managed RESTORE registry in accordance with the final study protocol and SAP for the AbD in order to be able to use evaluations based on the RESTORE registry together with the present registry study, e.g. in the form of a meta-analysis for the AbD. | No |
| 7 | Data source | SMArtCARE centers outside Germany should not be excluded as a data source in principle, since they can also provide prospective data for symptomatic patients. | No |
| 8 | Data source | There should be no exclusive restriction to centers that fulfil the quality assurance guideline of the G-BA for the use of onasemnogene abeparvovec. Rather, the decision whether or not to include a center should depend on the quality or care actually implemented in that center. | No |
| 9 | Evaluation of the data collection; planning of the number of cases | The description of the recalculation of the case number planning (36-month analysis) in the SAP should be much more detailed; in addition, the exact use of the measure $R^2$and its precise definition should be added. The description of the recalculation should be based on a shifted hypothesis boundary for the assessment of the effects. | No |

| No. | Topic | G-BA Request | Depicted in 4 February 2021 resolution |
|---|---|---|---|
| 10 | Evaluation of the data collection: Confounder adjustment | The division of patients into the proposed "treatment groups" for confounder adjustment should be changed. A division of patients must be made by information available at the beginning of the study. | No |
| 11 | Evaluation of the data collection: Confounder adjustment | Missing details for the propensity score analysis should be added (verification of goodness, concrete criteria for sufficient overlap and balance). | No |
| 12 | Evaluation of the data collection: Confounder adjustment | A description of a decision algorithm to adjust the propensity score analysis in case of missing overlap and balance after application of the first procedure should be added. Likewise, the correct consequence should be named if no propensity score procedure can be found.<br><br>A definition should be given with which a sufficient overlap and a sufficient balance of the groups to be compared can be achieved.<br><br>In such a case, it makes no sense to attempt to estimate the effect using either propensity scores or regression models. | No |
| 13 | Evaluation of the data collection: Analysis of the endpoints | The models for effect estimation should be presented in detail.<br><br>The center effect should not be included in the analysis as either a random or a fixed effect. A possible center effect should be investigated in a sensitivity analysis. | No |
| 14 | Evaluation of the data collection: Analysis of the endpoints | The SAP should describe in detail the form in which the confounders are to be included as fixed effects in the respective endpoint model. | No |
| 15 | Evaluation of the data collection: Analysis of the endpoints | Information on how to check whether temporally parallel and non-parallel data or data from different data sources can be used for pooled analyses is missing and should be added. | Yes |
| 16 | Evaluation of data collection: consideration of shifted hypothesis boundaries | The consideration of a shifted hypothesis boundary in the evaluation of the data is missing and should be supplemented. These additions could be made, for example, in the (previously missing) formulation of a hypothesis. | Yes |
| 17 | Evaluation of data collection: | Due to the expected small number of cases, it is proposed to calculate and present all relevant | No |

| No. | Topic | G-BA Request | Depicted in 4 February 2021 resolution |
|---|---|---|---|
| | subgroup analyses | subgroup analyses without the requirement of a statistically significant interaction. | |
| 18 | Evaluation of the data collection: Dealing with missing confounders | For the consideration of data, the corresponding registers/data sets should in principle contain information on all relevant baseline confounders. However, an exclusion of individual patients with remaining missing data from all analyses that take these confounders into account does not appear appropriate in view of the small number of cases.<br><br>It is suggested that remaining missing values for individual patients should be replaced by the multiple imputation approach. In addition, information on the extent to which or the reasons for which missing data are to be expected and information on how to deal with implausible data or outliers should be added.<br><br>Furthermore, a description of the proportions of missing data should be provided. | No |
| 19 | Evaluation of data collection: dealing with changes in treatment | The division of patients into the proposed "treatment groups" should be changed, as an adequate division of patients must be made by information available at the beginning of the study. | No |
| 20 | Evaluation of data collection: dealing with changes in treatment | A Cox model with time-dependent covariates is not considered an adequate method for dealing with treatment changes in the present case.<br><br>An allocation of treatment-naïve patients to the respective initial treatment (new-user design) is recommended. As a sensitivity analysis, supplementary evaluations should be performed with censoring in the case of treatment changes, whereby the time of censoring should be varied in order to take into account "carry-over" effects for the previous treatment.<br><br>If the initial question can no longer be answered due to a high proportion of treatment changes, a prevalent-new-user design can be used as an alternative for the evaluation. Whether this option should be used can be decided in each case after data on the course of AbD (see following point) have been submitted to the G-BA and implemented in an amendment to the protocol and SAP. | No |

| No. | Topic | G-BA Request | Depicted in 4 February 2021 resolution |
|---|---|---|---|
| 21 | Evaluation of data collection: dealing with changes in treatment | Information on the number of patients changing treatment, including the respective times under the different treatments, should be part of the information on the course of AbD to be submitted regularly to the G-BA. | No |
| 22 | Evaluation of data collection: Planned analyses | The planned dates for the interim and final analyses differ from those set out in the decision.<br>The analyses to be submitted should be planned in relation to the date of the decision, not in relation to the start of the study, and should be carried out as specified in the decision. A futility check should also be performed for each interim analysis. | Yes |

Source: (42)

### 1.3.3 Depiction of change requests from 28 September 2021 in study protocol and SAP version 2.02

In the context of a non-randomized, non-interventional trial, the exact statistical methodology used for analysis is of critical importance both for the feasibility of the study as well as its ability to generate valid results in light of the specific framework of routine care in Germany for the relevant indication. Accordingly, the German parliamentary health committee pointed out that "G-BA has to define as specifically as possible the form in which the data collection should be carried out" as part of its rationale and report on the law for more safety in the supply of medicines (Gesetz für mehr Sicherheit in der Arzneimittelversorgung - GSAV), which provides the legal basis for the Routine Data Collection and Evaluations (44). This is also reflected in § 35a section 3b sentence 4 SGB V, which mandates G-BA to especially define methodological aspects of the study.

In line with these legal requirements, G-BA code of procedure mandates that the concept for the Routine Data Collection and Evaluations is to include requirements on the "methodology of the data collection" (G-BA Code of Procedure, Chapter 5, § 56, section 1 No. 3). Accordingly, the G-BA resolution mandating a Routine Data Collection and Evaluations is to include "requirements for the data collection and for evaluations on the basis of the concept" (G-BA Code of Procedure, Chapter 5, § 58, section 1 No. 1). This procedure would allow for relevant stakeholders (e.g. medical societies and the pharmaceutical entrepreneurs) to weigh in on methodological aspects of the Routine Data Collection and Evaluations as part of a public consultation procedure (G-BA Code of Procedure, Chapter 5, § 57, section 1).

Neither the IQWiG concept (33) nor the 4 February 2021 G-BA resolution (28) include methodological requirements on key study design aspects (e.g. handling of treatment switches, handling of missing and unplausible data, eligibility of non-

parallel data). An inclusion of methodological aspects in the resolution mandating the study according to § 35a section 3b sentence 4 would have allowed for a public consultation procedure to also address key questions on the methodology of the study as well as the impact of methodological aspects on study feasibility. By also shifting the methodological aspects from a resolution-making procedure to a letter, a public consultation did not take place, although such a consultation would have been very valuable precisely in view of the absolute novelty of the procedure and the methodological principles.

Novartis Gene Therapies believes that the Routine Data Collection and Evaluations would have benefited from a dialog and involvement of medical societies on methodological questions – especially in light of the pilot character of this particular study. Proposals on dialog formats, e.g. via an expert workshop to address methodological questions not covered in the IQWIG concept and G-BA resolution, were put forward both during G-BA advice meetings and in writing by Novartis Gene Therapies but not pursued by G-BA.

With protocol version 2.02, Novartis Gene Therapies included methodological requests put forward by G-BA on 28 September 2021 in the study concept. Key aspects of the study design could not be consented between G-BA and Novartis Gene Therapies. As a consequence, Novartis Gene Therapies will also conduct statistical analysis according the originally submitted study design, which was developed to incorporate the recommendations of German SMA clinical experts.

Both approaches are depicted in the protocol starting from version 2.02 and will be submitted to G-BA at each status report, interim analysis, as well as with the value dossier scheduled for submission on 1 July, 2027. While an exchange on methodological questions including clinical SMA experts was not possible in the procedure on these Routine Data Collection and Evaluations, full transparency on different methodological approaches as well as their influence on the study feasibility and outcomes will support the process of utilizing the best available evidence in a benefit assessment in 2027.

### 1.3.4 Conditional approval of study protocol and SAP, implementation of additional change requests

After submission of protocol and SAP version 2.02, G-BA commissioned IQWiG with an assessment of the implementation of the 22 change requests provided to Novartis Gene Therapies on 28 September, 2021. Based on IQWiG's assessment (43), G-BA passed a resolution on a finding in the procedure (45) stating that Novartis Gene Therapies has fulfilled its obligation to submit a study protocol and SAP prior to study initiation under the condition that further changes are implemented in the protocol and SAP.

These additional change requests as well as some recommendations formulated by G-BA are implemented in versions 3.01 of the study protocol and SAP. Table 7 and Table 8 depict the change requests as well as a brief description of their implementation in the study protocol and SAP versions 3.01.

Table 7: G-BA change requests from 20 January 2022 concerning study protocol

| Topic | No. | G-BA Request | Implementation in protocol version 3.01 |
|---|---|---|---|
| Question according to PICO: Outcome (side effects) | a | The pharmaceutical entrepreneur plans to collect the serious adverse event (SAE) endpoint as adverse events (AEs) leading to hospitalization and deaths of any cause, as data on AEs leading to death are not collected in the SMArtCARE registry.<br><br>Regarding deaths from any cause, it must be documented whether they are due to AEs. Only those attributable to AEs should be included in the evaluation of SAE. If this is not possible, only AEs leading to hospitalization should be included. | SMArtCARE will provide information on cause of death that will be used to manually determine deaths due to AEs. Only such events – not deaths of any cause - will be included in SAE analyses. |
| Study design: prospective / retrospective data collection | b | The use of already collected data on nusinersen and onasemnogene abeparvovec (from the SMArtCARE registry and, if applicable, other registries) must be planned for the registry study, provided that they meet the stated requirements for data quality in the decision to require an application-accompanying data collection and evaluations for the active substance onasemnogene abeparvovec of February 4, 2021 (hereinafter: decision to require AbD for onasemnogene abeparvovec). The restriction of the consideration of retrospective data to nusinersen does not meet the requirements of the G-BA and is not appropriate.<br><br>The consideration of retrospective data on onasemnogene abeparvovec, provided that they meet the stated data quality requirements in the decision to require AbD for onasemnogene abeparvovec, must be | With protocol version 2.02, Novartis Gene therapies had included retrospective data on onasemnogene abeparvovec in the study. In this update, elimination of a date criterion to operationalize endpoints in the SMArtCARE CRF Table 23: Inclusion criteria and operationalization in SMArtCARE registry, criterion # 2) was missed and has been corrected. |

| Topic | No. | G-BA Request | Implementation in protocol version 3.01 |
|---|---|---|---|
| | | supplemented accordingly in the study protocol. | |
| Study design: selection of confounders | c | The adjustment of the list of relevant confounders to the subpopulations of the total study population is appropriate. However, the classification of the confounder "age at symptom onset" in the subpopulations of symptomatic patients as "less important" is not appropriate. This confounder must be classified as "very important". | The classification of confounders was not performed by Novartis Gene Therapies and the corresponding section in the study protocol is a documentation of the assessment performed by advising clinical experts. Novartis Gene Therapies thus cannot change the classification, as this would lead to an incorrect documentation of an external assessment.<br><br>The classification is also of no relevance to this study as all confounders categorized as “very” or “less” important are included in statistical analyses with no differentiation in any aspect of the study analysis.<br><br>This was depicted in more detail in the study protocol. |

Source: (Gemeinsamer Bundesausschuss 2022b)

Table 8: G-BA change requests from 20 January 2022 concerning SAP

| Topic | No. | G-BA Request | Implementation in SAP version 3.01 |
|---|---|---|---|
| Evaluation of the data collection: Confounder adjustment | 2a-aa | Criterion for sufficient overlap: It is stated that sufficient overlap exists if PS < 0.3 does not apply to 50% of patients in one treatment group and PS > 0.7 applies to 50% of patients in the other treatment group. This allows patient groups with 0% overlap to be considered sufficient and patient groups with 100% overlap to be considered not sufficiently overlapping. | Overlap will be assessed graphically with an overlap of 50% serving as guidance given a lack of an established criterion in the literature or recommended by G-BA and IQWiG. |
| | 2a-bb | Assessment of balance: the criteria for standardized mean differences (SMDs) of all confounders between treatment groups after weighting appear appropriate, but the criteria are weakened under certain conditions and then not applied. In addition, it is not stated that no PS analysis will be performed if severe imbalance is found for any of the confounders. | Criterion of abs(SMD) > 0.2 will be applied in all analyses. In case of violation, a naïve comparison will be performed. |
| | 2a-cc | There is no indication that the target population to which the treatment effect ultimately estimated in the PS analysis (after trimming and weighting) applies should be accurately described and that justification should be provided that this target population is appropriate for the initial question. | Reporting on baseline characteristics of both patients included in adjusted analysis as well as patients not included in adjusted analysis (e.g. trimming) is part of standard reporting and is now mentioned explicitly in the study protocol and SAP. |
| Evaluation of the data collection: Confounder adjustment | 2b-aa | The criteria for model selection (overlap and balance) are not appropriate, as shown in point 2a). | See 2a |
| | 2b-bb | There is no concrete indication of how the trimming specified in the decision algorithm should be performed. | Trimming described in more detail in sections 8.1.2 and 8.1.3 of the SAP |
| | 2b-cc | The decision algorithm also contains an approach via matching, where it is sufficient if only at least 50% of the | Matched-pair approach was removed from confounder adjustment strategy. |

| Topic | No. | G-BA Request | Implementation in SAP version 3.01 |
|---|---|---|---|
| | | confounders are considered. This approach is not appropriate per se. | |
| Evaluation of the data collection: Analysis of endpoints | 2c-aa | The criterion for sufficient overlap is not appropriate, as shown in point 2a). | See 2a |
| | 2c-bb | The change from the combined sample to the sample with only parallel data is done too early in the decision algorithm. The other procedures that can lead to improved overlap and balance (trimming, weighting method) must be applied first. | Parallel and non-parallel data will no longer be differentiated given relatively small share of patients enrolled before availability of onasemnogene abeparvovec through compassionate use programs. |
| | 2c-cc | It is not appropriate to use only the sample with exclusively parallel data in all further steps immediately after detecting insufficient overlap in the 1st step of the PS analysis. | See 2c-bb |
| | 2c-dd | The samples of data collected in parallel and not in parallel over time are also to be compared descriptively, and in centralized analyses of the combined or subsample, the other sample is to be used for sensitivity analyses. | See 2c-bb |
| Evaluation of the data collection: Planned analyses | 2d | In connection with the futility test, the pharmaceutical entrepreneur states that an insufficient number of cases may already be sufficient for a single "key endpoint" to terminate the observation for the respective population. In such a case, the results should not be evaluated. Neither is appropriate. The examination for futility must include the overall view of all data. The corresponding reports on the interim analyses must therefore contain all results collected up to that point and the associated analyses in full. Furthermore, the decision for or against a continuation of the observation of | Wording in SAP version 2.02 was not clear and interpreted differently by G-BA than it was meant by the sponsor. Study termination was always only planned if no key endpoint appears feasible to reach required patient numbers and results until that point are routinely reported to G-BA with each interim analysis. Clarification was added along with explicit mention of consultation with G-BA before any action is taken based on the results of the feasibility assessment. |

| Topic | No. | G-BA Request | Implementation in SAP version 3.01 |
|---|---|---|---|
| | | the population must be made in consultation with the G-BA on the basis of the respective interim report. | |

Source: (45)

### 1.3.5 Change requests from G-BA resolution of October 20, 2022

By decision of October 20, 2022 (46), the G-BA determined that the submitted version 3.01 of the study protocol and the SAP of July 13, 2022, for the implementation of the Routine Data Collection and Evaluations also contained changes that go beyond the requirements and recommendations in the resolution of January 20, 2022, and that these changes were not adequately identified. Any changes that exceed the requirements of the January 20, 2022 resolution should be reversed, separately identified, justified, and depicted into separate addenda to the study protocol and SAP as part of a resubmission. Therefore, this version 4.00 is also presented in track changes version, specifically identifying the revised study protocol and SAP version 3.01 and commenting the changes with an appropriate rationale (47).

Another requirement by decision of October 20 (46), 2022 was to reverse and outsource all definitions, operationalizations, and analyses for the RESTORE registry in a separate addendum (Addendum 1) to the study protocol and SAP. “The G-BA recommends that the requirements for the integration of further registries described in the resolution on the requirement of the AbD be listed in the study protocol and that the necessary references to the respective explanations in the study protocol for the AbD, e.g. on source data verification, be established. Study protocol and SAP for data collection in the SMArtCARE registry could then be the starting point for the inclusion of other international registries including the RESTORE registry."

Furthermore, important changes not mandated by the G-BA were additionally depicted in a second addendum (Addendum 2) to assure a better overview and to improve the traceability of those changes. Changes due to updates of the registry or due to insights from the first status report were not additionally reported in a separate addendum.

Last, the G-BA did request a change in study protocol and SAP regarding mandated change requests in the January 20, 2022 resolution not sufficiently depicted in the study protocol and SAP version 3.01:

- Requirement 1: The confounder "age at symptom onset" should be declared as "very important".
- Requirement 2: With regard to the examination of the suitability of non-parallel data on nusinersen, the pharmaceutical company was instructed in

resolution of 20 January 2022 to use the other sample for sensitivity analyses in the case of central evaluations of the samples of the data collected in parallel and non-parallel data were to use the respective other sample for sensitivity analyses. The required planning for sensitivity analyses with regard to the data collected in parallel and not in parallel is missing in the present SAP and in the study protocol.

### 1.3.6 Those requests were accordingly addressed in the study protocol and SAP version 4.00. Change request from G-BA resolution on September 21, 2023 regarding inclusion of risdiplam as comparator

On 21 September, 2023 (48) the G-BA passed a resolution on changing the study comparator in the PICO scheme. On the basis of the current evidence and after taking into account the written statement of medical societies and participating registries, risdiplam was defined as a new comparator for the routine data collections and evaluations besides nusinersen. Therefore, data from patients treated with nusinersen and risdiplam are to be collected in the comparator arm for the respective patient population for this Routine Date Collection and Evaluation.

Risdiplam was approved on 26 March 2021 for the treatment of 5q associated SMA in patients aged 2 months and older with a clinically diagnosed type 1, type 2 or type 3 SMA or with one to four copies of the SMN2 gene. Furthermore, the active substance received a positive opinion from the European Medicines Agency on July 2023 for the treatment of patients with SMA aged from 0 to 2 months.

Therefore, the G-BA mandated to change the comparator from only “nusinersen” to “therapy as determined by a physician, taking into account nusinersen and risdiplam”. As such, the comparator consists of the other two therapies authorized for the treatment of SMA. The modified comparator is to be implemented within the scope of an addendum to the study protocol and to the SAP and to be submitted for review together with the first interim analysis on 4 February 2024. Furthermore, changes were additionally implemented in track change mode in the existing study documents in order to ensure better traceability of the changes.

Also, the G-BA requested to provide data analyses based on the adapted study protocol and SAP for the modified comparator “therapy as determined by a physician, taking into account nusinersen and risdiplam” in the course of the second interim analysis.

# 2. Overview of study design and study schematic

## 2.1 Pre-specification of two analysis approaches

The study is a non-interventional, non-randomized, registry-based data collection. The study is based on secondary use of data from the SMArtCARE registry as primary data source. Furthermore, secondary use of data from the RESTORE registry's (49) de-novo sites as a secondary data source with its changes and adaptations to the AbD is displayed in a separate addendum (Addendum 1) to the actual study protocol.

Participants are enrolled when they first meet the inclusion and exclusion criteria of the study (sections 7.1, 7.2) and are observed until the date of data cut for final analysis or loss to follow-up.

It was not possible to reach an alignment on key aspects of the study methodology between Novartis Gene Therapies and G-BA/IQWiG incorporating recommendations from medical societies and clinical SMA experts (section 1.3.2, 1.3.3). The study concept depicted in the revised versions of protocol and SAP thus includes two approaches: (1) a methodology developed by Novartis Gene Therapies based on a broad involvement of external clinical and methodological experts (hereafter: "NGT approach") and (2) the methodology requested by G-BA based on IQWiG's assessment of study protocol and SAP (hereafter: "G-BA approach"). Table 9 gives an overview of key study design aspects for both approaches.

Table 9: Overview of key similarities and differences between NGT approach and G-BA approach

| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| Inclusion and exclusion criteria | Key inclusion criteria:<br>▪ Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA OR<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene<br>▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to body weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC)<br>▪ Body weight at treatment initiation ≤ 21 kg<br><br>Key exclusion criteria: | |

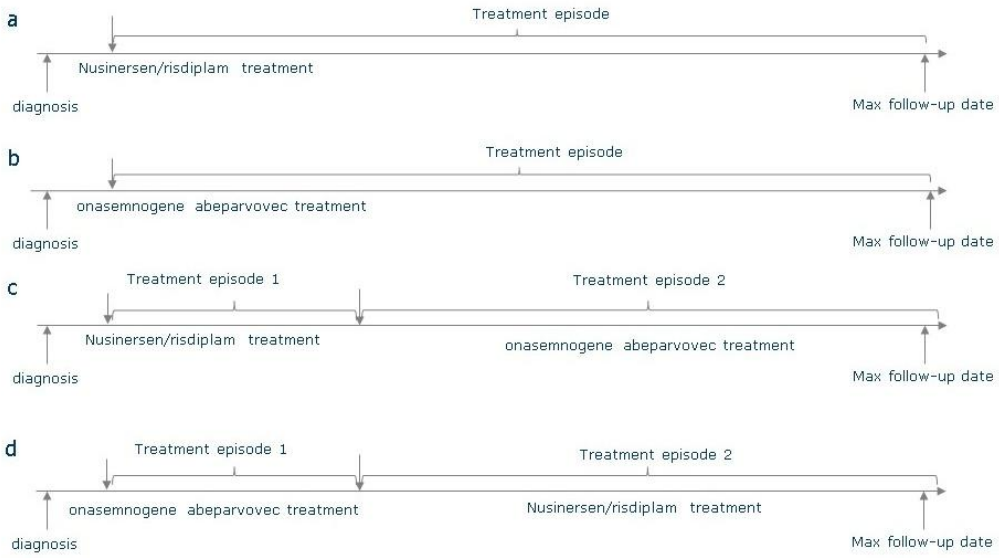
| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| | ▪ Pretreatment with disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam)<br>▪ Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | |
| Analysis populations | ▪ NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene<br>▪ NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene | ▪ GBA-A: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene<br>▪ GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br>▪ GBA-C: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene<br>▪ GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene |
| Handling of treatment switches | Treatment episodes, no censoring for treatment switches | Allocation to initial treatment, no censoring for treatment switches |
| Confounder adjustment | Propensity score methods or conditional regression based on the best suitability for the actual data available | Propensity score methods only |
| Sensitivity analyses | Comparative analysis of treatment patterns:<br>▪ Nusinersen/risdiplam monotherapy<br>▪ Onasemnogene abeparvovec monotherapy<br>▪ Treatment switch from nusinersen/risdiplam to | Censoring for treatment switches<br><br>Pooled analysis of populations GBA-A and GBA-B (2 copy SMN2) as well as populations GBA-C and GBA-D (3 copy SMN2) |

| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| | onasemnogene abeparvovec<br>▪ Add-on therapy of nusinersen/risdiplam after onasemnogene abeparvovec (few to no patients expected) | |
| Utilization of parallel retrospective data, i.e. collected after availability of onasemnogene abeparvovec | Yes | |
| Utilization of non-parallel retrospective data, i.e. collected before availability of onasemnogene abeparvovec | Yes | |
| Data sources | Primary: SMArtCARE<br><br>*In case of participation of a treatment center in both SMArtCARE and other registries as secondary data source, only data documented in SMArtCARE will be used to avoid duplication of patient records.* | |
| Study sites | SMArtCARE: Germany and Austria<br>Any registry:<br>▪ Experience with drug therapy for SMA: use of approved drugs (nusinersen, onasemnogene abeparvovec, risdiplam) in ≥ 10 patients under 18 years of age and ≥ 5 patients under 10 years within 3 years<br>o At study start and for retrospective data: 2019-2021 period<br>o Annual review thereafter to see if new sites are added. No exclusion of sites once included.<br>▪ Performance of standardized motor function tests for diagnosis by physical therapists with at least two years of experience in physical therapy diagnosis and treatment of children with neuromuscular diseases and training in the performance of standardized, disease-specific muscle function tests. | |
| Sample size calculation | Standard null-hypothesis | Shifted null-hypothesis |
| Interim analysis | 36 and 54 months after G-BA resolution from 4 February 2021 | |

Four types of treatment patterns regarding onasemnogene abeparvovec and nusinersen are theoretically possible (Figure 1) of which three are expected in the SMArtCARE registry data covering German patients. In addition to subjects who are (a) treated exclusively with nusinersen/risdiplam or (b) with onasemnogene abeparvovec according to the SmPC, there will also be (c) patients who switch from nusinersen/risdiplam to onasemnogene abeparvovec at a given time point.

Patients (d) treated with nusinersen/risdiplam after receiving onasemnogene abeparvovec are theoretically possible but expected to not occur at all or in very limited numbers in SMArtCARE because combination therapy is not routinely reimbursed by the Statutory Health Insurance in Germany. Regarding the inclusion of international registries (e.g. RESTORE), treatment patterns may differ due to differences in healthcare and reimbursement systems.

Figure 1: Expected treatment schemes




## 2.2 NGT approach

Due to the non-interventional nature of Routine Data Collection and Evaluations, it is not possible to regulate therapy changes within the study protocol. Novartis Gene Therapies expects that a significant number of patients included in this study will be characterized by a treatment switch, especially from nusinersen to onasemnogene abeparvovec or risdiplam. No methodological approach exists, which can completely exclude possible bias of treatment effects due to therapy changes.

In an effort to generate the best possible evidence in a situation with high patient shares with treatment switches, a treatment episode design is used for main analysis. Patients without treatment switches are characterized by only one treatment episode for the single treatment they have received from inclusion in the study to end of observation. Patients switching from nusinersen/risdiplam to onasemnogene abeparvovec (group c) or receiving nusinersen/risdiplam after onasemnogene abeparvovec (group d) are characterized by two treatment episodes and is analyzed in terms of treatment episodes under each treatment (section 7.3 of the SAP). A treatment episode starts with the day of first administration

and ends with the first administration of the respective follow-up intervention or the date of analysis.

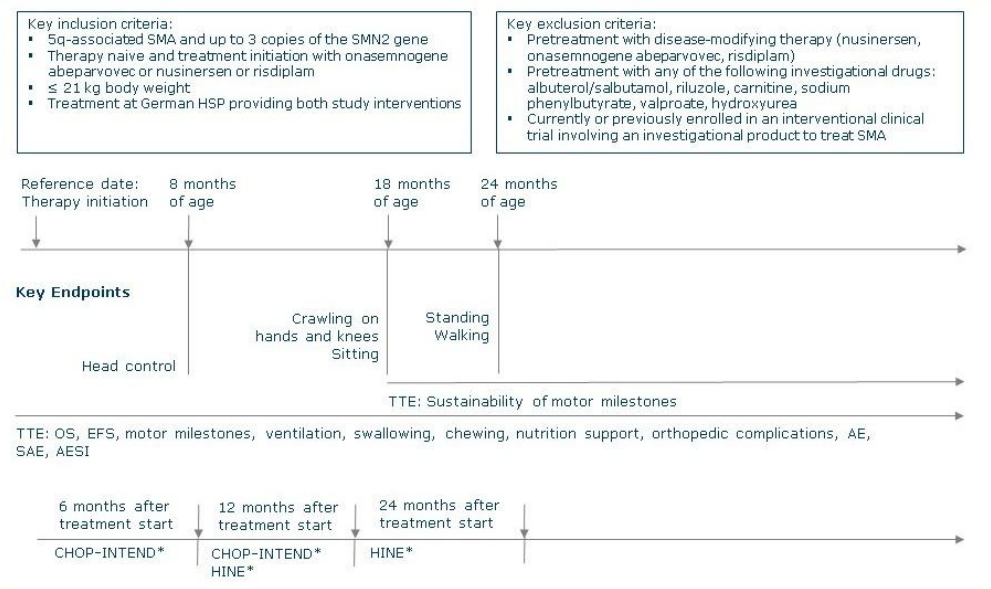
Furthermore, switches from nusinersen to risdiplam and risdiplam to onasemnogene abeparvovec as well as combination therapy of onasemnogene abeparvovec and risdiplam are expected. However, treatment switches between nusinersen and risdiplam do not trigger change of treatment episodes. No treatment switching will be censored.

In case of substantial number of patients switching from nusinersen/risdiplam to other therapies suggesting a potential deterioration under treatment that might not have been reflected yet into the key study outcomes, missing data handling approaches that consider patients as missing not at random (MNAR) would be considered via an amendment and discussed with G-BA to ensure that appropriate methodology to handle such patients is defined.

For sensitivity analysis, comparative analysis of treatment patterns (a-d) will be performed (section 8.5.1 of the SAP). Interpretation of results, especially on the effects of treatment switching, will be based on both the main analysis (treatment episodes) as well as the sensitivity analysis (comparative analysis of treatment patterns).

Figure 2 shows an overview of the study design.

Figure 2: Overview study design: NGT approach



## 2.3 G-BA approach

As per change requests No. 10, 19, 20, and 21 from 28 September 2021 (Table 6), the main analysis will allocate patients into two treatment arms depending on their initial treatment: 1) nusinersen/risdiplam or 2) onasemnogene abeparvovec.

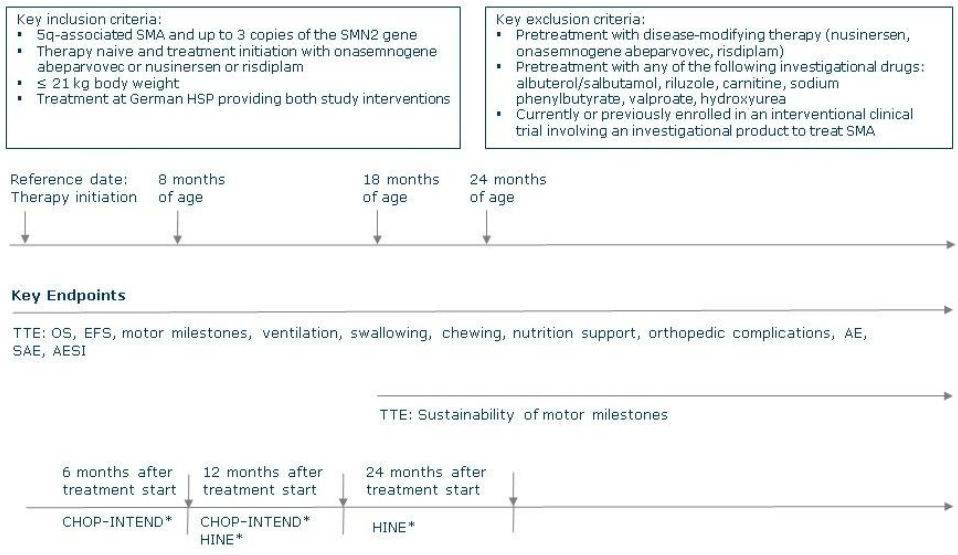
If treatment with risdiplam is less than 2 weeks before treatment with onasemnogene abeparvovec, treatment will be allocated to onasemnogene abeparvovec as initial treatment.

Treatment switches from nusinersen to onasemnogene abeparvovec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec are ignored for main analysis of treatment effects. Accordingly, no censoring, exclusion or any other type of methodological handling of treatment switches is performed.

For sensitivity analysis, patients switching from nusinersen to onasemnogene abeparvovec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec will be censored (section 7.4 of the SAP).

Figure 3 shows an overview of the study design.

Figure 3: Overview study design: G-BA approach



# 3. Compared therapies

## 3.1 Onasemnogene abeparvovec

### 3.1.1 Mechanism of action

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human SMN protein. It is designed to introduce a functional copy of the SMN1 gene in the transduced cells to address the monogenic root cause of SMA. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons (50).

Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype (AAV) vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal deoxyribonucleic acid (DNA) in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken-β-actin-hybrid), which results in continuous and sustained SMN protein expression (50).

### 3.1.2 Method of administration and dosage

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. It should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus (50).

It is recommended to initiate an immunomodulatory regimen with oral prednisolone starting 24 hours prior to infusion of onasemnogene abeparvovec and continue for 30 days post infusion (including the day of infusion). The further immunomodulatory therapy with gradually lower doses lasts 28 days and can be conducted with oral prednisolone or systemic corticosteroids, depending on the patient´s liver function (50).

The SmPC recommends a dose of nominal 1.1 x $10^{14}$ vg/kg onasemnogene abeparvovec and determines the total volume by patient body weight (32).

## 3.2 Nusinersen

### 3.2.1 Mechanism of action

Nusinersen acts to enhance the amount of functional SMN protein in infants/children and adults with SMA. It replaces the SMN protein deficit which causes SMA, by increasing the splicing efficiency of the SMN2 pre-messenger ribonucleic acid.

More specifically, nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-mRNA. By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein (51).

### 3.2.2 Method of administration and dosage

Nusinersen is for intrathecal use by lumbar puncture. It is administered as an intrathecal bolus injection for over 1 to 3 minutes, using a spinal anesthesia needle. Sedation may be required for administration, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of nusinersen, particularly in younger patients and in patients with scoliosis (51).

The recommended dosage is 12 mg (5 ml) per administration. Nusinersen treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter (51).

An ongoing study on nusinersen (DEVOTE) is currently investigating the clinical efficacy and safety of higher doses of nusinersen in a different regimen (52). For example, in deviation from the approved dose, treatment-naïve patients with SMA receive 50 mg nusinersen on days 0 and 14 as a loading dose followed by a maintenance dose of 28 mg after 4-5 months. Patients who have already received the maintenance dose of 12 mg nusinersen for one year will receive 50 mg once 4 months after their last dose and 28 mg every 4 months thereafter.

In case of a positive benefit-risk ratio of the results of the DEVOTE study, a corresponding adjustment of the approval is conceivable. In this case, an amendment of the protocol and SAP of this study will be initiated to depict the exact changes of nusinersen's marketing authorization that may arise.

## 3.3 Risdiplam

### 3.3.1 Mechanism of action

Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations of the SMN1 gene in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is directly linked to the SMA pathophysiology which includes progressive loss of motor neurons and muscle weakness. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels (53).

### 3.3.2 Method of administration and dosage

Each bottle contains 60 mg risdiplam in 2 g powder for oral solution. Each mL of the constituted solution contains 0.75 mg risdiplam. Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA. The recommended once daily dose of Evrysdi is determined by age and body weight. Evrysdi is taken orally once a day after a meal at approximately the same time each day, using the reusable oral syringe provided. Evrysdi must be constituted by a healthcare professional (e.g. pharmacist) prior to being dispensed. It is recommended healthcare professionals (HCP) discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose. In infants who are breastfed, Evrysdi should be administered after breastfeeding. Evrysdi should be taken immediately after it is drawn up into the oral syringe. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, Evrysdi can be administered via the tube (53).

# 4. Objectives

The objective of this study is to evaluate the overall effectiveness and safety in therapy-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as symptomatic patients with 5q-associated SMA type I treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to therapy as determined by a physician, taking into account Spinraza® (nusinersen) and Evrysdi® (risdiplam). As such, the comparator consists of the other two therapies authorized for the treatment of SMA.

The effectiveness and safety will be assessed based on patient-relevant endpoints, which are derived from the G-BA resolution mandating this study (28).

Effectiveness covers the following:

- Survival
- Motor function
- Nutrition
- Orthopedic complications
- Respiratory function
- Planned hospitalizations

Safety covers the following:

- Adverse events (AE)
- Serious adverse events (SAE)
- Adverse events of special interest (AESI)

The outcomes of this study are to be used in a future benefit assessment according to § 35a SGB V in Germany. It is acknowledged that G-BA recommended the formulation of a formal hypothesis using a shifted null hypothesis building on IQWiG's proposed effect thresholds (33). However, decisions on an additional benefit are the sole responsibility of G-BA's decision making processes in the benefit assessment procedures and have always been independent from any potential hypotheses formulated in confirmatory clinical studies. In the setting of this non-interventional, non-confirmatory study, all endpoints will thus be analyzed and reported to G-BA for its decision-making without formulation of a formal hypothesis.

# 5. Endpoints

Due to the non-interventional nature of this real world data collection, the definition of endpoints as primary or secondary is omitted formally. This is in line with the general methods of the German benefit assessment according to § 35a SGB V, which requires the assessment of patient relevant endpoints irrespective of their character as primary vs. secondary in a specific study (54, 55). An endpoint is considered patient relevant if it depicts how a patient feels, can perform his or her functions and activities, or whether he or she survives (55).

The endpoints depicted in this study are based on the Patient-Intervention-Comparator-Outcome (PICO)-Scheme included in the G-BA resolution mandating this study (28). As per the justification to the resolution, mortality and at least one endpoint per morbidity category depicted in the PICO-Scheme is covered in this study:

*"In particular, deaths (mortality category) and at least one endpoint from each of the following patient-relevant morbidity categories should be surveyed: Motor functioning (surveyed with age-appropriate instruments), achievement of motor development milestones of the WHO, respiratory function (need for [continuous] ventilation), bulbar function (e.g. ability to swallow and speak), need for oral nutritional support), and further complications of the disease (e.g. pain, orthopedic complications)" (37).*

All endpoints and in particular their definitions were coordinated and validated with clinical experts as well as representatives from the SMArtCARE registry. The endpoints EFS / ventilatory support and motor milestones are considered key endpoints and provide reliable results independent of the age of the treated children. They were thus used for initial sample size calculations (section 8.2).

In addition to the endpoints mandated by G-BA, planned hospitalizations are included upon recommendation by clinical experts. Reasons for planned hospitalizations may include – but are not limited to – the administration of disease modifying therapies, the placement of a gastric tube, or orthopedic complications. This combined endpoint thus depicts a patient relevant burden of the disease and its therapy. This is in line with IQWiG's general methods, which clarify that "the intervention- and disease-related effort of the treatment can be taken into account" in assessing the additional benefit of an intervention (55).

The following sections list endpoints and definitions used for the comparison. G-BA requested that endpoints on motor function are reduced and put into a hierarchy to reduce multiplicity (change request No. 2 from 28 September 2021, Table 6) Novartis Gene Therapies acknowledges the issue of multiplicity but regards it as a secondary issue to the more serious challenge of limited power of the study. Novartis Gene Therapies has proposed a study design with only two study populations and linking the time of outcome analysis to reaching sample size required for sufficient power. G-BA has rejected this approach and mandated a design with four analysis populations and fixed times for outcome analysis irrespective of reaching

required sample sizes. As a consequence, it is significantly less likely that sufficient power will be reached in the G-BA approach. Irrespective of these concerns, a reduced list of motor function endpoints used for G-BA mandated analyses (G-BA approach) is depicted in section 5.1.2.2. All other endpoints will be applied for both NGT and G-BA approaches.

Health-related quality of life (HRQoL) is not surveyed in German routine care and not included in the SMArtCARE registry. HRQoL thus cannot be depicted in this registry-based, non-interventional study.

Information on endpoints as well es depictability in RESTORE registry as potential secondary data source is displayed in the RESTORE addendum (Addendum 1), section 5. Additionally, the conduction of a meta-analysis together with RESTORE registry will be presented.

Tables in sections 5.1 and 5.2 show the operationalization of endpoints in SMArtCARE registry. Depictability of endpoints (previously reported in version 3.01 of the study protocol) is now reported in the second addendum (Addendum 2) to the study protocol version 4.00.

## 5.1 Effectiveness

### 5.1.1 Survival

Table 10: Effectiveness endpoints: Survival

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Overall Survival (OS) | Time from the date of first treatment to the date of death due to any cause | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ End of data collection: Date of death<br>Medical assessment: Visit date |
| Event Free Survival (EFS) | Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ End of data collection: Date of death<br>▪ Medical assessment: Visit date<br>Medical assessment: Time of ventilator use = Continuous (>16h/day) |

### 5.1.2 Motor function

#### 5.1.2.1 NGT approach

Table 11: Effectiveness endpoints: Motor function (NGT approach)

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Achievement of motor milestones according to age | Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis<br><br>Age limits per milestone (based on WHO (57))<br>▪ Sitting without support: 9.2 months<br>▪ Crawl on hands and knees: 13.5 months<br>▪ Standing without support: 16.9 months<br>▪ Walking without support: 17.6 months | ▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>▪ *Note: SMArtCARE refers to the WHO performance criteria (58) as guidance.* |
| Head control at the age of 8 months | Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age | ▪ Medical assessment: Age at visit<br>▪ Medical Assessment: HINE: Head control |
| Crawl on hands and knees at the age of 18 months | Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months | ▪ Medical assessment: Best current motor function = Crawl on hands and knees or higher motor milestone (Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>▪ *Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least three in a row."* |
| Sitting without support | Proportion of patients | ▪ Medical assessment: Best current |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| at the age of 18 months | achieving the motor milestone of sitting without support at or before the age of 18 months | motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Standing without support at the age of 24 months | Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months | ▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Walking without support at the age of 24 months | Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months | ▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child takes at least five steps independently in upright position with the* |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | *back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Medical assessment: Visit date<br>▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Changes in motor milestones<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age lost of previous motor milestone<br>▪ Baseline: Sitting without support (if gained: Age gained)<br>▪ Baseline: Standing without support (if gained: Age gained)<br>▪ Baseline: Walking without support (if gained: Age gained)<br><br>Note: SMArtCARE refers to the WHO performance criteria (58) as guidance. |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Score |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical Assessment: HINE: Visit date<br>▪ Medical Assessment: HINE: Score |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support<br><br>*Note: Endpoint of exploratory nature due to* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Walking without support or higher motor |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | *uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |

For TTE analyses of motor milestones, there are uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed) as well as potential bias from different frequencies of visits between the study interventions.

#### 5.1.2.2 G-BA approach

Table 12: Effectiveness endpoints: Motor function (G-BA approach)

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>▪ *Note: SMArtCARE refers to the WHO performance* |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | *criteria (58) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br>▪ *Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | filled)<br><br>▪ *Note: SMArtCARE refers to the WHO performance criteria (58) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Medical assessment: Visit date<br>▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Changes in motor milestones<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age lost of previous motor milestone<br>▪ Baseline: Sitting without support (if gained: Age gained)<br>▪ Baseline: Standing without support (if gained: Age gained)<br>▪ Baseline: Walking without support (if gained: Age gained) |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Score |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical Assessment: HINE: Visit date<br>▪ Medical Assessment: HINE: Score |

For TTE analyses of motor milestones, there are uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed) as well as potential bias from different frequencies of visits between the study interventions.

### 5.1.3 Nutrition

Table 13: Effectiveness endpoints: Nutrition

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Difficulties in swallowing | Time from the date of first treatment to the first documented difficulties in swallowing | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Swallowing? = With difficulties |
| Difficulties in chewing | Time from the date of first treatment to the first documented difficulties in chewing | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Chewing? = With difficulties |
| Gastric or nasal feeding tube | Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations<br>▪ Any type of tube feeding (supplementary or exclusively)<br>▪ Supplementary (e.g. for fluids)<br>▪ Exclusively | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube<br>▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids<br>▪ Medical assessment: Start of tube feeding (date)<br>Medical assessment: Visit date (if start date of feeding tube not filled) |

### 5.1.4 Orthopedic complications

Table 14: Effectiveness endpoints: Orthopedic complications

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Scoliosis or orthopedic surgery | Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient have scoliosis?<br>▪ Medical assessment: Orthopedic surgery since last visit? |
| Scoliosis | Time from the date of first treatment to first documentation of scoliosis | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient have scoliosis? |
| Orthopedic surgery | Time from the date of first treatment to first documentation of orthopedic surgery | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Orthopedic surgery since last visit? |

### 5.1.5 Respiratory function

Table 15: Effectiveness endpoints: Respiratory function

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Time of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of<br>▪ Any ventilator support<br>▪ Ventilator support at night (during sleep)<br>▪ Intermittent ventilator support at day time and continuous at night | ▪ Nusinersen/ Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Start of ventilator use<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support? |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | ▪ Permanent ventilator support (≥16 hours per day)<br>▪ Intermittent ventilator support with acute illnesses<br><br>Documentation of same or higher ventilator support time required at two consecutive visits. | ▪ Medical assessment: Time of ventilator use<br>o Night (during sleep)<br>o Intermittent day time and continuous at night<br>o Continuous (>16h/day)<br>o Intermittent with acute illnesses |
| Type of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of (each separately)<br>▪ Non-invasive ventilation<br>▪ Invasive ventilation<br><br>Documentation of same or higher ventilator support type required at two consecutive visits. | ▪ Nusinersen/ Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support?<br>▪ Medical assessment: Type of ventilation<br>o Non-invasive<br>o Invasive |
| Improvement in time of ventilator support from baseline | Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following<br>▪ Change from permanent ventilator support (≥16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR<br>▪ Change from intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR<br>▪ Change from ventilator support at night (during sleep) to no ventilator | ▪ Nusinersen/ Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support?<br>▪ Medical assessment: Time of ventilator use<br>o Night (during sleep)<br>o Intermittent day time and continuous at night<br>o Continuous (>16h/day) |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | support | |

### 5.1.6 Planned hospitalizations

Table 16: Effectiveness endpoints: Planned hospitalizations

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Planned hospitalizations | Cumulative number of planned hospitalizations across all patients per patient-year of being at risk including planned hospitalizations for administration of SMA treatments | ▪ Nusinersen/ Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Planned hospitalisation since last visit (except for treatment administration)?<br>▪ Medical assessment: Reason for hospitalisation<br>▪ Nusinersen/ Risdiplam/Zolgensma: Care Setting = Inpatient (overnight)<br><br>*Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE SAP accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.* |

## 5.2 Safety

### 5.2.1 Adverse events

Table 17: Safety endpoints: Adverse events

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Any Adverse events with or without hospitalization | Cumulative number of patients with and number of adverse events with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Type of unexpected event<br>▪ Adverse events: Start date<br>▪ Adverse events: Date recorded (in case start date is not filled)<br>▪ Adverse events: name of drug |
| Any Adverse events with or without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Type of unexpected event<br>▪ Adverse events: Start date<br>▪ Adverse events: Date |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | recorded (in case start date is not filled)<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |
| Adverse events without hospitalization | Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/ Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Adverse events without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/ Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |

### 5.2.2 Serious adverse events

Serious adverse events (SAE) are not directly documented in SMArtCARE (59). SMArtCARE supports documenting adverse events that lead to unplanned or

prolonged hospitalization, which is considered the most common criterion for an adverse event being classified as serious in SMA by clinical SMA experts. Furthermore, SMArtCARE has agreed to provide free-text information on cause of death, which will be used to determine AEs leading to death and incorporated into SAE analyses.

SMArtCARE does not, however, document the following, remaining criteria for serious adverse events:

- Life-threatening adverse events
- Adverse events leading to permanent or serious disability or invalidity
- Development of a congenital anomaly or birth defect

It is assumed that most – if not all – life-threatening adverse events as well as those leading to permanent or serious disability or invalidity will coincide with an unplanned or prolonged hospitalization and would thus be captured. Developments of a congenital anomaly or birth defect is not expected to play a role for the study population of infants and young children.

To approximate SAEs in the primary data source (SMArtCARE), they are defined as adverse events leading to hospitalization or death due to AEs.

Table 18: Safety endpoints: Serious adverse events

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Serious adverse events with hospitalization | Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/ Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Serious adverse events with hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |
| Serious adverse events with hospitalization or death | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br>▪ End of data collection: Date of death<br><br>Note: SAEs are not directly documented in SMArtCARE. Unplanned or prolonged hospitalizations as well as death due to AES are used as proxy for SAEs. SMArtCARE captures cause of death separately from AE information. AEs resulting in death will be derived from information on cause of death. |
| Serious adverse events with hospitalization or death related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment (yes/possibly) across all patients per | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug<br>▪ End of data collection: Date of death<br><br>Note: SAEs are not directly documented in SMArtCARE. Unplanned or prolonged hospitalizations as well as death due to AES are used as proxy for SAEs. SMArtCARE captures cause of death separately from AE information. AEs resulting in death will be derived from information on cause of death. |

### 5.2.3 Adverse events of special interest

According to the G-BA resolution (28) and justification of resolution (37) mandating this study, serious specific unwanted side effects identified on the basis of the information provided in the Risk Management Plan and the European Public Assessment Report (EPAR) of the intervention onasemnogene abeparvovec and the comparator nusinersen/risdiplam should be surveyed. This should include hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, renal toxicity, and hydrocephalus (36).

This requirement was discussed with clinical experts as well as representatives from the SMArtCARE registry to evaluate if there are generally accepted clinical thresholds or criteria that can be applied. This is currently not the case and Novartis Gene Therapies had considered it sufficient to cover these adverse events of special interest in the MedDRA-based reporting of adverse events that is planned for this study.

SMArtCARE has documented the following specific adverse events and adverse events with hospitalization using specific checkboxes from its initiation, which were based on specific reporting needs for nusinersen/risdiplam:

- Respiratory tract infection
- Hydrocephalus
- Epileptic seizure
- Post lumbar puncture syndrome

Based on G-BA change request No. 3 from 28 September 2021 (Table 6) SMArtCARE will add checkboxes for the following adverse events and adverse events with hospitalization to its CRF:

- Hepatotoxicity
- Thrombocytopenia
- Cardiac events
- Dorsal root ganglia cell inflammation
- Renal toxicity

In general, SMArtCARE requires documented adverse events if, in the investigator's opinion, they are considered clinically significant. Clinical significance is defined as any abnormality that causes a deviation from standard care (e.g. additional tests or measures).

Table 19: Safety endpoints: Adverse events of special interest

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| Hydrocephalus with or without hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hydrocephalus<br>▪ Adverse events: Start date |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | ▪ Adverse events: name of drug |
| Hydrocephalus with hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hydrocephalus<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Hepatotoxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hepatotoxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Hepatotoxicity with hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk<br><br>*Analysis based on specific* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | *checkbox in SMArtCARE CRF post CRF update.* | event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hepatotoxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Thrombocytopenia with or without hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Thrombocytopenia<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Thrombocytopenia with hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Thrombocytopenia<br>▪ Adverse events: Start date |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | ▪ Adverse events: name of drug |
| Cardiac events with or without hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Cardiac events<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Cardiac events with hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Cardiac events<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Dorsal root ganglia cell inflammation with or without hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>*Analysis based on specific* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | *checkbox in SMArtCARE CRF post CRF update.* | event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Dorsal root ganglia cell inflammation with hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Renal toxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation? |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | ▪ Adverse events: Type of unexpected event = Renal toxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Renal toxicity with hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Renal toxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Respiratory tract infection with or without hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Respiratory tract infection<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Respiratory tract infection with hospitalization | Cumulative number of patients with and number of | ▪ Nusinersen/Risdiplam/Zolgensma: |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | adverse events of respiratory tract infection per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Respiratory tract infection<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Epileptic seizure with or without hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Epileptic seizure<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Epileptic seizure with hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation? |

| Endpoint | Definition | Fields of SMArtCARE CRF (56) |
|---|---|---|
| | | ▪ Adverse events: Type of unexpected event = Epileptic seizure<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Post lumbar puncture syndrome with or without hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Post lumbar puncture syndrome with hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk<br><br>*Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* | ▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |

The specific documentation of hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, and renal toxicity in SMArtCARE can only be applied prospectively following the update of SMArtCARE's CRF. Analysis of these AESI is thus limited to the time from depiction in SMArtCARE's CRF to the end of study.

All adverse events possibly relating to the five AESIs mandated by G-BA that require an update of SMArtCARE's CRF are generally covered retrospectively in the MedDRA-based reporting of AEs (section 5.2.1, 5.2.2).

# 6. Data sources

IQWiG identified the RESTORE registry (49), the German Patient SMA registry (as part of the Global TREAT-NMD SMA Global Registry (60–62) and the SMArtCARE registry (63) as potentially suitable registries via literature research (30). Their suitability for the present Routine Data Collection and Evaluations was evaluated in detail.

The German Patient SMA registry (as part of the Global TREAT-NMD SMA Registry) does not collect longitudinal data, i.e. no data on effectiveness, and is therefore not eligible as data source (30).

According to IQWiG, the RESTORE registry bears risk of selection bias as there are differences in the completeness of patients treated with onasemnogene abeparvovec and nusinersen. Moreover, the recruiting centers that collect patient level data on both interventions ("de-novo sites") are predominantly located in the United States of America, whereas no such recruiting centers exist in Germany so far (30). As such, differences in standard of care between the United States and Germany are expected to manifest in the RESTORE data.

In its 4 February 2021 G-BA resolution (28) and its justification (37), G-BA thus defined SMArtCARE as the primary data source and required the "use of an indication register in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany". The integration of other registries was defined as possible – not mandatory – if the quality criteria depicted Table 5 were fulfilled. It was also noted that "if there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present Routine Data Collection and Evaluations". This concern was also put forward by the Drug Commission of the German Medical Association, which expressed concern that an inclusion of non-national registries might induce bias due to different national regulations of reimbursement.

Based on the conclusions of the IQWiG concept as well as the provisions of the G-BA resolution mandating this study, Novartis Gene Therapies had defined SMArtCARE as the exclusive data source for this study and further restricted to data from study sites in Germany that fulfil the quality criteria defined by G-BA for the use of onasemnogene abeparvovec (64).

## 6.1 SMArtCARE registry

The SMArtCARE registry is a joined initiative of academic institutions and patient organizations and supported by the pharmaceutical industry. The contractual framework is set up in a way that the academic network has full data ownership and publication rights. SMArtCARE does not transfer patient level data to pharmaceutical companies. If data analysis is needed for regulatory purposes, this is done via an independent third party. All studies and data analysis require prior approval of the SMArtCARE steering committee.

Data for the SMArtCARE registry is collected mainly in German centers and includes information on potential confounders. Data quality is ensured by standardized data collection, staff training at the participating centers, plausibility checks and queries. Physiotherapeutic evaluation is performed by appropriately trained physiotherapists and according to WHO criteria (59). SDV will be implemented as described in section 10.2 of this protocol. IQWiG concludes that the SMArtCARE registry sufficiently meets the quality criteria and qualifies as data source for the mandated Routine Data Collection and Evaluations (30).

Details of IQWiG's assessment of SMArtCARE are listed in Table 20.

Table 20: Fulfillment of quality criteria by SMArtCARE registry

| No. | Quality criterion | Fulfillment by SMArtCARE |
|---|---|---|
| | **Consistent systematics** | |
| 1 | Detailed description of registry (registry protocol) | Yes |
| | **Standardization** | |
| 2 | Exact definition/ operationalization of expositions, clinical events, endpoints and confounders | Yes |
| 3 | Current data plan/ coding list | Yes |
| 4 | Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA) | Yes |
| 5 | Use of validated standard assessment instruments (questionnaires, scales, tests) | Yes, but no assessment of health-related quality of life |
| 6 | Training on data collection and - acquisition | Yes |
| 7 | Implementation of a disease-specific core data set | Yes |
| 8 | Use of exact patient-specific dates (e.g. birth, death, pregnancy) | Yes |
| 9 | Use of exact dates in medical history (e.g. diagnosis, clinical relevant events) | Yes |
| 10 | Use of exact dates of important medical assessments | Yes |
| 11 | Use of exact dates for treatments and interventions (e.g. start/stop, dosage, dosage adjustment) | Yes, with limitations (no documentation of nusinersen dosage) |
| | **Achievement of recruitment target/sample collection** | |
| 12 | Clearly defined inclusion/exclusion criteria for registry population | Yes |
| 13 | Completeness of registry patients (complete registration or representative sample) | Unclear |
| 14 | Strategies to avoid unintentional recruitment bias to attain representative status | Yes (consecutive inclusion) |

| No. | Quality criterion | Fulfillment by SMArtCARE |
|---|---|---|
| | **Validity of data collection** | |
| 15 | Completeness of data per assessment | Shall be assured through standards |
| 16 | Completeness of assessments (loss to follow-up, drop outs) | Shall be assured through standards |
| 17 | Accuracy of data | Limited as there is actually no source data verification[a] |
| 18 | Consistency of data over time | Yes |
| 19 | Source data verification (e.g. for 10% randomly selected patients per participating center) | Yes, starting in 2022 as described in section 10.2 |
| 20 | Internal audits | No |
| 21 | External audits | No |
| 22 | Quality management system (with regular evaluation of quality indicators, where appropriate) | Yes |
| 23 | Standard Operating Procedures regarding data collection | Yes |
| | **Superordinate quality criteria** | |
| 24 | Transparency of the registry (including funding, decision-making, conflict of interest, amongst others) | Yes |
| 25 | Scientific independence | Yes |
| 26 | Secured funding (for planned study period) | Yes |
| 27 | Steering committee | Yes |
| 28 | Up-to-date registry documents (e.g. protocol, data plan, statistical analysis plan, informed consent etc.) | Yes |
| 29 | Protection of patients´ rights and data protection, consideration of ethical aspects | Yes |
| 30 | Timeliness (current status/quick availability/timeliness of requested results) | Yes |
| 31 | Flexibility and adaptability (e.g. implementation of trials, further assessments, changing medical care situation) | Yes |
| 32 | Documentation trail - documentation of all changes to processes and definitions | Yes |
| 33 | Audit trail - documentation and attribution of all data transactions | Yes |
| 34 | Interconnectability with other data sources | Planned |

| No. | Quality criterion | Fulfillment by SMArtCARE |
|---|---|---|
| | **Further possible criteria from a regulatory point of view** | |
| 46 | Assessment and handling of adverse events (AE) in accordance with regulatory requirements | Yes |

[a]SDV will be performed starting in 2022 as described in section 10.2.1

Source: (30)

## 6.2 RESTORE registry

Information on RESTORE registry as well as its performed adaptations to fulfill G-BA requirements is displayed in RESTORE addendum (Addendum 1), section 6.

## 6.3 Study sites

Due to the design of a registry-based, non-interventional study, available data in SMArtCARE is provided by all HSPs participating in the registries.

The criteria depicted in Table 21 will be applied that are possible for Novartis Gene Therapies to evaluate based on data of the SMArtCARE registry s as well as individual surveying and contracting activities with SMArtCARE sites. They are derived from the quality criteria put forward in the G-BA resolution of 20 November 2020 (32).

Table 21: SMArtCARE center inclusion criteria

| # | Center inclusion criterion | Rationale |
|---|---|---|
| 1 | Experience with drug therapy for SMA: Use of approved drugs (nusinersen, zolgensma, risdiplam) in ≥ 10 patients under 18 years of age and ≥ 5 patients under 10 years of age within 3 years<br>▪ For study start and retrospective data: 2019-2021 period<br>▪ Annual review thereafter to check if new centers are added. No exclusion of centers once included. | G-BA quality criteria for onasemnogene abeparvovec require at least 15 patients treated with an approved SMA therapy within 3 years (§ 3 section 2). In addition, G-BA requires at least 5 SMA treatments of patients less than one year of age within the last 3 years. However, this criterion is explicitly dropped for follow-up care after one year (§ 10 section 2). In order to ensure a uniform pool of centers for treatment and follow-up and at the same time to maximize patient numbers as much as possible, the additional criterion for initial treatment is dropped. In an effort to fulfill G-BA requests to maximize patient numbers for this study, the minimum patient number was reduced from 15 to 10.<br><br>The G-BA quality criteria also consistently focus on neuropediatrics. Unlike G-BA, Novartis Gene Therapies cannot verify the qualifications of the treating physicians in detail. While the fulfillment of the G-BA quality criteria separately |

| # | Center inclusion criterion | Rationale |
|---|---|---|
| | | requires certain minimum quantities as well as the neuropediatric qualification, the separate verification of the latter is not possible for Novartis Gene Therapies. Therefore, the required minimum quantities are applied to the age group of under 18-year-olds.<br><br>The inclusion criteria of ≤ 21kg for this study effectively limits initial treatment to patients less than 5 years of age. Given a follow-up period of 5 years, it can be assumed that the included patients will be under 10 years of age. An additional experience criterion of ≥ 5 patients under 10 years of age was thus applied to ensure adequate experience and routine, especially regarding the performance of motor function tests. |
| 2 | Performance of standardized motor function tests for diagnosis by physical therapists with at least two years of experience in physical therapy diagnosis and treatment of children with neuromuscular diseases and training in the performance of standardized, disease-specific muscle function tests. | In its justification of the quality criteria for onasemnogene abeparvovec, G-BA explicitly regulates experience and training requirements for physiotherapeutic staff in order to ensure the validity of the Routine Data Collection and Evaluations:<br>*"In order to ensure that data collection is uniform and comparable and that valid follow-up with comparably collected baseline values can be performed across treatment facilities, it is important that the physicians and physiotherapists collecting the findings are appropriately trained. Therefore, the requirements for physiotherapeutic care apply in accordance with § 6 paragraph 2 sentences 1 and 2. Reference is made to the comments on § 6 paragraph 2 sentences 1 and 2."*<br><br>The referenced criteria of § 6 section 2 sentences 1 and 2 define:<br>"*In the treatment facilities within the meaning of this resolution, it must be ensured that the performance of standardized motor function tests for diagnosis is carried out by physiotherapists with at least two years of experience in the physiotherapeutic diagnosis and treatment of children with neuromuscular diseases. They must be trained in the performance of standardized, disease-specific muscle function tests (e.g., CHOP-INTEND, HFMSE, RULM,* |

| # | Center inclusion criterion | Rationale |
|---|---|---|
| | | *6MWT)."*<br><br>The restriction to centers that meet the appropriate experience and training requirements is therefore consistent with the G-BA's resolutions and justifications. Novartis Gene Therapies will survey fulfillment of this criterion. |

### 6.3.1 SMArtCARE

According to public information, 53 entities of 46 hospitals are currently participating in the SMArtCARE registry, of which 41 entities of 34 hospitals are located within Germany and 9 entities of 8 hospitals are located in Austria (65). Two hospitals located in Spain and one hospital located in Switzerland are also listed on the SMArtCARE website. However, SMArtCARE informed Novartis Gene Therapies that these sites only use the documentation forms and database design of SMArtCARE and do not actually provide data to SMArtCARE. Thus, centers located in Germany and Austria can be included in this study and are depicted in Table 22.

Centers fulfilling the quality criteria depicted in Table 21 will be included in the study. Based on the data in SMArtCARE as of November 2021, 22 HSPs would be included in the study, of which 19 are located in Germany and 3 are located in Austria. It is expected that additional HSPs can be included in the study after systematically evaluating backlog of paper-CRFs and supporting sites in addressing backlog for this study (section 10.3).

Table 22: Participating German and Austrian HSPs in SMArtCARE and current fulfillment of patient number inclusion criterion

| Country | City | HSP | Fulfillment of patient number inclusion criterion (as of 11/2021) |
|---|---|---|---|
| **Germany** | Augsburg | Universitätsklinikum Augsburg<br>▪ Klinik für Kinder und Jugendliche / Mutter-Kind-Zentrum Schwaben | No |
| | Berlin | Charité Universitätsmedizin Berlin: Campus Virchow Klinikum<br>▪ Sozialpädiatrisches Zentrum Neuropädiatrie | Yes |
| | Berlin | DRK Kliniken Berlin Westend<br>▪ Klinik für Kinder- und Jugendmedizin Epilepsiezentrum / Neuropädiatrie | Yes |

| Country | City | HSP | Fulfillment of patient number inclusion criterion (as of 11/2021) |
|---|---|---|---|
| | Bochum | Ruhruniversität Bochum im St. Josef Hospital<br>▪ Klinik für Kinder- und Jugendmedizin: Neuropädiatrie | Yes |
| | Bonn | Universitätsklinikum Bonn<br>▪ Zentrum für Kinderheilkunde Abteilung Neuropädiatrie | Yes |
| | Dresden | Universitätsklinikum Carl Gustav Carus Dresden an der Technischen Universität Dresden<br>▪ Klinik und Poliklinik für Neurologie<br>▪ Neuropädiatrie Klinik und Poliklinik für Kinder- und Jugendmedizin | Yes |
| | Erlangen | Universitätsklinikum Erlangen<br>▪ Neurologische Klinik<br>▪ Kinder und Jugendklinik Neuropädiatrie | Yes |
| | Essen | Universitätsklinikum Essen<br>▪ Neurologische Klinik und Poliklinik<br>▪ Klinik für Kinderheilkunde Neuropädiatrie | Yes |
| | Freiburg | Universitätsklinikum Freiburg<br>▪ Klinik für Neuropädiatrie und Muskelerkrankungen | Yes |
| | Gießen | Universitätsklinikum Gießen und Marburg GmbH - Klinikum der Justus-Liebig-Universität<br>▪ Zentrum für Kinderheilkunde und Jugendmedizin. Abteilung für Kinderneurologie, Sozialpädiatrie und Epileptologie | Yes |
| | Göttingen | Universitätsmedizin Göttingen<br>▪ Klinik für Neurologie<br>▪ Klinik für Kinder- und Jugendmedizin Sozialpädiatrisches Zentrum | Yes |
| | Halle | Universitätsklinikum Halle<br>▪ Klinik und Poliklinik für Neurologie | No |

| Country | City | HSP | Fulfillment of patient number inclusion criterion (as of 11/2021) |
|---|---|---|---|
| | Hamburg | Asklepios Klinik Nord Hamburg<br>▪ Neuropädiatrie | No |
| | Hamburg | Universitätsklinikum Hamburg-Eppendorf<br>Zentrum für Geburtshilfe, Kinder- und Jugendmedizin<br>▪ Klinik und Poliklinik für Kinder- und Jugendmedizin | Yes |
| | Hannover | Medizinische Hochschule Hannover<br>▪ Klinik für Neurologie<br>▪ Zentrum für Kinderheilkunde u. Jugendmedizin | Yes |
| | Heidelberg | Universitätsklinikum Heidelberg<br>▪ Neurologische Klinik<br>▪ Zentrum für Kinder- und Jugendmedizin | Yes |
| | Homburg | Universitätsklinikum des Saarlandes<br>▪ Klinik für Allgemeine Pädiatrie und Neonatologie | Yes |
| | Jena | Universitätsklinikum Jena<br>▪ Neurologische Klinik und Poliklinik<br>▪ Klinik für Neuropädiatrie Sozialpädiatrisches Zentrum | Yes |
| | Kassel | Klinikum Kassel<br>▪ Neuropädiatrie | Yes |
| | Kiel | Universitätsklinikum Schleswig-Holstein<br>▪ Klinik für Neurologie | No |
| | Cologne | Kliniken der Stadt Köln GmbH Kinderkrankenhaus<br>▪ Sozialpädiatrisches Zentrum | No |
| | Leipzig | Universitätsmedizin Leipzig<br>▪ Klinik und Poliklinik für Neurologie | No |
| | Mannheim | Universitätsmedizin Mannheim<br>▪ Neurologische Klinik | No |
| | Munich | Klinikum der Universität München<br>▪ Friedrich-Baur-Institut | No |

| Country | City | HSP | Fulfillment of patient number inclusion criterion (as of 11/2021) |
|---|---|---|---|
| | Munich | Dr. von Haunersches Kinderspital<br>▪ Kinderklinik und Kinderpoliklinik der Ludwig Maximilian Universität München | Yes |
| | Munich | Technische Universität München Klinikum rechts der Isar<br>▪ Klinik und Poliklinik für Neurologie | No |
| | Münster | Universitätsklinikum Münster<br>▪ Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie - Neuropädiatrie | Yes |
| | Oldenburg | Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie – Neuropädiatrie<br>▪ Klinik für neurologische Intensiv- medizin und Frührehabilitation | No |
| | Rostock | Universitätsklinikum Rostock<br>▪ Klinik und Poliklinik für Neurologie Zentrum für Nervenheilkunde | No |
| | Stuttgart | Klinikum Stuttgart Olgaspital<br>▪ Päd. Neurologie, Psychosomatik und Schmerztherapie | No |
| | Tübingen | Universitätsklinikum Tübingen<br>▪ Kinderklink Abteilung III | Yes |
| | Ulm | Universitätsklinikum Ulm<br>▪ Sektion Sozialpädiatrisches Zentrum und Pädiatrische Neurologie / Stoffwechsel | No |
| | Wiesbaden | DKD Helios Klinik Wiesbaden<br>▪ FB Neurologie und Klin. Neurophysiologie | No |
| | Würzburg | Universitätsklinikum Würzburg<br>▪ Kinderklinik und Poliklinik Sozial- pädiatrisches Zentrum Neuropädiatrie | No |

| Country | City | HSP | Fulfillment of patient number inclusion criterion (as of 11/2021) |
|---|---|---|---|
| | | ▪ Neurologische Klinik und Poliklinik | |
| **Austria** | Bregenz | Landeskrankenhaus Bregenz<br>Kinder und Jugendheilkunde Neuropädiatrie | No |
| | Graz | Universitätsklinikum Graz<br>Universitätsklinik für Kinder- und Jugendheilkunde, Klinik für Neuropädiatrie und angeborene Stoffwechselkrankheiten | Yes |
| | Innsbruck | Tirol Kliniken<br>Universitätsklinik für Pädiatrie I Department für Kinder - und Jugendheilkunde | Yes |
| | Klagenfurt | Klinikum Klagenfurt am Wörthersee<br>▪ Abteilung für Neurologie<br>▪ Abteilung für Kinder- und Jugendmedizin | No |
| | Linz | Kepler Universitätsklinikum Linz<br>Universitätsklinikum für Kinder- und Jugendheilkunde | No |
| | Linz | Ordensklinikum Linz GmbH Barmherzige Schwestern<br>Kinder- und Jugendheilkunde Neuropädiatrische Ambulanz | No |
| | Mödling | Landesklinikum Baden-Mödling<br>Abteilung für Kinder- und Jugendheilkunde | No |
| | Wels | Klinikum Wels-Grieskirchen<br>Abteilung für Kinder- und Jugendheilkunde | No |
| | Wien | Kaiser-Franz-Josef Spital mit G.v. Preyersches Kinderspital<br>Abteilung für Kinder- und Jugendheilkunde | Yes |

Source: SMArtCARE (65)

### 6.3.2 RESTORE

Information on study sites in the RESTORE registry is displayed in the RESTORE addendum (Addendum 1), section 6.

# 7. Population Selection

This analysis will use individual patient data from patients included in SMArtCARE registry, which are treated with onasemnogene abeparvovec or nusinersen/risdiplam and fulfill the inclusion and exclusion criteria.

Tables in section 7.1 and 7.2 show the operationalization of inclusion and exclusion criteria in SMArtCARE registry.

Information on population selection in the RESTORE registry as secondary data source is displayed in the RESTORE addendum (Addendum 1), section 7. Depictability of inclusion and exclusion in SMArtCARE (previously reported in version 3.01 of the study protocol) is now reported in the second addendum (Addendum 2) to the study protocol version 4.01.

## 7.1 Inclusion Criteria

Patients included in the study need to fulfill the criteria listed in Table 23.

Table 23: Inclusion criteria and operationalization in SMArtCARE registry

| # | Inclusion criteria | Fields of SMArtCARE (56) |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT<br>Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |

| # | Inclusion criteria | Fields of SMArtCARE (56) |
|---|---|---|
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: Age at symptom onset < 6 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Age at symptom onset ≥ 6 months<br>AND<br>▪ Baseline: Age at symptom onset < 18 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to body weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) | ▪ Medical Assessment: Is the patient on any approved medication for SMA? = no for all visits before |

| # | Inclusion criteria | Fields of SMArtCARE (56) |
|---|---|---|
| | | Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Name of drug = onasemnogene abeparvovec/Zolgensma OR nusinersen/Spinraza/risdiplam/Evrysdi |
| 3 | Body weight at treatment initiation ≤ 21 kg | ▪ Medical assessment: Body weight (kg) ≤ 21 AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |
| 4 | Appropriate consent/assent has been obtained for participation in the study | ▪ Enrolment: Date of consent <> "" |

The first inclusion criterion depicted in Table 23 depicts the population mandated for this study by G-BA (28). Pre-symptomatic patients are characterized by their symptom status at baseline, i.e. they are pre-symptomatic if diagnosis was made pre-symptomatically and there is no documentation of symptoms related to SMA prior to treatment initiation.

The second criterion depicted in Table 23 ensures compliance with the concept of "emulation of target trial" set forth by IQWiG. The IQWiG methodological framework for Real World Evidence (RWE) application in the benefit assessment (33) and the IQWiG concept for Routine Data Collection and Evaluations for onasemnogene abeparvovec (30) recommend the explicit emulation of the planning of randomized trials for planning of non-randomized RWE studies for the benefit assessment ("emulation of target trial"). Within the components of the emulation of the target trial from a non-randomized data set, a "new user design" is required:

*"Patients who meet the inclusion/exclusion criteria are assigned to the intervention they received at the beginning of their treatment for the disease or indication under investigation" (33).*

To implement these requirements, only therapy-naïve patients will be included in the study.

The third criterion depicted in Table 23 is introduced to ensure that only patients eligible for treatment with both interventions of this study are included. While the EU marketing authorization for onasemnogene abeparvovec does not recommend an age limit, the use of onasemnogene abeparvovec is expected to be almost exclusive to newborns and infants. This is also reflected in the G-BA's quality criteria

for the use of onasemnogene abeparvovec (32). Onasemnogene abeparvovec is administered by intravenous infusion. Patients receive a dosage based on body weight. The SmPC specifies a recommended dosage for patients with a body weight up to 21.0 kg body weight (50). For this reason, only patients ≤21 kg body weight are included in the in-use data collection to ensure the best possible comparability of the patient populations for both interventions.

The fourth criterion depicted in Table 23 serves to ensure compliance with all legal requirements of this study (see section 11).

## 7.2 Exclusion Criteria

Patients characterized by any of the criteria listed in Table 24 will not be included in the study.

Table 24: Exclusion criteria and operationalization in SMArtCARE registry

| # | Exclusion criteria | Fields in SMArtCARE CRF (56) |
|---|---|---|
| 1 | Pretreatment with disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) | Medical Assessment: Is the patient on any approved medication for SMA? = yes for any visit before Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |
| 2 | Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | ▪ Medical Assessment: Other medication taken on a regular basis? = Yes<br>AND<br>▪ Medical Assessment: Name of medication (other medication) includes albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, or hydroxyurea<br>AND<br>Medical Assessment: Start Date (other medication) ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |
| 3 | Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA | ▪ Baseline: Is the patient currently or was previously included in a clinical trial? = Yes<br>OR<br>Medical assessment: Is the patient currently in a clinical trial? = Yes for any visit before Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |

The first criterion depicted in Table 24 serves to ensure patients are not pre-treated with any authorized disease modifying drug (DMD) prior to their inclusion in the study.

The second and third criteria depicted in Table 24 ensures that patients are not treated with any disease modifying drug (DMD) not authorized but investigated for use in SMA prior to their inclusion in the study.

## 7.3 Criteria for historic data

The SMArtCARE registry has been enrolling patients since July 2018 (30) and prospectively collected data for patients treated with nusinersen/risdiplam since then. Data on risdiplam has been collected since its authorization in the EU on March 2021. Onasemnogene abeparvovec has been authorized in Germany since July 2020, i.e. two years later than nusinersen and one year earlier than risdiplam. However, a limited number of patients has been treated with onasemnogene abeparvovec on or after January 2020 and therefore prior to marketing authorization and may have been documented in SMArtCARE. As per G-BA request No. 4 of 28 September 2021 (Table 6), historical data, i.e. data prospectively captured in SMArtCARE prior to the start of this study, will be utilized in this study.

The use of data that was collected at different times per intervention generally results in a relevant potential for bias. Even if significant confounders are mapped and data was collected at the time of treatment, it cannot be ruled out that non-measurable confounders, e.g. in the form of changes in the standard of care over time, may have an impact on the results.

As per G-BA's position in the G-BA advice meeting of 11 August 2021, all historical data must meet the following criteria in addition to fulfilling the inclusion and exclusion criteria depicted in sections 7.1 and 7.2 (66):

1. Information must be available on all baseline confounders depicted in section 8.6.1.
2. Information on key endpoints of the study must be available, which are used for sample size calculation. This includes event free survival and motor milestones. Should other endpoints be used for final sample size calculations, which is possible and explicitly allowed by the G-BA resolution (28), information on these endpoints needs to be available.
3. The data on baseline confounders and endpoints used to calculate treatment effects must be quality assured retrospectively by 100% source data verification (section 10.2). As such, informed consent from living patients must have been obtained (section 11.2).

Fulfillment of all criteria required for inclusion of historic patients will be assessed to determine the number of eligible historic patients. The results regarding criteria 1 can be included in the first status report submitted to G-BA (section 12). The results regarding criteria 2 will be reported to G-BA with the first interim analysis.

As informed consent has to be obtained for all patients in order to allow for source data verification, information on the third criterion will be included in subsequent status reports submitted to G-BA (section 12).

Further information on the RESTORE registry as secondary data source is displayed in the RESTORE addendum (Addendum 1), section 7.

# 8. Study Design & Methods: Statistical Considerations

## 8.1 Analysis Populations

In the resolution of February 4 2021, G-BA defined the following patient groups within the PICO-scheme for the Routine Data Collection and Evaluations for inclusion (28):

- Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

Patients who are older than 6 months or 6 weeks at the time of gene therapy with onasemnogene abeparvovec are to be included. As part of the G-BA advice meeting on 29 June 2021, G-BA further specified that pre-symptomatic patients should be stratified by SMN2 copy number (67).

The stratification of patients within the study has been subject to intense exchange with clinical experts. The unanimous assessment of the external experts was that stratification of the study population according to symptom status at the start of treatment is common and feasible in clinical trials in SMA, but not in the Routine Data Collection and Evaluations in German/Austrian routine care based on the SMArtCARE registry. To the knowledge of Novartis Gene Therapies, this also applies to routine care in other geographies globally, regarding the inclusion of international registries as secondary data source (e.g. RESTORE).

Novartis Gene Therapies has explained the reasons for a stratification based solely on the copy number of the SMN2 gene with corresponding control for the characteristic of the symptom status at the start of treatment in the context of the confounder adjustment in the G-BA advice meeting of 11 August 2021 (66):

- As a consequence of early detection and immediate treatment, the importance of the copy number of the SMN2 gene versus the clinical phenotype of the disease is increasing from a clinical perspective (8, 9).
- Due to the introduction of nationwide newborn screening (68) and the results on the proportion of patients treated with disease modifying therapy immediately after diagnosis from the pilot screening (69), it can be assumed that hardly any symptomatic diagnoses and therapy initiations will be observed in Germany prospectively. Stratification based on symptom status at the start of treatment thus effectively prevents the inclusion of historic data to increase patient numbers within study populations. If stratified by symptom status at treatment initiation, it can be assumed

that the vast majority of historic data would be depicted in the study populations of symptomatic patients. In contrast, the vast majority of prospectively collected data will be attributable to the study populations of pre-symptomatic patients because of newborn screening.

- Furthermore, stratification into four instead of two study populations leads to a substantial increase in the required patient numbers for the study. For statistical significance, only the number of cases within a study population is relevant, which is why IQWiG's orienting case number calculation of 106-548 patients (30) applies per study population. Using the mean of the four IQWiG scenarios (282 patients), the required total number of approximately 500 patients would be understandable in case of a stratification into two study populations. Stratification into four study populations, on the other hand, would result in a required total number of more than 1,000 patients, which does not seem feasible given the epidemiological and temporal framework.
- Dichotomous assignment of symptom status, as would be required for stratification of the study population, is not clinically present in patients with SMA. Instead, clinical symptomatology manifests as a continuum. In the context of clinical trials, a stratification based on symptom status has been performed in the past, but due to the continuum character of clinical symptomatology based on predefined thresholds of specialized diagnostic procedures (esp. compound muscle action potential - CMAP). Contrary to the usual procedure for checking inclusion and exclusion criteria in the context of clinical trials, there is no comparable and systematic survey of symptom status in German routine care using specialized diagnostic procedures such as the measurement of specific CMAP amplitudes.

Irrespective of these challenges communicated by Novartis Gene Therapies, G-BA has requested that “the definition of the patient population and the evaluation of the data should be carried out separately for pre-symptomatic and symptomatic patients” (change request No. 1 from 28 September 2021, Table 6). While G-BA did not provide any further information on this change request, IQWIG noted that “a relevant number of patients are also available for retrospective data collection” and that “symptom status, in conjunction with age, contributes to clinical diagnosis and has a relevant impact on treatment outcome” (43).

Novartis Gene Therapies agrees that symptom status at treatment initiation is an important prognostic factor in SMA and had thus proposed to include it as a confounder for adjustment in statistical analysis. However, neither G-BA nor IQWiG speak to the practical challenges, e.g. the impossibility of characterizing symptom status by means of diagnostic information available in German routine care outside of clinical trials or the effective prevention of historic data to increase patient numbers within study populations. As a consequence, both the stratification approach proposed by Novartis Gene Therapies based on recommendations of clinical experts as well as the one requested by G-BA are implemented in this study.

### 8.1.1 NGT approach

In the setting of care for this study, it is appropriate to only stratify study populations based on the copy number of the SMN2 gene. Control of the influence of the symptom status at treatment initiation is achieved via adequate adjustment methods for confounders (section 8.6). In addition, possible effect modification in symptomatic patients will be investigated in the planned subgroup analyses for all confounders (section 8.7).

Main analysis

Patients with 5q-associated SMA with biallelic mutation in the SMN1 gene will thus be stratified by number of copies of the SMN2 gene: up to 2 copies vs. 3 copies. Therefore, the following study populations are defined for analyses:

- Population NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene
- Population NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene

All patients in each population are targeted for effectiveness and safety analyses. The analysis will not be performed on the combined overall population of A and B.

Sensitivity analysis

For sensitivity analysis, additional populations are defined per section 8.5.1 of the SAP.

### 8.1.2 G-BA approach

Main analysis

Per change request No. 1 (Table 6), analyses will also be stratified into the four populations requested by G-BA:

- Population GBA-A: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene
- Population GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA
- Population GBA-C: Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene
- Population GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

All patients in each population are targeted for effectiveness and safety analyses. The analysis will not be performed on the combined overall population of GBA-A, GBA-B, GBA-C, and GBA-D.

Sensitivity analysis

For sensitivity analysis, additional populations are defined per section 8.5.1 of the SAP.

It was originally planned to conduct a sensitivity analysis including ulnar compound muscle action potential (CMAP) as an additional confounder (47) as this was identified as a potential confounder. (70)The sensitivity analysis proved to be infeasible due to a very low degree of documentation in German routine care, leading to almost no data on this confounder in SMArtCARE. The resulting uncertainty, however, is addressed by the use of a “shifted null-hypothesis” when interpreting results.

## 8.2 Sample Size

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling the inclusion and exclusion criteria (section 7) will be included in the study.

As SMA is a rare disease, there is a finite number of patients that can be enrolled with the additional restriction that the study needs to be stratified into two analysis subsets for the NGT approach and four analysis subsets for the G-BA approach (section 8.1). Despite these limitations, sample size calculation and fulfillment of minimum patient numbers is essential to ensure that there will be sufficient numbers of patients to generate interpretable results. If patient numbers are too low compared to required sample size, statistically insignificant results are to be expected irrespective of the true treatment effect.

The sample size calculations provided in the following sections reflect the initial sample size calculations and are no longer up to date, as they have been replaced by the updated sample size calculation in Addendum 4 as mandated by G-BA.

### 8.2.1 NGT approach

Within the scope of the study planning, sample size calculations based on the best available evidence are performed. For a sample size estimation in non-interventional studies, assumptions on effect measure are required as well as assumptions on the available number of patients per treatment and the degree of association between treatment and confounders. The latter point is important because at the time of planning it cannot be assumed that structural comparability can be established using PS methods and confounders must be controlled for using regression-based methods.

In models with more than one covariate, the influence of covariates on the power of the test can be taken into account by using a correction factor. This factor depends on the proportion $R^2$ of the variance of the treatment explained by the regression relationship with the confounders. If $N$ is the sample size considering treatment alone, then the sample size in a setting with additional covariates is

$N' = N/(1 - R^2)$. This correction has been proposed by Hsieh, Bloch et al. (71) and is implemented in G*Power (72).

#### 8.2.1.1 Assumptions of effect measures and event rates

**Population NGT-A**

To derive an estimate for effect measures for population NGT-A, an adjusted indirect comparison of nusinersen and onasemnogene abeparvovec in patients with SMA type I was performed by Novartis Gene Therapies (73). This was based on the START and STR1VE-US studies for onasemnogene abeparvovec and SHINE for nusinersen. Sample size calculations for study population NGT-A are thus based on unpublished results of an ITC of study results from START, STR1VE-US, and SHINE trials, which was performed by Novartis Gene Therapies and used for the purpose of planning this study (73). Adjustments were made for the confounders CHOP-INTEND and ventilatory support at baseline; additional confounders could not be considered due to lack of convergence of the statistical models. The results are shown in Table 25.

Table 25: Effect measures and event rates: SMA type I used for population NGT-A

| Endpoint | Type | Effect measure [95% CI] | Overall event rate for patient ratio 1:1 |
|---|---|---|---|
| EFS until month 18 | TTE | HR: 0.19 [0.07-0.54] | 35.2% |
| Sitting without support to month 18 | binary | OR: 2.88 [0.95-8.73] | 41.6% |

Source: (73)

**Population NGT-B**

For population NGT-B, no results from indirect comparisons are available, which could be used as a basis for a sample size calculation. Against this background, sample size estimates were performed based on very rough assumptions.

Because of the high proportion of patients with 3 copies of the SMN2 gene who achieve unassisted sitting and the low proportion of patients who require permanent ventilation at a young age, other endpoints (e.g. standing, walking, or motor function in HFMSE & RULM) are more likely to show relevant differences. Because no evidence or assumptions are currently available for these endpoints, it was assumed that event rates and effect size for independent standing may be comparable to those observed for independent sitting in SMA type I. The resulting assumptions on effect measures and event rates are shown in Table 26.

Table 26: Assumed effect measures and event rates: Population NGT-B

| Endpoint | Type | Assumend effect measure [95% CI] | Assumend average event rate for patient ratio 1:1 |
|---|---|---|---|
| Standing without support to month 18 | binary | OR: 2.88 [0.95-8.73] | 41.6% |

8.2.1.2 Further assumptions and methods of case number calculation

Sample size calculations were performed for both TTE and binary endpoints. Due to unknown patient proportions in the non-interventional setting, calculations in SAP-Version 1 were performed for both a 1:1 ratio and a 1:2 ratio. Based on IQWiG's assessment of protocol and SAP resulting in the 28 September 2021 change requests from G-BA (Table 6) and its suggestion to reduce scenarios and results of sample size estimations (43), only a patient ratio of 1:1 is used for the purposes of sample size estimation. While unlikely in the prospective part of this study, the utilization of non-parallel nusinersen patients requested by G-BA (change request No. 4 from 28 September 2021) makes an even distribution of patient shares more likely.

The assumed association between treatment and baseline confounders after adjustment in terms of $R^2$ was assumed at two possible levels: 0 (perfect balance, "RCT-like") and 30% (strong association). The following assumptions were used for both types of endpoints:

- Alpha: 0.05 two-sided
- Power: 0.9
- Drop-out/loss-to-follow-up (LTFU): 20% (e.g., due to censoring when changing treatment to risdiplam).

For TTE endpoints, it was additionally assumed:

- Effect measure: HR
- Method for estimating sample size: Cox regression (74)

For binary endpoints, it was additionally assumed:

- Effect measure: OR
- Method for estimating sample size: logistic regression - binomial distribution, enumeration procedure (72, 75) if N < 100.000

8.2.1.3 Results of the sample size calculations

**Population NGT-A**

Based on the assumptions-, for patients with up to 2 copies of the SMN2 gene (population NGT-A), the sample sizes presented in Table 27 result.

Table 27: Required total sample size for patients with up to 2 copies of the SMN2 gene

| Endpoint | Input | $R^2$ between confounders and treatment | Patient ratio 1:1 |
|---|---|---|---|
| EFS until month 18 | HR=0.2,<br>event rate = 35% | 0%<br>30% | 48<br>68 |
| Sitting without support to month 18 | OR=3,<br>event rate = 40% | 0%<br>30% | 189<br>270 |

The calculations show that a statistical power of 0.9 for sitting at month 18 might require about 4 times more patients than for EFS. Changing the association between confounders and treatment from 0 to 30% results in a change of about 50% in the number of patients required.

**Population NGT-B**

For the study population of patients with 3 copies of the SMN2 gene, the sample sizes shown in Table 28 result.

Table 28: Required total sample size for patients with 3 copies of the SNM2 gene

| Endpoint | Input | Association between confounders and treatment $R^2$ | Ratio 1:1 |
|---|---|---|---|
| Standing without support to month 24 | OR=3.5,<br>event rate = 45% | 0%<br>30% | 155<br>221 |

8.2.1.4 Discussion

The sample sizes depicted in Table 27 and Table 28 would have to be targeted for enrollment to ensure adequate power. Based on current estimates of patient enrollment (section 8.3.1), the study will be powered for EFS and independent sitting in study population NGT-A (2 copy SMN2). The study will also likely be powered for independent standing in study population NGT-B (3 copy SMN2) based on current assumptions.

Due to the high degree of uncertainty regarding both effect measures and event rates used for sample size calculation as well as patient enrollment, NGT had

proposed to link sample size calculations along with their update to actual enrollment of patients by performing final outcome analysis only after sample size is reached in protocol version 1.01. However, G-BA requested that all planned outcome analyses are to be performed at fixed dates defined in the G-BA resolution and thus irrespective of the actual enrollment of patients compared to the number of patients needed to ensure adequate power for at least one key endpoint derived from sample size calculations (change request No. 22 from 28 September 2021, Table 6).

### 8.2.2 G-BA approach

8.2.2.1 Assumptions and methods of case number calculation

In its review of the study protocol and the SAP version 1.01 (43), IQWiG criticized that no shifted null hypothesis was used in sample size considerations. It was argued, that a statement on the benefit or harm of an intervention could only be derived from effects observed above or below a certain effect size because of potentially unknown confounders in this non-randomized study. According to IQWiG's review of the study protocol and SAP, statement on benefit or harm can only be made if the 95% confidence interval for the observed effect is above or below a threshold to be defined and refers to its rapid report (43) for a potential threshold.

IQWiG's rapid report (33) names the range $RR_0 = 2 \; to \; 5$ (or $RR_0 = 0.5 \; to \; 0.2$ for risk-reduction) as the spectrum of such thresholds for non-randomized trials. According to IQWiG's usual procedure the threshold has to be applied to the boundaries of the 95% confidence interval.

Since IQWiG derives this range from the effect measures defining a "dramatic effect" (RR = 5-10) in its general methods (55) by extending the range of values to 2-5, it would seem appropriate to apply the same rationale to this range as to the dramatic effect. IQWiG's general methods define the criteria for a dramatic effect to be (a) statistically significant on a .01 level and (b) a relative risk in the range 5-10. This is also depicted in G-BA's resolution practice, e.g. its resolution granting an additional benefit for cerliponase alfa due to a dramatic effect based on a HR of 0.1 with a 95% confidence interval of 0.03-0.38 and p=0.0005 (76).

However, IQWiG applies its relative risk threshold of 2-5 for the Routine Data Collection and Evaluations to the boundaries of the 95% confidence interval instead of the effect estimate. Such a threshold would require effect estimates to be well above the threshold of 2-5 and thus in or very close to the range of a "dramatic effect" (relative risk of 5-10). By applying the threshold to the boundaries of the 95% confidence interval, the criteria for the Routine Data Collection and Evaluations of onasemnogene abeparvovec would thus not be "well below the value for the 'dramatic effect'" but rather very much in the same range.

Irrespective of these circumstances, G-BA recommended that an orienting sample size calculation until month 36 is performed using a shifted null hypothesis (45). G-BA did not specify for which endpoint such an orienting sample size calculation is to be performed. Given the significant amount of uncertainty on event rates and effect sizes as well as the relatively high number of endpoints depicted in this study per the PICO scheme defined by G-BA, a general orienting sample size calculation for TTE effectiveness endpoints was performed. Initial assumptions are:

- $RR_0$/ $HR_0$=0.5
- alpha = 0.05 two-sided
- beta = 0.2
- negligible censoring

Sample sizes for RR are estimated using the formula of Farrington and Manning (77) in its implementation function *nBinomial* in the R-library *gsDesign* (78).

Since IQWiG only accepts non-randomized trials with balanced known confounders between treatment arms, no association between confounders and treatment in terms of $R^2$ is reflected in the following sample size calculations.

#### 8.2.2.2 Results of the sample size calculations

Since no estimator for the event rate under nusinersen treatment until month 36 as well initial guidance on treatment effects will only be available at the time of first interim analysis, three values for event rates in terms of “low”, “medium” and “high” are used in Table 29: 20% (low) 50% (medium) and 80% (high).

Table 29: Assumed effect sizes and event rates of nusinersen patients for the G-BA populations (Pop GBA-A – GBA-D)

| HR/RR | Event rate Nusinersen until month 36 | Sample Size | | | |
|---|---|---|---|---|---|
| 0.2 | 20% | 2 | x | 216 | = 432 |
| | 50% | 2 | x | 71 | = 142 |
| | 80% | 2 | x | 34 | = 68 |
| 0.4 | 20% | 2 | x | 2,359 | = 4,718 |
| | 50% | 2 | x | 744 | = 1,488 |
| | 80% | 2 | x | 336 | = 672 |

8.2.2.3 Discussion

The sample sizes depicted in Table 29 would have to be targeted for enrollment to ensure adequate power. Based on current estimates of patient enrollment (section 8.3.1), the study will only be powered for endpoints that show very substantial effect size (e.g. HR=0.2) and high event rates (around 50%).

Due to the high degree of uncertainty regarding both effect measures and event rates used for sample size calculation as well as patient enrollment, NGT had proposed to link sample size calculations along with their updates to actual enrollment of patients by performing final outcome analysis only after sample size is reached in protocol version 1.01 (64). However, G-BA requested that all planned outcome analyses are to be performed at fixed dates defined in the G-BA resolution and thus irrespective of the actual enrollment of patients compared to the number of patients needed to ensure adequate power for at least one key endpoint derived from sample size calculations (change request No. 22 from 28 September 2021, Table 6).

### 8.2.3 Update of sample size calculations with interim analyses

Due to substantial uncertainties regarding patient proportions, drop-out rates, event rates, effect sizes, and the association of confounders and treatment outcomes, sample size will be updated with the first interim analysis 36 months after the G-BA resolution date of 4 February 2021.

The first interim analysis will generate effect estimates and event rates as well as information on censoring events that will be reported to G-BA. Based on these results, sample size calculations as described in sections 8.2.1 and 8.2.2 can be performed for the respective study populations. For the most appropriate and feasible endpoint per analysis population (which need not necessarily be EFS or a motor function endpoint), a hypothesis is formulated, and sample size calculation is conducted according to section 5.4 of the SAP while considering additional interim analyses and adjustments of the alpha error.

The results of sample size update with the first interim analysis are depicted in detail in Addendum 4 and serve as the basis for the feasibility assessment (section 8.4) that will be reported to G-BA. Results will also be included in the submission of module 4 of the dossier template to G-BA.

Per G-BA resolution from 6 June 2024, a final sample size estimation and futility assessment is performed with the second interim analysis. This is depicted in Addendum 5 of this protocol.

## 8.3 Expected patient numbers

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling in inclusion and exclusion criteria (section 7) will be included in the study.

Nationwide newborn screening for SMA is performed in Germany starting from October 2021 (68) and pilot nationwide newborn screening was also introduced in Austria in 2021 (79). All prospective patients of this study are thus expected to be identified from newborn screening. However, per G-BA change request No. 4 from 28 September 2021 (Table 6), historic patients will also be included in the study. As a consequence, patients diagnosed predominantly symptomatically before the introduction of newborn screening will also be included in the study.

Estimates of expected patient numbers are performed exclusively for the primary data source (SMArtCARE) and based on the incidence of SMA based on the results of pilot newborn screening for SMA in Germany (69). Based on 297,163 screened newborns, the SMA incidence was determined to be 1 per 6,910 births. Based on approx. 780,000 live births in Germany (80) and approx. 85,000 live births in Austria per year (81), this results in a total of 125 patients with SMA being born in Germany and Austria together each year. Pilot newborn screening reports 40% of SMA incidence to show up to 2 copies of the SMN2 gene and 23% to show 3 copies of the SMN2 gene (69).

All estimates of the required case numbers as well as the included patient numbers are subject to considerable uncertainty, as Novartis Gene Therapies has no influence on the course of this non-interventional study. It was originally assumed that all patients diagnosed with SMA from 2022 onward are documented in SMArtCARE while an average of 75% of patients diagnosed with SMA between the start of enrollment in SMArtCARE in July 2018 to December 2021 are documented in

SMArtCARE. Results of the first status report (82) suggest that the assumptions used for until December 2021 were slightly conservative with a total of 252 patients included in SMArtCARE compared to an estimated number of 276 diagnosed cases and 206 cases expected to be enrolled. It also suggests that recruitment is generally in line with predictions and given an ideal assumption of 100% depiction of diagnosed cases in SMArtCARE starting in January 2022, it seems appropriate to hold up the originally estimated patient numbers depicted in the following sections (8.3.1, 8.3.1).

An update of the sample size calculations as well as a feasibility assessment was provided in Addendum 4.

Information on expected patient numbers in the RESTORE registry as secondary data source is displayed in the RESTORE addendum (Addendum 1), section 8.

### 8.3.1 NGT approach

#### 8.3.1.1 Population NGT-A

Table 30 summarizes the calculation of potential patient numbers for population NGT-A (up to 2 copies of the SMN2 gene).

Table 30: Expected patient numbers for Germany and Austria: Population NGT-A

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (2 copy SMN2) | 49 |
| 2 | Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 3.5*(1)* | 173 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 247 |
| 4 | Total number of potentially eligible patients enrolled in SMArtCARE<br>*Calculation: (2)*0.75+(3)* | 377 |
| 5 | Patients with less that 18 months of observation time at time of data cut for final analysis<br>*Calculation:* 1.5*(1) | 74 |
| 6 | Patients potentially available for outcome analysis at time of data cut for final analysis<br>Calculation: (4)-(5) | 303 |

*Note: Illustration of rounded numbers. Calculation based on exact numbers.*

Based on the stated assumptions, up to 377 patients for population NGT-A may be enrolled in SMArtCARE.

Due to limitations in analyzing motor function endpoints before an age of 18 months, 74 patients with treatment initiation within 18 months of the final data cut will not be fully available for outcome analysis. Up to 303 patients may thus be fully eligible for final outcome analysis.

#### 8.3.1.2 Population NGT-B

Table 31 summarizes the calculation of potential patient numbers for population NGT-A (3 copies of the SMN2 gene).

Table 31: Expected patient numbers for Germany and Austria: Population NGT-B

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (3 copy SMN2) | 29 |
| 2 | Patients diagnosed between July 2019 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 3.5*(1)* | 102 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 146 |
| 4 | Total number of potentially eligible patients enrolled in SMArtCARE<br>*Calculation: (2)*0.75+(3)* | 222 |
| 5 | Patients with less that 18 months of observation time at time of data cut for final analysis<br>*Calculation:* 1.5*(1) | 44 |
| 6 | Patients potentially available for outcome analysis at time of data cut for final analysis<br>Calculation: (4)-(5) | 178 |

*Note: Illustration of rounded numbers. Calculation based on exact numbers.*

Based on the stated assumptions, up to 222 patients for population NGT-B may be enrolled in SMArtCARE

Due to limitations in analyzing motor function endpoints before an age of 18 months, 44 patients with treatment initiation within 18 months of the final data cut will not be fully available for outcome analysis. Up to 178 patients may thus be fully eligible for final outcome analysis.

### 8.3.2 G-BA approach

An estimate of the distribution of patients based on a stratification by symptom status is subject to high uncertainty. It is assumed that 80% of patients were diagnosed symptomatically prior to the introduction of newborn screening, which is dated to January 2022 for both Germany and Austria for reasons of simplifying calculations. After the introduction of nationwide newborn screening, significant challenges remain in classifying patients by symptom status in routine clinical practice (section 8.1). For pilot newborn screening, children with normal muscle tone, a CHOP INTEND score of > 35 points, an ulnar CMAP amplitude > 1 mV, and no deterioration in their first 4 weeks of life were considered pre-symptomatic (69). 53% of 2 copy SMN2 children were pre-symptomatic while 47% of 2 copy SMN2 children were classified as symptomatic. 100% of 3 copy SMN2 children were diagnosed pre-symptomatically (69).

While these shares are used for estimating patient numbers for G-BA-mandated study populations, it is expected that the application of CHOP-INTEND and ulnar CMAP amplitude for determining symptom status, which is not performed in routine clinical practice in Germany, may have led to significantly higher shares of symptomatic patients compared to a purely clinical assessment on the presence of symptoms in newborns.

#### 8.3.2.1 Population GBA-A

Table 32 summarizes the calculation of potential patient numbers for population GBA-A (pre-symptomatic patients with up to 2 copies of the SMN2 gene).

Table 32: Expected patient numbers for Germany and Austria: Population GBA-A

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (2 copy SMN2) | 49 |
| 2 | Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 3.5*(1)* | 173 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 247 |
| 4 | Pre-symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 0.2*(2)* | 35 |
| 5 | Pre-symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 0.53*(3)* | 131 |
| 6 | Total number of potentially eligible patients enrolled in SMArtCARE | 157 |

| Step | Description | No. |
|---|---|---|
| | *Calculation: (4)*0.75+(5)* | |

*Note: Illustration of rounded numbers. Calculation based on exact numbers.*

8.3.2.2 Based on the stated assumptions, up to 157 patients for population GBA-A may be enrolled in SMArtCARE Population GBA-B

Table 33 summarizes the calculation of potential patient numbers for population GBA-B (symptomatic patients with a clinically diagnosed type 1 SMA).

Table 33: Expected patient numbers for Germany and Austria: Population GBA-B

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (2 copy SMN2) | 49 |
| 2 | Patients diagnosed between July 2018 (enrollment start of SMArt-CARE) and December 2021<br>*Calculation: 3.5*(1)* | 173 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 247 |
| 4 | Symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 0.8*(2)* | 139 |
| 5 | Symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 0.47*(3)* | 116 |
| 6 | Total number of potentially eligible patients enrolled in SMArtCARE<br>*Calculation: (4)*0.75+(5)* | 220 |

*Note: Illustration of rounded numbers. Calculation based on exact numbers.*

8.3.2.3 Based on the stated assumptions, up to 220 patients for population GBA-B may be enrolled in SMArtCARE Population GBA-C

Table 34 summarizes the calculation of potential patient numbers for population GBA-C (pre-symptomatic patients with 3 copies of the SMN2 gene).

Table 34: Expected patient numbers for Germany and Austria: Population GBA-C

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (3 copy SMN2) | 29 |
| 2 | Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 3.5*(1)* | 102 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 146 |
| 4 | Pre-symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 0.2*(2)* | 20 |
| 5 | Pre-symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 1*(3)* | 146 |
| 6 | Total number of potentially eligible patients enrolled in SMArtCARE<br>*Calculation: (4)*0.75+(5)* | 161 |

*Note: Illustration of rounded numbers. Calculation based on exact numbers.*

Based on the stated assumptions, up to 161 patients for population GBA-C may be enrolled in SMArtCARE.

#### 8.3.2.4 Population GBA-D

Table 35 summarizes the calculation of potential patient numbers for population GBA-D (symptomatic patients with a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene).

Table 35: Expected patient numbers for Germany and Austria: Population GBA-D

| Step | Description | No. |
|---|---|---|
| 1 | Patients diagnosed per year in Germany and Austria (3 copy SMN2) | 29 |
| 2 | Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021<br>*Calculation: 3.5*(1)* | 102 |
| 3 | Patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 5*(1)* | 146 |
| 4 | Symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 | 82 |

| Step | Description | No. |
|---|---|---|
| | *Calculation: 0.8*(2)* | |
| 5 | Symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis)<br>*Calculation: 0*(3)* | 0 |
| 6 | Total number of potentially eligible patients enrolled in SMArtCARE<br>*Calculation: (4)*0.75+(5)* | 61 |
| *Note: Illustration of rounded numbers. Calculation based on exact numbers.* | | |

Based on the stated assumptions, up to 61 patients for population GBA-D may be enrolled in SMArtCARE.

## 8.4 Feasibility assessment

Due to considerable uncertainties regarding the required number of cases (section 8.2) and the actual number of patients included, an a priori assessment of the study feasibility for each study population is impossible. G-BA has requested that a feasibility assessment is performed with each interim analysis, i.e. 36 and 54 months after its resolution in 4 February 2021 (28) (change request No. 22 from 28 September 2021, Table 6) and the change in submission requirements with its 20 January 2022 resolution (45).

The assessment will be made per study population based on the following information:

- Updated sample size calculations (section 8.2) based on interim analysis results
- Number of eligible patients fulfilling inclusion and exclusion criteria per study population and extrapolation of patient numbers for nusinersen/risdiplam and onasemnogene abeparvovec based on study enrollment until time of interim analysis

Novartis Gene Therapies will report the results of the feasibility assessment for all study populations to G-BA together with all interim analysis results 36 and 54 months after the 4 February 2021 resolution. Novartis Gene Therapies will include a recommendation on continuation or termination of each study population building on the results of updated sample size calculations as well as extrapolated enrollment numbers. Any decision on actual termination of a population via an amendment of the study protocol and SAP is only made after consultation with G-BA.

For G-BA populations (GBA-A, GBA-B, GBA-C, GBA-D), sample sizes will be calculated using the approach of a shifted null hypothesis ($RR_0 = 0.5$). For NGT populations, standard null hypothesis ($RR_0 = 1$) will be used.

An update of the sample size calculations as well as a feasibility assessment is depicted in Addendum 4 for the first interim analysis and in Addendum 5 for the second interim analysis.

## 8.5 Planned Analyses

Multiple analyses are planned for the Routine Data Collection and Evaluations and described in the following sections (8.5.1, 8.5.2, 8.5.3, 8.5.4).

In addition to statistical analyses performed for the described submissions, analyses defined in the SAP may be performed at any time based on data cuts supplied by SMArtCARE in order to develop and update statistical analysis programs as well as analytics on data quality. Results of such analyses are provided to Novartis Gene Therapies and the respective registry (i.e. SMArtCARE depending on the data source that is analyzed) in an aggregated format.

### 8.5.1 Status report 18 months after G-BA resolution

G-BA has changed the submission requirements with its resolution of 20 January 2022 (45). A first status report will be submitted to G-BA 18 months after its 4 February 2021 resolution, i.e. by 4 August 2022. The report will be submitted using module 4 of the dossier template to be consistent with interim analyses and will cover the following aspects:

- Description of assumptions and key steps of data processing that were required to generate status report results
- Patient numbers per study population and intervention as well as per included treatment center
- Baseline characteristics for all study populations for both interventions including extend of missing values
- Standardized mean differences per confounder for all study population
- Observation times and treatment switching on study population and endpoint level per intervention
- For patient populations, in which patient numbers and confounder data allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
  - Graphical illustration of overlap per patient population before adjustment using density plots
- For patient populations with sufficient overlap for adjusted analyses using propensity score matching (PSM):
  - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis

- Baseline characteristics for patients included in adjusted analysis after applying PS weights
- Standardized mean differences after applying PS weights

Data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA will require 6 months. This is due to the number of populations requested by G-BA a high need for alignment with SMArtCARE as well as queries on implausible data performed by SMArtCARE with the documenting treatment centers. As such, data for the first interim analysis is cut in January 2022 but updates as a results of queries are incorporated during the period of status report generation.

### 8.5.2 Status report and interim analysis 36 months after G-BA resolution

Per the G-BA resolution of 4 February 2021 (28) and 20 January 2022 (45), a first interim analysis will be submitted to G-BA 36 months after the resolution date, i.e. by 4 February 2024. This interim analysis will be submitted using module 4 of the dossier template and covers the following aspects:

- Description of assumptions and key steps of data processing that were required to generate status report results
- Patient numbers per study population and intervention as well as per included treatment center
- Baseline characteristics for all study populations for both interventions including extend of missing values and strategies pursued to address missing values in statistical analysis
- Standardized mean differences per confounder for all study population
- Observation times and treatment switching on study population and endpoint level per intervention
- For patient populations, in which patient numbers and confounder data allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
  - Graphical illustration of overlap per patient population before adjustment using density plots
- For patient populations with sufficient overlap for adjusted analyses using PSM:
  - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
  - Baseline characteristics for patients included in adjusted analysis after applying PS weights

- Standardized mean differences after applying PS weights

- Results of main and sensitivity analyses for all endpoints
- Results of subgroup analyses

In addition, sample size recalculation as described in section 8.2.2.3, potential deviations from expected patient numbers described in section 8.3, and results of the feasibility assessment described in section 8.4 will be provided via an annex to module 4 of the dossier template.

While it is acknowledged that G-BA recommended to shorten the time between data cut and submission, experience from the first status report shows that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA requires a minimum of 6 months. This is due to the number of populations, endpoints, and subgroup analyses requested by G-BA as well as a need for alignment with registry providers as well as queries on implausible data performed by registry providers with the documenting treatment centers. As such, data for the first interim analysis will be cut in August 2023 but updates as a results of queries are incorporated during the period of status report generation.

### 8.5.3 Status report and interim analysis 54 months after G-BA resolution

Per the G-BA resolution of 4 February 2021 (28) and 20 January 2022 (45), a second interim analysis will be submitted to G-BA 54 months after the resolution date, i.e. by 4 August 2025. This interim analysis will be submitted using module 4 of the dossier template and covers the following aspects:

- Description of assumptions and key steps of data processing that were required to generate status report results
- Patient numbers per study population and intervention as well as per included treatment center
- Futility check and final sample size estimation
- Baseline characteristics for all study populations for both interventions including extend of missing values and strategies pursued to address missing values in statistical analysis
- Standardized mean differences per confounder for all study population
- Observation times and treatment switching on study population and endpoint level per intervention
- For patient populations, in which patient numbers and confounder data allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
  - Graphical illustration of overlap per patient population before adjustment using density plots

- For patient populations with sufficient overlap for adjusted analyses using PSM:
  - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
  - Baseline characteristics for patients included in adjusted analysis after applying PS weights
  - Standardized mean differences after applying PS weights
- Results of main and sensitivity analyses for all endpoints
- Results of subgroup analyses

In addition, potential deviations from expected patient numbers described in section 8.3 and results of the feasibility assessment described in section 8.4 will be provided via an annex to module 4 of the dossier template.

While it is acknowledged that G-BA recommended to shorten the time between data cut and submission, experience from the first status report shows that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA requires a minimum of 6 months. This is due to the number of populations, endpoints, and subgroup analyses requested by G-BA as well as a need for alignment with registry providers as well as queries on implausible data performed by registry providers with the documenting treatment centers. As such, data for the second interim analysis will be cut in January 2025 but updates as a results of queries are incorporated during the period of status report generation.

### 8.5.4 Final analysis for benefit assessment (submission on July 1 2027)

Per the G-BA resolution of 4 February 2021 (28), a value dossier for the benefit assessment is to be submitted to G-BA by 1 July 2027. The value dossier will be based on the final analysis and include the following aspects:

- Description of assumptions and key steps of data processing that were required to generate status report results
- Patient numbers per study population and intervention as well as per included treatment center
- Baseline characteristics for all study populations for both interventions including extend of missing values and strategies pursued to address missing values in statistical analysis
- Standardized mean differences per confounder for all study population
- Observation times and treatment switching on study population and endpoint level per intervention

- For patient populations, in which patient numbers and confounder data allow for calculation of PS (i.e. if logistic regressions to calculate PS converge):
  - Graphical illustration of overlap per patient population before adjustment using density plots
- For patient populations with sufficient overlap for adjusted analyses using PSM:
  - Unweighted baseline characteristics of patients trimmed from adjusted analyses as well as for patients included in adjusted analysis along with a discussion on appropriateness of the resulting population included in adjusted analysis for the initial question
  - Baseline characteristics for patients included in adjusted analysis after applying PS weights
  - Standardized mean differences after applying PS weights
- Results of main and sensitivity analyses for all endpoints
- Results of subgroup analyses

Initially, a sensitivity analysis including ulnar compound muscle action potential (CMAP) was planned as an additional confounder (47).(70) However, this analysis turned out to be unfeasible due to a very low degree of documentation in German routine care and will therefore not be conducted. The omission of this planned sensitivity analysis leads to additional uncertainty regarding the results. These uncertainties will be covered in particular by the approach of applying a shifted null hypothesis.

All results will be reported and discussed in light of a shifted null-hypothesis, taking into account key aspects of the confounder adjustment like the extend of overlap, remaining heterogeneity in confounders after adjustment in terms of SMDs, as well as extend of missing values before imputation.

Experience from the first status report shows that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA requires a minimum of 6 months. This is due to the number of populations, endpoints, and subgroup analyses requested by G-BA, the need for alignment with registry providers, as well as queries on implausible data performed by registry providers with the documenting treatment centers. As such, data for final analysis will be cut in December 2026 but updates as a results of queries are incorporated during the period of value dossier generation.

## 8.6 Prognostic factors and potential confounders

### 8.6.1 Confounder identification and validation

Based on a systematic identification of potential confounders in national and international guidelines and publications as well as their validation by clinical experts, the convergence to structural comparability in the study arms is achieved by appropriate adjustment methods for pre-specified confounders. Validation of the identified confounders was performed by six German clinical SMA experts. Validation was performed by categorizing each confounder identified via systematic literature review (SLR) into one of the following three categories:

- **Very important:** These parameters have a significant effect on patient's outcomes and are essential for adjustment of statistical analyses in a non-randomized trial.
- **Less important:** These parameters have a moderate effect on patient's outcomes and should be controlled in statistical analysis. However, if selected confounders of this category cannot be controlled, results would still be considered valid.
- **Not important:** These parameters are not considered relevant for the specific study, e.g. due to coverage as endpoints or because of the specific study setting (quality controlled centers in Germany).

The confounders listed in Table 36 have been identified as clinically (very or less) important and are thus potentially relevant for the population included in this study. Categorization of confounders was exclusively performed by clinical experts with no influence from Novartis Gene Therapies. All confounders identified in the literature and categorized as clinically very important and less important for the population of this study are depictable in SMArtCARE and included in the study. While categorization as "not important" vs. "very/less important" by clinical experts determines inclusion in the study, categorization as "very important" vs. "less important" is of no relevance in the context of this study as both confounder categories are treated identically in statistical analysis. However, according to G-BA the classification also has potentially significant consequences for the interpretation of the results. Per G-BA resolution from 20 October 2022, the confounder of age at symptom onset was re-classified as very important.

All confounders identified via SLR and considered not important in the context of this study are depicted in annex A1.

With version 3.01 of study protocol and SAP, SMN2 copy number was added as a confounder applicable to populations GBA-B (clinically diagnosed type 1 SMA) and GBA-D (clinically diagnosed type 2 SMA) as well as sensitivity analysis populations GBA-Pool1 (A+B) and GBA-Pool2 (C+D) because data analysis for the first status report revealed that patients with more than two copies of the SMN2 gene are assigned to population GBA-B and patients with less than three copies of the SMN2 gene are assigned to population GBA-D in contrast to original expectations. Since

clinical experts declared this parameter as clinically very important, it is required to be depicted in confounder adjustment if population definitions do not yield stratification by this factor. For all other populations, all included patients are homogeneous with regard to their SMN2 copy number by definition of the populations.

Table 36 shows the operationalization of confounders in SMArtCARE registry.

Information on confounders in the RESTORE registry is displayed in the RESTORE addendum (Addendum 1), section 8. Depictability of confounders in SMArtCARE (previously reported in version 3.01 of the study protocol) is now reported in the second addendum (Addendum 2) to the study protocol version 4.01.

Table 36: Overview of identified confounders, their clinical relevance and corresponding availability in SMArtCARE

| Confounder | Clinical relevance[2] | Included in Study | Definition | Fields of SMArtCARE CRF (56) | Applicable to analysis populations |
|---|---|---|---|---|---|
| SMN2 copy number | Very important | Yes | Number of SMN2 copies assessed per genetic testing | ▪ Genetic Test Result: SMN2 copy number | Main analysis:<br>G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis:<br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at symptom onset | Very important | Yes | Age of symptom onset in months for symptomatic patients | ▪ Baseline: Age at symptom onset | Main analysis:<br>G-BA approach: GBA-B, GBA-D |
| Symptom status at treatment initiation | Very important | Yes | Symptomatic:<br>Diagnosis not made presymptomatically OR documentation of symptoms related to SMA at any medical assessment prior to AT | Symptomatic:<br>▪ Baseline: Was diagnosis made presymptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes | Main analysis:<br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: none (stratification parameter)<br><br>Sensitivity analysis: |

[2] According to the assessment of the six clinical experts consulted during the confounder validation process

| Confounder | Clinical relevance[2] | Included in Study | Definition | Fields of SMArtCARE CRF (56) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | treatment initiation<br><br><u>Pre-symptomatic:</u><br>Diagnosis made pre-symptomatically AND no symptoms related to SMA at any medical assessment prior to treatment initiation | ▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br><br><u>Pre-symptomatic:</u><br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at treatment initiation/treatment delay | Very important | Yes | Age in weeks at treatment initiation | ▪ Medical Assessment: Age at visit<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach:<br>▪ Directly: GBA-A, GBA-C<br>▪ Derived (treatment delay defined as time from symptom onset to treatment initiation: GBA-B, GBA-D<br><u>Sensitivity analysis:</u> |

| Confounder | Clinical relevance[2] | Included in Study | Definition | Fields of SMArtCARE CRF (56) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | | ▪ GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Nutrition support | Very important | Yes | Gastric tube or nasal feeding tube (exclusive/supplemental/none) at treatment initiation | ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube?<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Ventilation support | Very important | Yes | Duration of ventilator use (nighttime/intermittent/permanent (≥16h/day) at treatment initiation | ▪ Medical assessment: Does the patient receive ventilator support? = Yes<br>AND<br>▪ Medical assessment: Time of ventilator use<br>o Night (during sleep)<br>o Intermittent day time and continuous at night<br>o Continuous (>16h/day)<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Contractures | Less important | Yes | Contractures limiting function (yes/no) at treatment initiation | ▪ Medical Assessment: Are any contractures present? = Yes<br>AND | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D |

| Confounder | Clinical relevance[2] | Included in Study | Definition | Fields of SMArtCARE CRF (56) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | ▪ Medical assessment: Type of limitation = Severe (imposing limits to function)<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | <u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Motoric function: Highest motor milestone | Very important | Yes | Highest motor milestone at treatment initiation:<br>▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing without support<br>▪ Walking without support<br>▪ Climb stairs | ▪ Medical assessment: Best current motor function<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | All |
| Motoric function: CHOP-INTEND | Very important | Yes | CHOP-INTEND score at treatment initiation (≤ Median CHOP-INTEND, > Median CHOP-INTEND) | ▪ CHOP-INTEND: Score<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | All |

A detailed description of the process of confounder identification and validation is given in Annex 1 of this protocol. The clinically very important confounder of SMN2 copy number is depicted in this study via stratification of study populations (section 8.1) in both NGT and G-BA approaches.

Potential effects from different standards of care between HSPs will be addressed via sensitivity analysis (section 8.5 of the SAP).

For sensitivity analysis, ulnar compound muscle action potential (CMAP) amplitude was originally included in baseline confounders but experience from first status report showed that data is available for almost no patients. It was thus removed with version 3.01 of protocol and SAP (47). This removal will be discussed in the final analysis in light of a shifted null-hypothesis (see section 8.5.4).

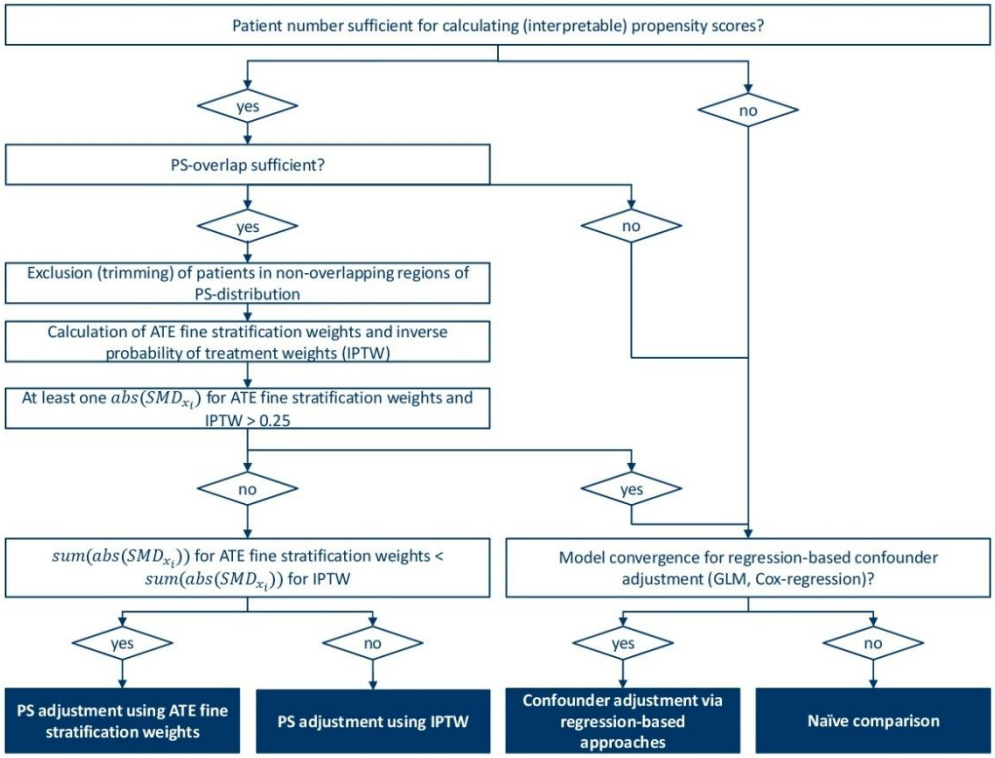
Due to limitations in data availability on CHOP-INTEND at the time of second interim analysis the RESTORE registry (>50% missing values in all populations), the confounder CHOP-INTEND is not included in adjustment for RESTORE in the second interim analysis. For all other analysis sources (SMArtCARE, IPD meta-analysis), CHOP-INTEND is included as a confounder and missing values in CHOP-INTEND are subject to standard imputation of missing values as described in SAP section 8.2.2. As retrospective data capture and SDV is ongoing in RESTORE, this handling may not be needed for final analysis.

### 8.6.2 Adjustment for confounders

Registry data are associated with several disadvantages: lack of randomization and thus unbalanced covariates and potentially different treatment time periods between study interventions. Bias due to time-shifts needs to be discussed in the study report, missing randomization will be countered with adjustment methods.

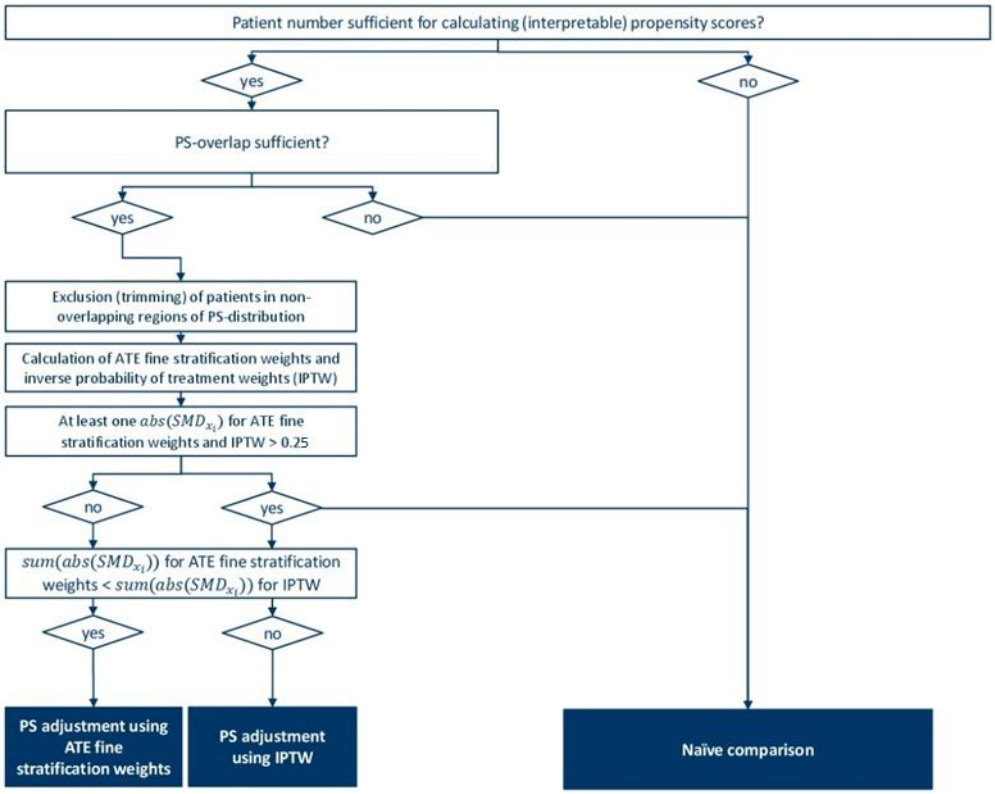
For both NGT and G-BA approaches, adjustment of confounders will take place using appropriate methods following a pre-specified decision tree. Figure 4 illustrates the decision tree for NGT approach, Figure 5 illustrates the decision tree for G-BA approach. See SAP section 8.1 for details.

Figure 4: Adjustment for confounders: NGT approach




*Overlap is assessed graphically. Intuitively, one would assume that the overlap should be ≥ 50% to call a minimum for the degree of overlap.

Figure 5: Adjustment of confounders: G-BA approach




* Overlap is assessed graphically. Intuitively, one would assume that the overlap should be ≥ 50% to call a minimum for the degree of overlap.

## 8.7 Subgroup analyses

### 8.7.1 Subgroups for baseline characteristics

As far as possible, subgroup analyses for all endpoints are planned based on the following patients' baseline characteristics. Table 37 contains all planned subgroup analyses in this study

Information on subgroups in the RESTORE registry as secondary data source is displayed in the RESTORE addendum (Addendum 1), section 8.7. Depictability of subgroups in SMArtCARE (previously reported in version 3.01 of the study protocol) is now reported in the second addendum (Addendum 2) to the study protocol version 4.01.

Table 37: Overview of planned subgroup analyses in this comparative analysis

| Planned subgroups | Patients' baseline status | Fields of SMArtCARE CRF (56) | Applicable for analysis populations |
|---|---|---|---|
| SMN2 copy number | ▪ 1<br>▪ 2<br>▪ 3<br>▪ 4 | ▪ Genetic Test Result: SMN2 copy number | Main analysis:<br>G-BA approach:<br>GBA-B,<br>GBA-D<br><br>Sensitivity analysis:<br>GBA-Pool1 (A+B),<br>GBA-Pool2 (C+D) |
| Age at treatment initiation | ▪ ≤ 4 weeks<br>▪ > 4 weeks | ▪ Enrolment: Date of birth<br>▪ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | All |
| Gender | ▪ Male<br>▪ Female<br>▪ Undifferentiated<br>▪ Unknown | ▪ Enrolment: Gender | All |
| Region | ▪ Germany<br>▪ Austria<br>▪ | ▪ N.a. (Treatment center information not part of SMArtCARE CRF but available in SMArtCARE database) | All |
| Symptom status at treatment initiation | ▪ Symptomatic<br>▪ Pre-symptomatic | Symptomatic:<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br><br>Pre-symptomatic:<br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT | NGT approach:<br>NGT-A,<br>NGT-B |

| Planned subgroups | Patients' baseline status | Fields of SMArtCARE CRF (56) | Applicable for analysis populations |
|---|---|---|---|
| | | Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | |
| Nutrition support (Does the patient use a gastric or nasal feeding tube?) | ▪ No<br>▪ Yes - exclusively fed by tube<br>▪ Yes – supplementary e.g. for fluids | ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? AT<br>▪ Medical Assessment: Visit Date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D |
| Ventilation support (Does the patient receive ventilator support?) | ▪ No<br>▪ Yes | ▪ Medical assessment: Does the patient receive ventilator support? AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D |
| Contractures (Contractures limiting function) | ▪ No<br>▪ Yes | ▪ Medical Assessment: Are any contractures present? = Yes AND<br>▪ Medical assessment: Type of limitation = Severe (imposing limits to function) AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D |
| Motor function: Highest motor milestone | ▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing with-out support<br>▪ Walking with-out support<br>▪ Climb stairs | ▪ Medical assessment: Best current motor function AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | All |
| Motor function: CHOP-INTEND score | ▪ ≤ Median CHOP-INTEND<br>▪ > Median CHOP-INTEND | ▪ CHOP-INTEND: Score AT<br>▪ Medical Assessment: Visit date = Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) | All |

### 8.7.2 Analysis methods

Subgroup analyses are planned for all endpoints in all analysis populations. Patients with missing values in subgroup variables will be discarded from analyses as well as patients in subgroup categories that are only present in one treatment arm.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived within the analytical framework as described in section 11 of the SAP.

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients.

Subgroup analyses for binary events per variable are conducted only if at least 10 events occurred in one of the subgroups.

# 9. Safety

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only; no reporting on an individual case level to NGT is required.

In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions will be summarized in the study report, i.e. the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

# 10. Data Handling and Monitoring

## 10.1 Data Management

All clinical data for this project are collected and stored exclusively in the SMArtCARE registry. Study site personnel are responsible for patient data collection and data entry into SMArtCARE. Data will be entered into electronic case report forms (eCRFs) of the SMArtCARE registry.

SMArtCARE uses a clinical database provided by OpenApp. According to SMArtCARE, the clinical database offers a query workflow for a documented and efficient data review process. Validation of patient data in the clinical database is carried out via automated edit checks as well as manual checks raised by clinical research associates during on-site routine monitoring visits (RMVs).

Information on data management of the RESTORE registry is displayed in the RESTORE addendum (Addendum 1), section 10.1.

## 10.2 Source Data verification

To minimize the potential for bias in the use of registry data as part of the Routine Data Collection and Evaluations, 100% on-site SDV will be performed for all data fields in the SMArtCARE registry that are applied to determine inclusion and exclusion criteria, confounders, and endpoints for the study (Annex 10).

Source data verification will be performed by CSG Clinische Studiengesellschaft mbH. A site initiation visit (SIV) will be performed at each study site. Approx. 18 routine monitoring visits (RMVs) at each study site will be conducted. It is expected that two visits per site will be carried out with a focus on the historical data and 16 RMVs (4 p.a. per site) for the prospective data. The frequency of RMVs will be dependent on the enrollment rate and the site's data documentation. A close-out visit (COV) at each study site will be performed at the end of the study.

SDV will be performed by clinical monitors on the basis of all available patient records. Novartis Gene Therapies will bear the financial expenses for the implementation of the source data verification.

The implementation of SDV in SMArtCARE requires (a) an update of the informed consent, (b) approval of the update from all involved ethics committees (one per site), and (c) implementation of contracts with each site. After ethics approval per site of the new informed consent, a time lag of up to 4 months occurs until a patient is scheduled for the next visit, at which the updated informed consent can be signed. Due to these lead times and administrative requirements, the first RMV will be performed in mid-2022.

At current, there are uncertainties regarding the possibilities and limitations of performing SDV as part of the study. The extent of archived documentation, especially for historical nusinersen/risdiplam patients, cannot be estimated at present and could differ between the participating centers. Based on the assessments of

clinical experts as well as those responsible for the SMArtCARE registry, the use of the paper-based CRF of the SMArtCARE registry has also become established in the care setting as part of the documentation for patient records. The extent to which independent documentation is carried out in paper-based or electronic patient records is also currently unclear and probably varies between individual centers. If necessary, changes to the possible extend of SDV will be depicted in an amendment to the study protocol.

Information on source data verification of the RESTORE registry is displayed in the RESTORE addendum (Addendum 1), section 10.2.

## 10.3 Minimization of missing data

Due to the non-interventional nature of a Routine Data Collection and Evaluations, complete avoidance of missing or implausible data is impossible. Source data verification as described in section 10.2 will significantly reduce the frequency of missing or implausible data. Remaining missing data will be addressed in statistical analysis (see section 8.2 of the SAP).

## 10.4 Data analysis

Data for analysis is transferred to IGES Institute GmbH via secure data transfer for statistical analysis. Data transfer is strictly limited to the purpose of the study and as far as required for intended statistical analysis.

# 11. Ethical and regulatory aspects

## 11.1 Regulatory and ethical compliance

This non-interventional, non-randomized, registry-based data collection will be performed in accordance with the ethical principles laid down in the Declaration of Helsinki and in consistence with applicable regulatory requirements.

According to the Professional Code for Physicians in Germany (Berufsordnung Ärzte, BO-Ä Art 15, the final study protocol will be reviewed and approved by an Independent Ethics Committee before study start depending on the local requirements.

## 11.2 Informed Consent

The legal guardian of prospective patients will be asked for informed consent at the time of the patients' initial enrollment in SMArtCARE. The legal guardian of historical patients will be contacted to give informed consent for this study, unless the patients are documented as deceased. Eligible patients may only be included in the study after written consent of their legal guardian.

To facilitate the Routine Data Collection and Evaluations, SMArtCARE updated their informed consent accordingly to also include all aspects of this study (including SDV).

Information on informed consent of the RESTORE registry is displayed in the RESTORE addendum (Addendum 1), section 11.2.

# 12. Outcome

Only aggregated data will be presented to Novartis Gene Therapies, no patient level data will be disclosed.

Results of status reports and interim analyses will be submitted using module 4 of the dossier template and contain the information described in sections 8.5.1, 8.5.2 and 8.5.3. Based on the results and in alignment with G-BA, an amendment to the study protocol may be required.

Results of final analysis (section 8.5.4) will be submitted to G-BA in form of a value dossier for benefit assessment on 1 July, 2027. Upon completion of the study, a study report is prepared and serves as the basis for the description of the results that will be submitted to G-BA with the value dossier.

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# Annex

## A1 Methodology for Confounder Identification

## A2 Relevant variables in SMArtCare Registry

# A 1 Methodology for Confounder Identification

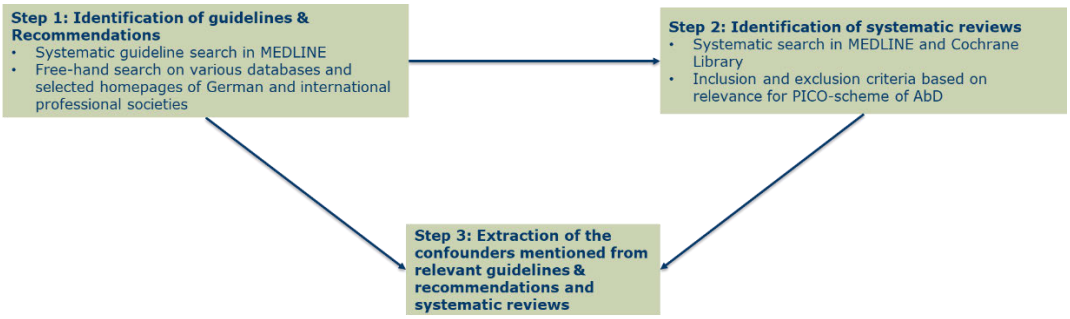
# 14. Methodical approaches for identifying confounders in SMA

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) rapid report „Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V“ (Concepts for the generation of data in health care settings and their evaluation for the purpose of assessing the benefit of drugs according to § 35a SGB V), version 1.1 as of May 13 2020, provides some guidance for the analysis of patient-specific data within the framework of the benefit assessment according to § 35a SGB V. Therein, IQWiG not only discusses various aspects of study and statistical analysis planning, but also the relevance of confounders in studies without randomization (1). It is stated that confounders putatively relevant for the research question must be defined *a priori* on the basis of scientific literature and, if necessary, by clinical expert validation.

In order to meet these requirements for confounder identification in non-randomized studies, a methodological 2-step-approach was applied (steps 1 and 2) as shown in Figure A 1. First, evidence-based guidelines and recommendations were identified via a systematic search of the MEDLINE bibliographic database. Further, a supplementary structured free-hand search on various databases and on selected websites of German and international professional societies was conducted, as this type of publication provides a broad and expert-validated data basis. Secondly, a systematic search was conducted in the bibliographic databases MEDLINE and the Cochrane Database of Systematic Reviews to identify systematic reviews and meta-analyses, since these documents would fundamentally supplement the data basis provided by the evidence-based guidelines.

The applied search strings have been designed analogously to the evidence search performed by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) to identify the appropriate comparator therapy (2). Literature search was followed by a literature selection process performed by two independent reviewers. This process comprised an initial title-abstract screening step as per pre-specified inclusion and exclusion criteria followed by an according full-text screening procedure.

Figure A 1: Overview of the methodical procedure




## 14.1 Indication/question

Confounders were identified specifically for the present indication according to the PICO scheme given in G-BA resolution of February 4 2021 (3):

- Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

## 14.2 Systematic research and data sources

A systematic evidence collection was carried out to identify relevant confounders in the above mentioned question. For this purpose, based on the systematic literature search carried out by G-BA to determine the appropriate comparator therapy according to § 35a SGB V for onasemnogene abeparvovec (2), systematic literature searches were carried out for evidence-based guidelines and recommendations (step 1) and systematic reviews and meta-analyses (step 2) in the indication of spinal muscular atrophy (SMA). The results were selected according to the previously defined inclusion and exclusion criteria (see section 15.3 and section 16.2). Two independent reviewers performed the screening of the retrieved results.

The bibliographic databases MEDLINE (PubMed) and the Cochrane Library (Cochrane Database of Systematic Reviews) were used for systematic information retrieval. Structured free-hand search was carried out in the databases and websites of the following organizations: AWMF, CMA Infobase, TRIP Database, google scholar. In addition, a free internet search was conducted for current German (Gesellschaft für Neuropädiatrie, Deutsche Gesellschaft für Muskelkranke e.V.) and international guidelines (Treat-NMD Neuromuscular Network, SMA Europe, Cure

SMA) as well as in PubMed. A detailed description of the search strategies is given in section 18.1 and section 18.2.

The research was completed on March 23th 2021.

Table A 1: Overview

| | |
|---|---|
| **Population** | ▪ Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene |
| **Intervention** | - |
| **Comparators** | - |
| **Endpoints** | Confounders, risk factors, prognostic factors |
| **Language** | German and English |
| **Publication types** | (I) Guidelines, recommendations<br>(II) Systematic reviews, meta-analyses |

Sections 2 (Identification of relevant guidelines and recommendations (step 1)) and 3 (Identification of systematic reviews and meta-analyses (step 2)) describe the procedure for identifying the confounders, the inclusion and exclusion criteria and the results of the two search areas in detail.

# 15. Identification of relevant guidelines and recommendations (step 1)

## 15.1 Bibliographic literature research – Guidelines and recommendations

In accordance with the above-mentioned specifications, the search was carried out on March 23th, 2021 in the MEDLINE bibliographic database. The search strategy was individually adapted and structured to the database. The detailed search strategy is described in section 18.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA). The PRISMA flow-chart representing the selection process as per pre-specified inclusion- and exclusion criteria (section 15.3) is shown in Figure A 2 and the final results of the search and selection process are listed in section 15.4.

## 15.2 Free-hand search – Guidelines and recommendations

In accordance with the above-mentioned specifications, the structured free-hand search was carried out on March 23th 2021 in the various databases and websites shown in Table A 2. The search strategies were individually adapted and structured to the respective databases and websites. The search results are presented in section 18.3.

Table A 2: Various Guidelines databases and selected websites

| **Guidelines databases** |
|---|
| AWMF Guidelines |
| CMA Infobase: (CPGs) – Clinical Practice Guidelines Database |
| TRIP Database |
| **Selected websites of German and international professional societies** |
| Gesellschaft für Neuropädiatrie |
| Deutsche Gesellschaft für Muskelkranke e.V. |
| Treat NMD Neuromuscular Network |
| SMA Europe |
| Cure SMA |
| **Additional Free-hand search & PubMed** |
| PubMed |
| Google |
| Google-Scholar |

## 15.3 Inclusion / exclusion criteria – Guidelines and recommendations

The identification of relevant guidelines and recommendations comprised the entire indication area of SMA. The applied inclusion- and exclusion criteria are listed in Table A 3.

Table A 3: Inclusion / exclusion criteria – Guidelines and recommendations

| | Inclusion criteria | | Exclusion criteria | |
|---|---|---|---|---|
| Patient population | I1 | Guideline for SMA<br>Recommendation for SMA | E1 | I1 not fulfilled. |
| Intervention | I2/E2 | No limitation | | |
| Appropriate comparator therapy | I3/E3 | No limitation | | |
| Endpoints | I4 | Information on prognostic factors contained in guideline | E4 | I4 not fulfilled. |
| (Study) guideline type | I5 | Current valid version | E5 | I5 not fulfilled. |
| Language | I6 | English or German | E6 | I6 not fulfilled. |

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

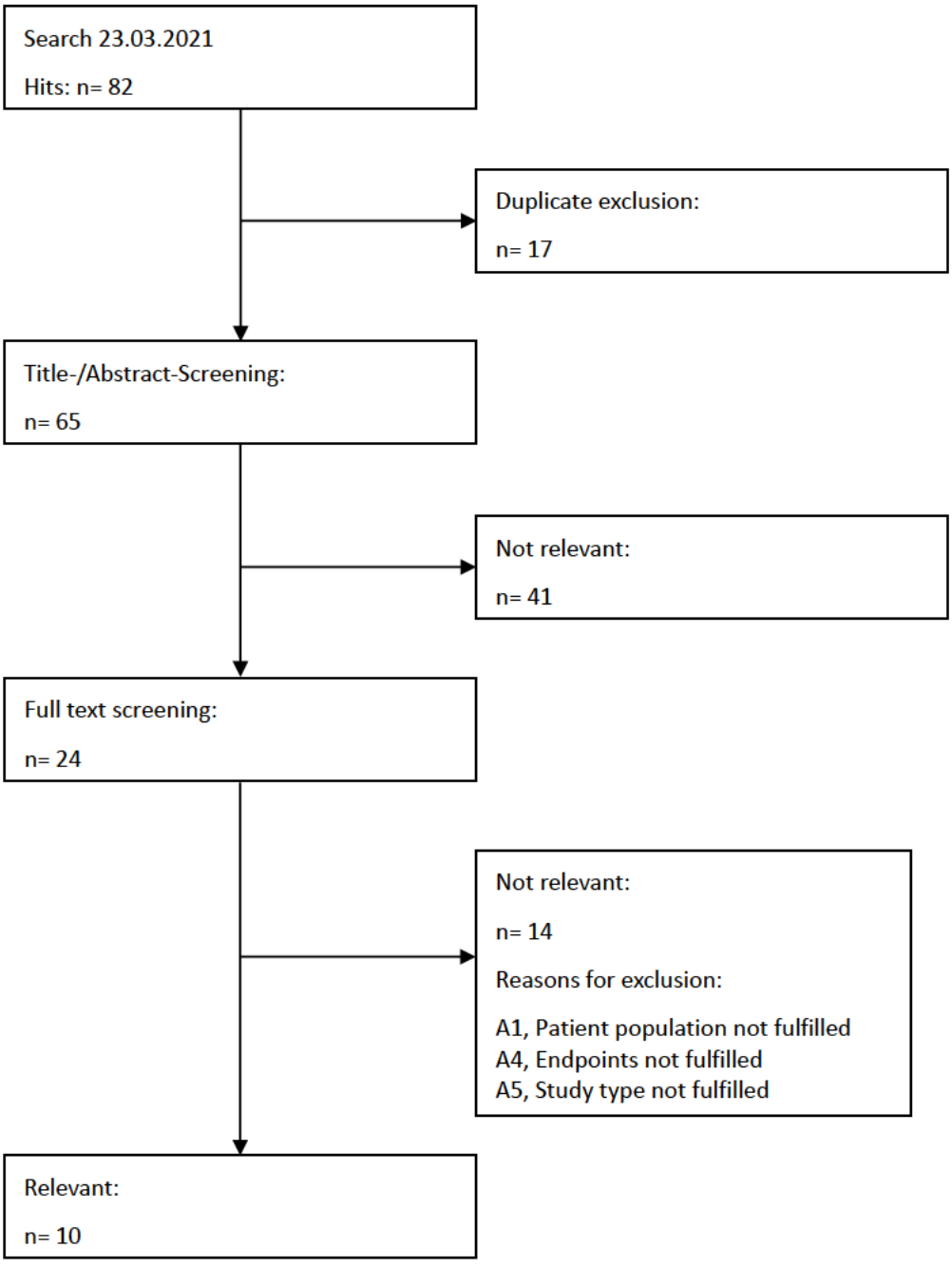
## 15.4 Results – Guidelines and recommendations

The PRISMA diagram shown in Figure A 2 illustrates the screening and selection process for relevant guidelines and recommendations, which form the basis for the identification of confounders.

The search yielded 34 hits in the MEDLINE bibliographic database. In the structured free-hand search, 48 potentially relevant publications were identified. After excluding duplicates, 65 hits remained to be evaluated via the 2-step selection/screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, study type and language. In total, 41 publications were excluded. In the second screening, full texts of publications remaining from the first screening (24 hits) were reviewed and checked for relevance. In addition to the criteria from the first screening, the full texts were also be checked for information on prognostic endpoints. As a result, a total of 10 guidelines and recommendations for the indication spinal muscle atrophy were included.

Figure A 2: PRISMA diagram – Guidelines and recommendations



# 16. Identification of relevant systematic reviews and Meta-analyses (step 2)

## 16.1 Bibliographic literature research – Systematic reviews and Meta-analyses

The bibliographic search was conducted in accordance with the above-mentioned specifications, the search was carried out on March 23th 2021 in the MEDLINE bibliographic database and in the Cochrane Database of Systematic Reviews. The search strategies were individually adapted and structured to each database. The detailed search strategy is described in section 18.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA).

## 16.2 Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

Inclusion / exclusion criteria for the literature selection have been designed analogously to the evidence search performed by the G-BA to identify the appropriate comparator therapy (2). The criteria listed in Table A 4 were taken into account for the inclusion of systematic reviews and meta-analyses as a basis for the identification of confounders.

Table A 4: Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

| | Inclusion criteria | | Exclusion criteria | |
|---|---|---|---|---|
| Patient population | I1 | ▪ Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | E1 | I1 not fulfilled. |
| Intervention | I2/E2 | No limitation | | |
| Appropriate comparator therapy | I3/E3 | No limitation | | |
| Endpoints | I4 | Collection of at least one patient-relevant outcome in the dimensions | E4 | I4 not fulfilled, or no separate evaluation for the |

| Inclusion criteria | | | Exclusion criteria | |
|---|---|---|---|---|
| | | of:<br>▪ Mortality<br>▪ Deaths<br>▪ Morbidity<br>▪ motor function (assessed with age-appropriate instruments, depending on disease severity, especially achievement of WHO milestones of motor development)<br>▪ respiratory function (need for [permanent] ventilation)<br>▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support)<br>▪ other complications of the disease (e.g., pain, orthopedic complications)<br>▪ Side effects<br>▪ Adverse events<br>▪ Health-related quality of life<br>▪ health-related quality of life (assessed with an age-appropriate instrument) | | relevant population. |
| Study type | I5 | ▪ Systematic reviews<br>▪ Meta-Analyses | E5 | I5 not fulfilled<br>▪ HTA report<br>▪ Dose-finding<br>▪ studies<br>▪ Non-interventional studies<br>▪ narrative reviews<br>▪ Case reports<br>▪ Retrospective studies and cohort study<br>▪ Opinions<br>▪ Animal studies / in vitro studies |
| Duration of study | I6 | No limitation | | |
| Type of documentation | I7 | Full text publication | E7 | Document types other than full text publication |

| Inclusion criteria | | | Exclusion criteria | |
|---|---|---|---|---|
| | | | | (e.g. conference abstracts, editorials, notes, letters to the editor) |
| Language | I8 | English or German | E8 | I8 not fulfilled |

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

## 16.3 Results – Systematic reviews and Meta-analyses

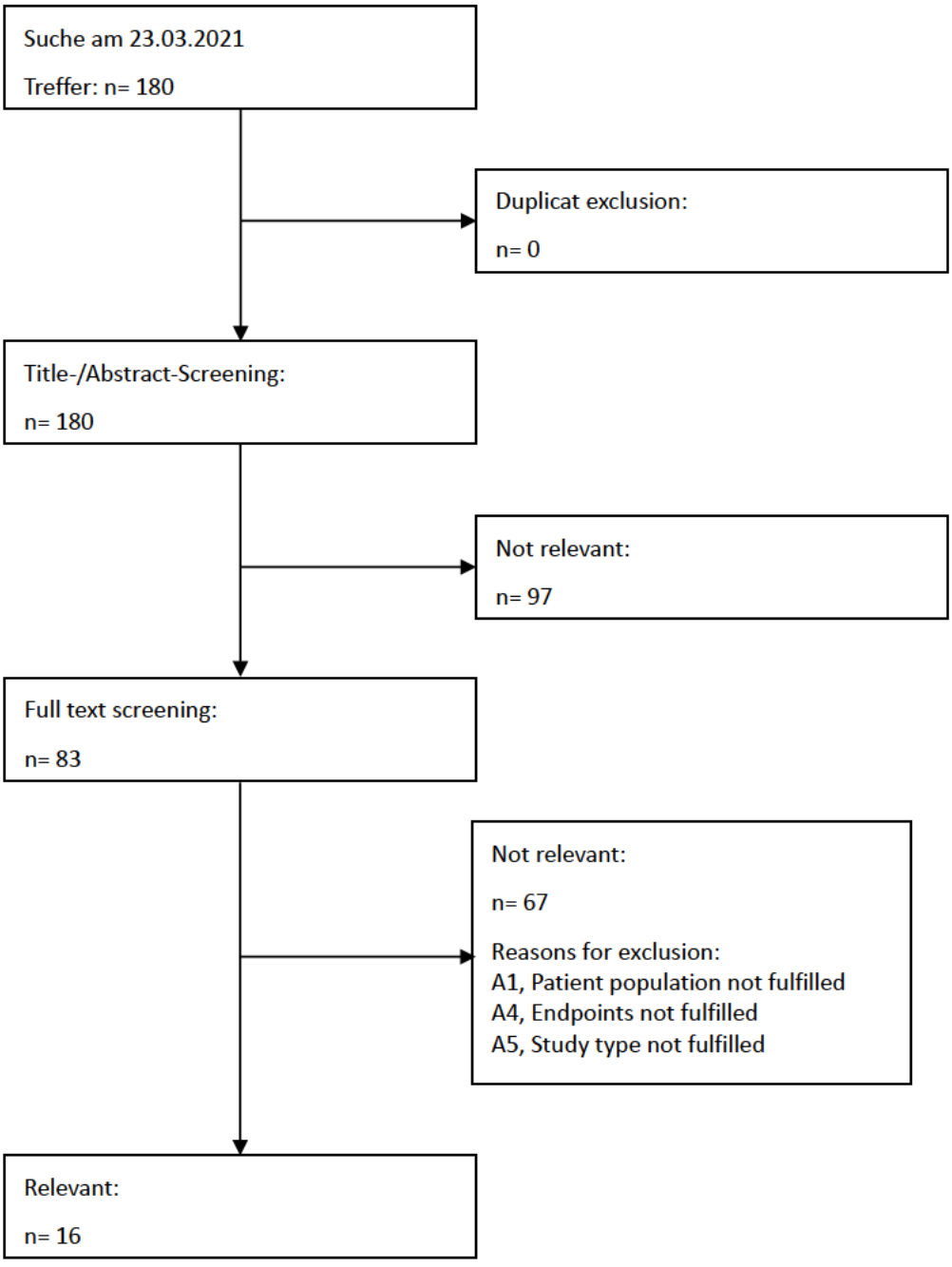
The PRISMA diagram shown in Figure A 3 illustrates the screening and selection process for relevant systematic reviews and meta-analyses, which form the second basis for the identification of confounders.

The search yielded 165 hits in the MEDLINE bibliographic database and 15 hits were identified in the Cochrane Library. After excluding duplicates, 180 hits remained to be evaluated via the 2-step selection / screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, endpoints, study type, documentation type and language. In total 97 publications were excluded.

In the second screening, full texts of publications remaining from the first screening (83 hits) were reviewed and checked for relevance. The same criteria were used as in the first screening. As a result, 16 systematic reviews were included for the indication.

Figure A 3: PRISMA diagram – Systematic reviews and Meta-analyses



# 17. Result presentation of the confounder identification and clinical perspective

After identification of the relevant national and international guidelines and recommendations as well as systematic reviews and meta-analyses, all confounders that were considered potentially relevant for SMA were identified and extracted.

The results were then validated by clinical experts in a joint workshop on May 12 2021. For this purpose, all identified and potentially relevant confounders were discussed regarding their importance for the target population with the following six clinical experts:

- Prof. Dr. Janbernd Kirschner (University Hospital Bonn, member of the SMArtCARE steering committee)
- Dr. Astrid Pechmann (University Hospital Freiburg, member of the SMArtCARE steering committee)
- Prof. Dr. Ulrike Schara-Schmidt (University Hospital Essen, member of the SMArtCARE steering committee)
- Prof. Dr. Andreas Hahn (University Hospital Giessen)
- Dr. Andreas Ziegler (Heidelberg University Hospital)
- Prof. Dr. Wolfgang Müller-Felber (University Hospital Munich, member of the SMArtCARE steering committee)

The systematic literature searches revealed two potential categories of confounders. The majority of potential confounders manifest at baseline (Table A 5 - Table A 10). The clinical experts agreed that baseline should be equated with the time of treatment initiation. Some confounders, called progression confounders, that occur after baseline during treatment were also identified in the systematic literature research (Table A 11 - Table A 14). According to clinical experts, the relevance of these confounders is not proven. For this reason, only baseline confounders are considered relevant and included in the study.

The assessment from a clinical perspective resulted in a categorization of the identified confounders into one of three groups:

- Very important: these confounders have a significant impact on the results and are essential for adjusting the statistical analyses in a non-randomized study
- Less important: These confounders have a minor influence on the results and should be controlled in the statistical analysis if possible. However, if selected confounders in this category cannot be controlled, the results are still considered valid
- Not important: These confounders are not considered relevant to this study, e.g., due to being captured as endpoints or due to the specific study setting

Operationalization of confounders for the study was directly proposed and whether they could currently be mapped in the SMArtCARE registry was queried.

Table A 5: Confounders at baseline - Category Patient characteristics

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Age onset | ▪ Age at symptom onset | n.a. | n.a. | X | X | ▪ Age at symptom onset | Less important | Yes | |
| Age Treatment initiation | ▪ Age at treatment<br>▪ Age at study start (first dose) | X | X | X<br>X | X<br>X | ▪ Age at study start (first dose) | Very important | Yes | (4–6) |
| Comorbidities | ▪ Comorbidities | X | X | X | X | ▪ Include as general flag (yes/no) specific ones? | Not relevant in routine care due to rarity | Yes | |
| Lean body mass | ▪ Lean body mass | n.a. | n.a. | X | X | ▪ BMI? | Not important | Yes<br>▪ Weight<br>▪ Height | |
| Race | ▪ Race | | | | X | Do not include | Not important | No | |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| Region | ▪ Regional and cultural standards | X | X | X | X | Do not include<br>▪ Study limited to Germany<br>If Austria were included: Potentially include Austria vs. Germany | Not important | Yes<br>▪ Place of birth<br>▪ Location of treatment center? | |

Table A 6: Confounders at baseline - Category Origin of SMA disease

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| SMA Type | ▪ SMA Type | n.a. | n.a. | X | X | Individual study populations:<br>▪ Pre-symptomatic 1-2 copy SMN2<br>▪ Pre-symptomatic 3 copy SMN2<br>▪ Symptomatic Type I<br>▪ Symptomatic Type II | Not important: Age at onset & highest motor milestone at baseline captured individually | SMA type not explicitly available? Derivation from age at symptom onset:<br>▪ <6M: Type I<br>▪ 6M-18M: Type II | |
| SMN2 copy number | ▪ SMN2 copy number | X | X | X | X | SNM2 copy number | Very Important[3] | Yes | |
| SMN2 genotype/ variants | ▪ Genotype of SMN2 | X | X | X | X | | Not important | No<br>▪ SNM1 mutation type only | |

[3] Due to the stratification according to SMN2 copy number, this confounder is not taken into account

Table A 7: Confounders at baseline - Category Impact on the Treatment response

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Pre-symptomatic/ symptomatic at treatment initiation | ▪ Pre-symptomatic vs. symptomatic at the time of disease-modifying therapy (DMT) | X | X | (X) | (X) | Individual study populations:<br>▪ Pre-symptomatic 1-2 copy SMN2<br>▪ Pre-symptomatic 3 copy SMN2<br>▪ Symptomatic Type I<br>▪ Symptomatic Type II<br>at treatment initiation | Very important | Yes | |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| Treatment delay | ▪ Time between diagnosis and start of treatment | X | X | X | X | Do not include<br>▪ Age at symptom onset and age at treatment initiation included | Not important:<br>▪ Age at symptom onset and age at treatment initiation relevant | No<br>▪ Time of diagnosis not specified? | (7–9)<br>(8) |
| | ▪ Time between symptom onset and 1st DMT | X | X | X | X | | | | |

Table A 8: Confounders at Baseline - Category Nutrition manifestations

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Gastroesophageal reflux | ▪ Gastroesophageal reflux | X | X | X | X | ? | Not important | No | |
| Gastrostomy | ▪ Gastrostomy tube feeding<br>▪ Gastrostomy placement | (X) | (X) | X<br>X | X<br>X | Nutritional support:<br>▪ Proportion with nutritional support part-time<br>▪ Proportion with Nutritional support full time<br>Use gastric/ nasal feeding tube information? | Nutritional Support general: Very important<br>Gastrostomy vs. nasal feeding: not important | Does the patient use a gastric or nasal feeding tube?<br>▪ Exclusively<br>▪ Supplementary | (7, 10, 11) |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-atic 1/2 SMN2 copies | Pre-symp-tom-atic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| Nutrition | ▪ Growth and Undernutrition<br>▪ Overnutrition problems | X | X | X | X | Weight at or above the 3rd percentile of age group<br>à If included likely other percentile relevant for SMA, (above 1st?)<br>Nutrition support via gastric/nasal feeding tube (see above) | Not important because captured via nutritional support<br>Suggestion: Eliminate weight at or above the 3rd percentile of age group because not influenced by DMD but by standard of care | Yes<br>▪ Weight<br>▪ Height<br>▪ Age | (7, 12)<br>(13) |
| | ▪ Nutrition | X | X | X | X | | | | |
| | ▪ Nutrition support | | | X | X | | | | |
| Bone mineral density | ▪ Bone mineral density | X | X | X | X | Do not include | Not important | No | |

Table A 9: Confounders at Baseline - Category Orthopedic and motoric manifestations

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Contractures | ▪ Contractures | (X) | (X) | X | X | Yes/No<br>▪ Limit to selected localizations / types? | Less important | Yes<br>▪ Are any contractures present? (including limitations by contrature and localisation/ type) | (7) |
| | ▪ Flexion Contractures | X | X | X | X | | | | |
| Motoric function | ▪ CHOP-INTEND score at baseline | X | X | X | X | ▪ Mean CHOP-INTEND score at baseline (as applicable) à Include for all (also pre-symptomatic)<br>▪ Mean Hammersmith score at baseline (as applicable) à Do not include | Very important | Yes?<br>▪ Physiotherapy assessment on day 1, 30, 60, 180, followed by 4-monthly examinations **à CHOP-INTEND, HMFSE?** | (14)<br>(4) |
| | ▪ HFMSE score from baseline | | | X | X | | | | |
| | ▪ Highest motor milestone at baseline | | | | | | | | |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| | | | | | | (only measured at age 2+)<br>▪ Highest motor milestone at baseline à include | | ▪ Motor Function:<br>Best current motor function:<br>Sitting without support;<br>Crawl on hands an knees;<br>Standing without support;<br>Walking without support;<br>Climb stairs;<br>Other | |
| Physical activity | ▪ Physical activity | X | X | X | X | ▪ Do not include | Not important | No | |
| Orthotics | ▪ Scoliosis | (X) | (X) | X | X | ▪ Yes/no | Not important | Yes.<br>Does the | |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| | | | | | | | | Patient have scoliosis? | |

Table A 10: Confounders at Baseline - Category Access to and quality of treatment

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symptom-matic 3 SMN2 copies | SMA Type I | SMA Type II | | | | |
| Access/ Quality | ▪ COVID-19 Pandemic | X | X | X | X | Not relevant for study?<br>▪ Inclusion in case of treatment requires access<br>▪ Application of G-BA quality criteria for participating centers | Not important if study only includes HSPs qualifying for Zolgensma<br>If other HSPs are included for Nusinersen: potentially important and should be included | No | |
| | ▪ Medical practitioners' knowledge | X | X | X | X | | | | (7) |
| | ▪ Multidisciplinary or interdisciplinary team | X | X | X | X | | | | (7, 15) |
| | ▪ Treatment Center | | | X | X | | | | (7) |

Table A 11: Confounders after Baseline – Category Access to and quality of treatment

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| Access/ Quality | ▪ Engagement with health care | X | X | X | X | No./Proportion of missed routine visits And | Not important | Yes ▪ Date of each visit | |
| | ▪ Providing families with information | X | X | X | X | No. of missed doses for nusinersen | | | (7) |
| | ▪ Access to therapeutic interventions | X | X | X | X | Discussion: ▪ All routine visits performed at participating treatment center? | | | (16) |
| Adaptation | ▪ Mechanical ventilation | | | X | | Do not include ▪ Changes in ventilator and ▪ nutritional support represent endpoints | Not important (endpoint, not confounder) | Yes | |
| | ▪ Tracheostomy | | | X | | | | | (16) |
| | ▪ Gastrostomy | | | X | | | | | (16) |
| | ▪ Motor and respiratory physiotherapy | | | X | | | | | (16) |
| | ▪ Nursing care | | | X<br>X | | | | | (16) |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| | ▪ Occupational therapy | | | X | | | | | (16) |
| | ▪ Speech therapy for alternative communication and dysphagia | | | | | | | | (16) |

Table A 12: Confounders after Baseline – Category Assistive equipment

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Assistive equipment | ▪ Assistive equipment<br>▪ Wheelchair | X | X | X<br>X | X<br>X | Do not include | Not important | Yes<br>▪ Assistance in airway clearance and secretion mobilization (type, frequency)<br>▪ Wheelchair use (including type and frequency of use) | (7) |

Table A 13: Confounders after Baseline – Category Orthopedic and motoric manifestations

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symptomatic 1/2 SMN2 copies | Pre-symptomatic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Orthotics | ▪ Kneeankle- foot orthoses | | | | X | Do not include<br>▪ Contractures at baseline included<br>▪ Baseline motor function included<br>Discussion:<br>▪ Confounder on pain? | Not important | Yes<br>▪ Orthoses/ Devices (incl. Type, type of use, and frequency) | (12)<br>(7)<br>(7) |
| | ▪ Limb orthotics | | | | | | | | |
| | ▪ Orthosis | | | X | X | | | | |
| | ▪ Positioning and seating alterations and orthotic devices | X | X | X | X | | | | |
| | ▪ Posture management | X | X | X | X | | | | (7) |
| | ▪ Surgical correction of scoliosis | | | X | X | | | | (7) |
| Physiotherapy | ▪ Occupational therapy | | | X | X | Yes/no (per time between visits)<br>Reliable operationalization not possible, | Less important:<br>No evidence on effect of physio-therapy | Yes<br>▪ Therapy interventions (physio, feeding/ | (7) |
| | ▪ Physical therapy | | | X | X | | | | |
| | ▪ Physiotherapy | X | X | X | X | | | | |

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies | SMA Type I 3 | SMA Type II | | | | |
| | ▪ Regular exercise | X | X | X | X | because it would require quantity and quality<br>à Do not include in study | | speech, occupational, other) | (7)<br>(7) |
| Motoric function | ▪ Position (supine/ seated) | X | X | X | X | Do not include<br>▪ Baseline confounder and end-point | Not important (endpoint, not confounder) | | |

Table A 14: Confounders after Baseline – Category Others

| Confounder/ prognostic factor | Characteristics | Relevant for (according to literature) | | | | Proposed operationalization in study | Importance for study (very important, less important, not important) | Currently depictable in SMArtCARE | Sources |
|---|---|---|---|---|---|---|---|---|---|
| | | Pre-symp-tom-matic 1/2 SMN2 copies | Pre-symp-tom-matic SMN2 copies 3 | SMA Type I | SMA Type II | | | | |
| Nutrition | ▪ Education about nutrition | X | X | X | X | Do not include? | Not important | Unclear<br>▪ Therapy interventions: feed/speech includes Education? | |
| Pain management | ▪ Pain management | | | X | X | Do not include? | Not important | Unclear<br>▪ May be partly covered by "Other medication taken on a regular basis?" | |
| Support | ▪ Support<br>▪ support from family | X<br>X | X<br>X | X<br>X | X<br>X | Do not include | Not important | No | (17)<br>(18, 19) |

# 18. Detailed presentation of the search strategy

## 18.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA)

Table A 15: Search string for guidelines and recommendations

| Database | MEDLINE | |
|---|---|---|
| Search interface | PubMed | |
| Search date | 24.03.2021 | |
| # | Search terms | Results |
| 1 | "Muscular Atrophy, Spinal"[mh] OR "Motor Neuron Disease"[mh:noexp] | 9.563 |
| 2 | motor[Title/Abstract] AND neuron*[Title/Abstract] AND disease*[Title/Abstract] | 22.950 |
| 3 | spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR myelopath*[tiab] OR progressiv*[tiab] OR spinobulbar[tiab] AND (muscular[tiab] OR muscle[tiab]) AND atroph*[tiab] | 10.585 |
| 4 | (spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab] | 5.453 |
| 5 | (Spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab] | 289 |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 | 36.514 |
| 7 | (#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title]) | 95 |
| 8 | (#7) AND ("2015/06/01"[PDAT] : "3000"[PDAT]) | 34 |
| 9 | (#8) NOT (retracted publication [pt] OR retraction of publication [pt]) | 34 |

## 18.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA)

Table A 16: Search string for systematic reviews in MEDLINE

| Database | MEDLINE | |
|---|---|---|
| Search interface | PubMed | |
| Search date | 24.03.2021 | |
| # | Search terms | Results |
| 1 | "muscular atrophy, spinal"[MeSH Terms] | 5.299 |
| 2 | ("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "myelopath*"[Title/Abstract] OR "progressiv*"[Title/Abstract] OR "spinobulbar"[Title/Abstract]) AND ("muscular"[Title/Abstract] OR "muscle"[Title/Abstract]) AND "atroph*"[Title/Abstract] | 10.585 |
| 3 | ("spinal"[Title/Abstract] OR "neurogenic scapuloperonea*"[Title/Abstract]) AND "amyotroph*"[Title/Abstract] | 5.453 |
| 4 | ("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "spinobulbar"[Title/Abstract] OR | 289 |

| | | |
|---|---|---|
| | "spinopontin*"[Title/Abstract] OR "hereditary motor"[Title/Abstract]) AND "neuronopath*"[Title/Abstract] | |
| 5 | #1 OR #2 OR #3 OR #4 | 16.385 |
| 6 | (#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab])) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) | 278 |
| 7 | (#6) AND ("2015/06/01"[PDAT] : "3000"[PDAT]) | 169 |
| 8 | (#7) NOT "The Cochrane database of systematic reviews"[Journal] | 165 |
| 9 | (#8) NOT (retracted publication [pt] OR retraction of publication [pt]) | 165 |

Table A 17: Search string for systematic reviews in Cochrane.

| Database | Cochrane Database of Systematic Reviews | |
|---|---|---|
| Search interface | Cochrane Library | |
| Search date | 24.03.2021 | |
| # | Search terms | Results |
| 1 | [mh "spinal muscular atrophy"] | 91 |
| 2 | [mh "motor neuron disease"] | 718 |
| 3 | (motor NEXT neuron* NEXT disease*):ti,ab,kw | 459 |
| 4 | (spinal OR "bulbo spinal" OR bulbospinal OR myelopath* OR progressiv* OR spinobulbar):ti,ab,kw AND (Muscular OR muscle):ti,ab,kw AND (Atroph*):ti,ab,kw | 520 |
| 5 | (Spinal OR (neurogenic NEXT scapuloperonea*)):ti,ab,kw AND (Amyotroph*):ti,ab,kw | 127 |
| 6 | (Spinal OR "bulbo spinal" OR bulbospinal OR spinobulbar OR spinopontin* OR "hereditary motor"):ti,ab,kw AND (Neuronopath*):ti,ab,kw | 2 |
| 7 | {OR #1-#6} | 1310 |
| 8 | #7 with Cochrane Library publication date from Jun 2015 to Jun 2020, in Cochrane Reviews and Cochrane Protocols | 15 |

## 18.3 Search Results – Free-hand search (Guidelines and recommendations for the indication SMA)

Table A 18: List of guidelines found by the freehand search and their reasons for inclusion and exclusion

| Plattform | Hits | Inclusion/exclusion |
|---|---|---|
| **Systematic search - various databases** | | |
| **AWMF Leitlinien Suche** | Guideline application:<br>**S1: Spinale Muskelatrophie (SMA), Diagnostik und Therapie**<br>Registration number: 022-030<br>Planned completion: 15.01.2021 | Exclusion<br>No current version available |
| **CMA Infobase: Clinical Practice Guidelines Database (CPGs)** | **1. Pediatric home mechanical ventilation: a Canadian Thoracic Society clinical practiceguideline executive summary**<br>Amin et al.<br>Canadian Thoracic Society<br>Published on: 2017 | Inclusion |
| **Trip Database** | **Evidence in focus: Nusinersen use in spinal muscular atrophy**<br>Michelson et al.<br>Neurology<br>Published on: 2018 | Exclusion<br>Duplicate |

| | | |
|---|---|---|
| | **Pediatric home mechanical ventilation: A Canadian Thoracic Society clinical practiceguideline executive summary**<br>Amin et al.<br>Respiratory, critical care and Sleep Medicine<br>Published on: 2017 | Exclusion<br>Duplicate |
| | **Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis**<br>Anonym<br>Published on: 2020 | Exclusion<br>A4, Endpoints not fulfilled |
| | **Carrier Screening for Genetic Conditions**<br>Committee on Genetics<br>Published on: 2011 | Exclusion<br>A4, Endpoints not fulfilled |
| **Google-Suche** | **Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.**<br>Hagenacker et al.<br>Published on: 2017<br>Fortschritte Neurologie Psychiatrie | Exclusion<br>Duplicate |
| | **Spinale Muskelatrophie – Expertenempfehlungen zur Behandlung von erwachsenen Patienten mit Nusinerse**<br>Hagenacker et al.<br>Published on: 2019<br>Fortschritte Neurologie Psychiatrie | Exclusion<br>Duplicate |
| | **Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.**<br>Ziegler et al.<br>Published on: 2017<br>Der Nervenarzt | Exclusion<br>Duplicate |
| **Google-Scholar** | **Best practice guidelines for molecular analysis in spinal muscular atrophy**<br>Scheffer et al.<br>Published on: 2001<br>European Journal of Human Genetics | Inclusion |

| | |
|---|---|
| **Spinal Muscular Atrophy**<br>Prior et al.<br>Published on: 2020<br>GeneReviews® | Inclusion |
| **Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.**<br>Ziegler et al.<br>Published on: 2017<br>Der Nervenarzt | Exclusion<br>Duplicate |
| **Recommendations for the diagnosis and management of typical childhood spinal muscular Atrophy Recommandations pour le diagnostic et la prise en charge de l'amyotrophie spinale typique de l'enfant**<br>Cuisset et al.<br>Published on: 2012<br>Revue Neurologique | Inclusion |
| **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics**<br>Finkel et al.<br>Published on: 2018<br>Neuromuscular Disorder | Exclusion<br>Duplicate |
| **1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I–III**<br>Sansone et al.<br>Published on: 2015<br>Neuromuscular Disorder | Exclusion<br>Duplicate |
| **Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2**<br>Glascock et al.<br>Published on: 2020<br>Journal of Neuromuscular Diseases | Exclusion<br>Duplicate |
| **Management of children with spinal muscular atrophy type 1 in Australia**<br>Tassie et al.<br>Published on: 2013<br>Journal of Pediatrics and Child Health | Exclusion<br>A5, Study type not fulfilled |

| | | |
|---|---|---|
| | **Special Considerations in the Respiratory Management of Spinal Muscular Atrophy**<br>Schroth et al.<br>Published on: 2009<br>Pediatrics | Inclusion |
| | **Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening**<br>Glascock et al.<br>Published on: 2018<br>Journal of Neuromuscular Diseases | Inclusion |
| | **Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy**<br>Cuscó et al.<br>Published on: 2020<br>Neurology Genetics | Exclusion<br>Duplicate |
| | **Carrier screening for spinal muscular atrophy**<br>Prior et al.<br>Published on: 2008<br>genetics in medicine | Inclusion |
| | **Evidence in focus: Nusinersen use in spinal muscular atrophy**<br>Michelson et al.<br>Published on: 2018<br>Neurology | Exclusion<br>Duplicate |
| | **Consensus Statement for Standard of Care in Spinal Muscular Atrophy**<br>Wang et al.<br>Published on: 2007<br>Sage Open | Exclusion<br>Duplicate |
| **Cochrane Deutschland** | | No guideline found for the indication SMA. |
| **Pubmed** | **Treatment Advances in Spinal Muscular Atrophy**<br>Bharucha-Goebel et al.<br>Published on: 2017<br>Current neurology and neuroscience reports | Exclusion<br>A5, Study type not fulfilled |
| | **Spinal muscular atrophy care in the COVID-19 pandemic era**<br>Veerapandiyan et al.<br>Published on: 2020<br>Muscle & Nerve | Exclusion<br>A5, Study type not fulfilled |

| | | |
|---|---|---|
| | **Spinal muscular atrophy**<br>D´Amico et al.<br>Published on: 2011<br>Orphanet Journal of Rare Diseases | Exclusion<br>A5, Study type not fulfilled |
| | **Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)]**<br>Ziegler et al.<br>Published on: 2020<br>Der Nervenarzt | Exclusion<br>Duplicate |
| **Selected homepages of German and international professional societies** | | |
| **NHS - Protocol and Guidelines** | | No guideline found for the indication SMA. |
| **NICE Guidelines** | | No guideline found for the indication SMA. |
| **Gesellschaft für Neuropädiatrie** | **Diagnosestellung und Behandlung bei SMA Patienten** | Exclusion<br>A5, Study type not fulfilled |
| **Treat-NMD Neuromuscular Network** | **Behandlungsstandards für Spinale Muskelatrophie**<br>Wang et al.<br>Journal of Child Neurology<br>Published on: 2007 | Inclusion |
| | **Diagnosestellung und Behandlung bei SMA Patienten**<br>Translation of Wang et al. by Schwersenz et al. | Exclusion<br>A5, Study type not fulfilled |
| **Deutsche Gesellschaft für Muskelkranke e.V.** | **Leitfaden zu den Internationalen Therapiestandards für Spinale Muskelatrophie**<br>Published on: 2017 | Exclusion<br>A5, Study type not fulfilled |
| | **Diagnosis and management of spinal muscular atrophy: Part 1:Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care**<br>Mercuri et al.<br>Published on: 2018<br>Neuromuscular Disorders | Exclusion<br>Duplicate |
| | **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonaryand acute care; medications, supplements and immunizations; other organsystems; and ethics**<br>Mercuri et al.<br>Published on: 2018<br>Neuromuscular Disorders | Exclusion<br>Duplicate |

| | | |
|---|---|---|
| | **Management of Neuromuscular Diseases Spinale Muskelathrophie**<br>Deutsche Gesellschaft für Muskelkranke e.V.<br>Published on: 2005 | Exclusion<br>A5, Study type not fulfilled |
| **Initiative SMA** | | No guideline found for the indication SMA. |
| **Schweizerischen Muskelgesellschaft** | | No guideline found for the indication SMA. |
| **Neurologienetz** | | No guideline found for the indication SMA. |
| **Deutsche Gesellschaft für Humangenetik e.V.** | | No guideline found for the indication SMA. |
| **Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.** | | No guideline found for the indication SMA. |
| **Deutsche Muskelstiftung** | | No guideline found for the indication SMA. |
| **Deutsche Muskelschwund-Hilfe e.V.** | | No guideline found for the indication SMA. |
| **Muskeln für Muskeln** | | No guideline found for the indication SMA. |
| **Patientenstimme SMA** | | No guideline found for the indication SMA. |
| **SMA Europe** | **SPINAL MUSCULAR ATROPHY:PATHOLOGY, DIAGNOSIS,CLINICAL PRESENTATION,THERAPEUTIC STRATEGIES & TREATMENTS**<br>Published on: 11/2020 | Exclusion<br>A5, Study type not fulfilled |
| | **Consensus Statement for Standard of Care in Spinal Muscular Atrophy**<br>Wang et al.<br>Published on: 2007<br>Journal of Child Neurology | Exclusion<br>Duplicate |
| **Marathon** | | No guideline found for the indication SMA. |
| **CTM-austria** | | No guideline found for the indication SMA. |
| **AFM Telethon** | | No guideline found for the indication SMA. |

| | | |
|---|---|---|
| **Spierziekten Nederland** | | This website is not available in English or German. |
| **European Neuro Muscular Centre** | | No guideline found for the indication SMA. |
| **Asami – Associazione per lo Studio delle Atrofie Muscolari Spinali Infantili** | | This website is not available in English or German. |
| **Muscular Dystrophy UK** | | No guideline found for the indication SMA. |
| **Cure SMA** | **Respiratory muscle function in infants with spinal muscular atrophy type I**<br>Finkel et al.<br>Published on: 2014<br>Pediatric Pulmonology | Exclusion<br>A5, Study type not fulfilled |
| | **Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care**<br>Mecuri et al.<br>Published on: 2018<br>Neuromuscular Disorders | Exclusion<br>Duplicate |
| | **Assessing the Needs of the SMA Population: Survey Results of Health Care Providers and Families**<br>Halanski et al.<br>Published on: 2014<br>SAGE Open | Exclusion<br>A5, Study type not fulfilled |
| | **The Experience of Families With Children With Spinal Muscular Atrophy Type I Across Health Care Systems**<br>Murrell et al.<br>Published on: 2016<br>Journal of Child Neurology | Exlusion<br>A5, Study type not fulfilled |
| | **Opening the window: The case for carrier and perinatal screening for spinal muscular atrophy**<br>Burns et al.<br>Published on: 2016<br>Neuromuscular Disorders | Exclusion<br>A5, Study type not fulfilled |
| | **What Matters Most: A Perspective From Adult Spinal Muscular Atrophy Patients**<br>Hunter et al.<br>Published on: 2016<br>Journal of Neuromuscular Diseases | Exclusion<br>A5, Study type not fulfilled |

| | | |
|---|---|---|
| | **Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy**<br>Metha et al.<br>Published on: 2015<br>Pediatric Neurology | Exclusion<br>A5, Study type not fulfilled |
| | **Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study**<br>Kolb et al.<br>Published on: 2016<br>Annals of Clinical an Translational Neurology | Exclusion<br>A5, Study type not fulfilled |
| | **Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study**<br>Qian et al.<br>Published on: 2015<br>BMC Neurology | Exclusion<br>A5, Study type not fulfilled |
| | **Responses to Fasting and Glucose Loading in a Cohort of Well Children with Spinal Muscular**<br>**Atrophy Type II**<br>Davis et al.<br>Published on: 2015<br>Journal of pediatrics | Exclusion<br>A5, Study type not fulfilled |
| | **209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands**<br>Finkel et al.<br>Published on: 2015<br>Neuromuscular Disorders | Exclusion<br>A5, Study type not fulfilled |
| | **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics**<br>Mecuri et al.<br>Published on: 2018<br>Neuromuscular Disorders | Exclusion<br>Duplicate |
| **Spinal Muscular Atrophy Foundation**<br>**My Care Plus** | | No guideline found for the indication SMA.<br>No guideline found for the indication SMA. |
| **World Muscle Society** | | No guideline found for the indication SMA. |

## 18.4 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – Guidelines and recommendations)

Table A 19: List of guidelines and recommendations viewed in full text and excluded

| Ongoing number | Excluded reference | Reason for exclusion |
|---|---|---|
| 1 | Anonym, ADDENDUM: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2016:18(7):752. | A5, Study type not fulfilled |
| 2 | Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Common Drug Reviews 2017. | A5, Study type not fulfilled |
| 3 | Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Com-mon Drug Reviews 2017. | A4, Endpoints not fulfilled |
| 4 | Bergin et al. Recommendations to support informal carers of people living with motor neurone disease. Br J Community Nurs 2016:21(10):518-524. | A1, Patient population not fulfilled |
| 5 | Deignan et al. Addendum: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2020. | A5, Study type not fulfilled |
| 6 | Glascock et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2.J Neuromuscul Dis 2020:7(2):97-100. | A5, Study type not fulfilled |
| 7 | Hagenacker et al. [Spinal Muscular Atrophy - expert recommendations for the use of nusinersen in adult patients]. Fortschr Neurol Psychiatr 2019:87(12):703-710. | A4, Endpoints not fulfilled |
| 8 | Harvey et al. ACR Appropriateness Criteria® Movement Disorders and Neurodegenerative Diseases. J Am Coll Radiol 2020:17(5):175-187. | A1, Patient population not fulfilled |
| 9 | Mercuri et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018:28(2):103-115. | A5, Study type not fulfilled |
| 10 | Anonym, Motor Neurone Disease: Assessment and Management. NICE Guideline 2016:42:1-7. | A1, Patient population not fulfilled |
| 11 | Oliver et al. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotroph Lateral Scler Frontotemporal Degener 2017:18:5-6:313-323. | A1, Patient population not fulfilled |
| 12 | Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen. Rev Assoc Med Bras (1992) 2018:64(6):484-491. | A4, Endpoints not fulfilled |
| 13 | Writing Group For Practice Guidelines For et al. [Clinical practice guidelines for spinal muscular atrophy]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi Actions 2020:37(3):263-268 | A6, Language |

## 18.5 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – systematic reviews and Meta-analyses)

Table A 20: List of systematic reviews and Meta-analyses viewed in full text and excluded

| Ongoing number | Excluded reference | Reason for exclusion |
|---|---|---|
| 1 | Anonym. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018:17(12):1083-1097. | A1, Patient population not fulfilled |
| 2 | Abati et al. Pregnancy outcomes in women with spinal muscular atrophy: A review. J Neurol Sci 2018:388():50-60. | A1, Patient population not fulfilled |
| 3 | Ahmadian-Moghadam et al. Therapeutic potential of stem cells for treatment of neurodegenerative diseases. Biotechnol Lett 2020:42(7):1073-1101. | A5, Study type not fulfilled |
| 4 | Alhammoud et al. The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review. Spine Deform 2021. | A4, Endpoints not fulfilled |
| 5 | Ali et al. Healthcare utilisation in children with SMA type 1 treated with nusinersen: a single centre retrospective review. BMJ Paediatr Open 2019:3(1):e000572. | A5, Study type not fulfilled |
| 6 | Azadinia et al. Can lumbosacral orthoses cause trunk muscle weakness? A systematic review of literature. Spine J 2017:17(4):589-602. | A1, Patient population not fulfilled |
| 7 | Bartels et al. Physical exercise training for type 3 spinal muscular atrophy. Cochrane Database of Systematic Reviews 2019: (3). | A1, Patient population not fulfilled |
| 8 | Bernardes Neto et al. Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review. BMJ Open 2019:9(11):e029890. | A1, Patient population not fulfilled |
| 9 | Bharucha-Goebel et al. Treatment Advances in Spinal Muscular Atrophy. Curr Neurol Neurosci Rep 2017:17(11):91 | A5, Study type not fulfilled |
| 10 | Boardman et al. Impairment Experiences, Identity and Attitudes Towards Genetic Screening: the Views of People with Spinal Muscular Atrophy. J Genet Couns 2018:27(1):69-84. | A4, Endpoints not fulfilled |
| 11 | Boentert et al. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol 2017:30(5):529-537. | A5, Study type not fulfilled |
| 12 | Bowerman et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 2017:10(8):943-954. | A5, Study type not fulfilled |
| 13 | Bray et al. Preference-based measures of health-related quality of life in congenital mobility impairment: a systematic review of validity and responsiveness. Health Econ Rev. 2020:10(1):9. | A4, Endpoints not fulfilled |
| 14 | Butchbach et al. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016:3():7. | A4, Endpoints not fulfilled |
| 15 | Calder et al. Small Molecules in Development for the Treatment of Spinal Muscular Atrophy. J Med Chem 2016:59(22):10067-10083. | A4, Endpoints not fulfilled |

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|---|---|---|
| 16 | Castro-Codesal et al. Long-term non-invasive ventilation therapies in children: A scoping review. Sleep Med Rev 2018:37():148-158. | A1, Patient population not fulfilled |
| 17 | Chiriboga et al. Nusinersen for the treatment of spinal muscular atrophy. Expert Rev Neurother 2017:17(10):955-962. | A5, Study type not fulfilled |
| 18 | Cohen et al. Diffusion MRI of the spinal cord: from structural studies to pathology. NMR Biomed 2017:30(3). | A1, Patient population not fulfilled |
| 19 | Dangouloff et al. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis 2021:16(1):47. | A4, Endpoints not fulfilled |
| 20 | Dial et al. The Role of AMPK in Neuromuscular Biology and Disease. Trends Endocrinol Metab 2018:29(5):300-312. | A5, Study type not fulfilled |
| 21 | Dubowitz et al. Critical Review Ahead of Publication. Neuromuscul Disord 2019:29(6):412. | A5, Study type not fulfilled |
| 22 | Dunaway Young et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve 2016:54(5): 836-842. | A1, Patient population not fulfilled |
| 23 | Elshafay et al. Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. CNS Drugs. 2019:33(3):239-250. | A4, Endpoints not fulfilled |
| 24 | Finsterer et al. Fasciculations in human hereditary disease. Acta Neurol Belg 2015:115(2):91-95. | A4, Endpoints not fulfilled |
| 25 | Göhl et al. [Respiratory Muscle Training: State of the Art]. Pneumologie 2016:70(1):37-48. | A1, Patient population not fulfilled |
| 26 | Grayev et al. A Systematic Review of Procedural Complications from Transforaminal Lumbar Puncture for Intrathecal Nusinersen Administration in Patients with Spinal Muscular Atrophy. AJNR Am J Neuroradiol 2021. | A1, Patient population not fulfilled |
| 27 | Grotto et al. Type 0 Spinal Muscular Atrophy: Further Delineation of Prenatal and Postnatal Features in 16 Patients. J Neuromuscul Dis 2016:3(4):487-495. | A1, Patient population not fulfilled |
| 28 | Grychtol et al. The role of sleep diagnostics and non-invasive ventilation in children with spinal muscular atrophy. Paediatr Respir Rev 2018:28():18-25. | A5, Study type not fulfilled |
| 29 | Hensel et al. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? Neuroscientist 2018:24(1):54-72. | A5, Study type not fulfilled |
| 30 | Hu et al. Gene therapeutic strategies and relevant clinical trials in neuromuscular disorder in China. Gene Ther 2020:27(7-8):321-328. | A5, Study type not fulfilled |
| 31 | Iftikhar et al. Current and emerging therapies for Duchenne muscular dystrophy and spinal muscular atrophy. Pharmacol Ther 2021:220: 107719. | A5, Study type not fulfilled |
| 32 | Jablonka et al. Developmental regulation of SMN expression: pathophysiological implications and perspectives for therapy development in spinal muscular atrophy. Gene Ther 2017:24(9):506-513. | A5, Study type not fulfilled |
| 33 | Janoudi et al. Nusinersen for Adolescents and Adults with Spinal Muscular Atrophy: A Review of Clinical Effectiveness. CADTH Rapid Response Reports 2020. | A1, Patient population not fulfilled |
| 34 | Kennedy et al. Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. J Foot Ankle Res 2020:13(1):10. | A1, Patient population not fulfilled |

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|---|---|---|
| 36 | Kilcher et al. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss Med Wkly 2017:147():w14463. | A4, Endpoints not fulfilled |
| 36 | Kreider et al. Creatine in Health and Disease. Nutrients 2021:13(2). | A4, Endpoints not fulfilled |
| 37 | Kremer et al. Transcriptomics: molecular diagnosis of inborn errors of metabolism via RNA-sequencing. J Inherit Metab Dis 2018:41(3):525-532. | A4, Endpoints not fulfilled |
| 38 | Lager et al. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. Eur J Paediatr Neurol 2015:19(5):537-546. | A1, Patient population not fulfilled |
| 39 | Landfeldt et al. Costs of Illness of Spinal Muscular Atrophy: A Systematic Review. Appl Health Econ Health Policy 2021. | A4, Endpoints not fulfilled |
| 40 | Lanigan et al. Comparative Pathology of the Peripheral Nervous System. Vet Pathol 2021:58(1):10-33. | A5, Study type not fulfilled |
| 41 | Li et al. The prevalence of spinal muscular atrophy carrier in China: Evidences from epidemiological surveys. Medicine (Baltimore) 2020:99(5):e18975. | A4, Endpoints not fulfilled |
| 42 | Lin et al. Molecular Therapies for Muscular Dystrophies. Curr Treat Options Neurol 2018:20(7):27. | A5, Study type not fulfilled |
| 43 | Long et al. Genome Editing of Monogenic Neuromuscular Diseases: A Systematic Review. JAMA Neurol 2016:73(11):1349-1355. | A1, Patient population not fulfilled |
| 44 | MacDonald et al. The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines - An Update. CADTH Rapid Response Reports 2019. | A1, Patient population not fulfilled |
| 45 | Magalhães et al. Is transcutaneous electrical muscle stimulation an alternative for preventing acquired muscle weakness in the pediatric intensive care unit? A scoping review. Pediatr Pulmonol 2019:54(8):1108-116. | A1, Patient population not fulfilled |
| 46 | Mandarakas et al. Functional outcome measures for infantile Charcot-Marie-Tooth disease: a systematic review. J Peripher Nerv Syst 2018:23(2):99-107. | A4, Endpoints not fulfilled |
| 47 | Martin et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: A systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. Neuroimage Clin 2016:10():192-238. | A1, Patient population not fulfilled |
| 48 | Mensch et al. Instruments for the evaluation of motor abilities for children with severe multiple disabilities: A systematic review of the literature. Res Dev Disabil 2015:47():185-198. | A4, Endpoints not fulfilled |
| 49 | Messina et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. Neuromuscul Disord 2019:29(12):940-950. | A4, Endpoints not fulfilled |
| 50 | Miladi et al. Minimally Invasive Surgery for Neuromuscular Scoliosis: Results and Complications in a Series of One Hundred Patients. Spine (Phila Pa 1976) 2018:43(16):E968-E975. | A1, Patient population not fulfilled |
| 51 | Nidetz et al. Adeno-associated viral vector-mediated immune responses: Understanding barriers to gene delivery. Pharmacol Ther 2020:207():107453. | A5, Study type not fulfilled |
| 52 | O'Sullivan et al. Effect of Lung Volume Recruitment on Pulmonary Function in Progressive Childhood-Onset Neuromuscular Disease: A Systematic Review. Arch Phys Med Rehabil 2020. | A1, Patient population not fulfilled |
| 53 | Paganoni et al. Evidence-Based Physiatry: Pediatric Neuromuscular Rehabilitation in the Era of Precision Medicine. | A5, Study type not fulfilled |

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|---|---|---|
| | Cochrane Database of Systematic Reviews 2018:97(12):920. | |
| 54 | Payne et al. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017:(4). | A1, Patient population not fulfilled |
| 55 | Perez et al. Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurodegenerative Diseases. Brain Sci 2020:10(2). | A5, Study type not fulfilled |
| 56 | Sansone et al. 1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I-III, Rome, Italy, 30-31 January 2015. Neuromuscul Disord 2015:25(12)979-989. | A5, Study type not fulfilled |
| 57 | Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen.Rev Assoc Med Bras (1992) 2018:64(6):484-491. | A5, Study type not fulfilled |
| 58 | Simon et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews 2016:(10). | A1, Patient population not fulfilled |
| 59 | Simonds et al. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc 2016:13(11):2035-2044. | A1, Patient population not fulfilled |
| 60 | Tizzano et al. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. Neuromuscul Disord 2017:27(10):883-889. | A1, Patient population not fulfilled |
| 61 | Uchitel et al. Viral-Mediated Gene Replacement Therapy in the Developing Central Nervous System: Current Status and Future Directions.Pediatr Neurol 2020:110():5-19. | A5, Study type not fulfilled |
| 62 | Vaidya et al. Correction to: Measuring quality of life in children with spinal muscular atrophy: a systematic literature review. Qual Life Res 2018:27(12):3095. | A5, Study type not fulfilled |
| 63 | Van Geel et al. Measuring walking-related performance fatigability in clinical practice: a systematic review. Eur J Phys Rehabil Med 2020:56(1):88-103. | A1, Patient population not fulfilled |
| 64 | Waldboth et al. Living a normal life in an extraordinary way: A systematic review investigating experiences of families of young people's transition into adulthood when affected by a genetic and chronic childhood condition. Int J Nurs Stud 2016:(62). | A1, Patient population not fulfilled |
| 65 | Wei et al. Notable Carrier Risks for Individuals Having Two Copies of SMN1 in Spinal Muscular Atrophy Families with 2-copy Alleles: Estimation Based on Chinese Meta-analysis Data. J Genet Couns 2017:26(1):72-78. | A1, Patient population not fulfilled |
| 66 | Wiffen et al. Systematic Reviews Published in the Cochrane Library January-March 2017. J Pain Palliat Care Pharmacother 2017:31(2):167-169. | A1, Patient population not fulfilled |

## A 2 Relevant variables in SMArtCare Registry

Table A 21: Relevant variables in SMArtCARE Registry

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| **Enrolment** | | Date of consent | x | |
| | | Genetically proven 5q SMA | x | |
| | | Date of Birth | x | |
| | | Gender | x | |
| **Baseline** | | Date recorded | x | |
| | Genetic Test Result | SMN2 copy number | x | |
| | | Was diagnosis made pre-symptomatically? | x | |
| | Clinical diagnosis | Age at symptom onset | x | |
| | Motor function | Sitting without support | x | |
| | | Sitting without support: Age gained | x | |
| | | Crawl on hands and knees | x | |
| | | Crawl on hands and knees: Age gained | x | |
| | | Standing without support | x | |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Standing without support: Age gained | x | |
| | | Walking without support | x | |
| | | Walking without support: Age gained | x | |
| | | Climb stairs | x | |
| | | Climb stairs: Age gained | x | |
| | Registries, clinical trials | Is the patient currently or was previously included in a clinical trial? | x | |
| **Medical Assessment** | | Visit date | x | x |
| | | Age at visit | x | x |
| | Pulmonary | Does the patient receive ventilator support? | x | x |
| | | Type of ventilation | | x |
| | | Time of ventilator use | x | x |
| | | Start of ventilator use | | x |
| | Nutrition | Does the patient use a gastric or nasal feeding tube? | x | x |
| | | Start of tube feeding | x | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Swallowing? | | x |
| | | Chewing? | | x |
| | Orthopedics | Does the patient have scoliosis? | | x |
| | | Orthopedic surgery since last visit? | | x |
| | Hospitalisation | Planned hospitalisation since last visit (except for treatment administration)? | | x |
| | | Admission date | | x |
| | | Reason for hospitalisation | | x |
| | Medication | Is the patient on any approved medication for SMA? | x | x |
| | | Name of drug | x | x |
| | | Start date | x | x |
| | | Other medication taken on a regular basis? | x | x |
| | | Name of medication | x | x |
| | Clinical Trial | Is the patient currently in a clinical trial? | x | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Start Date | x | x |
| | Motor function | Any changes in motor milestones? | x | x |
| | | Age gained of new motor milestone | x | x |
| | | Age loss of previous motor milestone | x | x |
| | | Best current motor function | x | x |
| | HINE | Score | x | x |
| | | Head control | x | x |
| | Clinical examination | Body weight | x | |
| | | Neurology: Symptoms related to SMA | x | |
| | | Are any contractures present? | x | |
| | | Type of limitation | x | |
| **Physiotherapeutic Assessment** | CHOP-INTEND | Date of Evaluation | x | x |
| | | Score | x | x |
| **Zolgensma** | Admission day | Date of treatment | x | |
| **Nusinersen** | | Date of treatment | x | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Care setting | x | x |
| **Risdiplam** | | Date of treatment | x | x |
| **Adverse Events** | | Date recorded | | x |
| | | Type of unexpected event: Hydrocephalus | | x |
| | | Type of unexpected event: Hepatotoxicity | | x (to be added) |
| | | Type of unexpected event: Thrombocytopenia | | x (to be added) |
| | | Type of unexpected event: Cardiac events | | x (to be added) |
| | | Type of unexpected event: Dorsal root ganglia cell inflammation | | x (to be added) |
| | | Type of unexpected event: Renal toxicity | | x (to be added) |
| | | Type of unexpected event: Respiratory tract infection | | x |
| | | Type of unexpected event: Epileptic seizure | | x |
| | | Type of unexpected event: Post lumbar puncture | | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | syndrome | | |
| | | Has there been any adverse event since the last visit? | | x |
| | | Has there been unplanned or prolonged hospitalisation? | | x |
| | | Any unexpected events without hospitalisation? | | |
| | | Type of unexpected event | | x |
| | | MedDRA code of acute event | | x |
| | | Admission date | | x |
| | | Is the adverse event related to drug treatment? | | x |
| | | Name of drug | | x |
| | | Start date | | x |
| **End of data collection** | | Date recorded | | x |
| | | Is the patient deceased? | | x |
| | | Date of death | | x |

Source: SMArtCARE Case Report Form 2021 (20)

Relevant variables for RESTORE registry are displayed in RESTORE addendum (Addendum 1).

# Addendum 1

# Inclusion of RESTORE registry as secondary data source

# Addendum 1 – Inclusion of RESTORE registry as secondary data source

Addendum 1 to study protocol version 4.01 of routine data collection and evaluations of onasemnogene abeparvovec in Germany

Protocol Number: COAV101A1DE01

Study protocol version 4.01

26 January, 2024

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# Purpose of the addendum for RESTORE registry

*According to G-BA resolution on 20 October 2022, the integration of the RESTORE registry alone was not explicitly mandated by the G-BA. Instead, study protocol and SAP should be seen as the starting point of possible integration of other registries including RESTORE.*

*Therefore, information on RESTORE registry was extracted from the study protocol version 3.01 and was displayed in this addendum for the new study protocol version 3.1.*

*For better orientation, the structure of this addendum was designed analogous to the study protocol and only filled with information or changes that do only affect the RESTORE registry as secondary data source. General information regarding RESTORE as well as SMArtCARE registry were only depicted in the actual study protocol version 3.1.*

*Information on SMArtCARE registry or general information on the study can be retrieved from the study protocol version 3.1.*

***Amendment 1.1 (study protocol version 4.01)***

*This RESTORE addendum was amended to include risdiplam as comparator besides treatment with nusinersen. Further information can be found in study protocol version 4.01.*

# Revision History

*For more information see study protocol version 4.01.*

# Synopsis and Milestones

*For more information see study protocol version 4.01.*

# 1. Background

## 1.1 Spinal muscular atrophy

*For more information see study protocol version 4.01.*

## 1.2 Benefit assessments for onasemnogene abeparvovec

*For more information see study protocol version 4.01.*

## 1.3 Routine Data Collection and Evaluations for onasemnogene abeparvovec

### 1.3.1 G-BA resolutions and procedures

*For more information see study protocol version 4.01.*

### 1.3.2 Written change requests from G-BA based on IQWiG assessment of study protocol and SAP

*For more information see study protocol version 4.01.*

### 1.3.3 Depiction of change requests from 28 September 2021 in study protocol and SAP version 2.02

*For more information see study protocol version 4.01.*

### 1.3.4 Conditional approval of study protocol and SAP, implementation of additional change requests

*For more information see study protocol version 4.01.*

# 2. Overview of study design and study schematic

## 2.1 Pre-specification of two analysis approaches

*For more information see study protocol version 4.01.*

*Information on RESTORE was included in the following table:*

Table A1 1: Overview of key similarities and differences between NGT approach and G-BA approach

| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| Inclusion and exclusion criteria | *For more information see study protocol version 4.01.* | |
| Analysis populations | *For more information see study protocol version 4.01.* | |
| Handling of treatment switches | *For more information see study protocol version 4.01.* | |
| Confounder adjustment | *For more information see study protocol version 4.01.* | |
| Sensitivity analyses | *For more information see study protocol version 4.01.* | |
| Utilization of parallel retrospective data, i.e. collected after availability of onasemnogene abeparvovec | *For more information see study protocol version 4.01.* | |
| Utilization of non-parallel retrospective data, i.e. collected before availability of onasemnogene abeparvovec | *For more information see study protocol version 4.01.* | |
| Data sources | Secondary: RESTORE (de-novo sites only) | |
| Study sites | RESTORE: De-novo sites (currently predominantly located in the United States but additional sites continuously added globally) | |
| Sample size calculation | *For more information see study protocol version 4.01.* | |
| Interim analysis | *For more information see study protocol version 4.01.* | |
| Status report | *For more information see study protocol version 4.01.* | |

## 2.2 NGT approach

*For more information see study protocol version 4.01.*

## 2.3 G-BA approach

*For more information see study protocol version 4.01.*

# 3. Compared therapies

## 3.1 Onasemnogene abeparvovec

### 3.1.1 Mechanism of action

*For more information see study protocol version 4.01.*

### 3.1.2 Method of administration and dosage

*For more information see study protocol version 4.01.*

## 3.2 Nusinersen

### 3.2.1 Mechanism of action

*For more information see study protocol version 4.01.*

### 3.2.2 Method of administration and dosage

*For more information see study protocol version 4.01.*

# 4. Objectives

*For more information see study protocol version 4.01.*

# 5. Endpoints

*Health-related quality of life (HRQoL) will not be depicted in the Routine Data Collection and Evaluations (see study protocol version 4.01 for details on SMArtCARE). Information on HRQoL in RESTORE registry is the following:*

*HRQoL* is generally included in the form of the Pediatric Quality of Life Inventory™ 4.0 (PedsQL™ 4.0) questionnaire. However, age-appropriate versions of the PedsQL™ 4.0 only start at an age of 2 years, while the vast majority of patients included in this study are younger at treatment initiation (baseline). HRQoL is thus not included in the Routine Data Collection and Evaluations as it is only depictable in the secondary data source and baseline data would only be available for a very small share of patients (significantly less than 70% required by G-BA).

A detailed description of the operationalization of endpoints in RESTORE is provided in section 5.1 and 5.2. The depictability of confounders in RESTORE registry is shown in annex A3. Additionally, it was assessed whether meta-analysis with SMArtCARE registry is feasible.

## 5.1 Effectiveness

### 5.1.1 Survival

Table A1 2: Effectiveness endpoints in RESTORE Registry: Survival

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Overall Survival (OS) | Time from the date of first treatment to the date of death due to any cause | ▪ Nusinersen Treatment: MIN(Date of dose)/Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ End of Registry Summary: Date of death |
| Event Free Survival (EFS) | Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ End of Registry Summary: Date of death<br>▪ Ventilatory Support: Tracheostomy: Date of procedure/Other Ventilatory Support: Start date<br>▪ Ventilatory Support: Tracheostomy: Ongoing? = Yes/Other Ventilatory Support: Ongoing? = Yes<br>▪ Ventilatory Support: Other Ventilator Support: Average daily use ≥ 16 hours/day<br><br>*Note: Operationalization may change* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *after CRF update to harmonize ventilator data capture with SMArtCARE categories.* |

### 5.1.2 Motor function

#### 5.1.2.1 NGT approach

Table A1 3: Effectiveness endpoints in RESTORE Registry: Motor function (NGT approach)

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Achievement of motor milestones according to age | Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis<br><br>Age limits per milestone (based on WHO) (22)<br>▪ Sitting without support: 9.2 months<br>▪ Crawl on hands and knees: 13.5 months<br>▪ Standing without support: 16.9 months<br>▪ Walking without support: 17.6 months | ▪ Developmental milestones: Hands and Knees Crawling: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Hands and Knees crawling: Age in months at first achieved (months)<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestone: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestone: Walking Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note:*<br>▪ *RESTORE refers both to WHO performance criteria (23) and Bayley Scales Infant and Toddler Development (24) criteria as guidance.*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *seconds) via a CRF update* |
| Head control at the age of 8 months | Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age | ▪ HINE: Age at evaluation (months)<br>▪ HINE: Item 1: Head control |
| Crawl on hands and knees at the age of 18 months | Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months | ▪ Developmental milestones: Hands and Knees Crawling: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Hands and Knees Crawling: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the Bayley Scales Infant and Toddler criteria (24) as guidance: "Child makes forward progress of at least 5 feet by crawling on hands and knees"* |
| Sitting without support at the age of 18 months | Proportion of patients achieving the motor milestone of sitting without support at or before the age of 18 months | ▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Standing without support at the age of 24 months | Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months | ▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestone: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled) |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *Notes:*<br>▪ *RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child stands alone for at least 3 seconds after you release his or her hands."*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10 seconds) via CRF update* |
| Walking without support at the age of 24 months | Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months | ▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone? = yes<br>▪ Developmental milestones: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly"* |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone?<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Did the patient lose the milestone?<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at lost (months)<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone?<br>▪ Developmental milestones: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Standing Alone: Did the patient lose the milestone?<br>▪ Developmental milestones: Standing Alone: Age in months at lost (months) |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | ▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone?<br>▪ Developmental milestones: Walking Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Walking Alone: Did the patient lose the milestone?<br>▪ Developmental milestones: Walking Alone: Age in months at lost (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved or lost not filled)<br><br>*Notes:*<br>▪ *RESTORE refers both to WHO performance criteria (23) and Bayley Scales Infant and Toddler Development criteria (24) as guidance.*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10 seconds) via a CRF update* |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | ▪ Nusinersen Treatment: MIN(Date of dose) Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Final Score |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ HINE: Evaluation Date<br>▪ HINE: Total Score |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | *scoring instrument* | |
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestone: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Notes:*<br>▪ *RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child stands alone for at least 3 seconds after you release his or her hands."*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10 seconds) via a CRF update* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly"* |

5.1.2.2 G-BA approach

Table A1 4: Effectiveness endpoints in RESTORE Registry: Motor function (G-BA approach)

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestone: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Notes:*<br>▪ *RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child stands alone for at least 3 seconds after you release his or her hands."*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10 seconds) via a CRF update* |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone? = Yes<br>▪ Developmental milestones: Age in months at first achieved (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved not filled)<br><br>*Note: RESTORE refers to the Bayley Scales Infant and Toddler Development criteria (24) as guidance: "Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly"* |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support | ▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | ▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved (months)<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Did the patient lose the milestone?<br>▪ Developmental milestones: Child sits up straight with head erect for at least 10 seconds: Age in months at lost (months)<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone?<br>▪ Developmental milestones: Standing Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Standing Alone: Did the patient lose the milestone?<br>▪ Developmental milestones: Standing Alone: Age in months at lost (months)<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone?<br>▪ Developmental milestones: Walking Alone: Age in months at first achieved (months)<br>▪ Developmental milestones: Walking Alone: Did the patient lose the milestone?<br>▪ Developmental milestones: Walking Alone: Age in months at lost (months)<br>▪ Developmental milestones: Age at assessment (if age at first achieved or lost not filled)<br><br>*Note:*<br>▪ *RESTORE refers both to WHO performance criteria (23) and Bayley Scales Infant and Toddler Development criteria (24).*<br>▪ *RESTORE will add developmental milestone of standing without support per WHO performance criteria (10 seconds) via a CRF update* |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Neuromuscular Disorders): Change from baseline | ▪ 12 months after initial treatment | MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Final Score |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ HINE: Evaluation Date<br>▪ HINE: Total Score |

### 5.1.3 Nutrition

Table A1 5: Effectiveness endpoints in RESTORE Registry: Nutrition

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Difficulties in swallowing | Time from the date of first treatment to the first documented difficulties in swallowing | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Bulbar Function: Date of evaluation<br>▪ Bulbar Function: Swallow evaluation result<br>o Aspiration<br>o Dysphagia (coughing, sputtering, wet sound with feeds)<br>o Able to tolerate thick liquids by mouth<br>o Other<br>▪ Bulbar function: Other swallow evaluation result specify (text field) |
| Difficulties in chewing | Time from the date of first treatment to the first documented difficulties in chewing | *Note: Difficulties in chewing was originally not captured in RESTORE but will be added via CRF update.* |
| Gastric or nasal feeding tube | Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations<br>▪ Any type of tube feeding (supplementary or exclusively)<br>▪ Supplementary (e.g. for fluids)<br>▪ Exclusively | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Nutritional Assessment: Has the patient had any non-oral feeding support used to administer nutrition? = Yes<br>▪ (Nutritional Assessment: Non-oral feeding support used to administer nutrition (select)<br>▪ Nutritional Assessment: Other non-oral feeding support, specify) |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | AND<br>▪ Nutritional assessment: Nutritional intake<br>o All food via non-oral method<br>o Able to eat some food by mouth<br>o Able to eat all food by mouth<br>▪ Nutritional Assessment: Date of placement |

### 5.1.4 Orthopedic complications

Table A1 6: Effectiveness endpoints in RESTORE Registry: Orthopedic complications

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Scoliosis or orthopedic surgery | Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Musculoskeletal Findings: Spinal curvature = Scoliosis<br>OR<br>▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Relevant Surgical Procedures: Date of surgery<br>▪ Relevant Surgical Procedures Question: Has the patient had any surgical procedures since initial SMA diagnosis?<br>▪ Relevant Surgical Procedures: Procedure<br>o Hip surgery<br>o Scoliosis surgery<br>o Spinal fusion with bone windows<br>o Spinal fusion without bone windows<br>o Tendon surgery |
| Scoliosis | Time from the date of first treatment to first documentation of scoliosis | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Musculoskeletal Findings: Spinal curvature = Scoliosis |
| Orthopedic surgery | Time from the date of first treatment to first documentation of orthopedic surgery | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Relevant Surgical Procedures: Date of surgery<br>▪ Relevant Surgical Procedures Question: Has the patient had any surgical procedures since initial SMA diagnosis?<br>▪ Relevant Surgical Procedures: Procedure<br>o Hip surgery<br>o Scoliosis surgery<br>o Spinal fusion with bone windows<br>o Spinal fusion without bone windows<br>o Tendon surgery |

### 5.1.5 Respiratory function

Table A1 7: Effectiveness endpoints in RESTORE Registry: Respiratory function

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Time of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of<br>▪ Any ventilator support<br>▪ Ventilator support at night (during sleep)<br>▪ Intermittent ventilator support at day time and continuous at night<br>▪ Permanent ventilator support (≥16 hours per day)<br>▪ Intermittent ventilator support with acute illnesses<br><br>Documentation of same or | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Ventilatory Support Question: Has the patient had any ventilatory support since birth?<br>▪ Ventilatory Support: Tracheostomy: Date of procedure/Other Ventilatory Support: Start date<br>▪ Ventilatory Support: Tracheostomy: Reason for procedure/ Other Ventilatory Support: Reason for use |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | higher ventilator support time required at two consecutive visits. | ▪ Ventilatory Support: Tracheostomy: Ongoing?/Other Ventilatory Support: Ongoing?<br>▪ Ventilatory Support: Other Ventilatory Support: Frequency: daily/as needed<br>▪ Ventilatory Support: Other Ventilatory Support: Average daily use<br><br>*Note: RESTORE currently does not differentiate between day and night time use of ventilator. To approximate SMArtCARE categories the following average daily use times are used in retrospective data:*<br><br>▪ *Night (during sleep): < 12 hours*<br>▪ *Intermittent at day time and continuous at night: ≥ 12 hours < 16 hours*<br>▪ *Continuous: ≥16 hours*<br><br>*Via an update of the CRF, categories in line with SMArtCARE definitions on nightly use and intermittent ventilator support at day time and continuous at night will be added to RESTORE.* |
| Type of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of (each separately)<br>▪ Non-invasive ventilation<br>▪ Invasive ventilation<br><br>Documentation of same or higher ventilator support type required at two consecutive visits. | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Ventilatory Support Question: Has the patient had any ventilatory support since birth?<br>▪ Ventilatory Support: Record Ventilatory Support. Specify type(s) of ventilator support used.<br>o Tracheostomy<br>o Other invasive ventilatory support<br>▪ Ventilatory Support: Other Ventilatory Support: Type =<br>o Bi-level positive airway pressure ventilators (i.e. BiPAP)<br>o CPAP<br>o Endotracheal type via mouth or nose<br>o Other |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | ▪ Ventilatory Support: Tracheostomy: Date of procedure/Other Ventilatory Support: Start date |
| Improvement in time of ventilator support from baseline | Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following<br>▪ Change from permanent ventilator support (≥16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR<br>▪ Change from intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR<br>▪ Change from ventilator support at night (during sleep) to no ventilator support | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Ventilatory Support Question: Has the patient had any ventilatory support since birth?<br>▪ Ventilatory Support: Tracheostomy: Date of procedure/ Other Ventilatory Support: Start date<br>▪ Ventilatory Support: Tracheostomy: Reason for procedure/Ventilatory Support: Reason for use<br>▪ Ventilatory Support: Other Ventilatory Support: Frequency: daily/as needed<br>▪ Ventilatory Support: Other Ventilatory Support: Average daily use<br>*Note: RESTORE currently does not differentiate between day and night time use of ventilator. To approximate SMArtCARE categories the following average daily use times are used in retrospective data:*<br>▪ *Night (during sleep): < 12 hours*<br>▪ *Intermittent at day time and continuous at night: ≥ 12 hours < 16 hours*<br>▪ *Continuous: ≥16 hours*<br>*Via an update of the CRF, categories in line with SMArtCARE definitions on nightly use and intermittent ventilator support at day time and continuous at night will be added to RESTORE.* |

### 5.1.6 Planned hospitalizations

Table A1 8: Effectiveness endpoints in RESTORE Registry: Planned hospitalizations

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Planned hospitalizations | Cumulative number of planned hospitalizations across all patients per patient-year of being at risk including planned hospitalizations for administration of SMA treatments | *Note: RESTORE captures data on care setting of drug administration via the system metadata of submissions on nusinersen/risdiplam doses / AVXS-101 treatment. This information will be used for endpoint analysis.* |

## 5.2 Safety

### 5.2.1 Adverse events

In RESTORE AEs are collected in the first year from treatment, after that only AESIs and SAEs are collected.

Table A1 9: Safety endpoints in RESTORE Registry: Adverse events

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Any Adverse events with or without hospitalization | Cumulative number of patients with and number of adverse events with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse event: [text field]<br>▪ Adverse Events: Start date |
| Any Adverse events with or without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse event: [text field]<br>▪ Adverse events: Start date<br>▪ Adverse events: Relationship to SMA treatment<br>▪ Adverse events: Specify which |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | treatment |
| Adverse events without hospitalization | Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event? |
| Adverse events without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse event: Relationship to SMA treatment<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event? |

### 5.2.2 Serious adverse events

RESTORE as the secondary data source uses standard SAE criteria, which are used for analyses.

Table A1 10: Safety endpoints in RESTORE Registry: Serious adverse events

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Serious adverse events with hospitalization | Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event? |
| Serious adverse events with hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Relationship to SMA treatment<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event? |
| Serious adverse events with hospitalization or death | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse Event: [text field] |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | *MedDRA code was documented.* | ▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: Results in death<br>▪ Adverse Events: Serious criteria: it requires in-patient hospitalization or prolongation of existing hospitalization |
| Serious adverse events with hospitalization or death related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: Results in death<br>▪ Adverse Events: Serious criteria: it requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Adverse Events: Relationship to SMA treatment |
| Serious adverse events (RESTORE only) | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious AE?<br><br>*Note: RESTORE captures additional seriousness criteria that cannot be depicted in SMArtCARE (i.e. immediately life-threatening, permanent disability, congenital abnormalities or birth defects).* |
| Serious adverse events related to treatment (RESTORE only) | Cumulative number of patients with and number of serious adverse events related to treatment (yes/possibly) across all patients per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol? |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious AE?<br>▪ Adverse Events: Relationship to SMA treatment<br><br>*Note: RESTORE captures additional seriousness criteria that cannot be depicted in SMArtCARE (i.e. immediately life-threatening, permanent disability, congenital abnormalities or birth defects).* |

### 5.2.3 Adverse events of special interest

RESTORE did not explicitly capture the AESIs required for this study at the time of registry initiation but uses standardized MedDRA queries (SMQs) to identify potential instances of AESIs that are evaluated by the marketing authorization holder for reporting to regulatory authorities. This very sensitive search approach, however, leads to almost 100% "overshooting", i.e. almost no adverse event identified via the corresponding SMQs is actually an instance of an AESI.

In order to depict the AESIs included in this study consistently across both the primary and secondary data sources, an explicit selection field will be added to RESTORE's AE reporting CRF page asking the investigator if the reported AE could be characterized as any of the AESIs included in this study. Information from this CRF update will be available prospectively and used for AESI analyses in the secondary data source.

The specific documentation of all AESIs in RESTORE will start after completion of a protocol and CRF update performed to fulfill all data source requirements and data documentation needs of this study. Novartis Gene Therapies expects that this process will be completed by the end of 2023.

All adverse events possibly relating to the five AESIs mandated by G-BA that require a CRF update are generally covered retrospectively in the MedDRA-based reporting of AEs.

Table A1 11: Safety endpoints in RESTORE Registry: Adverse events of special interest

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| Hydrocephalus with or without hospitalization | Cumulative number of patients with and number of adverse events of | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | hydrocephalus per patient-year of being at risk | MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Hydrocephalus with hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Hepatotoxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Hepatotoxicity with hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note:* CRF *will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Thrombocytopenia with or without hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse Event: [text field] |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *Note:* CRF *will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Thrombocytopenia with hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note:* CRF *will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Cardiac events with or without hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Cardiac events with hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Dorsal root ganglia cell inflammation with or without hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>. | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven* |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | *documentation will be used for analysis.* |
| Dorsal root ganglia cell inflammation with hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>. | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Renal toxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Renal toxicity with hospitalization | Cumulative number of patients with and number of | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | adverse events of renal toxicity per patient-year of being at risk | MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Respiratory tract infection with or without hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk<br><br>. | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Respiratory tract infection with hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Epileptic seizure with or without hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Epileptic seizure with hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Post lumbar puncture syndrome with or without hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |
| Post lumbar puncture syndrome with hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization<br>▪ Hospitalizations Question: Was the patient admitted to hospital more |

| Endpoint | Definition | Fields of RESTORE CRF (21) |
|---|---|---|
| | | than 24 hours?<br>▪ Hospitalizations: Date of hospitalization<br>▪ Hospitalizations: Was visit for an Adverse Event?<br>▪ Adverse Events: Adverse Event: [text field]<br><br>*Note: CRF will be updated to explicitly collect information on AESI of this study. Investigators will be asked if the AE reported is any of the AESI defined for this study. Once implemented, information from this direct, investigator-driven documentation will be used for analysis.* |

# 6. Data sources

*For more information see study protocol version 4.01.*

With its resolution from 20 January 2022 (25), G-BA recommended explicitly the inclusion of RESTORE as a secondary data source under the condition that structural changes are performed in order to fulfill the data source requirements set forth in its 4 February 2021 resolution (Gemeinsamer Bundesausschuss 2021. Previously, G-BA has requested that "the pharmaceutical company should make the necessary adjustments to the self-managed RESTORE registry in accordance with the final study protocol and SAP for the Routine Data Collection and Evaluations in order to be able to use evaluations based on the RESTORE registry together with the present registry study, e.g. in the form of a meta-analysis for the Routine Data Collection and Evaluations" with its 28 September 2021 change requests (Change request No. 6 from 28 September 2021, Table 6). With protocol version 3.01, RESTORE was added as a secondary data source per G-BA's explicit recommendation and transferred to a separate addendum due to the G-BA request in the resolution on 20 October 2022 (Gemeinsamer Bundesausschuss 2022c). Novartis Gene Therapies is also implementing major structural changes in RESTORE and its more than 100 de-novo sites globally to fulfill the data source requirements set forth in G-BA's 4 February 2021 resolution (3).

Novartis Gene Therapies cannot influence that healthcare systems and reimbursement situations differ between Germany and the United States of America as well as other global geographies that are continuously added to RESTORE. Novartis Gene Therapies thus assumes that G-BA's explicit recommendation to include RESTORE as a secondary data source in an effort to increase patient numbers of this study implicates a commitment by G-BA to include this data in a future benefit assessment despite the limitations of differences in healthcare systems originally depicted in its 4 February 2021 resolution (3).

Analyses will be conducted within each data source and presented to G-BA. If the results meet homogeneity criteria, meta-analysis will be performed. Information on the RESTORE registry as secondary data source is provided in Table 20: Fulfillment of quality criteria by SMArtCARE registry.

## 6.1 SMArtCARE registry

*For more information see study protocol version 4.01.*

## 6.2 RESTORE registry

### 6.2.1 Overview

The RESTORE registry is a prospective, multicenter, non-interventional disease registry for SMA. The registry is sponsored by Novartis Gene Therapies and governed by an international steering committee of SMA experts, who are committed to

ensuring the quality of the data and to sharing findings through publication. Clinical care is not dictated by a research protocol and no additional visits or investigations are performed beyond those consistent with normal clinical practice. Patients were originally planned to be enrolled over a 5-year period and followed for 15 years, or until death (26). With the inclusion of RESTORE in this study, a protocol amendment will be performed to continue enrolling patients until at least 31 December 2026, i.e. until the time of final data cut of this study.

The RESTORE registry is part of the requirements in the EMA's Risk Management Plan for onasemnogene abeparvovec (27). A minimum of 500 subjects were originally the recruitment target, which will be exceeded significantly due to the global expansion of the registry as well as the significant extension of enrollment period performed for this study. Recruitment started in September 2018.

Table A1 12 depicts RESTORE inclusion and exclusion criteria.

Table A1 12: RESTORE eligibility criteria

| Inclusion Criteria | Exclusion criteria |
|---|---|
| ▪ Patients not treated with AVXS-101 with SMA genetically confirmed on or after 24 May 2018 OR<br>▪ Patients treated with AVXS-101 with SMA genetically confirmed regardless of the date of diagnosis AND<br>▪ Appropriate consent/assent has been obtained for participation in the registry. | ▪ Currently enrolled in an interventional clinical trial involving an investigational product to treat SMA. |

Note: patients that are participating in a CUP for AVXS-101 (Zolgensma) such as a MAP, an EAP, SPI or NPP are eligible to enroll in the registry regardless of the date of genetic confirmation of SMA. Patients that are participating in long-term follow-up studies of Zolgensma (such as LT-001 or LT-002) are not eligible to enroll in the registry. However, patients who have completed clinical trials and are not participating in the long-term follow up studies may enroll in this registry.

Sources: (28)

RESTORE data is sourced both from de-novo study sites and consortia. From de-novo sites, patient level data on both onasemnogene abeparvovec and nusinersen/risdiplam is available and will be used for the Routine Data Collection and Evaluations. Consortia are study groups or other international SMA registries that contractually agreed to share their data in the RESTORE registry. While some consortia agreed to provide patient level data for onasemnogene abeparvovec, no consortia partner has agreed to also sharing patient level data on nusinersen/risdiplam. Since only aggregated data on nusinersen/risdiplam is thus available from consortia, only data from de-novo RESTORE sites can and will be used for the Routine Data Collection and Evaluations.

At current, no RESTORE de-novo site is participating in SMArtCARE. Should any center participate in both RESTORE and SMArtCARE (as a de-novo site) in the future, RESTORE data from this center will not be included in the analysis. Instead, the center's data documented in the primary data source (SMArtCARE) will be used to avoid duplicate patient inclusion in the Routine Data Collection and Evaluations.

### 6.2.2 Changes performed to fulfill G-BA's data source requirements

With its explicit recommendation to include RESTORE as a secondary data source in the Routine Data Collection and Evaluations, G-BA mandated that changes to the registry are performed. A number of measures have thus been initiated by the registry's steering committee and are supported by Novartis Gene Therapies.

Enrollment of nusinersen/risdiplam patients

G-BA and IQWiG have expressed concerns that strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness may not be sufficient in RESTORE. While RESTORE eligibility criteria have never restricted or differentiated between therapies, it is acknowledged that to date, the majority of RESTORE enrolled patients have been treated with onasemnogene abeparvovec. To increase the number of patients initially treated with nusinersen/risdiplam or exclusively treated with nusinersen/risdiplam, the following measures will be performed:

- Implement a formal feasibility to identify and a focused plan to enroll additional nusinersen/risdiplam patients from existing sites that fulfill the inclusion and exclusion criteria of the Routine Data Collection and Evaluations – where all the active de-novo sites will be requested to review their site records and provide a summary count of their nusinersen/risdiplam patients. The individual site counts will be compared against the number of nusinersen/risdiplam patients fulfilling the inclusion and exclusion criteria of the Routine Data Collection and Evaluations that each center has already enrolled in the registry.
- Building on the results of the feasibility, Novartis Gene Therapies will optimize the site investigators' ability to attract these potential patients to consent to participate in the RESTORE study.
- Re-training of sites will be performed to focus on enrolling additional nusinersen/risdiplam patients meeting the inclusion and exclusion criteria for the Routine Data Collection and Evaluations. Each site will be given a RESTORE engagement package of tools, which will consist of standard messaging and materials to be provided to caregivers/patients focused on the value of the RESTORE registry.

The results of these activities will be provided to G-BA as part of the interim analyses. Should patient numbers for nusinersen/risdiplam continue to be below expectations, additional steps (e.g. identification and activation of new sites in RESTORE with substantial numbers of nusinersen/risdiplam patients that fulfill the

inclusion and exclusion criteria of the Routine Data Collection and Evaluations) will be discussed with G-BA.

Optimization of enrollment time and retrospective data capture

In addition to measures ensuring minimization of selection bias and maximization of representativeness, measures on timely inclusion of patients after diagnosis and full data documentation from the time of initial SMA therapy onward will be undertaken. Due to differences in healthcare systems across different regions globally, enrollment of patients in RESTORE frequently occurs after initiation of the first SMA therapy. To increase the number of patients in RESTORE that can be included in the Routine Data Collection and Evaluations, Novartis Gene Therapies will optimize the engagement among RESTORE operations and treating sites to enroll patients closer to the time of their first dose of first SMA treatment.

- The RESTORE protocol, CRF, and data collection tools will be amended to require the retrospective collection of data from all enrolled patients fulfilling the inclusion and exclusion criteria of the Routine Data Collection and Evaluations from the time of initiating first dose of first SMA therapy up to the date of registry enrollment. The implementation operations will include approval of the protocol amendment by regional authorities / local ethics committees, updates to site agreements, and reconsent of patients. Once all in place, sites will be trained to and requested to provide this retrospective data for patients fulfilling the inclusion and exclusion criteria of the Routine Data Collection and Evaluations already enrolled in RESTORE, as well as for newly included patients
- RESTORE operations will develop and disseminate new RESTORE materials to increase registry interest from commercial prescribers and patients not involved with RESTORE.
- All current and potential treated patients will be approached, with documented confirmations on an ongoing basis.

Source data verification

100% source data verification will also be implemented across all RESTORE de-novo sites globally (see section 10.2). This will involve modifications with site contracts and approval of ethics committees for all 100+ de-novo sites globally. As such, SDV is expected to start in first sites in end of 2023 after EMA approval of the protocol amendment but be implemented consecutively over the next years.

CRF update

Finally, changes to the RESTORE CRF will be performed to optimize availability of data for the Routine Data Collection and Evaluations as well as harmonize definitions with SMArtCARE to allow for best possible meta-analysis of results.

Fulfillment of quality criteria by RESTORE registry

Table A1 13 summarizes the fulfillment of G-BA data source requirements.

Table A1 13: Fulfillment of quality criteria by RESTORE registry

| No. | Quality criterion | Fulfillment by RESTORE |
|---|---|---|
| | **Consistent systematics** | |
| 1 | Detailed description of registry (registry protocol) | Yes |
| | **Standardization** | |
| 2 | Exact definition/ operationalization of expositions, clinical events, endpoints and confounders | Yes |
| 3 | Current data plan/ coding list | Yes |
| 4 | Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA) | Yes |
| 5 | Use of validated standard assessment instruments (questionnaires, scales, tests) | Yes |
| 6 | Training on data collection and - acquisition | Yes |
| 7 | Implementation of a disease-specific core data set | Yes |
| 8 | Use of exact patient-specific dates (e.g. birth, death, pregnancy) | Yes |
| 9 | Use of exact dates in medical history (e.g. diagnosis, clinical relevant events) | Yes |
| 10 | Use of exact dates of important medical assessments | Yes |
| 11 | Use of exact dates for treatments and interventions (e.g. start/stop, dosage, dosage adjustment) | Yes (retrospective documentation of all information from treatment start to enrollment will be implemented starting in 2023) |
| | **Achievement of recruitment target/sample collection** | |
| 12 | Clearly defined inclusion/exclusion criteria for registry population | Yes |
| 13 | Completeness of registry patients (complete registration or representative sample) | Zolgensma: yes (completeness intended)<br>Nusinersen/Risdiplam: unclear (no completeness but significantly increased patient numbers and representativeness expected from structural changes implemented in RESTORE for this study) |
| 14 | Strategies to avoid unintentional recruitment bias to attain representative status | Yes (open for inclusion of patients with any intervention at de-novo sites, substantial activities to increase |

| No. | Quality criterion | Fulfillment by RESTORE |
|---|---|---|
| | | nusinersen/risdiplam patient inclusion starting in 2022) |
| | **Validity of data collection** | |
| 15 | Completeness of data per assessment | Shall be assured through standards |
| 16 | Completeness of assessments (loss to follow-up, drop outs) | Shall be assured through standards |
| 17 | Accuracy of data | Ensured by automated quality checks and possibility of audits |
| 18 | Consistency of data over time | Yes |
| 19 | Source data verification (e.g. for 10% randomly selected patients per participating center) | Yes, starting in end of 2023 as described in section 10.2. |
| 20 | Internal audits | Yes |
| 21 | External audits | Yes |
| 22 | Quality management system (with regular evaluation of quality indicators, where appropriate) | Yes |
| 23 | Standard Operating Procedures regarding data collection | Yes |
| | **Superordinate quality criteria** | |
| 24 | Transparency of the registry (including funding, decision-making, conflict of interest, amongst others) | Yes |
| 25 | Scientific independence | Yes (steering committee with charter) |
| 26 | Secured funding (for planned study period) | Yes |
| 27 | Steering committee (SC) | *Yes (listed below) :*<br>▪ ***Richard Finkel, (SC Chair)*** *MD - St. Jude Children's Research - Memphis, TN, USA*<br>▪ ***Laurent Servais (SC Co-Chair),*** *MD, PhD, MDUK Oxford Neuromuscular Centre, Oxford, UK*<br>▪ ***John Day,*** *MD, PhD Stanford University Medical Center Palo Alto, CA, USA*<br>▪ ***Isabelle Desguerre,*** *MD, PhD - Assistance Publique, Hôpitaux de Paris –APHP -Paris, France*<br>▪ ***Darryl De Vivo,*** *MD-Columbia University Medical Center - New York, NY, USA* |

| No. | Quality criterion | Fulfillment by RESTORE |
|---|---|---|
| | | ▪ ***Nicole Gusset,*** *PhD- Patient Representative - SMA Europe, Switzerland*<br>▪ ***Janbernd Kirschner,*** *MD - Universität Freiburg, Germany*<br>▪ ***Eugenio Mercuri,*** *MD, PhD-Università Cattolica del Sacro Cuore - Roma, Italy*<br>▪ ***Francesco Muntoni,*** *MD Univeristy College - London, UK*<br>▪ ***Crystal Proud****, MD, Children's Hospital of The King's Daughters, Norfolk, VA, USA*<br>▪ ***Susana Quijano-Roy****, MD, PhD, University Hôpital Raymond Poincaré, Paris, France*<br>▪ ***Kayoko Saito,*** *MD, Tokyo's Women's Medical University School of Medicine, Tokyo, Japan*<br>▪ ***Perry Shieh,*** *MD, PhD, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA*<br>▪ ***Eduardo Tizzano,*** *MD, PhD, Hospital Valle Hebron, Barcelona, Spain)* |
| 28 | Up-to-date registry documents (e.g. protocol, data plan, statistical analysis plan, informed consent etc.) | Yes |
| 29 | Protection of patients´ rights and data protection, consideration of ethical aspects | Yes |
| 30 | Timeliness (current status/quick availability/timeliness of requested results) | Yes |
| 31 | Flexibility and adaptability (e.g. implementation of trials, further assessments, changing medical care situation) | Yes |
| 32 | Documentation trail - documentation of all changes to processes and definitions | Yes |
| 33 | Audit trail - documentation and attribution of all data transactions | Yes |
| 34 | Interconnectability with other data sources | Yes |
| | **Further possible criteria from a regulatory point of view** | |
| 46 | Assessment and handling of adverse events (AE) in accordance with regulatory requirements | Yes |

## 6.3 Study sites

*The criteria depicted in section 6.3 of the study protocol version 4.01 do also apply to the RESTORE registry. See study protocol version 4.01 for more details.*

### 6.3.1 SMArtCARE

*For more information see study protocol version 4.01.*

### 6.3.2 RESTORE

The RESTORE registry is currently enrolling SMA patients across 113 de-novo sites globally, from which patient level data on both onasemnogene abeparvovec and nusinersen/risdiplam is available. The majority of de-novo sites currently participating in RESTORE are located in the United States but additional sites are continuously added across various global geographies. Table A1 14 depicts RESTORE de-novo sites as of 29 June 2022.

Table A1 14: RESTORE de-novo sites

| Country | City, State | HSP |
|---|---|---|
| **Greece** | Thessaloniki | General Hospital of Thessaloniki Ippokrateio |
| | Pendeli | Pendeli Children's Hospital |
| | Athens | University General Hospital Attikon |
| **Ireland** | Dublin | UCD School of Medicine Scoil an Leighis |
| **Israel** | Petah Tikva | Clalit Health Services |
| | Holon | Wolfson Medical Center |
| | Tel Aviv | Tel-Aviv Sourasky Medical Center |
| | Beer Sheva | Soroka Medical Centre |
| **Japan** | Toon-shi | Ehime University Hospital |
| | Kyoto-shi | University Hospital, Kyoto Prefectural University of Medicin |
| | Yokohama-shi | Kanagawa Children's Medical Center |
| | Osaka-shi | Osaka Metropolitan University Hospital |
| | Shimotsuke-shi | Jichi Medical University Hospital |
| | Chiba-shi | Chiba Children's Hospital |
| | Mito-shi | Ibaraki Children's Hospital |
| | Shinjuku-ku | Center Hospital of the National Center for Global Health and |

| Country | City, State | HSP |
|---|---|---|
| | Gifu-shi | Gifu Prefectural General Medical Center |
| | Konan-shi | Konan Kosei Hospital |
| | Kurume-shi | Kurume University Hospital |
| | Kobe-shi | Kobe University Hospital |
| | Izumi-shi | Osaka Women's and Children's Hospital |
| | Tsukuba-shi | University of Tsukuba Hospital |
| | Kumamoto-shi | Kumamoto University Hospital |
| | Moriyama-shi | Shiga Medical Center for Children |
| | Hamamatsu-shi | Hamamatsu University School of Medicine, University Hospital |
| | Saitama-shi | Saitama Children's Medical Center |
| | Ube-shi | Yamaguchi University Hospital |
| | Toyoake-shi | Fujita Health University Hospital |
| | Tokyo | Keio University Hospital |
| | Nagakute-shi | Aichi Medical University Hospital |
| | Sendai-shi | Miyagi Children's Hospital |
| | Hokkaido | Obihiro-Kosei General Hospital |
| | Koshigaya-shi | Dokkyo Medical University Saitama Medical Center |
| | Kawasaki-shi | Hospital of St. Marianna University School of Medicine |
| | Bunkyo-ku | Tokyo Medical and Dental University Hospital |
| | Fuchu-shi | Tokyo Metropolitan Neurological Hospital |
| | Kodaira-shi | National Center of Neurology and Psychiatry |
| | Obu-Shi | Aichi Children’s Health and Medical Center |
| | Hokkaido | Sapporo Medical University Hospital |
| | Kawasaki-shi | Kawasaki Municipal Tama Hospital |
| | Nagoya-shi | Nagoya University Hospital |
| | Kanazawa-shi | Kanazawa University Hospital |
| | Kita-gun | Kagawa University Hospital |
| | Setagaya-ku | National Center for Child Health and |

| Country | City, State | HSP |
|---|---|---|
| | | Development |
| | Muroran-shi | Nikko Memorial Hospital |
| | Shinjuku-ku | Tokyo Medical University Hospital |
| | Fukui | Fukui Prefectural Hospital |
| **Portugal** | Lisboa | Centro Hospitalar Universitario Lisboa Norte, EPE |
| | Coimbra | Centro Hospitalar e Universitario de Coimbra, EPE |
| | Lisboa | Centro Hospitalar Universitário de Lisboa Central, EPE |
| | Porto | Centro Universitario Hospitalar de São João, EPE |
| **Romania** | Bucharest | Spitalul Clinic de Psihiatrie „Profesor Doctor Alexandru Obr |
| **Russian Federation** | Moscow | Research Clinical Institute of Pediatrics n.a. Veltishchev |
| | Saint Petersburg | Almazov National Medical Research Centre |
| | Moscow | National Medical Research Center for Children's Health |
| **South Korea** | Seoul | Samsung Medical Center |
| | Seongnam-si | Seoul National University Bundang Hospital |
| | Daegu | Kyungpook National University Hospital |
| | Yangsan-si | Pusan National University Yangsan Hospital |
| | Jung-dong | Yongin Severance Hospital |
| | Seoul | Severance Hospital |
| **Taiwan** | Taipei City | National Taiwan University Hospital |
| | Kaohsiung City | Kaohsiung Medical University Chung-Ho Memorial Hospital |
| | Taipei City | Taipei Veterans General Hospital |
| | Taoyuan City | Chang Gung Memorial Hospital Linkou Branch |
| **United States** | Salt Lake City, UT | University of Utah |
| | Aurora, CO | Children's Hospital Colorado |
| | Houston , TX | Texas Children's Hospital |

| Country | City, State | HSP |
|---|---|---|
| | Louisville, KY | University of Louisville |
| | Dallas, TX | Children's Health |
| | Farmington, CT | Connecticut Children's Medical Center |
| | Rochester, NY | University of Rochester Medical Center |
| | Cincinnati, OH | Cincinnati Children's Hospital Medical Center |
| | Madison, WI | University of Wisconsin |
| | Los Angeles, CA | University of California Los Angeles Health |
| | St. Louis , Mo | Washington University School of Medicine in St. Louis |
| | Columbus, OH | Nationwide Children's Hospital |
| | Seattle, WA | Seattle Children's |
| | Durham, NC | Duke Health |
| | Portland , OR | CHRISTUS Health |
| | Portland , OR | Oregon Health and Science University |
| | Greenville, SC | Prisma Health |
| | Sacarmento, CA | University of California Davis Health System |
| | Kansas City, KS | University of Kansas Medical Center |
| | Little Rock, AR | Arkansas Children's Hospital |
| | Sacarmento, CA | Virginia Commonwealth University Health System |
| | Phoenix, AZ | Phoenix Children's Hospital |
| | Memphis, TN | Methodist Le Bonheur Healthcare |
| | Columbia, MO | University of Missouri Health System |
| | Cleveland, OH | University Hospitals |
| | Norfolk, VA | Children's Hospital of The King's Daughters |
| | Milwaukee, WI | Children's Hospital of Wisconsin |
| | New Haven, CT | Yale-New Haven Health System |
| | Indianapolis, IN | Indiana University Health |
| | Madera, CA | Valley Children's Healthcare |
| | Minneapolis, MN | University of Minnesota |
| | Fort Worth, TX | Cook Children's |

| Country | City, State | HSP |
|---|---|---|
| | Charlottesville, VA | University of Virginia Health System |
| | Loma Linda, CA | Loma Linda University Health |
| | Miami, FL | Nicklaus Children's Hospital |
| | La Jolla, CA | Rady Children's Hospital San Diego |
| | Albany, NY | Atlantic Health System |
| | Pittsburgh, PA | University of Pittsburgh Medical Center |
| | Oklahoma City, OK | Oklahoma University Medical Center |
| | Austin, TX | Child Neurology Consultants of Austin |
| | Orlando, FL | AdventHealth Altamonte Springs |
| | Fort Myers, FL | Lee Health |
| | Tacoma, WA | MultiCare Health System |
| | Hershey, PA | Penn State Hershey |
| | Stony Brook, NY | The State University of New York |
| | Los Angeles, CA | Children's Hospital of Los Angeles |
| | Orange, CA | Children's Hospital of Orange County |
| | Iowa City, IA | University of Iowa |

Source: Novartis Gene Therapies

# 7. Population Selection

This analysis will use individual patient data from patients included in RESTORE registry as potential secondary data source, which are treated with onasemnogene abeparvovec or nusinersen or risdiplam and fulfill the inclusion and exclusion criteria.

Tables in section 7.1 and 7.2 show the operationalization of inclusion and exclusion criteria in RESTORE registry. A detailed description on depictability of inclusion and exclusion criteria in RESTORE is presented in annex A3.

## 7.1 Inclusion Criteria

A detailed description of the operationalization of inclusion and exclusion criteria in RESTORE is provided in Table A1 15 and Table A1 16. The depictability of confounders in RESTORE registry is shown in annex A3.

Table A1 15: Inclusion criteria in RESTORE Registry

| # | Inclusion criteria | Fields of RESTORE CRF (21) |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | ▪ SMA Medical History: Genetic testing result for SMN1 = SMN1 homozygous deletion of exon 7 (or 7&8)<br>AND<br>▪ SMA Medical History: Did the patient display symptoms at the time of diagnosis? = no<br>AND<br>▪ SMA Medical History: SMN2 copy number ≤ 3 |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | ▪ SMA Medical History: Genetic testing result for SMN1 = SMN1 homozygous deletion of exon 7 (or 7&8)<br>AND<br>▪ SMA Medical History: Did the patient display symptoms at the time of diagnosis? = Yes<br>AND<br>▪ SMA Medical History: Age at first symptoms onset < 6 months<br><br>*Note: Age at first symptoms onset in months is derived from the following fields:*<br>▪ *SMA Medical History: Age in years at first symptoms onset [0-99]*<br>▪ *SMA Medical History: Age in months at first symptoms onset [0-11]* |

| # | Inclusion criteria | Fields of RESTORE CRF (21) |
|---|---|---|
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | ▪ SMA Medical History: Genetic testing result for SMN1 = SMN1 homozygous deletion of exon 7 (or 7&8)<br>AND<br>▪ SMA Medical History: Did the patient display symptoms at the time of diagnosis? = Yes<br>AND<br>▪ SMA Medical History: SMN2 copy number ≤ 3<br>AND<br>▪ SMA Medical History: Age at first symptoms onset ≥ 6 months<br>AND<br>▪ SMA Medical History: Age at first symptoms onset < 18 months<br><br>*Note: Age at first symptoms onset in months is derived from the following fields:*<br>▪ *SMA Medical History: Age in years at first symptoms onset [0-99]*<br>▪ *SMA Medical History: Age in months at first symptoms onset [0-11]* |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to body weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) | ▪ Nusinersen Treatment: MIN(Date of dose) = Nusinersen Treatment: Dosing stage = Dose 1 AND<br>▪ Risdiplam Treatment: Start Date<br>OR<br>▪ AVXS-101 Treatment: MIN (Date of treatment)<br><br>*Note: Retrospective documentation of all visits including AEs and relevant endpoints from the time of first dose/ first SMA treatment to enrollment planned for RESTORE.* |
| 3 | Body weight at treatment initiation ≤ 21 kg | ▪ Patient Growth: weight ≤ 21 kg<br>1. AT<br>▪ Patient Growth: MAX (Date of growth assessment) ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment) |
| 4 | Appropriate consent/assent has been obtained for participation in the study | ▪ Date of consent: Earliest Date of Consent for RESTORE Registry <> “”. |

## 7.2 Exclusion Criteria

Table A1 16: Exclusion criteria in RESTORE Registry

| # | Exclusion criteria | Fields of RESTORE CRF (21) |
|---|---|---|
| 1 | Pretreatment with disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) | ▪ Assessments Prior to Initial SMA Treatment: Has the patient received any approved SMA Treatment? = Yes |
| 2 | Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | ▪ Pulmonary Medications: Other medication, specify: contains albuterol/salbutamol<br>AND<br>▪ Pulmonary Medications: Start date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br><br>*Note: RESTORE currently only records approved SMA treatments and pulmonary medications.*<br>*Necessary information will be depicted via CRF update/protocol amendment.* |
| 3 | Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA | *Note: Eligibility criteria restrict patients not enrolled in a clinical trial at time of registry enrollment. Participation in a clinical trial prior to or after registry enrollment currently cannot be depicted in RESTORE.*<br>*Necessary information will be depicted via CRF update/protocol amendment.* |

## 7.3 Criteria for historic data

The RESTORE registry has been enrolling patients since September 2018. Onasemnogene abeparvovec has been authorized in the United States since May 2019. However, a limited number of patients has been treated with onasemnogene abeparvovec prior to marketing authorization and may have been documented in RESTORE. As per G-BA request No. 4 of 28 September 2021 historical data, i.e. data prospectively captured in RESTORE prior to the start of this study, will be utilized in this study.

*Criteria on historic data is further displayed in study protocol version 4.01.*

# 8. Study Design & Methods: Statistical Considerations

## 8.1 Analysis Populations

### 8.1.1 NGT approach

*Regarding the conduct of sensitivity analyses, information on centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene) will be additionally sourced from secondary data source RESTORE and updated with each submission to G-BA (see section 8.5 of the study protocol version 4.01.)*

*For more information see protocol version 4.01.*

*The following sensitivity analysis was added for RESTORE analysis:*

- Population NGT-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE
- Population NGT-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE

### 8.1.2 G-BA approach

*Regarding the conduct of sensitivity analyses, information on centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene) will be additionally sourced from secondary data source RESTORE and updated with each submission to G-BA (see section 8.5 of the study protocol version 4.01.)*

*The following sensitivity analysis was added for RESTORE analysis:*

- Population GBA-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE
- Population GBA-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE
- Population GBA-C-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE
- Population GBA-D-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.06.2018 as documented in RESTORE

## 8.2 Sample Size

*For more information see protocol version 4.01.*

### 8.2.1 NGT approach

*For more information see protocol version 4.01.*

8.2.1.1 Assumptions of effect measures and event rates

*For more information see protocol version 4.01.*

8.2.1.2 Further assumptions and methods of case number calculation

*For more information see protocol version 4.01.*

8.2.1.3 Results of the sample size calculations

*For more information see protocol version 4.01.*

8.2.1.4 Discussion

*For more information see protocol version 4.01.*

### 8.2.2 G-BA approach

*For more information see protocol version 4.01.*

8.2.2.1 Discussion

*For more information see protocol version 4.01.*

### 8.2.3 Update of sample size calculations with interim analysis at 36 months

*For more information see protocol version 4.01.*

## 8.3 Expected patient numbers

Patient numbers in RESTORE are subject to more uncertainty, and thus no prognosis is possible at current. A number of structural changes are performed to increase both patient numbers in RESTORE in general (e.g. additional sites and incentives for increased inclusion of nusinersen/risdiplam patients) as well as patients eligible for inclusion in the Routine Data Collection and Evaluations (e.g. retrospective documentation of time between initiation of first SMA therapy to enrollment in RESTORE). Given a later start of full data capture in RESTORE but the significantly

higher number of participating sites, patient numbers similar to those in SMArt-CARE seem a reasonable assumption.

### 8.3.1 NGT approach

8.3.1.1 Population NGT-A

*For more information see protocol version 4.01.*

8.3.1.2 Population NGT-B

*For more information see protocol version 4.01.*

### 8.3.2 G-BA approach

*For more information see protocol version 4.01.*

8.3.2.1 Population GBA-A

*For more information see protocol version 4.01.*

8.3.2.2 Population GBA-B

*For more information see protocol version 4.01.*

8.3.2.3 Population GBA-C

*For more information see protocol version 4.01.*

8.3.2.4 Population GBA-D

*For more information see protocol version 4.01.*

## 8.4 Feasibility assessment

*For more information see protocol version 4.01.*

## 8.5 Planned Analyses

*Information in section 8.5 of the study protocol version 4.01 does also apply to RE-STORE registry.*

### 8.5.1 Status report 18 months after G-BA resolution

As the secondary data source (RESTORE) is only added with version 3.1 of the protocol and SAP, the first status report that is submitted to G-BA at the same time as

the corresponding update of study protocol and SAP is exclusively based on the primary data source (SMArtCARE).

### 8.5.2 Status report and interim analysis 36 months after G-BA resolution

Analysis will be performed and reported based on both the primary and secondary data source (SMArtCARE and RESTORE).

### 8.5.3 Status report and interim analysis 54 months after G-BA resolution

Analysis will be performed and reported based on both the primary and secondary data source (SMArtCARE and RESTORE).

### 8.5.4 Final analysis for benefit assessment (submission on July 1, 2027)

Analysis will be performed and reported based on both the primary and secondary data source (SMArtCARE and RESTORE).

## 8.6 Prognostic factors and potential confounders

### 8.6.1 Confounder identification and validation

A detailed description of the operationalization of confounders in RESTORE is provided in Table A1 17. The depictability of confounders in RESTORE registry is shown in annex A3.

Table A1 17: Overview of identified confounders in RESTORE Registry

| Confounder | Clinical relevance[4] | Included in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analysis populations |
|---|---|---|---|---|---|
| SMN2 copy number | Very important | Yes | Number of SMN2 copies assessed per genetic testing | ▪ SMA Medical History: SMN2 copy number | Main analysis: G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis: GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

[4] According to the assessment of the six clinical experts consulted during the confounder validation process

| Confounder | Clinical relevance[4] | Included in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analysis populations |
|---|---|---|---|---|---|
| Age at symptom onset | Very important | Yes | Age of symptom onset in months for symptomatic patients | ▪ SMA Medical History: Age at symptoms onset<br><br>*Note: Age at first symptoms onset is derived from the following fields:*<br><br>▪ *SMA Medical History: Age in years at first symptoms onset [0-99]*<br>▪ *SMA Medical History: Age in months at first symptoms onset [0-11]* | <u>Main analysis:</u><br>G-BA approach: GBA-B, GBA-D |
| Symptom status at treatment initiation | Very important | Yes | <u>Symptomatic:</u><br><br>Diagnosis not made pre-symptomatically OR documentation of symptoms related to SMA at any medical assessment prior to treatment initiation<br><br><u>Pre-symptomatic:</u><br><br>Diagnosis made pre-symptomatically AND no symptoms related to SMA at any medical assessment prior to treatment initiation | <u>Symptomatic:</u><br><br>▪ SMA Medical History: Did the patient display symptoms at the time of diagnosis? = Yes<br>OR<br>▪ Age at first symptoms onset ≤ Nusinersen Treatment: MIN(Age at dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Age at treatment (months))<br>▪ SMA Medical History: Has the patient ever displayed SMA symptoms? = Yes<br><br><u>Pre-symptomatic:</u> | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: none (stratification parameter)<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

| Con-founder | Clinical rele-vance[4] | In-cluded in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analy-sis populations |
|---|---|---|---|---|---|
| | | | | ▪ SMA Medical History: Did the patient display symptoms at the time of diagno-sis? = No<br>OR<br>▪ Age at first symptoms onset > Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treat-ment: MIN(Start date)/ AVXS-101 Treatment: MIN(Age at treatment (months))<br>OR<br>SMA Medical History: Has the patient ever dis-played SMA symptoms? = No<br><br>*Note: Age at first symptoms onset in months is derived from the following fields:*<br>▪ *SMA Medical History: Age in years at first symptoms onset [0-99]*<br>▪ *SMA Medical History: Age in months at first symptoms onset [0-11]* | |
| Age at treat-ment ini-tiation | Very im-portant | Yes | Age in weeks at treatment initiation | ▪ Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treat-ment: MIN(Start | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: |

| Confounder | Clinical relevance[4] | Included in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | date)/ AVXS-101 Treatment: MIN(Age at treatment (months)) | ▪ Directly: GBA-A, GBA-C<br>▪ Derived (treatment delay defined as time from symptom onset to treatment initiation: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>▪ GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Nutrition support | Very important | Yes | Gastric tube or nasal feeding tube (exclusive/supplemental/none) at treatment initiation | ▪ Nutritional Assessment: Has the patient had any non-oral feeding support used to administer nutrition? AT<br>▪ Nutritional Assessment: Date of placement ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment) | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Ventilation support | Very important | Yes | Duration of ventilator use (nighttime/intermittent/permanent (≥16h/day) at treatment initiation | ▪ Ventilatory Support Question: Has the patient had any ventilator support since birth? = Yes<br>▪ Ventilatory Support: Tracheostomy: Ongoing?/Other Ventilatory | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

| Con-founder | Clinical rele-vance[4] | In-cluded in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analy-sis populations |
|---|---|---|---|---|---|
| | | | | Support: Ongo-ing? = Yes<br>▪ Ventilatory Sup-port: Other Ven-tilatory Support: Average daily use ≥ 16 Hours/Day<br>▪ Ventilatory Sup-port: Other Ven-tilatory Support: Frequency = daily/as needed AT<br>▪ Ventilatory Sup-port: Tracheost-omy: Date of procedure /Other Ventila-tory Support: Start date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdip-lam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment)<br>▪ Ventilatory Sup-port: Tracheost-omy: Date of re-moval/Other Ventilatory Sup-port: Stop date ≥ Nusinersen Treatment: MIN(Date of dose)/ Risdip-lam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment)<br>*Note: RESTORE does not differentiate be-tween day and night* | |

| Con-founder | Clinical rele-vance[4] | In-cluded in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analy-sis populations |
|---|---|---|---|---|---|
| | | | | *time use of ventila-tor. To approximate SMArtCARE catego-ries the following av-erage daily use times are used:*<br>▪ *Night (during sleep): < 12 hours*<br>▪ *Intermittent day time and contin-uous at night: ≥ 12 hours < 16 hours*<br>▪ *Continuous: ≥ 16 hours*<br><br>*Via an update of the CRF, categories in line with SMArtCARE definitions on nightly use and intermittent ventilator support at day time and contin-uous at night will be added to RESTORE.* | |
| Contrac-tures | Less im-portant | Yes | Contractures limiting func-tion (yes/no) at treatment initiation | ▪ HFMSE: Test item 2: Long sit-ting: Scoring de-tail limited by contractures = Yes<br>OR<br>▪ HFMSE: Test item 11: Props on forearms: Scoring detail limited by con-tractures = Yes<br>OR<br>▪ HFMSE: Test item 13: Prop on extended arms: Scoring detail limited by con-tractures = Yes<br>AT | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

| Con-founder | Clinical rele-vance[4] | In-cluded in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analy-sis populations |
|---|---|---|---|---|---|
| | | | | ▪ HFMSE: Evalua-tion Date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdip-lam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment) OR<br>▪ CHOP INTEND: Contractures AT<br>▪ CHOP-Intend: Date of evalua-tion ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdip-lam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment) OR<br>▪ Musculoskeletal Findings: Type of orthopedic issue = Contracture<br>▪ Muscoloskeletal Findings: Con-tracture (select) AT<br>▪ Musculoskeletal Findings: Start date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdip-lam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment) | |

| Confounder | Clinical relevance[4] | Included in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analysis populations |
|---|---|---|---|---|---|
| Motoric function: Highest motor milestone | Very important | Yes | Highest motor milestone at treatment initiation:<br>▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing without support<br>▪ Walking without support<br>▪ Climb stairs | ▪ Developmental milestones: child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: hands and knees crawling: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone?<br>AT<br>▪ Developmental Milestones: Date of assessment ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br>AND<br>▪ HFMSE: Test item 30: | All |

| Confounder | Clinical relevance[4] | Included in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | Ascends 4 stairs with railing OR<br>▪ HFMSE: Test item 32: Ascends 4 stairs without arm support AT<br>▪ HFMSE: Evaluation date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br>*Notes:*<br>▪ *RESTORE refers both to WHO performance and Bayley Scales Infant and Toddler Development criteria*<br>▪ *"climb stairs" not depicted as developmental milestone in RESTORE. If ability to climb stairs is reported in HFMSE, this information is used.* | |
| Motoric function: CHOP-INTEND | Very important | Yes | CHOP-INTEND score at treatment initiation | ▪ CHOP-INTEND: Final Score AT<br>▪ CHOP-INTEND: Date of evaluation ≤ Nusinersen Treatment: MIN(Date of | All |

| Con-founder | Clinical rele-vance[4] | In-cluded in Study | Definition | Fields of RESTORE CRF (21) | Applicable to analy-sis populations |
|---|---|---|---|---|---|
| | | | | dose/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treat-ment: MIN(Date of treatment) | |

### 8.6.2 Adjustment for confounders

*For more information see study protocol version 4.01.*

## 8.7 Subgroup analyses

### 8.7.1 Subgroups for baseline characteristics

A detailed description of the operationalization of subgroups in RESTORE is provided in Table A1 18. The depictability of confounders in RESTORE registry is shown in annex A3.

Table A1 18: Overview of planned subgroup analyses in RESTORE Registry

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| SMN2 copy number | ▪ 1<br>▪ 2<br>▪ 3<br>▪ 4 | ▪ SMA Medical History: SMN2 copy number | Main analysis:<br>G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis:<br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at treatment initiation | ▪ ≤ 4 weeks<br>▪ > 4 weeks | ▪ Nusinersen Treatment: MIN(Date of dose/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment) | All |
| Gender | ▪ Male<br>▪ Female<br>▪ Undifferentiated<br>▪ Unknown | ▪ Patient socio-demographics: Patient gender | All |
| Region | ▪ Germany<br>▪ Austria<br>▪ North America<br>▪ Asia Pacific<br>▪ Europe<br>▪ Rest of world | ▪ N.a (Countries in analyses are determined by site number) | All |
| Symptom status at treatment initiation | ▪ Symptomatic<br>▪ Pre-symptomatic | Symptomatic: | NGT approach: NGT-A, NGT-B |

- SMA Medical History: Did the patient display symptoms at the time of diagnosis? = Yes
  OR
- Age at first symptoms onset ≤ Nusinersen Treatment: MIN(Age at dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Age at treatment (months))
- SMA Medical History: Has the patient ever displayed SMA symptoms? = Yes

<u>Pre-symptomatic:</u>

- SMA Medical History: Did the patient display symptoms at the time of diagnosis? = No
  OR
- Age at first symptoms onset > Nusinersen Treatment: MIN(Age at dose (months))/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Age at treatment (months))
  2. OR
- SMA Medical History: Has the patient ever displayed SMA symptoms? = No

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| | | *Note: Age at first symptoms onset in months is derived from the following fields:*<br>▪ *SMA Medical History: Age in years at first symptoms onset [0-99]*<br>▪ *SMA Medical History: Age in months at first symptoms onset [0-11]* | |
| Nutrition support (Does the patient use a gastric or nasal feeding tube?) | ▪ No<br>▪ Yes - exclusively fed by tube<br>▪ Yes – supplementary e.g. for fluids | ▪ Nutritional Assessment: Has the patient had any non-oral feeding support used to administer nutrition? AT<br>▪ Nutritional Assessment: Date of placement ≤ Nusinersen Treatment: MIN (Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-10 Treatment: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |
| Ventilation support (Does the patient receive ventilator support?) | ▪ No<br>▪ Yes | ▪ Ventilatory Support Question: Has the patient had any ventilator support since birth? AT<br>▪ Ventilatory Support: Tracheostomy: Date of procedure /Other Ventilatory Support: Start date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| | | MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br><br>*Note: RESTORE does not differentiate between day and night time use of ventilator. To approximate SMArtCARE categories the following average daily use times are used:*<br>▪ *Night (during sleep): < 12 hours*<br>▪ *Intermittent day time and continuous at night: ≥ 12 hours < 16 hours*<br>▪ *Continuous: ≥ 16 hours*<br><br>*Via an update of the CRF, categories in line with SMArtCARE definitions on nightly use and intermittent ventilator support at day time and continuous at night will be added to RESTORE.* | |
| Contractures (Contractures limiting function) | ▪ No<br>▪ Yes | ▪ HFMSE: Test item 2: Long sitting: Scoring detail limited by contractures = Yes OR<br>▪ HFMSE: Test item 11: Props on forearms: Scoring detail limited by contractures = Yes OR<br>▪ HFMSE: Test item 13: Prop on extended arms: Scoring detail limited by contractures = Yes | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| | | AT<br>▪ HFMSE: Evaluation Date ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br>OR<br>▪ CHOP INTEND: Contractures<br>AT<br>▪ CHOP-INTEND: Date of evaluation ≤ Nusinersen Treatment: MIN (Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br>OR<br>▪ Musculoskeletal Findings: Type of orthopedic issue = Contracture<br>▪ Muscoloskeletal Findings: Contracture (select)<br>AT<br>Musculoskeletal Findings: Start date ≤ Nusinersen Treatment: MIN (Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment) | |

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| Motor function: Highest motor milestone | ▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing with-out support<br>▪ Walking with-out support<br>▪ Climb stairs | ▪ Developmental milestones: child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: hands and knees crawling: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: Standing Alone: Has the patient achieved this milestone?<br>OR<br>▪ Developmental milestones: Walking Alone: Has the patient achieved this milestone?<br>AT<br>▪ Developmental Milestones: Date of assessment ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br>AND<br>▪ HFMSE: Test item 30: Ascends 4 stairs with railing<br>▪ HFMSE: Test item 32: Ascends 4 stairs without arm support | All |

| Planned subgroups | Patients' baseline status | Fields of RESTORE CRF (21) | Applicable for analysis populations |
|---|---|---|---|
| | | AT<br>▪ HFMSE: Date of evaluation ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment)<br><br>*Notes:*<br>▪ *RESTORE refers both to WHO performance and Bayley Scales Infant and Toddler Development criteria as guidance*<br>▪ *"climb stairs" not depicted as developmental milestone in RESTORE. If ability to climb stairs is reported in HFMSE, this information is used.* | |
| Motor function: CHOP-INTEND score | ▪ ≤ Median CHOP-INTEND<br>▪ > Median CHOP-INTEND | ▪ CHOP-INTEND: Final Score AT<br>▪ CHOP-INTEND: Date of evaluation ≤ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/ AVXS-101 Treatment: MIN(Date of treatment) | All |

### 8.7.2 Analysis methods

*For more information see study protocol version 4.01.*

# 9. Safety

*For more information see study protocol version 4.01.*

# 10. Data Handling and Monitoring

## 10.1 Data Management

In order to minimize the burden to investigators, the RESTORE registry uses an electronic data capture (EDC) system for de-novo sites. Some or all patient data (e.g., PROs) may be directly entered into an electronic device (ePRO). For electronic clinical outcome assessment (eCoA) data, where there is no prior written or electronic record of the data, the EDC form serves as the source and the investigator receives an archival copy at the end of the registry for retention. Site personnel is trained on the EDC, ePRO and eCoA technologies.

Data verification takes place and any data verification activities are executed in compliance with a Data Management Plan (including electronic edit checks). As medical coding is required, this is reviewed by qualified personnel. Data verification requirements can be amended based on any observed data trends. This is only done for any data entered directly into the registry eCRF and not from data transferred from current registries.

Patients who are lost to follow-up or who withdraw from the registry are discontinued from the registry following confirmation from site and a reason for withdrawal is collected when available.

## 10.2 Source Data verification

SDV will be performed by UBC, Novartis Gene Therapies' CRO vendor managing the registry. For all RESTORE sites that enroll patients which meet the G-BA protocol criteria, RMVs will be conducted. It is expected that two visits per site / per year will be carried out with a focus on both historical and prospective data.

Each enrolling site on RESTORE will have a RMV conducted in Q1 and Q3 each year starting in Q3 2022, timed to be completed prior to two data cuts and transfers each year.

SDV will be performed by clinical monitors on the basis of all available patient records. Novartis Gene Therapies will bear the financial expenses for the implementation of the SDV.

Regular submissions to G-BA are planned with corresponding data-cut-off dates around 6 months prior submission date. After the data cut planned for 31 December 2026, UBC will complete SDV to reach 100% of SDV's data. Therefore Q1/2027 RMVs shall be performed in January 2027, to ensure last query resolved 28 February 2027.

## 10.3 Minimization of missing data

*For more information see study protocol version 4.01.*

## 10.4 Data analysis

*For more information see study protocol version 4.01.*

# 11. Ethical and regulatory aspects

## 11.1 Regulatory and ethical compliance

*For more information see study protocol version 4.01.*

## 11.2 Informed Consent

Prior to any data collection under this protocol, a written ICF and a privacy statement, if required, must be signed by the parent/guardian and, where appropriate if assent is required, by the patient, in accordance with local practice and regulations. Information about the registry will be explained to the parent/guardian and patient where appropriate. A copy of the ICF, signed and dated by the parent/guardian and patient where appropriate, must be given to the parent/guardian/patient. Confirmation of a parent/guardian's informed consent and where appropriate the patients' assent must be documented in the patient's medical records prior to any data collection under this protocol.

# 12. Outcome

*For more information see study protocol version 4.01.*

# Annex

## A1 Methodology for Confounder Identification

## A2 Relevant variables in SMArtCare Registry

## A 1.1 Relevant variables in RESTORE Registry

Table A1 19: Relevant variables in RESTORE Registry

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| **Date of consent** | Earliest Date of Consent for RESTORE Registry | x | |
| **SMA Medical History** | Age in years at first symptoms onset | x | |
| | Age in months at first symptoms onset | x | |
| | Has the patient ever displayed SMA symptoms? | x | |
| | Did the patient display symptoms at the time of diagnosis? | x | |
| | SMN2 copy number | x | |
| | Genetic testing result for SMN1 | x | |
| **Patient socio-demographics** | Patient gender | x | |
| **Patient Growth** | Date of growth assessment | x | |
| | weight | x | |
| **Assessments Prior to Initial SMA Treatment** | Has the patient received any approved SMA treatment? | x | |
| **Nusinersen Treatment** | Date of dose | x | x |
| | Dosing stage | x | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | Age at dose (months) | x | x |
| **AVXS-101 Treatment** | Date of treatment | x | x |
| | Age at treatment (months) | x | x |
| **Risdiplam Treatment** | Start date | x | x |
| **Pulmonary Medications** | Start date | x | x |
| | Other medication, specify: | x | x |
| **Nutritional Assessment** | Date of placement | x | x |
| | Has the patient had any non-oral feeding support used to administer nutrition? | x | x |
| | Non-oral feeding support used to administer nutrition (select) | x | x |
| | Other non-oral feeding support, specify | x | x |
| | Nutritional intake | x | x |
| **Ventilatory Support Question** | Has the patient had any ventilator support since birth? | x | x |
| **Ventilatory Support** | Record Ventilatory Support. Specify type(s) of ventilator used | x | x |
| | Tracheostomy: Date of procedure | x | x |
| | Tracheostomy: Ongoing? | x | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | Tracheostomy: Date of removal | | x |
| | Tracheostomy: Reason for procedure | x | x |
| | Other Ventilatory Support: Type | x | x |
| | Other Ventilatory Support: Start date | x | x |
| | Other Ventilatory Support: Ongoing? | x | x |
| | Other Ventilatory Support: Stop date | | x |
| | Other Ventilatory Support: Frequency | x | x |
| | Other Ventilatory Support: Average daily use | x | x |
| | Other Ventilatory Support: Reason for use | x | x |
| **CHOP INTEND** | Date of evaluation | x | x |
| | Contractures | x | x |
| | Final Score | x | x |
| **HFMSE** | Evaluation date | x | x |
| | Test item 2: Long sitting | x | x |
| | Test item 11: Props on forearms | x | x |
| | Test item 13: Prop on extended arms | x | x |
| | Test item 30: Ascends 4 stairs with railing | x | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | Test item 32: Ascends 4 stairs without arm support | x | x |
| **Developmental Milestones (V2)** | Hands and Knees Crawling: Has the patient achieved this milestone? | x | x |
| | Hands and Knees Crawling: Age in months at first achieved | x | x |
| | Hands and Knees Crawling: Did the patient lose the milestone? | x | x |
| | Hands and Knees Crawling: Age in months at lost | x | x |
| | Child sits up straight with head erect for at least 10 seconds: Has the patient achieved this milestone? | x | x |
| | Child sits up straight with head erect for at least 10 seconds: Age in months at first achieved | x | x |
| | Child sits up straight with head erect for at least 10 seconds: Did the patient lose the milestone? | x | x |
| | Child sits up straight with head erect for at least 10 seconds: Age in months at lost | x | x |
| | Standing Alone: Has the patient achieved this milestone? | x | x |
| | Standing Alone: Age in months at first achieved | x | x |
| | Standing Alone: Did the patient lose the milestone? | x | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | Standing Alone: Age in months at lost | x | x |
| | Walking Alone: Has the patient achieved this milestone? | x | x |
| | Walking Alone: Age in months at first achieved | x | x |
| | Walking Alone: Did the patient lose the milestone? | x | x |
| | Walking Alone: Age in months at lost | x | x |
| **HINE** | Age at evaluation (months) | x | x |
| | Evaluation date | x | x |
| | Item 1: Head control | x | x |
| | Total Score | x | x |
| **Relevant Surgical Procedures Question** | Has the patient had any surgical procedures since initial SMA diagnosis? | x | x |
| **Relevant Surgical Procedures** | Date of surgery | x | x |
| | Procedure | x | x |
| **Bulbar Function (V2)** | Date of evaluation | x | x |
| | Swallow evaluation result | x | x |
| | Other swallow evaluation result specify | x | x |
| **Musculoskeletal Findings (V2)** | Type of orthopedic issue | x | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | Contracture | x | x |
| | Spinal curvature | x | |
| **Adverse Events Question** | Has the patient experienced any Adverse Events as noted in the protocol? | | x |
| **Adverse Events** | Start date | | x |
| | Adverse Event | | x |
| | AESI: Hepatotoxicity | | x (to be added) |
| | AESI: Thrombocytopenia | | x (to be added) |
| | AESI: Cardiac events | | x (to be added) |
| | AESI: Dorsal root ganglia cell inflammation | | x (to be added) |
| | AESI: Renal toxicity | | x (to be added) |
| | AESI: Respiratory tract infection | | x (to be added) |
| | AESI: Epileptic seizure | | x (to be added) |
| | AESI: Post lumbar puncture syndrome | | x |

| CRF Section (Module) | CRF Item | at (or before) baseline | after baseline |
|---|---|---|---|
| | | | (to be added) |
| | Relationship to SMA treatment | | x |
| | Specify which treatment | | x |
| | Serious AE? | | x |
| | Serious criteria: It requires in-patient hospitalization or prolongation of existing hospitalization | | x |
| **Hospitalizations Question** | Was the patient admitted to hospital more than 24 hours? | | x |
| **Hospitalizations** | Date of hospitalization | | x |
| | Was visit for an Adverse Event? | | x |
| | Reason for hospitalization | | x |
| **End of Registry Summary** | Date of death | | x |

Source: RESTORE Case Report Form 2022

## A 1.2 Depictability in RESTORE Registry

# 13. Inclusion Criteria and Exclusion Criteria

Table A1 20: Inclusion criteria and operationalization in RESTORE registry

| # | Inclusion criteria | Depictable in RESTORE |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | Yes |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | Yes |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | Yes |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to body weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) | Yes |
| 3 | Body weight at treatment initiation ≤ 21 kg | Yes |
| 4 | Appropriate consent/assent has been obtained for participation in the study | Yes |

Table A1 21: Exclusion criteria and operationalization in RESTORE registry

| # | Exclusion criteria | Depictable in RESTORE |
|---|---|---|
| 1 | Pretreatment with disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) | Yes |
| 2 | Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | After CRF update to capture information on pre-treatments with investigational drugs for the treatment of SMA |
| 3 | Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA | Eligibility criteria always restricted patients enrolled in a clinical trial at time of registry enrollment to participate.<br><br>Participation in a clinical trial after enrollment in RESTORE will be captured after CRF update. |

# 14. Confounder

Table A1 22: Overview of identified confounders, their clinically relevance and corresponding availability in RESTORE registry

| Confounder | Clinical relevance[a] | Definition | Depictable in RESTORE | Applicable to analysis populations |
|---|---|---|---|---|
| SMN2 copy number | Very important | Number of SMN2 copies assessed per genetic testing | Yes | Main analysis: G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis: GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at symptom onset | Very important | Age of symptom onset in months for symptomatic patients | Yes | Main analysis: G-BA approach: GBA-B, GBA-D |
| Symptom status at treatment initiation | Very important | Symptomatic: Diagnosis not made pre-symptomatically OR documentation of symptoms related to SMA at any medical assessment prior to treatment initiation<br><br>Pre-symptomatic: Diagnosis made pre-symptomatically AND no symptoms related to SMA at any medical assessment prior to treatment initiation | Yes | Main analysis: NGT approach: NGT-A, NGT-B<br><br>G-BA approach: none (stratification parameter)<br><br>Sensitivity analysis: GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at treatment initiation | Very important | Age in weeks at treatment initiation | Yes | Main analysis: NGT approach: NGT-A, NGT-B<br><br>G-BA approach: |

| Confounder | Clinical relevance[a] | Definition | Depictable in RESTORE | Applicable to analysis populations |
|---|---|---|---|---|
| | | | | ▪ Directly: GBA-A, GBA-C<br>▪ Derived (treatment delay defined as time from symptom onset to treatment initiation: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Nutrition support | Very important | Gastric tube or nasal feeding tube (exclusive/supplemental/none) at treatment initiation | Yes | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Ventilation support | Very important | Duration of ventilator use (nighttime/intermittent/permanent (≥16h/day) at treatment initiation | Derived from hours per day until CRF update | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Contractures | Less important | Contractures limiting function (yes/no) at treatment | Yes | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B |

| Confounder | Clinical relevance[a] | Definition | Depictable in RESTORE | Applicable to analysis populations |
|---|---|---|---|---|
| | | initiation | | G-BA approach: GBA-B, GBA-D<br><br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Motoric function: Highest motor milestone | Very important | Highest motor milestone at treatment initiation:<br>▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing without support<br>▪ Walking without support<br>▪ Climb stairs | Yes<br><br>Harmonization of standing definition (WHO) after CRF update | All |
| Motoric function: CHOP-INTEND | Very important | CHOP-INTEND score at treatment initiation | Yes | All |

# 15. Subgroup analyses

Table A1 23: Overview of planned subgroup analyses in this comparative analysis

| Planned subgroups | Patients' baseline status | Depictable in RESTORE | Applicable for analysis population |
|---|---|---|---|
| SMN2 copy number | ▪ 1<br>▪ 2<br>▪ 3<br>▪ 4 | Yes | GBA-B, GBA-D |
| Age at treatment initiation | ▪ ≤ 4 weeks<br>▪ > 4 weeks | Yes | All |
| Gender | ▪ Male<br>▪ Female<br>▪ Undifferentiated<br>▪ Unknown | Yes | All |
| Region | ▪ Germany<br>▪ Austria<br>▪ North America<br>▪ Asia Pacific<br>▪ Europe<br>▪ Rest of world<br><br>*Regions were added due to integration of RESTORE registry.* | N.a. | All |
| Symptom status at treatment initiation | ▪ Symptomatic<br>▪ Pre-symptomatic | Yes | NGT-A, NGT-B |
| Nutrition support (Does the patient use a gastric or nasal feeding tube?) | ▪ No<br>▪ Yes - exclusively fed by tube<br>▪ Yes – supplementary e.g. for fluids | Yes | NGT-A, NGT-B, GBA-B, GBA-D |
| Ventilation support (Does the patient receive ventilator support?) | ▪ No<br>▪ Yes | Yes | NGT-A, NGT-B, GBA-B, GBA-D |
| Contractures (Contractures limiting function) | ▪ No<br>▪ Yes | Yes | NGT-A, NGT-B, GBA-B, GBA-D |

| Planned subgroups | Patients' baseline status | Depictable in RESTORE | Applicable for analysis population |
|---|---|---|---|
| Motor function: Highest motor milestone | ▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing without support<br>▪ Walking without support<br>▪ Climb stairs | Yes, using WHO standing definition after CRF update | All |
| Motor function: CHOP-INTEND score | ▪ ≤ Median CHOP-INTEND<br>▪ > Median CHOP-INTEND | Yes | All |

# 16. Endpoints

## 16.1 Effectiveness

### 16.1.1 Survival

Table A1 24: Effectiveness endpoints: Survival

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Overall Survival (OS) | Time from the date of first treatment to the date of death due to any cause | Yes | Yes |
| Event Free Survival (EFS) | Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day | Yes | Yes |

### 16.1.2 Motor function

#### 16.1.2.1 NGT Approach

Table A1 25: Effectiveness endpoints: Motor function (NGT approach)

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Achievement of motor milestones according to age | Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis<br><br>Age limits per milestone (based on WHO)<br>▪ Sitting without support: 9.2 months<br>▪ Crawl on hands and knees: 13.5 months<br>▪ Standing without support: 16.9 months<br>▪ Walking without support: 17.6 months | After CRF update to include WHO standing definition | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Head control at the age of 8 months | Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age | Yes | Yes |
| Crawl on hands and knees at the age of 18 months | Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months | Yes | Yes |
| Sitting without support at the age of 18 months | Proportion of patients achieving the motor milestone of sitting without support at or before the age of 18 months | Yes | Yes |
| Standing without support at the age of 24 months | Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months | Yes, using WHO standing definition only after CRF update | Yes |
| Walking without support at the age of 24 months | Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months | Yes | Yes |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | Yes, using WHO standing definition only after CRF update | Yes |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment<br><br>*Note: Endpoint of* | Yes | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| baseline | *exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | | |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | Yes | Yes |
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | Yes | Yes |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | Yes, using WHO standing definition only after CRF update | Yes |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | Yes | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | | |

### 16.1.2.2 G-BA Approach

Table A1 26: Effectiveness endpoints: Motor function (G-BA approach)

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | Yes | Yes |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support | Yes, using WHO standing definition only after CRF update | Yes |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | Yes | Yes |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support | Yes, using WHO standing definition only after CRF update | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | Documentation of the new (worsened) highest motor milestone at two consecutive visits is required. | | |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment | Yes | Yes |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment | Yes | Yes |

### 16.1.3 Nutrition

Table A1 27: Effectiveness endpoints: Nutrition

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Difficulties in swallowing | Time from the date of first treatment to the first documented difficulties in swallowing | Yes | Yes |
| Difficulties in chewing | Time from the date of first treatment to the first documented difficulties in chewing | After CRF update | Yes |
| Gastric or nasal feeding tube | Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations<br>▪ Any type of tube feeding (supplementary or exclusively)<br>▪ Supplementary | Yes | Yes |

| Endpoint | Definition | Depictable in RE-STORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | (e.g. for fluids)<br>▪ Exclusively | | |

### 16.1.4 Orthopedic complications

Table A1 28: Effectiveness endpoints: Orthopedic complications

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Scoliosis or orthopedic surgery | Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery | Yes | Yes |
| Scoliosis | Time from the date of first treatment to first documentation of scoliosis | Yes | Yes |
| Orthopedic surgery | Time from the date of first treatment to first documentation of orthopedic surgery | Yes | Yes |

### 16.1.5 Respiratory function

Table A1 29: Effectiveness endpoints: Respiratory function

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Time of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of<br>▪ Any ventilator support<br>▪ Ventilator support at night (during sleep)<br>▪ Intermittent ventilator support at day time and continuous at night<br>▪ Permanent ventilator support | Any ventilator support and permanent ventilator support from start, other categories after CRF update | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | (≥16 hours per day)<br>▪ Intermittent ventilator support with acute illnesses<br><br>Documentation of same or higher ventilator support time required at two consecutive visits. | | |
| Type of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of (each separately)<br>▪ Non-invasive ventilation<br>▪ Invasive ventilation<br><br>Documentation of same or higher ventilator support type required at two consecutive visits. | Yes | Yes |
| Improvement in time of ventilator support from baseline | Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following<br>▪ Change from permanent ventilator support (≥16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR<br>▪ Change from | Any ventilator support and permanent ventilator support from start, other categories after CRF update | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR<br>▪ Change from ventilator support at night (during sleep) to no ventilator support | | |

### 16.1.6 Planned hospitalizations

Table A1 30: Effectiveness endpoints: Planned hospitalizations

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Planned hospitalizations | Cumulative number of planned hospitalizations across all patients per patient-year of being at risk including planned hospitalizations for administration of SMA treatments | Yes (from metadata) | Yes |

## 16.2 Safety

### 16.2.1 Adverse events

Table A1 31: Safety endpoints: Adverse events

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Any Adverse events with or without | Cumulative number of patients with and | Yes | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| hospitalization | number of adverse events with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | | |
| Any Adverse events with or without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes | Yes |
| Adverse events without hospitalization | Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes | Yes |
| Adverse events without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment | Yes | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | (yes/possibly) without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | | |

### 16.2.2 Serious adverse events

Table A1 32: Safety endpoints: Serious adverse events

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Serious adverse events with hospitalization | Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes | Yes |
| Serious adverse events with hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no* | Yes | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | *MedDRA code was documented.* | | |
| Serious adverse events with hospitalization or death | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the protocol?<br>▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: Results in death Adverse Events: Serious criteria: it requires in-patient hospitalization or prolongation of existing hospitalization | Yes |
| Serious adverse events with hospitalization or death related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen Treatment: MIN(Date of dose)/ Risdiplam Treatment: MIN(Start date)/AVXS-101 Treatment: MIN(Date of treatment)<br>▪ Adverse Events Question: Has the patient experienced any Adverse Events as noted in the | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| | | protocol?<br>▪ Adverse Events: Adverse Event: [text field]<br>▪ Adverse Events: Start date<br>▪ Adverse Events: Serious criteria: Results in death<br>▪ Adverse Events: it requires in-patient hospitalization or prolongation of existing hospitalization<br>Adverse Events: Relationship to SMA treatment | |
| Serious adverse events | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes | Yes |
| Serious adverse events related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment (yes/possibly) across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes | Yes |

### 16.2.3 Adverse events of special interest

Table A1 33: Safety endpoints: Adverse events of special interest

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Hydrocephalus with or without hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | After CRF update (2023) | Yes |
| Hydrocephalus with hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | After CRF update (2023) | Yes |
| Hepatotoxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | After CRF update (2023) | Yes |
| Hepatotoxicity with hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | After CRF update (2023) | Yes |
| Thrombocytopenia with or without hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | After CRF update (2023) | Yes |
| Thrombocytopenia with hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | After CRF update (2023) | Yes |
| Cardiac events with or without hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | After CRF update (2023) | Yes |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Cardiac events with hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | After CRF update (2023) | |
| Dorsal root ganglia cell inflammation with or without hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk | After CRF update (2023) | |
| Dorsal root ganglia cell inflammation with hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk | After CRF update (2023) | |
| Renal toxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | After CRF update (2023) | |
| Renal toxicity with hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | After CRF update (2023) | |
| Respiratory tract infection with or without hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | After CRF update (2023) | |
| Respiratory tract infection with hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | After CRF update (2023) | |

| Endpoint | Definition | Depictable in RESTORE | Meta-analysis with SMArtCARE possible |
|---|---|---|---|
| Epileptic seizure with or without hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | After CRF update (2023) | |
| Epileptic seizure with hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | After CRF update (2023) | |
| Post lumbar puncture syndrome with or without hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | After CRF update (2023) | |
| Post lumbar puncture syndrome with hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | After CRF update (2023) | |

# Addendum 2

# Additional changes to study protocol

# Addendum 2 – Additional changes to study protocol

## Addendum 2 to study protocol version 4.01 of routine data collection and evaluations of onasemnogene abeparvovec in Germany

Protocol Number: COAV101A1DE01

Study protocol version: 4.01

26 January, 2024

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# Purpose of the addendum for additional changes to study protocol

*This document serves as an addendum to the study protocol version 3.1. It contains important changes relevant to the study protocol in version 3.01 compared to version 2.02, which were not mandated by the G-BA in any of the resolutions regarding routine data collection and evaluations for onasemnogene abeparvovec. However, changes were kept in the new version of the study protocol 3.1 and additionally displayed in this addendum for better clarity and traceability.*

***Amendment 2.1 (study protocol version 4.01)***

*This addendum was amended to include risdiplam as comparator besides treatment with nusinersen. Further information can be found in study protocol version 4.01.*

# 1. Depictability of endpoints in SMArtCARE

These tables were previously depicted in study protocol version 3.01 in section 5. but later reversed in study protocol version 3.1. Depictability of endpoints in RESTORE registry are included in the RESTORE addendum (Addendum 1).

## 1.1 Effectiveness

### 1.1.1 Survival

Table A2 1: Effectiveness endpoints: Survival

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Overall Survival (OS) | Time from the date of first treatment to the date of death due to any cause | Yes |
| Event Free Survival (EFS) | Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day | Yes |

### 1.1.2 Motor function

#### 1.1.2.1 NGT approach

Table A2 2: Effectiveness endpoints: Motor function (NGT approach)

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Achievement of motor milestones according to age | Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis<br><br>Age limits per milestone (based on WHO)<br>▪ Sitting without support: 9.2 months<br>▪ Crawl on hands and knees: 13.5 months<br>▪ Standing without support: 16.9 months<br>▪ Walking without support: 17.6 months | Yes |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Head control at the age of 8 months | Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age | Yes |
| Crawl on hands and knees at the age of 18 months | Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months | Yes |
| Sitting without support at the age of 18 months | Proportion of patients achieving the motor milestone of sitting without support at or before the age of 18 months | Yes |
| Standing without support at the age of 24 months | Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months | Yes |
| Walking without support at the age of 24 months | Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months | Yes |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | Yes |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the* | Yes |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| | *scoring instrument* | |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | Yes |
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | Yes |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | Yes |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | Yes |

#### 1.1.2.2 G-BA approach

Table A2 3: Effectiveness endpoints: Motor function (G-BA approach)

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | Yes |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support | Yes |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | Yes |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at two consecutive visits is required. | Yes |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment | Yes |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment | Yes |

### 1.1.3 Nutrition

Table A2 4: Effectiveness endpoints: Nutrition

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Difficulties in swallowing | Time from the date of first treatment to the first documented difficulties in swallowing | Yes |
| Difficulties in chewing | Time from the date of first treatment to the first documented difficulties in chewing | Yes |
| Gastric or nasal feeding tube | Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations<br>▪ Any type of tube feeding (supplementary or exclusively)<br>▪ Supplementary (e.g. for fluids)<br>▪ Exclusively | Yes |

### 1.1.4 Orthopedic complications

Table A2 5: Effectiveness endpoints: Orthopedic complications

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Scoliosis or orthopedic surgery | Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery | Yes |
| Scoliosis | Time from the date of first treatment to first documentation of scoliosis | Yes |
| Orthopedic surgery | Time from the date of first treatment to first documentation of orthopedic surgery | Yes |

### 1.1.5 Respiratory function

Table A2 6: Effectiveness endpoints: Respiratory function

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Time of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of<br>▪ Any ventilator support<br>▪ Ventilator support at night (during sleep)<br>▪ Intermittent ventilator support at day time and continuous at night<br>▪ Permanent ventilator support (≥16 hours per day)<br>▪ Intermittent ventilator support with acute ill-nesses<br><br>Documentation of same or higher ventilator support time required at two consec-utive visits. | Yes |
| Type of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of (each separately)<br>▪ Non-invasive ventilation<br>▪ Invasive ventilation<br><br>Documentation of same or higher ventilator support type required at two consecutive visits. | Yes |
| Improvement in time of venti-lator support from baseline | Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improve-ment is defined as any of the following<br>▪ Change from permanent ventilator support (≥16 hours per day) to ventila-tor support at night (dur-ing sleep) or intermittent ventilator support at day time and continuous at | Yes |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| | night or no ventilator support OR<br>▪ Change from intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR<br>▪ Change from ventilator support at night (during sleep) to no ventilator support | |

### 1.1.6 Planned hospitalizations

Table A2 7: Effectiveness endpoints: Planned hospitalizations

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Planned hospitalizations | Cumulative number of planned hospitalizations across all patients per patient-year of being at risk including planned hospitalizations for administration of SMA treatments | Yes |

## 1.2 Safety

### 1.2.1 Adverse events

Table A2 8: Safety endpoints: Adverse events

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Any Adverse events with or without hospitalization | Cumulative number of patients with and number of adverse events with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no* | Yes |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| | *MedDRA code was documented.* | |
| Any Adverse events with or without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes |
| Adverse events without hospitalization | Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes |
| Adverse events without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes |

### 1.2.2 Serious adverse events

Table A2 9: Safety endpoints: Serious adverse events

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Serious adverse events with hospitalization | Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes |
| Serious adverse events with hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Yes |
| Serious adverse events with hospitalization or death | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | Approximation via adverse events with hospitalization or death due to adverse events |
| Serious adverse events with hospitalization or death related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment (yes/possibly) across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was* | Approximation via adverse events with hospitalization or death due to adverse events |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| | *documented.* | |

### 1.2.3 Adverse events of special interest

Table A2 10: Safety endpoints: Adverse events of special interest

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| Hydrocephalus with or without hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | Yes |
| Hydrocephalus with hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | Yes |
| Hepatotoxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | After CRF update (2022) |
| Hepatotoxicity with hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | After CRF update (2022) |
| Thrombocytopenia with or without hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | After CRF update (2022) |
| Thrombocytopenia with hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | After CRF update (2022) |
| Cardiac events with or without hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | After CRF update (2022) |
| Cardiac events with hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | After CRF update (2022) |
| Dorsal root ganglia cell inflammation with or without hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of | After CRF update (2022) |

| Endpoint | Definition | Depictable in SMArtCARE |
|---|---|---|
| | being at risk | |
| Dorsal root ganglia cell inflammation with hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk | After CRF update (2022) |
| Renal toxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | After CRF update (2022) |
| Renal toxicity with hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | After CRF update (2022) |
| Respiratory tract infection with or without hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | Yes |
| Respiratory tract infection with hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | Yes |
| Epileptic seizure with or without hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | Yes |
| Epileptic seizure with hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | Yes |
| Post lumbar puncture syndrome with or without hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | Yes |
| Post lumbar puncture syndrome with hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | Yes |

# 2. Population Selection

## 2.1 Inclusion Criteria

These tables were previously depicted in study protocol section 3.01 in section 7. but later reversed in study protocol version 3.1. Depictability of endpoints in RESTORE registry are included in the RESTORE addendum (Addendum 1).

Table A2 11: Inclusion criteria and depictability in SMArtCARE registry

| # | Inclusion criteria | Depictable in SMArtCARE |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | Yes |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | Yes |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | Yes |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to bidy weight and age as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) | Yes |
| 3 | Body weight at treatment initiation ≤ 21 kg | Yes |
| 4 | Appropriate consent/assent has been obtained for participation in the study | Yes |

## 2.2 Exclusion Criteria

Table A2 12: Exclusion criteria and depictability in SMArtCARE registry

| # | Exclusion criteria | Depictable in SMArtCARE |
|---|---|---|
| 1 | Pretreatment with disease modifying therapy | Yes |

| # | Exclusion criteria | Depictable in SMArtCARE |
|---|---|---|
| | (nusinersen, onasemnogene abeparvovec, risdiplam) | |
| 2 | Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | Yes |
| 3 | Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA | Yes |

# 3. Sensitivity analyses

All analysis populations including the sensitivity analyses in the NGT and G-BA approach were listed in study protocol version 3.01 for better clarity. These were kept in version 3.1 but stressed in this addendum as they were additionally included without mandates by G-BA.

The respective analyses population were included in tables in section 8.6 (confounders), in section 8.7 (subgroups) in study protocol version 3.1 as well as in this addendum section 4 as not every confounder/subgroup is relevant for every analysis population presented in this study.

### 3.1.1 NGT approach

For sensitivity analysis, additional populations are defined per section 8.5.1 of the SAP version 3.1:

- Population NGT-A-S: Patients included in population NGT-A from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population NGT-B-S: Patients included in population NGT-B from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population NGT-A-CompMono: Patients included in population NGT-A that are treated exclusively with nusinersen/risdiplam
- Population NGT-B-CompMono: Patients included in population NGT-B that are treated exclusively with nusinersen/risdiplam
- Population NGT-A-OnaMono: Patients included in population NGT-A that are treated exclusively with onasemnogene abeparvovec

- Population NGT-B-OnaMono: Patients included in population NGT-B that are treated exclusively with onasemnogene abeparvovec
- Population NGT-A-CompOna: Patients included in population NGT-A that are initially treated with nusinersen/risdiplam and then switched to onasemnogene abeparvovec
- Population NGT-B-CompOna: Patients included in population NGT-B that are initially treated with nusinersen/risdiplam and then switched to onasemnogene abeparvovec
- Population NGT-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population NGT-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE

### 3.1.2 G-BA approach

For sensitivity analysis, additional populations are defined per section 8.5.2 of the SAP version 3.1:

- Population GBA-Pool1: Pooled patients included in populations GBA-A and GBA-B
- Population GBA-Pool2: Pooled patients included in populations GBA-C and GBA-D
- Population GBA-A-S: Patients included in population GBA-A from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-B-S: Patients included in population GBA-B from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-C-S: Patients included in population GBA-C from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-D-S: Patients included in population GBA-D from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-Pool1_S: Patients from population GBA-Pool1 from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)

- Population GBA-Pool2_S: Patients from population GBA-Pool2 from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population GBA-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population GBA-C-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population GBA-D-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE

# 4. Elimination of discrepancies within study protocol considering operationalization and other criteria

## 4.1 Prognostic factors

The confounder SMN2 copy number was identified and reported in the annex A1 of the study protocol describing the methodology of confounder identification. It was categorized as very important confounder but not included by mistake for all relevant populations in G-BA approach (main analysis: GBA B, GBA-D, sensitivity analysis: G-BA Pool 1 (A+B), G-BA Pool 2 (C+D)).

It was always displayed and declared as very important confounder by clinicians but not mentioned in the sections in the synopsis, section 8.6 prognostic factors and 8.7 subgroups in version 2.02 of the study protocol. This was also added in the respective section of the RESTORE addendum (Addendum 1).

Furthermore, the variable Ulnar CMAP was deleted in section 8.6 (as well as in section 8.7 and in annex A2 depicting relevant variables for operationalization) of the study protocol version 3.01, due to insights from the first status report indicating lack of data availability for this variable.

## 4.2 Operationalization in SMArtCARE

**Inclusion and exclusion criteria**

In version 3.01 of the study protocol, fields of SMArtCARE were added for better operationalization in criteria 1. An operationalization was deleted in criteria 2 as it was previously left by mistake in version 2.02.

Table A2 13: Inclusion criteria and operationalization in SMArtCARE registry

| # | Inclusion criteria | Fields of SMArtCARE (20) |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ **Medical Assessment: Neurology: Symptoms related to SMA = No**<br>**AT**<br>**Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)** |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: Age at symptom onset < 6 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ **Medical Assessment: Neurology: Symptoms related to SMA = Yes**<br>**AT**<br>**Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)** |

| # | Inclusion criteria | Fields of SMArtCARE (20) |
|---|---|---|
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Age at symptom onset ≥ 6 months<br>AND<br>▪ Baseline: Age at symptom onset < 18 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>**OR**<br>▪ **Medical Assessment: Neurology: Symptoms related to SMA = Yes**<br>**AT**<br>▪ **Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)** |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according toor onasemnogene abeparvovec (dosage according to body weight as per SmPC) | ▪ Medical Assessment: Is the patient on any approved medication for SMA? = no for all visits before Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br>▪ Name of drug = onasemnogene abeparvovec/Zolgensma OR nusinersen/Spinraza OR risdiplam/Evrysdi<br>~~▪ Nusinersen/Zolgensma: MIN(Date of treatment) ≥ study start date (not applied to nusinersen if historic data is used, see section 8.4)~~ |

**Subgoup analyses**

For the subgroup symptom status at treatment initiation, a more detailed operationalization was used for SMArtCARE fields compared to version 2.02 dividing the definition in symptomatic and pre-symptomatic:

| | |
|---|---|
| Symptom status at treatment initiation | Symptomatic:<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment)<br><br>Pre-symptomatic:<br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT<br>Medical Assessment: Visit date ≤ Nusinersen/Risdiplam/Zolgensma: MIN(Date of treatment) |

**Relevant variables in SMArtCARE registry**

The overview of relevant variables in SMArtCARE registry annex A2 of the study protocol version 3.01 was modified compared to version 2.02:

- Deletion of variables if they were not used for operationalization of endpoints or other relevant criteria
  - CRF Sections: RULM, HFMSE, Ulnar CMAP
  - CRF field: name of drug in CRF sections: registries, clinical trial
  - CRF field: SMN2 copy number performed? in CRF section: Genetic Test Result
- Correction of variables relevant for the operationalization
  - Age gained of new motor milestone, age loss of previous motor milestone in CRF section: Motor function

# Addendum 3

# Inclusion of risdiplam as comparator besides nusinersen

# Addendum 3 - Inclusion of risdiplam as comparator besides nusinersen

Addendum 3 to study protocol version 4.01 of routine data collection and evaluations of onasemnogene abeparvovec in Germany

Protocol Number: COAV101A1DE01

Study protocol version: 4.01

26 January, 2024

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# Purpose of the addendum for inclusion of risdiplam as comparator besides nusinersen

*This document serves as an addendum to the study protocol version 4.01.*

*On 21 September, 2023 the G-BA passed a resolution on changing the study comparator in the PICO scheme. On the basis of the current evidence and after taking into account the written statement of medical societies and participating registries, risdiplam was defined as a new comparator for the routine data collections and evaluations besides nusinersen. Therefore, data from patients treated with nusinersen and risdiplam are to be collected in the comparator arm for the respective patient population for this Routine Date Collection and Evaluation.*

## Revision History

*For more information see study protocol version 4.01.*

## Synopsis and Milestones

*For more information see study protocol version 4.01.*

# 1. Background

## 1.1 Spinal muscular atrophy

*For more information see study protocol version 4.01.*

## 1.2 Benefit assessments for onasemnogene abeparvovec

*For more information see study protocol version 4.01.*

## 1.3 Routine Data Collection and Evaluations for onasemnogene abeparvovec

### 1.3.1 G-BA resolutions and procedures

*Information on risdiplam was included in the following section:*

"As required by the G-BA code of procedure, four out of six G-BA resolutions on onasemnogene abeparvovec included a public consultation procedure allowing for a participation of stakeholders, including clinical SMA experts."

*Information in risdiplam was included in the following table:*

Table A3 1: Relevant G-BA procedures concerning the Routine Data Collection and Evaluations for onasemnogene abeparvovec

| G-BA procedure | Resolution date | Public consultation |
|---|---|---|
| *For more information see study protocol version 4.01.* | | |
| *For more information see study protocol version 4.01.* | | |
| *For more information see study protocol version 4.01.* | | |
| *For more information see study protocol version 4.01.* | | |
| *For more information see study protocol version 4.01.* | | |
| Change of comparator: inclusion of risdiplam besides nusinersen | 21 September 2023 | 24 August 2023: Consultation on the written statements; no oral hearing |

*Information in Risdiplam was included in the following table:*

Table A3 2: PICO scheme for Routine Data Collection and Evaluations for onasemnogene abeparvovec

| | |
|---|---|
| **Population** | *For more information see study protocol version 4.01.* |
| **Intervention** | *For more information see study protocol version 4.01.* |
| **Comparator** | Therapy as determined by a physician, taking into account nusinersen and risdiplam.<br><br>*Note: As such, the comparator consists of the other two therapies authorized for the treatment of SMA.* |
| **Outcome** | *For more information see study protocol version 4.01.* |

*Information in Risdiplam was included in the following table:*

Table A3 3: Requirements on data source, study protocol, and SAP per G-BA resolution

| Aspect | Requirements of G-BA resolution |
|---|---|
| Data Source | *For more information see study protocol version 4.01.* |
| Protocol & SAP | *For more information see study protocol version 4.01.*<br>▪ Information on the extent to which the data on nusinersen/risdiplam collected in parallel and not collected in parallel are suitable for a pooled analysis<br>▪ Information on the extent to which data, if any, comparing onasemnogene abeparvovec and nusinersen/risdiplam from different data sources are suitable for a pooled analysis |

### 1.3.2 Written change requests from G-BA based on IQWiG assessment of study protocol and SAP

*For more information see study protocol version 4.01.*

### 1.3.3 Depiction of change requests from 28 September 2021 in study protocol and SAP version 2.02

*For more information see study protocol version 4.01.*

### 1.3.4 Conditional approval of study protocol and SAP, implementation of additional change requests

*For more information see study protocol version 4.01.*

### 1.3.5 Change requests from G-BA resolution of October 20, 2022

*For more information see study protocol version 4.01.*

*Information on Risdiplam was included in a newly written paragraph 1.3.6:*

### 1.3.6 Change request from G-BA resolution on September 21, 2023 regarding inclusion of risdiplam as comparator

On 21 September 2023 the G-BA passed a resolution on changing the study comparator in the PICO scheme. On the basis of the current evidence and after taking into account the written statement of medical societies and participating registries, risdiplam was defined as a new comparator for the routine data collections and evaluations besides nusinersen. Therefore, data from patients treated with nusinersen and risdiplam are to be collected in the comparator arm for the respective patient population for this Routine Date Collection and Evaluation.

Risdiplam was approved on 26 March 2021 for the treatment of 5q associated SMA in patients aged 2 months and older with a clinically diagnosed type 1, type 2 or type 3 SMA or with one to four copies of the SMN2 gene. Furthermore, the active substance received a positive opinion from the European Medicines Agency on July 2023 for the treatment of patients with SMA aged from 0 to 2 months.

Therefore, the G-BA mandated to change the comparator from only “nusinersen” to “therapy as determined by a physician, taking into account nusinersen and risdiplam”. As such, the comparator consists of the other two therapies authorized for the treatment of SMA. The modified comparator is to be implemented within the scope of an addendum to the study protocol and to the SAP and to be submitted for review together with the first interim analysis on 4 February 2024. Furthermore, changes were additionally implemented in track change mode in the existing study documents in order to ensure better traceability of the changes.

Also, the G-BA requested to provide data analyses based on the adapted study protocol and SAP for the modified comparator “therapy as determined by a physician, taking into account nusinersen and risdiplam” in the course of the second interim analysis.

# 2. Overview of study design and study schematic

## 2.1 Pre-specification of two analysis approaches

*Risdiplam was included in the following table:*

Table A3 4: Overview of key similarities and differences between NGT approach and G-BA approach

| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| Inclusion and exclusion criteria | Key inclusion criteria:<br>▪ Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA OR<br>▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene<br>▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to age and body weight as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC)<br>▪ Body weight at treatment initiation ≤ 21 kg<br>*For more information see study protocol version 4.01.* | |
| Analysis populations | *For more information see study protocol version 4.01.* | |
| Handling of treatment switches | Treatment episodes, no censoring for treatment switches | Allocation to initial treatment, no censoring for treatment switches |
| Confounder adjustment | *For more information see study protocol version 4.01.* | |
| Sensitivity analyses | Comparative analysis of treatment patterns:<br>▪ Nusinersen/risdiplam monotherapy/Onasemnogene abeparvovec monotherapy<br>▪ Treatment switch from nusinersen/ risdiplam to onasemnogene abeparvovec/Add-on therapy of nusinersen/risdiplam after onasemnogene abeparvovec (few to no patients expected) | Censoring for treatment switches<br><br>Pooled analysis of populations GBA-A and GBA-B (2 copy SMN2) as well as populations GBA-C and GBA-D (3 copy SMN2) |
| Utilization of parallel retrospective data, i.e. collected after availability of onasemnogene | Yes | |

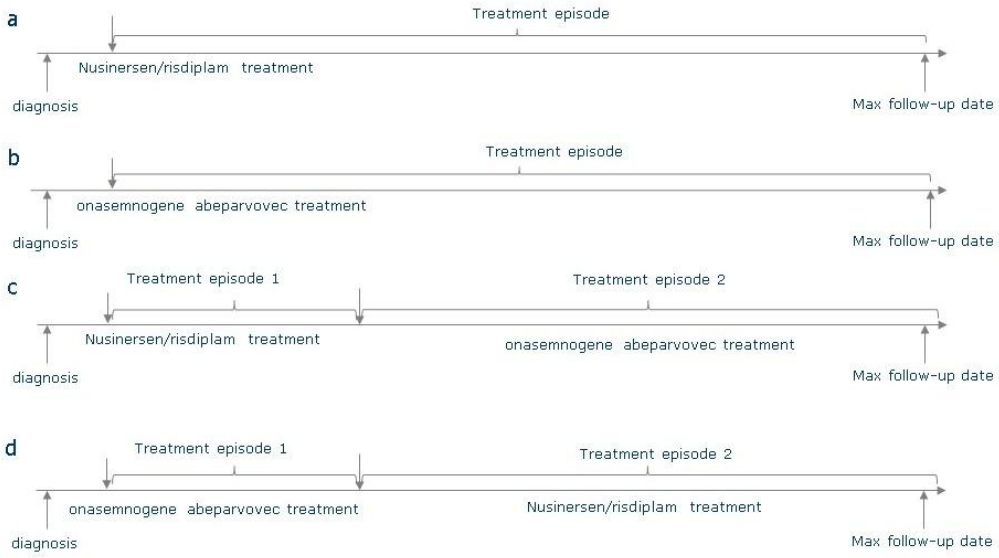
| Study design aspect | NGT approach | G-BA approach |
|---|---|---|
| abeparvovec | | |
| Utilization of non-parallel retrospective data, i.e. collected before availability of onasemnogene abeparvovec | Yes | |
| Data sources | *For more information see study protocol version 4.01.* | |
| Study sites | *For more information see study protocol version 4.01.* | |
| Sample size calculation | *For more information see study protocol version 4.01.* | |
| Interim analysis | *For more information see study protocol version 4.01.* | |
| Status report | *For more information see study protocol version 4.01.* | |

*Risdiplam was included in the following table:*

"Four types of treatment patterns regarding onasemnogene abeparvovec and nusinersen/risdiplam are theoretically possible (Figure 1), of which three are expected in the SMArtCARE registry data covering German patients. In addition to subjects who are (a) treated exclusively with nusinersen/risdiplam or (b) with onasemnogene abeparvovec according to the SmPC, there will also be (c) patients who switch from nusinersen/risdiplam to onasemnogene abeparvovec at a given time point. Patients (d) treated with nusinersen/risdiplam after receiving onasemnogene abeparvovec are theoretically possible, but expected to not occur at all or in very limited numbers in SMArtCARE because combination therapy is not routinely reimbursed by the Statutory Health Insurance in Germany."

*Risdiplam was included in the following figure:*

Figure A3 1: Expected treatment schemes




*Risdiplam was included in the following section:*

## 2.2 NGT approach

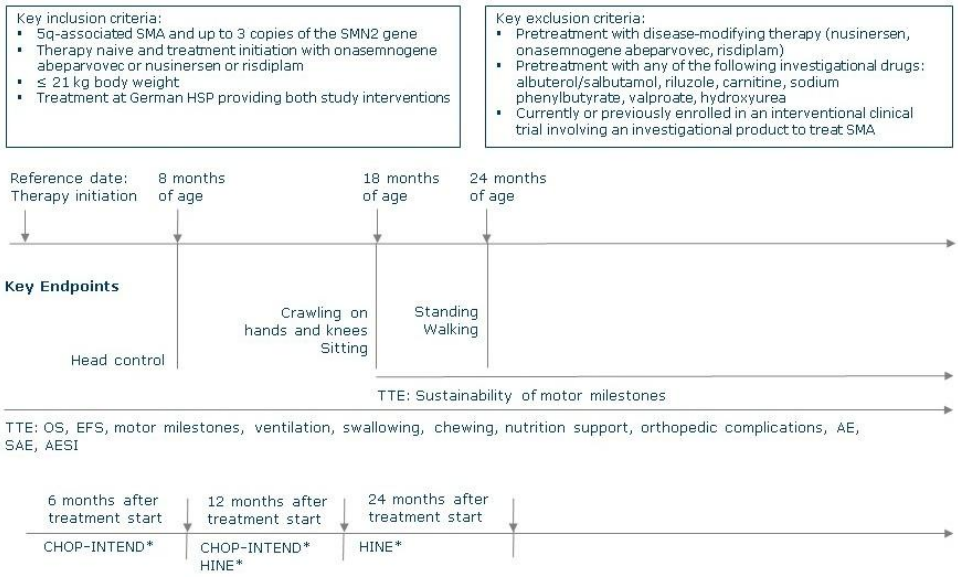
Patients switching from nusinersen/risdiplam to onasemnogene abeparvovec (group c) or receiving nusinersen/risdiplam after onasemnogene abeparvovec (group d) are characterized by two treatment episodes and are analyzed in terms of treatment episodes under each treatment (section 7.3 of the SAP). A treatment episode starts with the day of first administration and ends with the first administration of the respective follow-up intervention or the date of analysis.

Furthermore, switches from nusinersen to risdiplam and risdiplam to onasemnogene abeparvovec as well as combination therapy of onasemnogene abeparvovec and risdiplam are expected. However, treatment switches between nusinersen and risdiplam do not trigger change of treatment episodes. No treatment switching will be censored.

In case of substantial number of patients switching from nusinersen/risdiplam to other therapies suggesting a potential deterioration under treatment that might not have been reflected yet into the key study outcomes, missing data handling approaches that consider patients as missing not at random (MNAR) would be considered via an amendment and discussed with G-BA to ensure that appropriate methodology to handle such patients is defined.

*Risdiplam was included in the following figure:*

Figure A3 2: Overview study design: NGT approach




## 2.3 G-BA approach

*Risdiplam was included in the following section:*

As per change requests No. 10, 19, 20, and 21 from 28 September 2021, main analysis will allocate patients into two treatment arms depending on their initial treatment: 1) nusinersen/risdiplam or 2) onasemnogene abeparvovec.

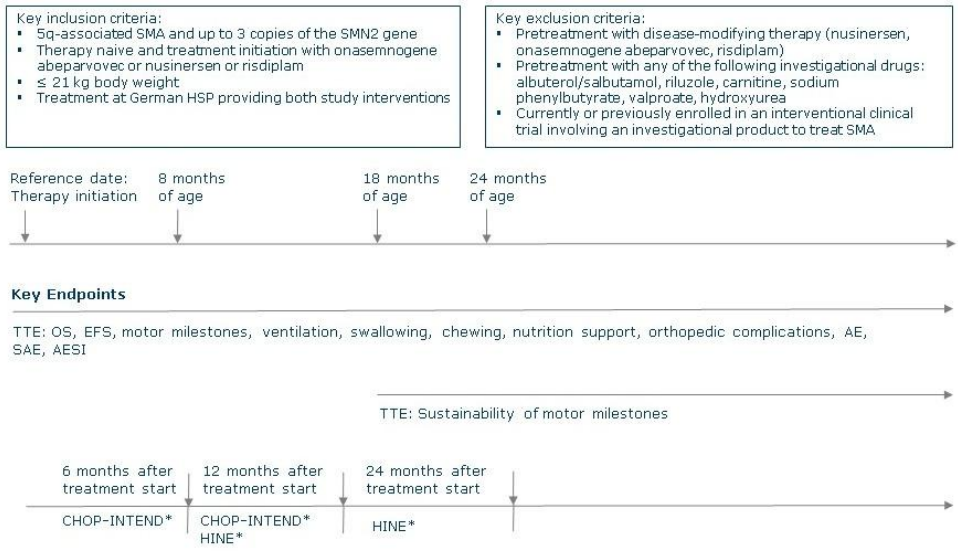
If treatment with risdiplam is less than 2 weeks before treatment with onasemnogene abeparvovec, treatment will be allocated to onasemnogene abeparvovec as initial treatment.

Treatment switches from nusinersen to onasemnogene abeparvovec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec are ignored for main analysis of treatment effects. Accordingly, no censoring, exclusion or any other type of methodological handling of treatment switches is performed.

For sensitivity analysis, patients switching from nusinersen to onasemnogene abeparvovec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec will be censored (section 7.4 of the SAP).

*Risdiplam was included in the following figure:*

Figure A3 3: Overview study design: G-BA approach



# 3. Compared therapies

## 3.1 Onasemnogene abeparvovec

### 3.1.1 Mechanism of action

*For more information see study protocol version 4.01.*

### 3.1.2 Method of administration and dosage

*For more information see study protocol version 4.01.*

## 3.2 Nusinersen

### 3.2.1 Mechanism of action

*For more information see study protocol version 4.01.*

### 3.2.2 Method of administration and dosage

*For more information see study protocol version 4.01.*

*Information on Risdiplam was included in a newly written paragraph 3.3:*

## 3.3 Risdiplam

### 3.3.1 Mechanism of action

Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations of the SMN1 gene in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is directly linked to the SMA pathophysiology which includes progressive loss of motor neurons and muscle weakness. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

### 3.3.2 Method of administration and dosage

Each bottle contains 60 mg risdiplam in 2 g powder for oral solution. Each mL of the constituted solution contains 0.75 mg risdiplam. Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA. The recommended once daily dose of Evrysdi is determined by age and body weight. Evrysdi is taken orally once a day after a meal at approximately the same time each

day, using the reusable oral syringe provided. Evrysdi must be constituted by a healthcare professional (e.g. pharmacist) prior to being dispensed. It is recommended healthcare professionals (HCP) discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose. In infants who are breastfed, Evrysdi should be administered after breastfeeding. Evrysdi should be taken immediately after it is drawn up into the oral syringe. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, Evrysdi can be administered via the tube.

# 4. Objectives

*Risdiplam was included in the following section:*

"The objective of this study is to evaluate the overall effectiveness and safety in therapy-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as symptomatic patients with 5q-associated SMA type I treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to therapy as determined by a physician, taking into account Spinraza® (nusinersen) and Evrysdi® (risdiplam). As such, the comparator consists of the other two therapies authorized for the treatment of SMA."

*For more information see study protocol version 4.01.*

# 5. Endpoints

## 5.1 Effectiveness

### 5.1.1 Survival

*Risdiplam was included in the following table:*

Table A3 5: Effectiveness endpoints SMArtCARE Registry: Survival

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Overall Survival (OS) | Time from the date of first treatment to the date of death due to any cause | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ End of data collection: Date of death<br>▪ Medical assessment: Visit date |
| Event Free Survival (EFS) | Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ End of data collection: Date of death<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Time of ventilator use = Continuous (>16h/day) |

### 5.1.2 Motor function

*Risdiplam was included in the following table:*

Table A3 6: Effectiveness endpoints SMArtCARE Registry: Motor function (NGT approach)

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Achievement of motor milestones according to age | Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis<br><br>Age limits per milestone (based on WHO (22))<br>▪ Sitting without support: 9.2 months<br>▪ Crawl on hands and knees: 13.5 months<br>▪ Standing without support: 16.9 months<br>▪ Walking without support: 17.6 months | ▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance.* |
| Head control at the age of 8 months | Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age | ▪ Medical assessment: Age at visit<br>▪ Medical Assessment: HINE: Head control |
| Crawl on hands and knees at the age of 18 months | Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months | ▪ Medical assessment: Best current motor function = Crawl on hands and knees or higher motor milestone (Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least three in a row."* |
| Sitting without support at the age of 18 months | Proportion of patients achieving the motor milestone of sitting without | ▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | support at or before the age of 18 months | on hands and knees, Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Standing without support at the age of 24 months | Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months | ▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Walking without support at the age of 24 months | Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months | ▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Medical assessment: Visit date<br>▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Any changes in motor milestones?<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age loss of previous motor milestone<br>▪ Baseline: Sitting without support (if gained: Age gained)<br>▪ Baseline: Standing without support (if gained: Age gained)<br>▪ Baseline: Walking without support (if gained: Age gained)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance.* |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Score |
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument* | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical Assessment: HINE: Visit date<br>▪ Medical Assessment: HINE: Score |
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Sitting without |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support<br><br>*Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)* | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO* |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | *performance criteria (23) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |

G-BA Approach

*Risdiplam was included in the following table:*

Table A3 7: Effectiveness endpoints SMArtCARE Registry: Motor function (G-BA approach)

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Time to sitting without support | Time from the age at first treatment to the age at reaching motor milestone of sitting without support | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."* |
| Time to standing without support | Time from the age at first treatment to the age at reaching motor milestone of standing without support | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | *Note: SMArtCARE refers to the WHO performance criteria (23)as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."* |
| Time to walking without support | Time from the age at first treatment to the age at reaching motor milestone of walking without support | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs)<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)<br><br>*Note: SMArtCARE refers to the WHO performance criteria (23) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."* |
| Sustainability of motor milestones | Time from gaining motor milestone to permanent loss of milestone ability<br>▪ Loss of the ability to sit without support<br>▪ Loss of the ability to stand without support<br>▪ Loss of the ability to walk without support<br><br>Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. | ▪ Medical assessment: Visit date<br>▪ Medical assessment: Best current motor function<br>▪ Medical assessment: Changes in motor milestones<br>▪ Medical assessment: Age gained of new motor milestone<br>▪ Medical assessment: Age lost of previous motor milestone<br>▪ Baseline: Sitting without support (if gained: Age gained)<br>▪ Baseline: Standing without support (if gained: Age gained)<br>▪ Baseline: Walking without support (if gained: Age gained) |
| CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline | Change in CHOP-INTEND score from baseline at<br>▪ 6 months after initial treatment<br>▪ 12 months after initial treatment | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ CHOP-INTEND: Date of evaluation<br>▪ CHOP-INTEND: Score |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| HINE (Hammersmith Infant Neurological Examination): Change from baseline | Change in HINE score from baseline at<br>▪ 12 months after initial treatment<br>▪ 24 months after initial treatment | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical Assessment: HINE: Visit date<br>▪ Medical Assessment: HINE: Score |

### 5.1.3 Nutrition

*Risdiplam was included in the following table:*

Table A3 8: Effectiveness endpoints SMArtCARE Registry: Nutrition

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Difficulties in swallowing | Time from the date of first treatment to the first documented difficulties in swallowing | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Swallowing? = With difficulties |
| Difficulties in chewing | Time from the date of first treatment to the first documented difficulties in chewing | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Chewing? = With difficulties |
| Gastric or nasal feeding tube | Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations<br>▪ Any type of tube feeding (supplementary or exclusively)<br>▪ Supplementary (e.g. for fluids)<br>▪ Exclusively | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube<br>▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids<br>▪ Medical assessment: Start of tube feeding (date)<br>▪ Medical assessment: Visit date (if start date of feeding tube not filled) |

### 5.1.4 Orthopedic complications

*Risdiplam was included in the following table:*

Table A3 9: Effectiveness endpoints SMArtCARE Registry: Orthopedic complications

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Scoliosis or orthopedic surgery | Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient have scoliosis?<br>▪ Medical assessment: Orthopedic surgery since last visit? |
| Scoliosis | Time from the date of first treatment to first documentation of scoliosis | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient have scoliosis? |
| Orthopedic surgery | Time from the date of first treatment to first documentation of orthopedic surgery | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Orthopedic surgery since last visit? |

### 5.1.5 Respiratory function

*Risdiplam was included in the following table:*

Table A3 10: Effectiveness endpoints SMArtCARE Registry: Respiratory function

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Time of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of<br>▪ Any ventilator support<br>▪ Ventilator support at night (during sleep)<br>▪ Intermittent ventilator support at day time and continuous at night<br>▪ Permanent ventilator support (≥16 hours per day)<br>▪ Intermittent ventilator support with acute illnesses<br><br>Documentation of same or | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Start of ventilator use<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support?<br>▪ Medical assessment: Time of ventilator use<br>o Night (during sleep)<br>o Intermittent day time and continuous at night<br>o Continuous (>16h/day)<br>o Intermittent with acute illnesses |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | higher ventilator support time required at two consecutive visits. | |
| Type of ventilator use | Time from the date of first treatment to the first of two consecutive documentations of (each separately)<br>▪ Non-invasive ventilation<br>▪ Invasive ventilation<br><br>Documentation of same or higher ventilator support type required at two consecutive visits. | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support?<br>▪ Medical assessment: Type of ventilation<br>o Non-invasive<br>o Invasive |
| Improvement in time of ventilator support from baseline | Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following<br>▪ Change from permanent ventilator support (≥16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR<br>▪ Change from intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR<br>▪ Change from ventilator support at night (during sleep) to no ventilator support | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Does the patient receive ventilator support?<br>▪ Medical assessment: Time of ventilator use<br>o Night (during sleep)<br>o Intermittent day time and continuous at night<br>o Continuous (>16h/day) |

### 5.1.6 Planned hospitalizations

*Risdiplam was included in the following table:*

Table A3 11: Effectiveness endpoints SMArtCARE Registry: Planned hospitalizations

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Planned hospitalizations | Cumulative number of planned hospitalizations across all patients per patient-year of being at risk including planned hospitalizations for administration of SMA treatments | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Medical assessment: Visit date<br>▪ Medical assessment: Planned hospitalisation since last visit (except for treatment administration)?<br>▪ Medical assessment: Reason for hospitalisation<br>▪ Nusinersen/Zolgensma: Care Setting = Inpatient (overnight)<br><br>*Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE CRF accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.* |

## 5.2 Safety

### 5.2.1 Adverse events

*Risdiplam was included in the following table:*

Table A3 12: Safety endpoints in SMArtCARE Registry: Adverse events

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Any Adverse events with or without hospitalization | Cumulative number of patients with and number of adverse events with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Type of |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | unexpected event<br>▪ Adverse events: Start date<br>▪ Adverse events: Date recorded (in case start date is not filled)<br>▪ Adverse events: name of drug |
| Any Adverse events with or without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Type of unexpected event<br>▪ Adverse events: Start date<br>▪ Adverse events: Date recorded (in case start date is not filled)<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |
| Adverse events without hospitalization | Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Adverse events without hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) without hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: MedDRA code of acute event |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | *MedDRA code was documented.* | ▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |

### 5.2.2 Serious adverse events

*Risdiplam was included in the following table:*

Table A3 13: Safety endpoints SMArtCARE Registry: Serious adverse events

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Serious adverse events with hospitalization | Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug |
| Serious adverse events with hospitalization related to treatment | Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug |
| Serious adverse events with hospitalization or death | Cumulative number of patients with and number of serious adverse events across all patients per patient-year of being at risk | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br>▪ End of data collection: Date of death<br>▪ End of data collection: Cause of death<br><br>*Note: SAEs are not directly documented in SMArtCARE. Unplanned or prolonged hospitalizations as well as death due to AES are used as proxy for SAEs. SMArtCARE captures cause of death separately from AE information. AEs resulting in death will be derived from information on cause of death.* |
| Serious adverse events with hospitalization or death related to treatment | Cumulative number of patients with and number of serious adverse events related to treatment (yes/possibly) across all patients per patient-year of being at risk<br><br>*Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.* | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: MedDRA code of acute event<br>▪ Adverse events: Start date<br>▪ Adverse events: Is the adverse event related to drug treatment?<br>▪ Adverse events: name of drug<br>▪ End of data collection: Date of death<br>▪ End of data collection: Cause of death<br><br>*Note: SAEs are not directly documented in SMArtCARE. Unplanned or prolonged hospitalizations as well as death due to AEs are used as proxy for SAEs. SMArtCARE captures cause of death separately from AE information. AEs resulting in death will be derived from information on cause of death.* |

### 5.2.3 Adverse events of special interest

*Risdiplam was included in the following table:*

Table A3 14: Safety endpoints SMArtCARE Registry: Adverse events of special interest

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Hydrocephalus with or without hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk<br><br>. | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hydrocephalus<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>Note: *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update* |
| Hydrocephalus with hospitalization | Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hydrocephalus<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>Note: *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update* |
| Hepatotoxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment) |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | hepatotoxicity per patient-year of being at risk | ▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hepatotoxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Hepatotoxicity with hospitalization | Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Hepatotoxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Thrombocytopenia with or without hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | ▪ Nusinersen / Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Thrombocytopenia<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific* |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | *checkbox in SMArtCARE CRF post CRF update.* |
| Thrombocytopenia with hospitalization | Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Thrombocytopenia<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Cardiac events with or without hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Cardiac events<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Cardiac events with hospitalization | Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Cardiac events |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | ▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>Note: *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Dorsal root ganglia cell inflammation with or without hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>. | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update* |
| Dorsal root ganglia cell inflammation with hospitalization | Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk<br><br>. | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>Note: *Analysis based on specific checkbox in SMArtCARE CRF post CRF update* |
| Renal toxicity with or without hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit? |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | ▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Renal toxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Renal toxicity with hospitalization | Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Renal toxicity<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF post CRF update.* |
| Respiratory tract infection with or without hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk<br><br>. | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Respiratory tract infection<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update* |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| Respiratory tract infection with hospitalization | Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Respiratory tract infection<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* |
| Epileptic seizure with or without hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Epileptic seizure<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.* |
| Epileptic seizure with hospitalization | Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Epileptic seizure |

| Endpoint | Definition | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | | ▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific check-box in SMArtCARE CRF pre- and post CRF update.* |
| Post lumbar puncture syndrome with or without hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Any unexpected events without hospitalisation?<br>▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific check-box in SMArtCARE CRF pre- and post CRF update.* |
| Post lumbar puncture syndrome with hospitalization | Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk | ▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Adverse events: Date recorded<br>▪ Adverse events: Has there been any adverse event since the last visit?<br>▪ Adverse events: Has there been unplanned or prolonged hospitalisation?<br>▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome<br>▪ Adverse events: Start date<br>▪ Adverse events: name of drug<br><br>*Note: Analysis based on specific check-box in SMArtCARE CRF pre- and post CRF update.* |

*Risdiplam was included in the following sections:*

“According to the G-BA resolution and justification of resolution mandating this study, serious specific unwanted side effects identified on the basis of the information provided in the Risk Management Plan and the European Public Assessment Report (EPAR) of the intervention onasemnogene abeparvovec and the comparator nusinersen/risdiplam should be surveyed. This should include hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, renal toxicity, and hydrocephalus. “

“SMArtCARE has documented the following specific adverse events and adverse events with hospitalization using specific checkboxes from its initiation, which were based on specific reporting needs for nusinersen/risdiplam:

- Respiratory tract infection
- Hydrocephalus
- Epileptic seizure
- Post lumbar puncture syndrome“

# 6. Data sources

## 6.1 SMArtCARE registry

*For more information see study protocol version 4.01.*

## 6.2 RESTORE registry

## 6.3 Study sites

*For more information see study protocol version 4.01.*

# 7. Population Selection

*Risdiplam was added to the following sections and tables:*

"This analysis will use individual patient data from patients included in SMArtCARE registry, which are treated with onasemnogene abeparvovec or nusinersen/risdiplam and fulfill the inclusion and exclusion criteria."

## 7.1 Inclusion Criteria

*Risdiplam was included in the following table:*

Table A3 15: Inclusion criteria in SMArtCARE Registry

| # | Inclusion criteria | Fields of SMArtCARE CRF (20) |
|---|---|---|
| 1 | Pre-symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam /Zolgensma: MIN(Date of treatment) |
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA<br><br>OR | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: Age at symptom onset < 6 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen/Risdiplam /Zolgensma: MIN(Date of treatment) |

| # | Inclusion criteria | Fields of SMArtCARE CRF (20) |
|---|---|---|
| | Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene | ▪ Enrolment: Genetically proven 5q SMA<br>AND<br>▪ Baseline: SMN2 copy number ≤ 3<br>AND<br>▪ Baseline: Age at symptom onset ≥ 6 months<br>AND<br>▪ Baseline: Age at symptom onset < 18 months<br>AND<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) |
| 2 | Treatment initiation with nusinersen (12 mg / 5 ml per administration) or risdiplam (dosage according to age and body weight as per SmPC) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) | ▪ Medical Assessment: Is the patient on any approved medication for SMA? = no for all visits before Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br>▪ Name of drug = onasemnogene abeparvovec/Zolgensma OR nusinersen/Spinraza /Risdiplam /Evrysdi |
| 3 | Body weight at treatment initiation ≤ 21 kg | ▪ Medical assessment: Body weight (kg) ≤ 21<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) |
| 4 | Appropriate consent/assent has been obtained for participation in the study | ▪ Enrolment: Date of consent <> "" |

## 7.2 Exclusion Criteria

*Risdiplam was included in the following table:*

Table A3 16: Exclusion criteria in SMArtCARE Registry

| # | Exclusion criteria | Fields of SMArtCARE CRF (20) |
|---|---|---|
| 1 | Pretreatment with disease modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) | ▪ Medical Assessment: Is the patient on any approved medication for SMA? = Yes for any visit before Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) |
| 2 | Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea | ▪ Medical Assessment: Other medication taken on a regular basis? = Yes<br>AND<br>▪ Medical Assessment: Name of medication (other medication) includes albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, or hydroxyurea<br>AND<br>▪ Medical Assessment: Start Date (other medication) ≤ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) |
| 3 | Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA | ▪ Baseline: Is the patient currently or was previously included in a clinical trial? = Yes<br>OR<br>▪ Medical assessment: Is the patient currently in a clinical trial? = Yes for any visit before Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) |

## 7.3 Criteria for historic data

*Risdiplam was included in the following section:*

"The SMArtCARE registry has been enrolling patients since July 2018 and prospectively collected data for patients treated with nusinersen since then. Data on risdiplam has been collected since its authorization in the EU on March 2021. Onasemnogene abeparvovec has been authorized in the United States since May 2019 and in Germany since July 2020, i.e. two years later than nusinersen and one year earlier than risdiplam. However, a limited number of patients has been treated with onasemnogene abeparvovec prior to marketing authorization and may have been documented in SMArtCARE. "

# 8. Study Design & Methods: Statistical Considerations

## 8.1 Analysis Populations

*For more information see study protocol version 4.01.*

### 8.1.1 NGT approach

*Risdiplam was included in the following section:*

Sensitivity analysis

For sensitivity analysis, additional populations are defined per section 8.5.1 of the SAP:

- Population NGT-A-S: Patients included in population NGT-A from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population NGT-B-S: Patients included in population NGT-B from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population NGT-A-CompMono: Patients included in population NGT-A that are treated exclusively with nusinersen/risdiplam
- Population NGT-B-CompMono: Patients included in population NGT-B that are treated exclusively with nusinersen/risdiplam
- Population NGT-A-OnaMono: Patients included in population NGT-A that are treated exclusively with onasemnogene abeparvovec
- Population NGT-B-OnaMono: Patients included in population NGT-B that are treated exclusively with onasemnogene abeparvovec
- Population NGT-A-CompOna: Patients included in population NGT-A that are initially treated with nusinersen/risdiplam and then switched to onasemnogene abeparvovec
- Population NGT-B-CompOna: Patients included in population NGT-B that are initially treated with nusinersen/risdiplam and then switched to onasemnogene abeparvovec
- Population NGT-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population NGT-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE

### 8.1.2 G-BA approach

*Risdiplam was included in the following section:*

Sensitivity analysis

For sensitivity analysis, additional populations are defined per section 8.5.2 of the SAP:

- Population GBA-Pool1: Pooled patients included in populations GBA-A and GBA-B
- Population GBA-Pool2: Pooled patients included in populations GBA-C and GBA-D
- Population GBA-A-S: Patients included in population GBA-A from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-B-S: Patients included in population GBA-B from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-C-S: Patients included in population GBA-C from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-D-S: Patients included in population GBA-D from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-Pool1_S: Patients from population GBA-Pool1 from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-Pool2_S: Patients from population GBA-Pool2 from centers offering both interventions of this study (nusinersen/risdiplam and onasemnogene abeparvovec)
- Population GBA-A-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population GBA-B-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE
- Population GBA-C-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE

- Population GBA-D-parallel: The population of parallel patients is defined as any patient treated with index date starting on or after 01.01.2020 as documented in SMArtCARE

## 8.2 Sample Size

## 8.3 Expected patient numbers

*For more information see study protocol version 4.01.*

## 8.4 Feasibility assessment

*Risdiplam was included to the following section:*

"The assessment will be made per study population based on the following information:

- Updated sample size calculations (section 8.2) based on interim analysis results
- Number of eligible patients fulfilling inclusion and exclusion criteria per study population and extrapolation of patient numbers for nusinersen/risdiplam and onasemnogene abeparvovec based on study enrollment until time of interim analysis"

## 8.5 Planned Analyses

### 8.5.1 Status report 18 months after G-BA resolution

*For more information see study protocol version 4.01.*

### 8.5.2 Status report and interim analysis 36 months after G-BA resolution

*For more information see study protocol version 4.01.*

### 8.5.3 Status report and interim analysis 54 months after G-BA resolution

*Information on risdiplam was included in the following section:*

"During the course of the second interim analysis, results with the modified comparator "therapy as determined by a physician, taking into account nusinersen and risdiplam" will be provided for the first time, after the application of changes to SAP and protocol in the course of the first interim analysis."

### 8.5.4 Final analysis for benefit assessment (submission on July 1 2027)

*For more information see study protocol version 4.01.*

## 8.6 Prognostic factors and potential confounders

### 8.6.1 Confounder identification and validation

*Risdiplam was included in the following table:*

Table A3 17: Overview of identified confounders in SMArtCARE Registry

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| SMN2 copy number | Very important | Yes | Number of SMN2 copies assessed per genetic testing | ▪ Genetic Test Result: SMN2 copy number | Main analysis: G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis: GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Age at symptom onset | Very important | Yes | Age of symptom onset in months for symptomatic patients | ▪ Baseline: Age at symptom onset | Main analysis: G-BA approach: GBA-B, GBA-D |
| Symptom status at treatment initiation | Very important | Yes | Symptomatic:<br><br>Diagnosis not made presymptomatically OR documentation of symptoms related to SMA at any medical assessment prior to treatment initiation | Symptomatic:<br><br>▪ Baseline: Was diagnosis made presymptomatically? = No<br>OR<br>▪ Medical Assessment: | Main analysis: NGT approach: NGT-A, NGT-B<br><br>G-BA approach: none (stratification parameter)<br><br>Sensitivity analysis: GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

[5] According to the assessment of the six clinical experts consulted during the confounder validation process

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | <u>Pre-symptomatic:</u><br>Diagnosis made pre-symptomatically AND no symptoms related to SMA at any medical assessment prior to treatment initiation | Neurology: Symptoms related to SMA = Yes<br>AT<br>▪ Medical Assessment: Visit date ≤ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br><br><u>Pre-symptomatic:</u><br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT | |

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | ▪ Medical Assess-ment: Visit date ≤ Nusiners en /Risdip-lam /Zolgens ma: MIN(Dat e of treat-ment) | |
| Age at treatment in-itiation | Very important | Yes | Age in weeks at treatment initiation | ▪ Medical Assess-ment: Age at visit<br>AT<br>▪ Medical Assess-ment: Visit date = Nusiners en /Risdip-lam Zolgens ma: MIN(Dat e of treat-ment) | <u>Main analy-sis:</u><br>NGT ap-proach: NGT-A, NGT-B<br>G-BA ap-proach:<br>▪ Directly: GBA-A, GBA-C<br>▪ Derived (treat-ment de-lay de-fined as time from symp-tom on-set to treat-ment ini-tiation: GBA-B, GBA-D<br><u>Sensitivity analysis:</u><br>▪ GBA-Pool1 (A+B), GBA- |

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | | Pool2 (C+D) |
| Nutrition support | Very important | Yes | Gastric tube or nasal feeding tube (exclusive/supplemental/none) at treatment initiation | ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube?<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | Main analysis:<br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br>Sensitivity analysis:<br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |
| Ventilation support | Very important | Yes | Duration of ventilator use (nighttime/intermittent/permanent (≥16h/day) at treatment initiation | ▪ Medical assessment: Does the patient receive ventilator support? = Yes<br>AND<br>▪ Medical assessment: Time of ventilator use | Main analysis:<br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br>Sensitivity analysis:<br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | ▪ Night (during sleep)<br>▪ Intermittent day time and continuous at night<br>▪ Continuous (>16h/day)<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | |
| Contractures | Less important | Yes | Contractures limiting function (yes/no) at treatment initiation | ▪ Medical Assessment: Are any contractures present? = Yes<br>AND<br>▪ Medical assessment: Type of limitation = Severe (imposing limits to function) | <u>Main analysis:</u><br>NGT approach: NGT-A, NGT-B<br>G-BA approach: GBA-B, GBA-D<br><u>Sensitivity analysis:</u><br>GBA-Pool1 (A+B), GBA-Pool2 (C+D) |

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | |
| Motoric function: Highest motor milestone | Very important | Yes | Highest motor milestone at treatment initiation:<br>▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing without support<br>▪ Walking without support<br>▪ Climb stairs | ▪ Medical assessment: Best current motor function<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | All |
| Motoric function: CHOP-INTEND | Very important | Yes | CHOP-INTEND score at treatment initiation | ▪ CHOP-INTEND: Score<br>AT<br>▪ Medical Assessment: | All |

| Confounder | Clinical relevance[5] | Included in Study | Definition | Fields of SMArtCARE CRF (20) | Applicable to analysis populations |
|---|---|---|---|---|---|
| | | | | Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | |

### 8.6.2 Adjustment for confounders

*For more information see study protocol version 4.01.*

## 8.7 Subgroup analyses

### 8.7.1 Subgroups for baseline characteristics

*Risdiplam was included in the following table:*

Table A3 18: Overview of planned subgroup analyses in SMArtCARE Registry

| Planned subgroups | Patients' baseline status | Fields of SMArtCARE CRF (20) | Applicable for analysis populations |
|---|---|---|---|
| SMN2 copy number | ▪ 1<br>▪ 2<br>▪ 3<br>▪ 4 | ▪ Genetic Test Result: SMN2 copy number | Main analysis:<br>G-BA approach: GBA-B, GBA-D<br><br>Sensitivity analysis:<br>GBA-Pool1 (A+B),<br>GBA-Pool2 (C+D) |
| Age at treatment initiation | ▪ ≤ 4 weeks<br>▪ > 4 weeks | ▪ Enrolment: Date of birth<br>▪ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | All |
| Gender | ▪ Male<br>▪ Female<br>▪ Undifferentiated<br>▪ Unknown | ▪ Enrolment: Gender | All |
| Region | ▪ Germany<br>▪ Austria | ▪ N.a. (Treatment center information not part of SMArtCARE CRF but available in SMArtCARE database) | All |
| Symptom status at treatment initiation | ▪ Symptomatic<br>▪ Pre-symptomatic | Symptomatic:<br>▪ Baseline: Was diagnosis made pre-symptomatically? = No<br>OR<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes<br>AT | NGT approach: NGT-A, NGT-B |

| Planned subgroups | Patients' baseline status | Fields of SMArtCARE CRF (20) | Applicable for analysis populations |
|---|---|---|---|
| | | ▪ Medical Assessment: Visit date ≤ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment)<br><br><u>Pre-symptomatic:</u><br>▪ Baseline: Was diagnosis made pre-symptomatically? = Yes<br>AND<br>▪ Medical Assessment: Neurology: Symptoms related to SMA = No<br>AT<br>Medical Assessment: Visit date ≤ Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | |
| Nutrition support (Does the patient use a gastric or nasal feeding tube?) | ▪ No<br>▪ Yes - exclusively fed by tube<br>▪ Yes – supplementary e.g. for fluids | ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube?<br>AT<br>▪ Medical Assessment: Visit Date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |
| Ventilation support (Does the patient receive ventilator support?) | ▪ No<br>▪ Yes | ▪ Medical assessment: Does the patient receive ventilator support?<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |
| Contractures (Contractures limiting function) | ▪ No<br>▪ Yes | ▪ Medical Assessment: Are any contractures present? = Yes<br>AND<br>▪ Medical assessment: Type of limitation = Severe (imposing limits to function)<br>AT<br>▪ Medical Assessment: Visit date = Nusinersen | NGT approach: NGT-A, NGT-B<br><br>G-BA approach: GBA-B, GBA-D |

| Planned subgroups | Patients' baseline status | Fields of SMArtCARE CRF (20) | Applicable for analysis populations |
|---|---|---|---|
| | | /Risdiplam /Zolgensma: MIN(Date of treatment) | |
| Motor function: Highest motor milestone | ▪ None/n.a.<br>▪ Sitting without support<br>▪ Crawl on hands and knees<br>▪ Standing with-out support<br>▪ Walking with-out support<br>▪ Climb stairs | ▪ Medical assessment: Best current motor function AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | All |
| Motor function: CHOP-INTEND score | ▪ ≤ Median CHOP-INTEND<br>▪ > Median CHOP-INTEND | ▪ CHOP-INTEND: Score AT<br>▪ Medical Assessment: Visit date = Nusinersen /Risdiplam /Zolgensma: MIN(Date of treatment) | All |

### 8.7.2 Analysis methods

*For more information see study protocol version 4.01.*

# 9. Safety

*For more information see study protocol version 4.01.*

# 10. Data Handling and Monitoring

## 10.1 Data Management

*For more information see study protocol version 4.01.*

## 10.2 Source Data verification

*Risdiplam was included in the following section:*

"At current, there are uncertainties regarding the possibilities and limitations of performing SDV as part of the study. The extent of archived documentation, especially for historical nusinersen and risdiplam patients, cannot be estimated at present and could differ between the participating centers."

## 10.3 Minimization of missing data

*For more information see study protocol version 4.01.*

## 10.4 Data analysis

*For more information see study protocol version 4.01.*

# 11. Ethical and regulatory aspects

## 11.1 Regulatory and ethical compliance

*For more details see study protocol version 4.01 of the study protocol.*

## 11.2 Informed Consent

*For more details see study protocol version 4.01 of the study protocol.*

# 12. Outcome

*For more information see study protocol version 4.01.*

# Annex

## A1 Methodology for Confounder Identification

## A2 Relevant variables in SMArtCare Registry

## A 3.1 Relevant variables in SMArtCARE Registry

*Risdiplam was included in the following table:*

Table A3 19: Relevant variables in SMArtCARE Registry

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| **Enrolment** | | Date of consent | x | |
| | | Genetically proven 5q SMA | x | |
| | | Date of Birth | x | |
| | | Gender | x | |
| **Baseline** | | Date recorded | x | |
| | Genetic Test Result | SMN2 copy number | x | |
| | | Was diagnosis made pre-symptomatically? | x | |
| | Clinical diagnosis | Age at symptom onset | x | |
| | Motor function | Sitting without support | x | |
| | | Sitting without support: Age gained | x | |
| | | Crawl on hands and knees | x | |
| | | Crawl on hands and knees: Age gained | x | |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Standing without support | x | |
| | | Standing without support: Age gained | x | |
| | | Walking without support | x | |
| | | Walking without support: Age gained | x | |
| | | Climb stairs | x | |
| | | Climb stairs: Age gained | x | |
| | Registries, clinical trials | Is the patient currently or was previously included in a clinical trial? | x | |
| **Medical Assessment** | | Visit date | x | x |
| | | Age at visit | x | x |
| | Pulmonary | Does the patient receive ventilator support? | x | x |
| | | Type of ventilation | | x |
| | | Time of ventilator use | x | x |
| | | Start of ventilator use | | x |
| | Nutrition | Does the patient use a gastric or nasal feeding tube? | x | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Start of tube feeding | x | x |
| | | Swallowing? | | x |
| | | Chewing? | | x |
| | Orthopedics | Does the patient have scoliosis? | | x |
| | | Orthopedic surgery since last visit? | | x |
| | Hospitalisation | Planned hospitalisation since last visit (except for treatment administration)? | | x |
| | | Admission date | | x |
| | | Reason for hospitalisation | | x |
| | Medication | Is the patient on any approved medication for SMA? | x | x |
| | | Name of drug | x | x |
| | | Start date | x | x |
| | | Other medication taken on a regular basis? | x | x |
| | | Name of medication | x | x |
| | Clinical Trial | Is the patient currently in a | x | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | clinical trial? | | |
| | | Start Date | x | x |
| | Motor function | Any changes in motor milestones? | x | x |
| | | Age gained of new motor milestone | x | x |
| | | Age loss of previous motor milestone | x | x |
| | | Best current motor function | x | x |
| | HINE | Score | x | x |
| | | Head control | x | x |
| | Clinical examination | Body weight | x | |
| | | Neurology: Symptoms related to SMA | x | |
| | | Are any contractures present? | x | |
| | | Type of limitation | x | |
| **Physiotherapeutic Assessment** | CHOP-INTEND | Date of Evaluation | x | x |
| | | Score | x | x |
| **Zolgensma** | Admission day | Date of treatment | x | |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| **Nusinersen** | | Date of treatment | x | x |
| | | Care setting | x | x |
| **Risdiplam** | | Date of treatment | x | x |
| **Adverse Events** | | Date recorded | | x |
| | | Type of unexpected event: Hydrocephalus | | x |
| | | Type of unexpected event: Hepatotoxicity | | x (to be added) |
| | | Type of unexpected event: Thrombocytopenia | | x (to be added) |
| | | Type of unexpected event: Cardiac events | | x (to be added) |
| | | Type of unexpected event: Dorsal root ganglia cell inflammation | | x (to be added) |
| | | Type of unexpected event: Renal toxicity | | x (to be added) |
| | | Type of unexpected event: Respiratory tract infection | | x |
| | | Type of unexpected event: Epileptic seizure | | x |

| CRF | CRF Section | CRF Item | at or before Baseline | after Baseline |
|---|---|---|---|---|
| | | Type of unexpected event: Post lumbar puncture syndrome | | x |
| | | Has there been any adverse event since the last visit? | | x |
| | | Has there been unplanned or prolonged hospitalisation? | | x |
| | | Any unexpected events without hospitalisation? | | |
| | | Type of unexpected event | | x |
| | | MedDRA code of acute event | | x |
| | | Admission date | | x |
| | | Is the adverse event related to drug treatment? | | x |
| | | Name of drug | | x |
| | | Start date | | x |
| **End of data collection** | | Date recorded | | x |
| | | Is the patient deceased? | | x |
| | | Date of death | | x |

Source: SMArtCARE Case Report Form 2021

# Addendum 4

# Sample Size Re-Calculation and Feasibility Assessment

# Addendum 4: Sample Size Re-Calculation and Feasibility Assessment

Addendum 4 to study protocol version 4.01 of routine data collection and evaluations of onasemnogene abeparvovec in Germany

Protocol Number: COAV101A1DE01

Study protocol version: 4.01

26 January, 2024

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# 1. Introduction

Per sections 8.2.3 and 8.4 of the study protocol and in line with the G-BA resolution of 20 January 2022 (25) an update of the sample size calculations as well as a feasibility assessment is to be performed with the first interim analysis and submitted to G-BA 36 months after study start.

It was originally planned to select the most appropriate and feasible endpoint per analysis population (which need not necessarily be EFS or a motor function endpoint) and conduct sample size calculation according to section 5.4 of the SAP while considering additional interim analyses and adjustments of the alpha error (section 8.2.3). However, a number of developments render this approach unfeasible at the current time.

First, with its resolution of 21 September 2023 (29), the G-BA changed the comparator of this study from nusinersen to therapy as determined by a physician, taking into account nusinersen and risdiplam (section 1.3.6). Interim results for the new comparator definition are to be submitted to G-BA for the first time with the second interim analysis due for submission on 4 August 2025 (29). Since only patient numbers and interim results for the original comparator (nusinersen) are available at current, a final sample size update and feasibility assessment is not appropriate at this time as the inclusion of risdiplam is expected to have effects on the results as well as the patient numbers and shares. Both effects – but especially the expected effects on patient numbers and shares– are actually a key reason for changing the comparator of this study (30).

Second, the introduction of nationwide newborn screening in October 2021 (31) has significantly changed the distribution of patient enrollment between analysis populations. While analysis populations with symptomatic patients (GBA-B and GBA-D) show a significant reduction of new patients with the introduction of newborn screening, analysis populations with pre-symptomatic patients (GBA-A and GBA-C) are characterized by the majority of patients being diagnosed and initially treated after the introduction of NBS. This results in significant differences in patient numbers and observation times between analysis populations with pre-symptomatic populations currently showing smaller patient numbers and much shorter observation times (Table A4 1). Results for symptomatic populations are thus more robust than for pre-symptomatic populations while the majority of future patients is expected to be allocated to pre-symptomatic populations.

Third, observation times differ significantly between patients treated with onasemnogene abeparvovec and nusinersen. These differences in treatment arms make it difficult to interpret interim results currently available, especially for motor milestones in pre-symptomatic populations. The approximate mean age at the time of data cut is above or around the relevant WHO developmental milestone thresholds also used for endpoint definitions in this study (9.2 months for sitting, 13.5 months for crawling, 16.9 months for standing, 17.6 months for walking) for patients treated with nusinersen pre-symptomatically. The majority of patients treated with nusinersen are thus old enough to develop key motor milestones

according to age. This is not the case for patients treated with onasemnogene abeparvovec pre-symptomatically, where the majority of patients is still at an age where key motor milestones are expected to develop.

Table A4 1: Mean age at treatment and observation times by analysis populations and treatment arms

| Population | Mean age at treatment initiation (months) | | Mean observation time (months) | | Approximate mean age at data cut (months) | |
|---|---|---|---|---|---|---|
| | Ona | Nusi | Ona | Nusi | Ona | Nusi |
| GBA-A | 0.8 | 0.8 | 10.3 | 22.6 | 11.1 | 23.4 |
| GBA-B | 4.6 | 4.6 | 18.3 | 43.9 | 23.0 | 48.5 |
| GBA-C | 0.8 | 0.8 | 10.9 | 15.9 | 11.8 | 16.7 |
| GBA-D | 19.8 | 19.8 | 16.3 | 47.3 | 36.5 | 67.1 |

Source: (32)

Fourth, the number of nusinersen patients in pre-symptomatic analysis populations is currently very low after trimming and PS-weighting with results being based on 14 patients in population GBA-A and 9.7 comparator patients in population GBA-C, respectively. Interim results for pre-symptomatic populations are thus subject to significant uncertainty caused by the low number of comparator patients in adjusted analysis.

Fifth, results for the secondary data source (RESTORE registry) as well as meta-analysis of results from the primary and secondary data sources can only be generated and reported with the second analysis as the extend of missing values in baseline confounders was too high for the RESTORE registry at the time of data cut for the first interim analysis. This is currently being addressed by the RESTORE study sites after an amendment to the RESTORE registry protocol was completed that now warrants (retrospective) data capture of all baseline confounders required for this study. Inclusion of RESTORE may have significant effects on results and patient numbers of this study.

Due to the described challenges, a final sample size update and feasibility assessment is not possible based on the data of the first interim analysis. The described sources of uncertainties and bias are expected to be reduced significantly with the inclusion of risdiplam into the comparator arm of the study as well as the availability of adjusted results from the RESTORE registry. It is expected that patient numbers for the comparator arm in pre-symptomatic patients will increase while differences in observation times are expected to decrease. As the data becomes more mature with future data cuts, results will also become more robust.

For informational purposes, the development of patient numbers and a forecast is depicted in section 2 for the SMArtCARE registry. The forecast is subject to

significant uncertainties because it is based on nusinersen data for the comparator arm and effects of the inclusion of risdiplam currently cannot be quantified.

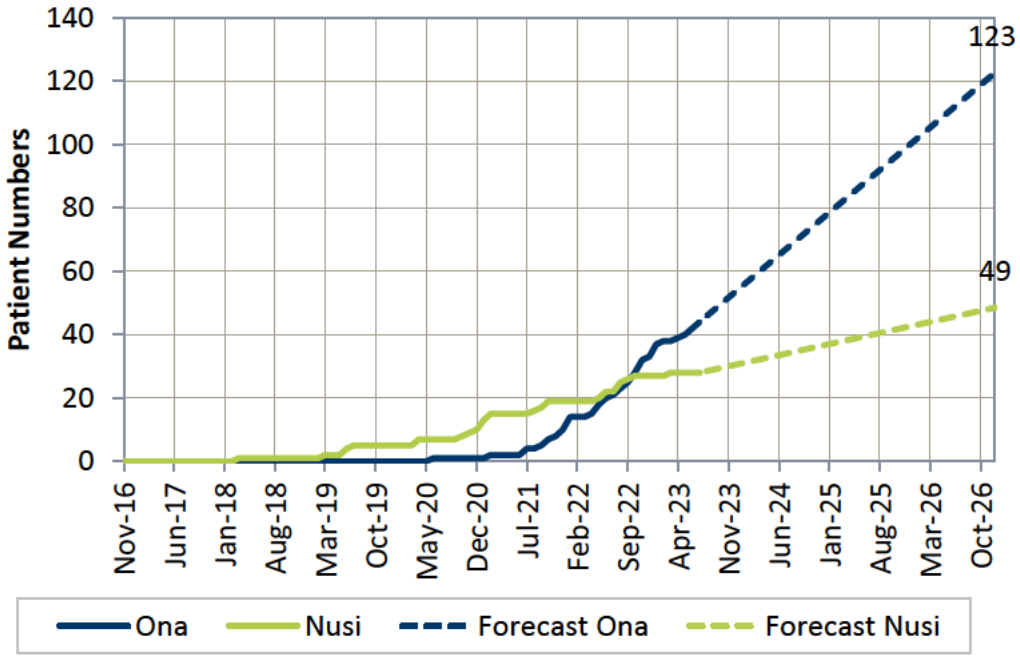
Based on the forecast results for patient shares between treatment arms at the time of final data cut (31 December, 2026) and interim results for selected endpoints, an updated sample size calculation was performed. Selection of endpoints was performed based on statistical significance of results. Especially in pre-symptomatic populations (GBA-A and GBA-C), non-significant endpoints with large effects were also included since statistical significance cannot be expected based on the current data with low patient numbers and short observation times.

## 2. Development of patient numbers and forecast

A key parameter for sample size calculations are the patient shares between treatment arms. At the time of initial study planning, this ratio was entirely unknown and a 1:1 distribution was assumed. Based on data for the first interim analysis, a forecast was performed by assuming that the average number of new patients per treatment arm and population observed in the last twelve months available in the data cut (August 2022 – July 2023) will be continued in the future. This approach is likely an underestimation of patient numbers in the comparator arm as risdiplam patients will also be included starting with the second interim analysis. Since this effect currently cannot be quantified and current sample size calculations are only informative due to the uncertainties described in section 1, this effect is not taken into account at this time. In addition, effects of trimming and weighting via standardized mortality weight ratios vs. fine stratification weights are ignored for the forecast as these are highly sensitive to the actual patient characteristics of included patients.

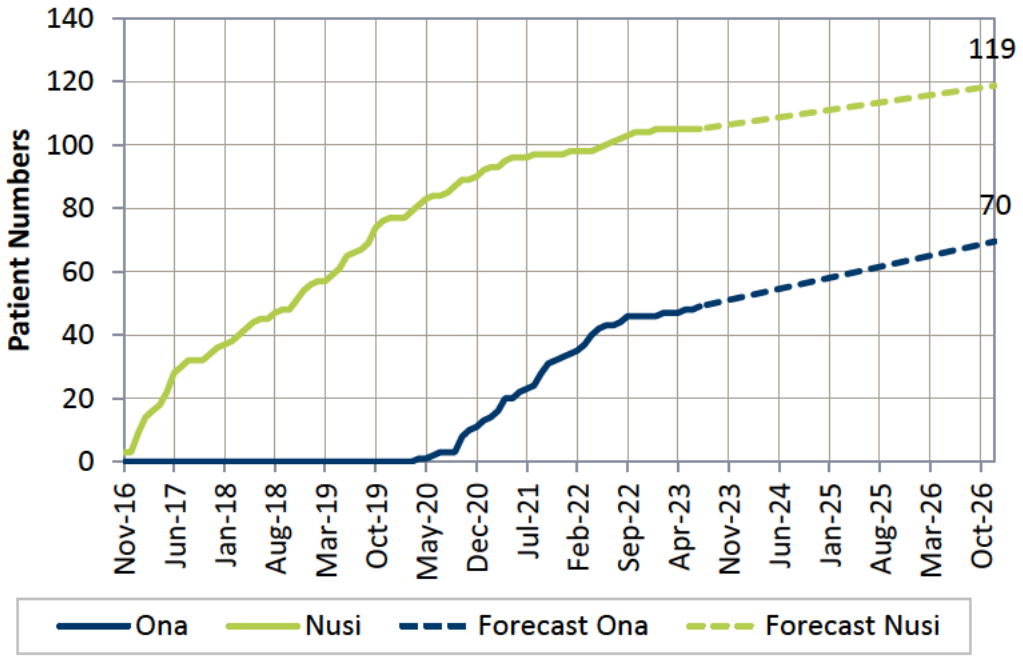
For population GBA-A, there are a total of 72 patients included at the time of data cut for first interim analysis (44 patients in the onasemnogene abeparvovec arm and 28 patients in the nusinersen arm). Based on the average numbers of patients included per treatment arm in the last 12 months before data cut, a total of 172 patients would result, of which 123 would be included in the intervention arm and 49 in the comparator arm. This would correspond to a ratio of 72% intervention to 28% control patients. The development and forecast for population GBA-A is depicted in Figure A4 1.

Figure A4 1: Patient Numbers and Forecast: Population GBA-A



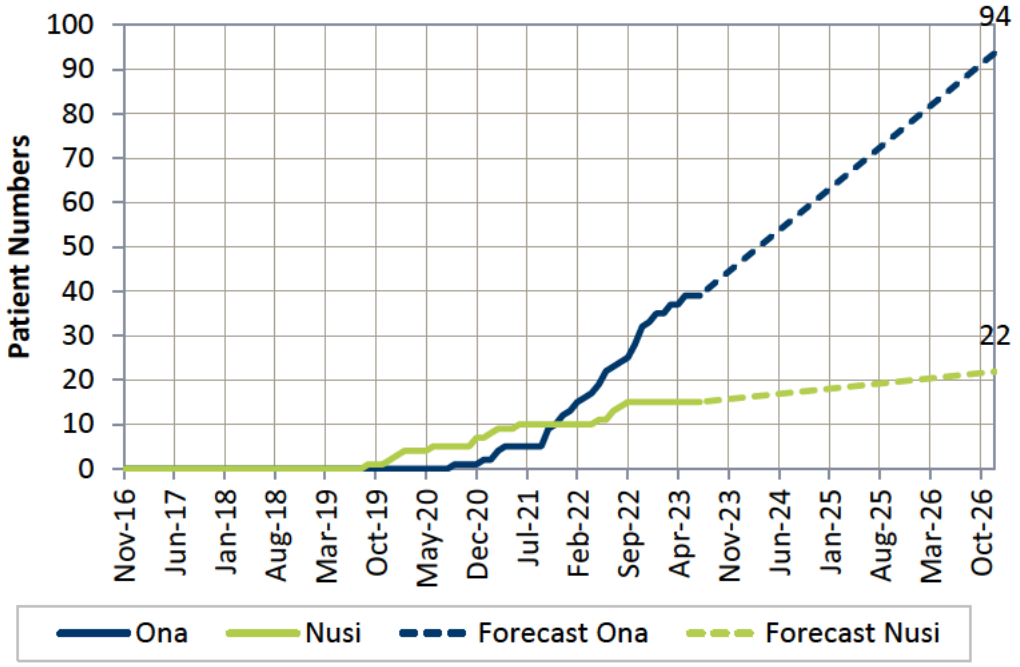
For population GBA-B, there are a total of 154 patients included at the time of data cut for first interim analysis (49 patients in the onasemnogene abeparvovec arm and 105 patients in the nusinersen arm). Based on the average numbers of patients included per treatment arm in the last 12 months before data cut, a total of 189 patients would result, of which 70 would be included in the intervention arm and 119 in the comparator arm. This would correspond to a ratio of 37% intervention to 63% control patients. The development and forecast for population GBA-B is depicted in Figure A4 2.

Figure A4 2: Patient Numbers and Forecast: Population GBA-B



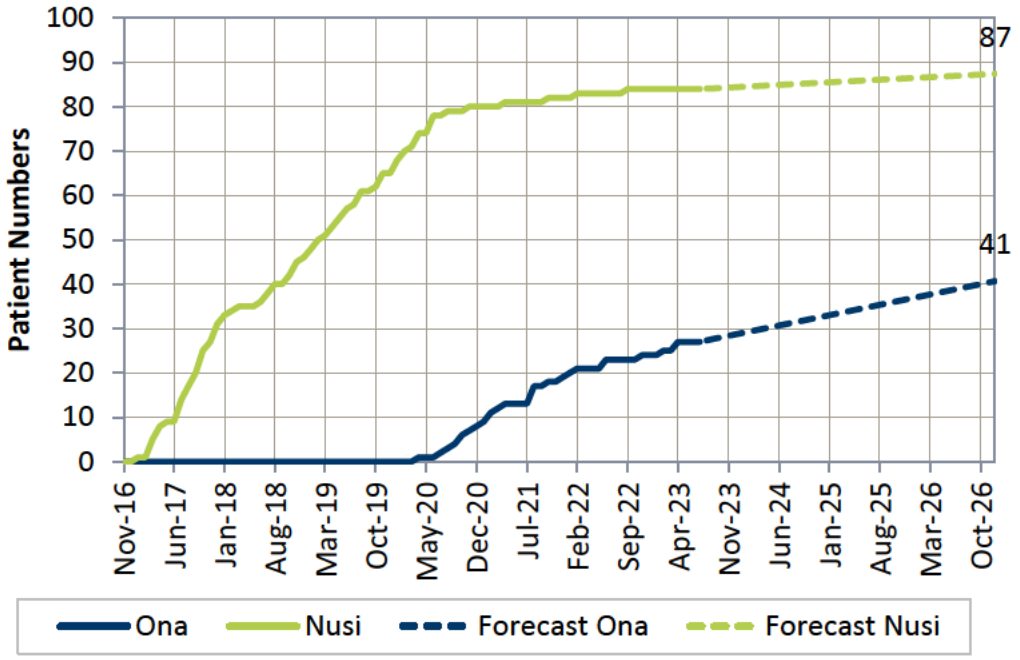

For population GBA-C, there are a total of 54 patients included at the time of data cut for first interim analysis (39 patients in the onasemnogene abeparvovec arm and 15 patients in the nusinersen arm). Based on the average numbers of patients included per treatment arm in the last 12 months before data cut, a total of 116 patients would result, of which 94 would be included in the intervention arm and 22 in the comparator arm. This would correspond to a ratio of 81% intervention to 19% control patients. The development and forecast for population GBA-C is depicted in Figure A4 3.

Figure A4 3: Patient Numbers and Forecast: Population GBA-C




For population GBA-D, there are a total of 109 patients included at the time of data cut for first interim analysis (26 patients in the onasemnogene abeparvovec arm and 83 patients in the nusinersen arm). Based on the average numbers of patients included per treatment arm in the last 12 months before data cut, a total of 128 patients would result, of which 41 would be included in the intervention arm and 87 in the comparator arm. This would correspond to a ratio of 32% intervention to 68% control patients. The development and forecast for population GBA-D is depicted in Figure A4 4.

Figure A4 4: Patient Numbers and Forecast: Population GBA-D




At the time of data cut for first interim analysis, the patient numbers are in line with the expectations formulated in section 8.3 of the protocol for populations GBA-A, GBA-B, and GBA-C (-12% to +9%). Patient numbers for population GBA-D are significantly higher than expected (+72%). Table A4 2 illustrates a comparison of expected patient numbers per section 8.3 of the protocol with actual patient numbers for first interim analysis. To estimate the patient numbers per assumptions of section 8.3, the total patients diagnosed from January 2022 to December 2026 were divided by 60 (total no. of months) and multiplied by 19 (no. of months between January 2022 and last month of data for first interim analysis, i.e. July 2023).

Expected patient numbers only cover the SMArtCARE registry in section 8.3 of the protocol. For informational purposes, the total number of RESTORE patients was also included in Table A4 2. These are generally comparable to those in SMArtCARE with the exception of population GBA-D, where there are only about half as many patients included in RESTORE compared to SMArtCARE. If the results of adjusted outcome analyses of RESTORE patients, which is planned to start with the second interim analysis, should allow for meta-analysis of the results, patient numbers could thus increase by a factor of about two due to the RESTORE patients.

Table A4 2: Comparison of expected and actual patient numbers at time of data cut for first interim analysis

| Step/Description | GBA-A | GBA-B | GBA-C | GBA-D |
|---|---|---|---|---|
| 75% of patients diagnosed between July 2018 and December 2021 (assumption: 75% of diagnosed cases enrolled in SMArtCARE) | 26 | 104 | 15 | 62 |
| Patients diagnosed from January 2022 to December 2026 | 131 | 116 | 146 | 0 |
| Total number of potentially eligible patients enrolled in SMArtCARE per section 8.3 of the protocol | 157 | 220 | 161 | 62 |
| Expected patient numbers at time of data cut for first interim analysis per assumptions in section 8.3 of the protocol | 68 | 141 | 61 | 62 |
| Actual patient numbers in SMArtCARE at time of data cut for first interim analysis | 72 | 154 | 54 | 109 |
| Actual patient numbers in RESTORE at time of data cut for first interim analysis | 57 | 193 | 53 | 58 |
| Actual patient numbers in SMArtCARE and RESTORE combined at time of data cut for first interim analysis | 129 | 347 | 107 | 167 |

# 3. Update of Sample Size Calculations

Sample size calculations were updated as described in section 8.2.3 of the protocol using the following assumptions:

- HR0=0.5 and 2, respectively
- alpha = 0.05, two-sided
- power = 0.8
- negligible/no censoring

Calculations were carried out with the software PASS 2023 using the option "Superiority by a Margin Tests for Two Survival Curves using Cox's Proportional Hazards Model". HR0 serves as the superiority hazard ratio. Hypotheses for HR0 = 0.5 are H0: HR ≥ HR0 vs. Ha: HR > HR0 and for HR0 = 2 the hypotheses are H0: HR ≤ HR0 vs. Ha: HR > HR0, respectively. Event rates and effect sizes from the first interim analysis were used for all calculations.

As mandated by G-BA, these assumptions represent a "shifted null-hypothesis". While not mandated by German Social law or G-BA code of procedure, it is acknowledged that this threshold and its application to the boundaries of the two-sided 95 % CI has been requested by IQWiG both in its initial Rapid Report (1), its general methods (33) as well as consistently applied in all AbD concepts to date (34–40).

While it is acknowledged that this approach guarantees a very high level of certainty, it is anticipated that it would also lead to patient numbers that often cannot realistically be included in the context of an AbD in rare diseases. An alternative could be to follow the principle of the "dramatic effect", i.e., $p < 0.01$ but with reduced effect thresholds (hazard ratio < 0.5).

To assess the effects of this alternative threshold, a second sample size calculation was performed using the following assumptions:

- power = 0.8
- $\alpha = 0.01$, two-sided
- negligible/no censoring

Calculations were carried out with the software PASS 2023 using the option "Tests for Two Survival Curves using Cox's Proportional Hazards Model". Hypotheses are H0: HR = 1 vs. Ha: HR ≠ 1

Event rates and effect sizes from the first interim analysis were used for all calculations. Patient shares were derived from forecast results depicted in section 2 of this addendum. Results for the calculations using a shifted null-hypothesis are illustrated in Table A4 3. Results for the calculations using a standard null-hypothesis but $\alpha = 0.01$ are illustrated in Table A4 4.

Table A4 3: Results of updated sample size calculations using a shifted null-hypothesis

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-A | Chewing | 16.3% | 0.35 | 28% | 3,833 | 2,760 | 1,073 |
| GBA-B | EFS | 19.8% | 0.21 | 63% | 252 | 94 | 158 |
| GBA-B | Any Tube Feeding | 41.4% | 0.48 | 63% | 48,392 | 17,906 | 30,486 |
| GBA-B | Supplemental Tube Feeding | 26.3% | 0.38 | 63% | 1,731 | 641 | 1,090 |
| GBA-B | Permanent Ventilation | 16.6% | 0.25 | 63% | 461 | 171 | 290 |
| GBA-C | Standing | 41.5% | 3.2 | 19% | 500 | 405 | 95 |
| GBA-D | Standing | 33.4% | 2.31 | 68% | 4,294 | 1,375 | 2,919 |

Event Rate Comparator: contains the assumed probabilities of an event in the control group
Hazard Ratio: is the assumed actual hazard ratio at which power is calculated
Patient share comparator: serves as the percent of the total sample size that is in the control group.

Table A4 4: Results of updated sample size calculations using a standard null-hypothesis with α = 0.01

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-A | Chewing | 16.3% | 0.35 | 28% | 840 | 605 | 235 |
| GBA-B | EFS | 19.8% | 0.21 | 63% | 148 | 55 | 93 |
| GBA-B | Any Tube Feeding | 41.4% | 0.48 | 63% | 283 | 105 | 178 |
| GBA-B | Supplemental Tube Feeding | 26.3% | 0.38 | 63% | 263 | 98 | 165 |
| GBA-B | Permanent Ventilation | 16.6% | 0.25 | 63% | 218 | 81 | 137 |
| GBA-C | Standing | 41.5% | 3.2 | 19% | 155 | 126 | 29 |
| GBA-D | Standing | 33.4% | 2.31 | 68% | 240 | 77 | 163 |

Event Rate Comparator: contains the assumed probabilities of an event in the control group
Hazard Ratio: is the assumed actual hazard ratio at which power is calculated
Patient share comparator: serves as the percent of the total sample size that is in the control group.

Application of a shifted null-hypothesis significantly increases required patient numbers compared to a scenario using a standard null-hypothesis with α = 0.01. As described in section 1 of this addendum, interim results and patient shares are subject to significant uncertainties and thus do not allow for a conclusion on study feasibility at this time. Even small changes in effect sizes and event rates can have a significant impact on required patient numbers, especially when using a shifted null-hypothesis. For example, the results of sample size calculations using a shifted null-hypothesis for EFS and permanent ventilation in population GBA-B differ by a factor of almost two (252 patients for EFS, 461 patients for permanent ventilation) despite relatively small differences in effect sizes and event rates.

Especially in pre-symptomatic analysis populations (GBA-A, GBA-C), effects from interim analysis are still very uncertain and based on very small patient numbers in the comparator arm. Results may still change significantly, leading to fewer required patients. Actual patient numbers available for final analysis are also uncertain and will be influenced by the inclusion of risdiplam in the comparator arm. In addition, the possibility of performing meta-analysis of SMArtCARE and RESTORE is dependent on the homogeneity of results and can only be assessed individually per data cut, population, and endpoint. Whether or not patient numbers can be

increased by about a factor of two through meta-analysis with RESTORE thus needs to be assessed with each future (interim) analysis and cannot be predicted.

# Addendum 5

# Sample Size Re-Calculation and Feasibility Assessment

# Addendum 5: Sample Size Re-Calculation and Feasibility Assessment

## Addendum 5 to study protocol version 4.01 of routine data collection and evaluations of onasemnogene abeparvovec in Germany

Protocol Number: COAV101A1DE01

Study protocol version: 5.01

01 August 2025

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# 1. Introduction

Per sections 8.2.3 and 8.4 of the study protocol and in line with the G-BA resolution of 20 January 2022 (41) an update of the sample size calculations as well as a feasibility assessment is to be performed with the second interim analysis.

With resolution of 21 September 2023 (42), the G-BA changed the comparator of this study from nusinersen to therapy as determined by a physician, taking into account nusinersen and risdiplam (section 1.3.6). Interim results for the new comparator definition are submitted to G-BA for the first time with the second interim analysis on 4 August 2025 (43).

The introduction of nationwide newborn screening (NBS) in October 2021 (44) has significantly changed the distribution of patient enrollment between analysis populations. While analysis populations with symptomatic patients (GBA-B and GBA-D) show a significant reduction of new patients with the introduction of newborn screening, analysis populations with pre-symptomatic patients (GBA-A and GBA-C) comprise mainly of patients who were diagnosed and initially treated after the introduction of NBS. This results in considerable differences in patient numbers and observation times between analysis populations. Currently the number of patients in the pre-symptomatic patients is still slower and the observation time shorter (Table A5 1).

Mean age at data cut in the intervention arm of pre-symptomatic populations (GBA-A and GBA-C) is also still relatively low with estimates of 21.2 and 20.0 months, respectively. Especially developmental milestones can thus be expected to still be achieved in the intervention arm, while significantly higher mean age at data cut in the control arm may suggest a lower probability of additional milestone achievement.

Overall, results for symptomatic populations are still more robust than those for pre-symptomatic populations. However, the number of patients to be allocated to pre-symptomatic populations has grown more considerably and will continue to do so in the future. With data maturing until the final analysis, current uncertainty is expected to reduce, especially in presymptomatic populations.

Table A5 1: Mean age at treatment and observation times by analysis populations and treatment arms

| Population | Number of patients | | Mean age at treatment initiation (months) | | Mean observation time (months) | | Approximate mean age at data cut (months) | |
|---|---|---|---|---|---|---|---|---|
| | Ona | Nusi/Ris | Ona | Nusi/Ris | Ona | Nusi/Ris | Ona | Nusi/Ris |
| **SMArtCARE** | | | | | | | | |
| GBA-A | 62 | 45 | 0.7 | 0.7 | 20.5 | 37.4 | 21.2 | 38.1 |
| GBA-B | 55 | 123 | 5.7 | 5.4 | 32.3 | 54.1 | 38.0 | 59.4 |
| GBA-C | 68 | 25 | 0.8 | 0.7 | 19.2 | 33.2 | 20.0 | 33.9 |
| GBA-D | 28 | 100 | 20.5 | 37.0 | 29.4 | 62.3 | 49.9 | 99.3 |
| **RESTORE** | | | | | | | | |
| GBA-A | 34 | 21 | 1.1 | 1.1 | 33.0 | 33.1 | 34.1 | 34.2 |
| GBA-B | 68 | 81 | 4.1 | 4.0 | 36.5 | 46.7 | 40.6 | 50.6 |
| GBA-C | 32 | 11 | 3.0 | 2.6 | 29.4 | 37.5 | 32.4 | 40.1 |
| GBA-D | 24 | 24 | 16.2 | 20.6 | 89.5 | 43.2 | 105.7 | 63.8 |
| **SMArtCARE + RESTORE** | | | | | | | | |
| GBA-A | 96 | 66 | 0.8 | 1.0 | 25.4 | 32.5 | 26.2 | 33.5 |
| GBA-B | 123 | 204 | 5.4 | 4.7 | 34.0 | 50.5 | 39.4 | 55.3 |
| GBA-C | 100 | 36 | 1.1 | 1.2 | 22.1 | 34.3 | 23.1 | 35.6 |
| GBA-D | 52 | 124 | 18.5 | 34.1 | 33.1 | 58.8 | 51.6 | 92.9 |

Source: (43)

The development of patient numbers and a forecast is depicted in section 2 for the SMArtCARE registry as well as the RESTORE registry.

Based on the forecast results for patient proportions between treatment arms at the time of final data cut (31 December 2026) and interim results for selected endpoints, an updated sample size calculation was performed. Selection of endpoints was based on statistical significance of results. Especially in pre-symptomatic populations (GBA-A and GBA-C), non-significant endpoints with large effects were also included since statistical significance cannot be expected based on the current data with partly still low patient numbers and short observation times.

Treatment switching to onasemnogene abeparvovec occurs frequently in patients who started initially with nusinersen. Thus, for a relevant proportion of nusinersen

patients the treatment effects in comparison to onasemnogene abeparvovec cannot be assessed soberly by the intention to treat approach applied in the main analyses. Sensitivity analyses were included to address this issue: The sensitivity analyses 2 (Sensi 2) according to the G-BA approach censors all patients at the time of an occurring treatment switch. The results of the interim analysis have shown that the effects from the Sensi 2 analyses are similar to those yielded from corresponding main analyses, but more pronounced in terms of effect and significance. Therefore, this updated sample size calculation was supplemented with calculations considering the Sensi 2 conditions.

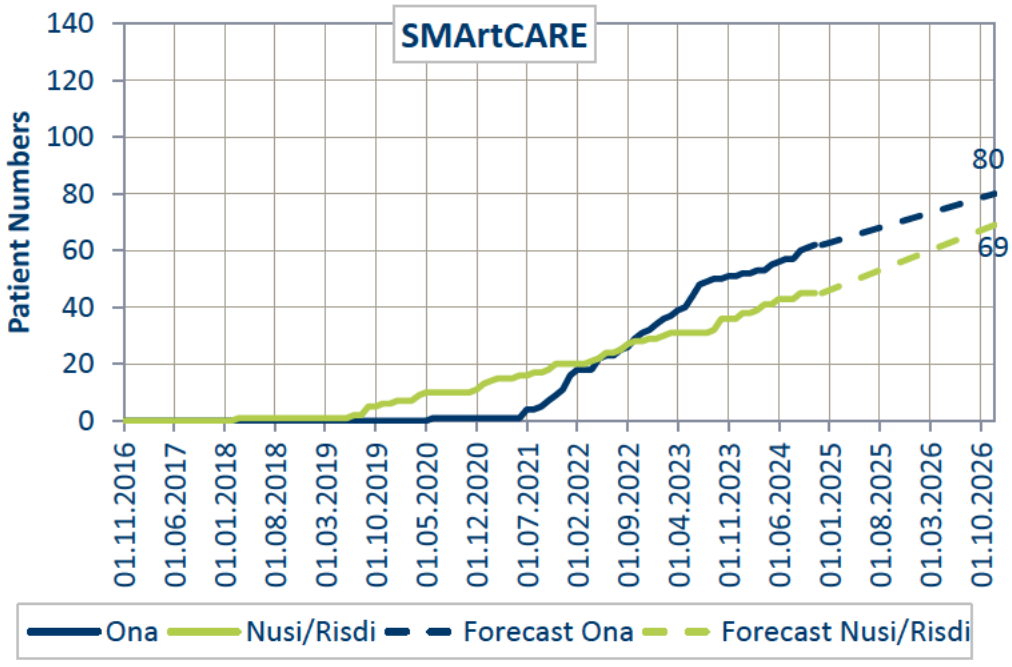
## 2. Development of patient numbers and forecast

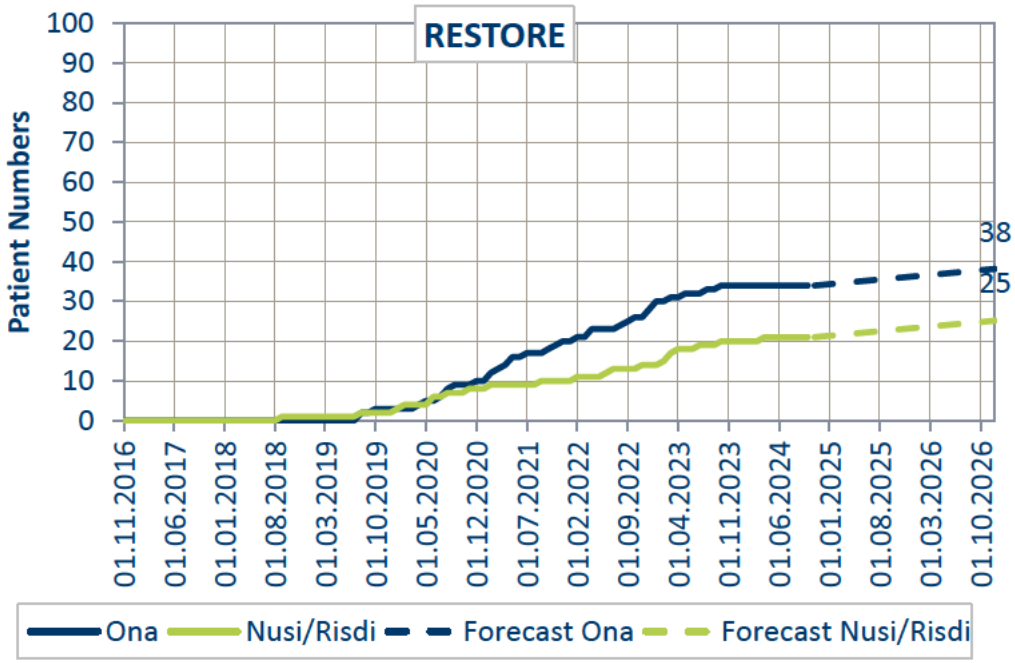
A key parameter for sample size calculations is the patient distribution between treatment arms. At the time of initial study planning, this ratio was entirely unknown and a 1:1 distribution was assumed. Based on data for the second interim analysis, a forecast was performed by assuming that the average number of new patients per treatment arm and population observed in the last twelve months available in the data cut (August 2023 – December 2024) will be included in the future. Effects of trimming and weighting via IPTW or fine stratification weights are ignored for the forecast as these are highly sensitive to the actual patient characteristics of included patients.

Expected patient numbers cover the SMArtCARE registry as described in section 8.3 of the protocol as well as the RESTORE registry which was included in the second interim analysis.

In population GBA-A, there are a total of 107 patients included at the time of data cut for second interim analysis from the SMArtCARE registry (SC) (62 patients in the onasemnogene abeparvovec arm and 45 patients in the nusinersen/risdiplam arm) and 55 from the RESTORE registry (RS) (34 patients in the onasemnogene abeparvovec arm and 21 patients in the nusinersen/risdiplam arm). Based on the number of recruited patients from the last twelve months that were carried forward, a total of 149 (RS: 63) patients would result for SC (RS), of which 80 (RS: 38) would be included in the intervention arm and 69 (RS: 25) in the comparator arm. This would correspond to a ratio of 54% (RS: 60%) intervention to 46% (RS: 40%) control patients. The development and forecast for population GBA-A is depicted in Figure A4 1.

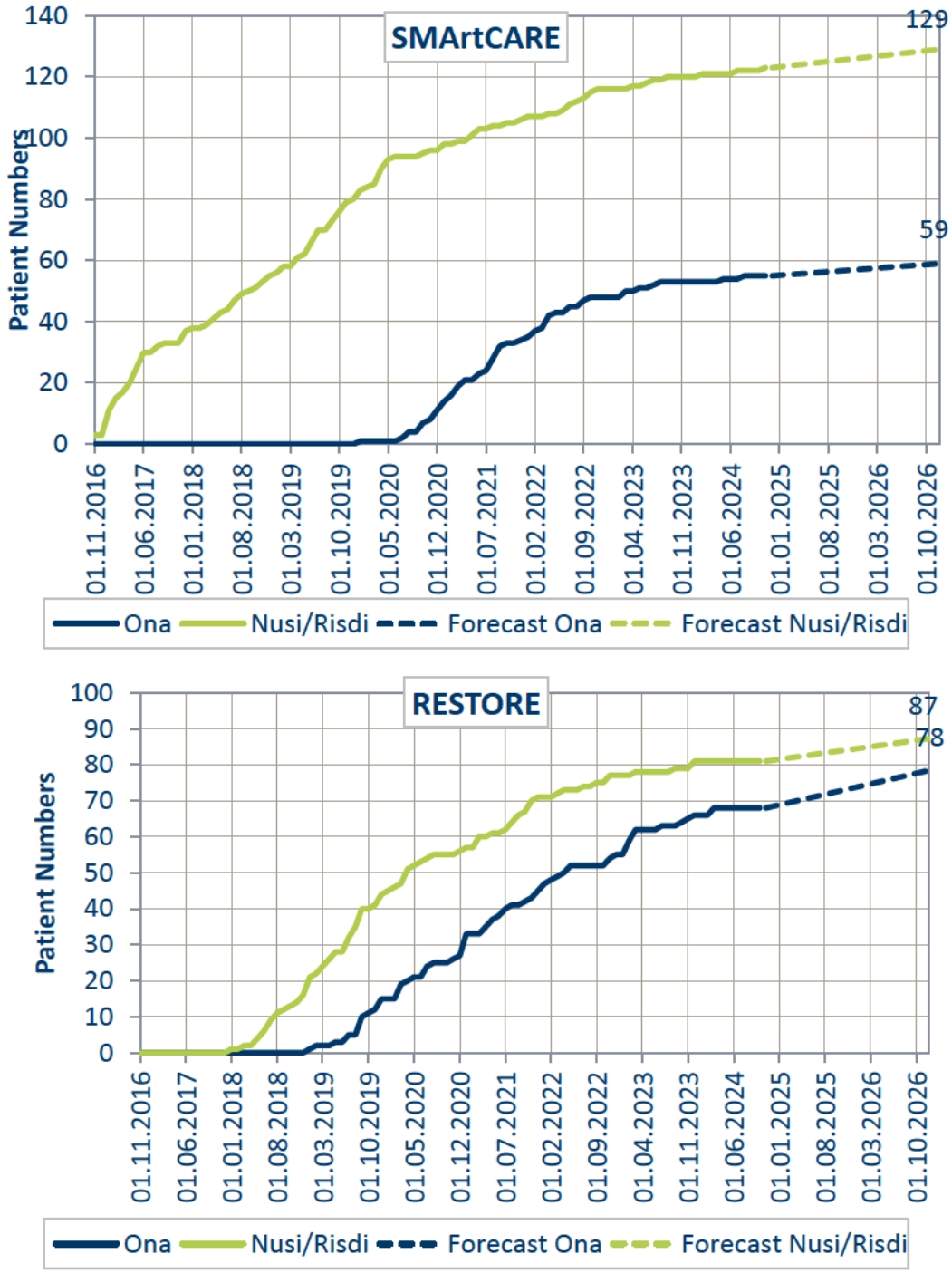
Figure A5 1: Patient Numbers and Forecast: Population GBA-A






For population GBA-B, there are 178 patients in total from SC (RS: 149) included at the time of data cut for second interim analysis (55 patients in the onasemnogene abeparvovec arm and 123 patients in the nusinersen/risdiplam arm; RS: 68 and 81, respectively). Based on the number of recruited patients from the last twelve months that were carried forward, a total of 188 (RS: 165) patients would result, of which 59 (RS: 78) would be included in the intervention arm and 129 (RS: 87) in the comparator arm. This would correspond to a ratio of 31% (RS: 47%) intervention to 69% (RS: 53%) control patients. The development and forecast for population GBA-B is depicted in Figure A4 2.

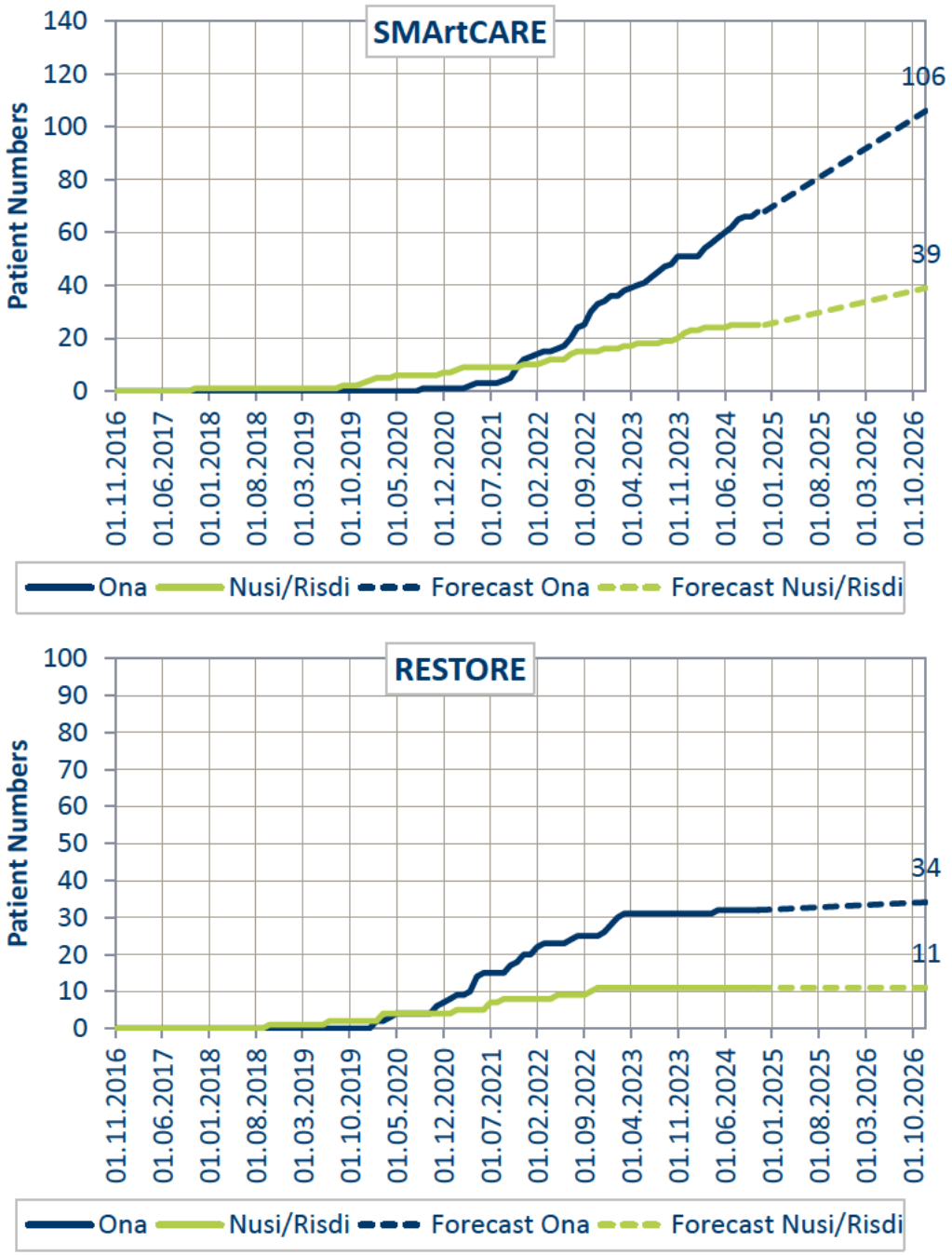
Figure A5 2: Patient Numbers and Forecast: Population GBA-B




For population GBA-C, there are a total of 93 patients included at the time of data cut for second interim analysis from SC (RS: 43), of which 68 (RS: 32) patients are assigned to the onasemnogene abeparvovec arm and 25 (RS: 11) patients to the nusinersen/risdiplam arm. Based on the number of recruited patients from the last twelve months that were carried forward, a total of 145 (RS: 45) patients would result, of which 106 (RS: 34) would be included in the intervention arm and 39 (RS:

11) in the comparator arm. This would correspond to a ratio of 73% (RS: 76%) intervention to 27% (RS: 24%) control patients. The development and forecast for population GBA-C is depicted in Figure A4 3.

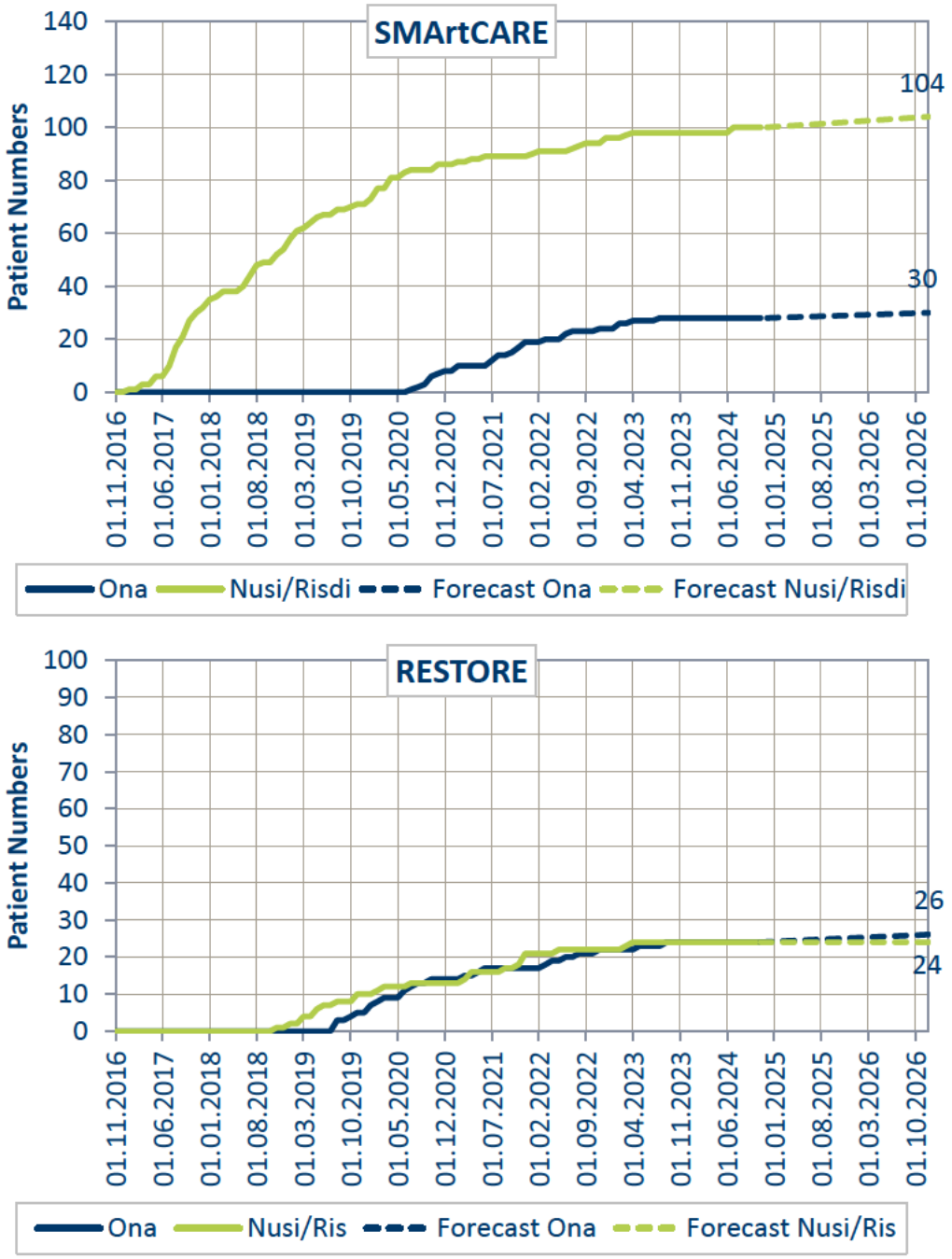
Figure A5 3: Patient Numbers and Forecast: Population GBA-C




For population GBA-D, there are a total of 128 SC patients (RS: 48) included at the time of data cut for second interim analysis (28 (RS: 24) patients in the onasemnogene abeparvovec arm and 100 (RS: 24) patients in the

nusinersen/risdiplam arm). Based on the number of recruited patients from the last twelve months that were carried forward, a total of 134 (RS: 50) patients would result, of which 30 (RS: 26) would be included in the intervention arm and 104 (RS: 24) in the comparator arm. This would correspond to a ratio of 22% (RS: 52%) intervention to 78% (RS: 48%) control patients. The development and forecast for population GBA-D is depicted in Figure A4 4.

Figure A5 4: Patient Numbers and Forecast: Population GBA-D



At the time of data cut for second interim analysis, the patient numbers are in line with the expectations formulated in section 8.3 of the protocol for populations GBA-A (expected vs. actual numbers are 107 vs. 107 patients), GBA-B (expected vs. actual numbers 176 vs. 178 patients; deviation +1,3%), and GBA-C (expected vs. actual numbers 105 vs. 93 patients; deviation −12%). Patient numbers for population GBA-D are higher than expected (expected vs. actual numbers 62 vs. 128 patients; deviation +108%). Regarding the total number of SMArtCARE patients, the deviation is +12% (expected vs. actual numbers 449 vs. 506 patients). Table A5 2 illustrates a comparison of expected patient numbers per section 8.3 of the protocol with patient numbers for first and second interim analysis. To estimate the patient numbers per assumptions of section 8.3, the total patients diagnosed from January 2022 to December 2026 were divided by 60 (total no. of months) and multiplied by 37 (no. of months between January 2022 and last month of data for second interim analysis, i.e. January 2024). Additionally, the patient numbers for the RESTORE registry as well as the total number of available patients at the time of the first and second data cut are presented.

Table A5 2: Comparison of expected and actual patient numbers at time of data cut for second interim analysis

| Step/Description | GBA-A | GBA-B | GBA-C | GBA-D |
|---|---|---|---|---|
| 75% of patients diagnosed between July 2018 and December 2021 (assumption: 75% of diagnosed cases enrolled in SMArtCARE) | 26 | 104 | 15 | 62 |
| Patients diagnosed from January 2022 to December 2026 | 131 | 116 | 146 | 0 |
| **Total number of potentially eligible patients enrolled in SMArtCARE per section 8.3 of the protocol** | **157** | **220** | **161** | **61** |
| Expected patient numbers at time of data cut for second interim analysis per assumptions in section 8.3 of the protocol | 107 | 176 | 105 | 61 |
| Actual patient numbers in SMArtCARE at time of data cut for second interim analysis | 107 | 178 | 93 | 128 |
| Actual patient numbers in RESTORE at time of data cut for second interim analysis | 55 | 149 | 43 | 48 |
| Actual patient numbers in SMArtCARE and RESTORE combined at time of data cut for second interim analysis | 162 | 327 | 136 | 176 |

Table A5 3: Summary of current patient numbers at data cut for second interim analysis and expected patient numbers at data cut for final analysis

| | GBA-A | GBA-B | GBA-C | GBA-D |
|---|---|---|---|---|
| Data cut second interim analysis | 107 | 178 | 93 | 128 |
| Forecast final data cut | 149 | 188 | 145 | 134 |
| Expected growth (%) until final data cut | 39% | 6% | 56% | 5% |
| Data cut second interim analysis | 55 | 149 | 43 | 48 |
| Forecast final data cut | 63 | 166 | 45 | 50 |
| Expected growth (%) until final data cut | 15% | 11% | 5% | 4% |
| Data cut second interim analysis | 162 | 327 | 136 | 176 |
| Forecast final data cut | 212 | 354 | 190 | 184 |
| Expected growth (%) until final data cut | 31% | 8% | 40% | 5% |

The summary of current and expected patient numbers for the SMArtCARE as well as the RESTORE registry shows that for the pre-symptomatic patient populations (GBA-A, GBA-C) considerable growth is expected until December 2026, the time of the final data cut. For the SMArtCARE registry the forecast shows a rise of up to 56% in patient numbers. This means that in the pre-symptomatic populations there are currently only two thirds of the patient numbers expected for the time at the final data cut. Due to the NBS the patient numbers are rising steadily, the probability that the expected patient numbers will finally be reached is high.

# 3. Update of Sample Size Calculations

Sample size calculations were updated as described in section 8.2.3 of the protocol using the following assumptions:

- HR0=0.5 and 2, respectively
- alpha = 0.05, two-sided
- power = 0.8
- negligible/no censoring

Calculations were carried out with the software PASS 2024 using the option "Superiority by a Margin Tests for Two Survival Curves using Cox's Proportional Hazards Model". HR0 serves as the superiority hazard ratio. Hypotheses for HR0 = 0.5 are H0: HR ≥ HR0 vs. Ha: HR > HR0 and for HR0 = 2 the hypotheses are H0: HR ≤ HR0 vs. Ha: HR > HR0, respectively. Event rates and effect sizes from the first interim analysis were used for all calculations.

As mandated by G-BA, these assumptions represent a "shifted null-hypothesis". While not mandated by German Social law or G-BA code of procedure, it is acknowledged that this threshold and its application to the boundaries of the two-sided 95 % CI has been requested by IQWiG both in its initial Rapid Report (45), its general methods (33) as well as consistently applied in all AbD concepts to date (46–62).

While it is acknowledged that this approach guarantees a very high level of certainty, it is anticipated that it would also lead to patient numbers that often cannot realistically be included in the context of an AbD in rare diseases. An alternative could be to follow the principle of the "dramatic effect", i.e., $p < 0.01$ but with reduced effect thresholds (hazard ratio < 0.5).

To assess the effects of this alternative threshold, a second sample size calculation was performed using the following assumptions:

- power = 0.8
- $\alpha = 0.01$, two-sided
- negligible/no censoring

Calculations were carried out with the software PASS 2024 using the option "Tests for Two Survival Curves using Cox's Proportional Hazards Model". Hypotheses are H0: HR = 1 vs. Ha: HR ≠ 1

Event rates and effect sizes from the second interim analysis were used for all calculations. Patient distribution was according to the forecast results depicted in section 2 of this addendum. As far as possible, endpoints for which a statistically significant difference was shown were chosen for the calculation. For the presymptomatic populations in particular, non-significant endpoints had to be regarded as well, since it cannot be expected that – due to partly still low patient

numbers and short observation times – the results from the current interim analysis show statistical significance. Therefore, insignificant endpoints with considerable high or low Hazard Ratios in combination with p-values close to significance were included, too.

Results for the calculations using a shifted null hypothesis are illustrated in Table A5 4. Results for the calculations using a standard null hypothesis but α = 0.01 are shown in Table A5 5.

Table A5 4: Results of updated sample size calculations (based on the results for the main analysis and the Sensi 2 analysis at the data cut for the second interim analysis) using a shifted null hypothesis with alpha = 0.05, two-sided

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| **SMArtCARE** | | | | | | | |
| GBA-A | Swallowing | 25.5% | 0.29 | 46% | 564 | 305 | 259 |
| GBA-A Sensi2 | | 15.0% | 0.15 | 46% | 237 | 128 | 109 |
| GBA-B | Swallowing | 41.1% | 0.66 | 69% | n.e. | n.e. | n.e. |
| GBA-B Sensi2 | | 30.7% | 0.69 | 69% | n.e. | n.e. | n.e. |
| GBA-B | Any Tube Feeding | 42.6% | 0.49 | 69% | 196 730 | 60 987 | 135 743 |
| GBA-B Sensi2 | | 38.8% | 0.42 | 69% | 2 849 | 884 | 1 965 |
| GBA-B | Supplemental Tube Feeding | 29.4% | 0.34 | 69% | 815 | 253 | 562 |
| GBA-B Sensi2 | | 29.4% | 0.28 | 69% | 361 | 112 | 249 |
| GBA-B | Orthopedic surgery | 26.2% | 2.76 | 69% | 1 185 | 368 | 817 |
| GBA-B Sensi2 | | 11.9% | 3.03 | 69% | 1 452 | 451 | 1001 |
| GBA-C | Standing | 76.0% | 1.53 | 27% | n.e. | n.e. | n.e. |
| GBA-C Sensi2 | | 36.0 | 1.64 | 27% | n.e. | n.e. | n.e. |
| GBA-D | Standing | 18.9% | 3.88 | 78% | 351 | 78 | 273 |
| GBA-D Sensi2 | | 15.06% | 4.01 | 78% | 360 | 80 | 280 |
| GBA-D | Walking | 12.8% | 3.32 | 78% | 860 | 190 | 670 |

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-D Sensi2 | | 10.6% | 3.5 | 78% | 787 | 174 | 6130 |
| **RESTORE** | | | | | | | |
| GBA-A | Any type tube feeding | 14.3% | 0.42 | 40% | 9 153 | 5 492 | 3 661 |
| GBA-A Sensi2 | | 9.5 | 0.07 | 40% | 114 | 64 | 50 |
| GBA-B | Walking | 32.7% | 2.86 | 53% | 780 | 367 | 413 |
| GBA-B Sensi2 | | 13.3 | 1.57 | 53% | n.e. | n.e. | n.e. |
| GBA-B | Permanent ventilator support | 1.3% | 8.05 | 53% | 237 | 112 | 125 |
| GBA-D | Any type tube feeding | 18.2% | 0.41 | 48% | 4 819 | 2 506 | 2 313 |
| GBA-D Sensi2 | | 13.6% | 0.44 | 48% | 15 001 | 4 501 | 10 500 |
| **SMArtCARE + RESTORE** | | | | | | | |
| GBA-A | Swallowing | 12.7% | 0.33 | 44% | 1 832 | 1026 | 806 |
| GBA-A Sensi2 | | 7.1 | 0.15 | 44% | 317 | 178 | 139 |
| GBA-B | Swallowing | 23.8% | 0.49 | 61% | 342 089 | 133 415 | 208 674 |
| GBA-B Sensi2 | | 17.7% | 0.46 | 61% | 25 101 | 9 790 | 15 311 |
| GBA-B | Tube feeding | 47.3% | 0.59 | 61% | n.e. | n.e. | n.e. |
| GBA-B Sensi2 | | 37.9% | 0.53 | 61% | n.e. | n.e. | n.e. |
| GBA-B | Supplemental tube feeding | 20.4% | 0.27 | 61% | 466 | 182 | 284 |
| GBA-B Sensi2 | | 19.8% | 0.21 | 61% | 241 | 94 | 147 |
| GBA-B | Invasive ventilation | 3.8% | 0.26 | 61% | 2 245 | 876 | 1 369 |
| GBA-B Sensi2 | | 2.3% | 0.3 | 61% | 5 555 | 2 167 | 3 388 |
| GBA-C | Standing | 84.6% | 1.41 | 26% | n.e. | n.e. | n.e. |

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-C Sensi2 | | 43.8% | 1.43 | 26% | n.e. | n.e. | n.e. |
| GBA-D | Standing | 19.2% | 4.61 | 70% | 160 | 48 | 160 |
| GBA-D Sensi2 | | 16.7% | 4.61 | 70% | 170 | 51 | 119 |
| GBA-D | Walking | 13.6% | 4.24 | 70% | 274 | 83 | 191 |
| GBA-D Sensi2 | | 11.0% | 4.65 | 70% | 241 | 73 | 168 |

n.e. = not estimable
Event Rate Comparator: contains the assumed probability of an event in the control group. Hazard Ratio: is the assumed actual hazard ratio at which power is calculated.
Patient share comparator: serves as the percentage of the total sample size that is in the control group.

Table A5 5: Results of updated sample size calculations (based on the results for the main analysis and the Sensi 2 analysis at the data cut for the second interim analysis) using a standard null hypothesis with $\alpha = 0.01$

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| **SMArtCARE** | | | | | | | |
| GBA-A | Swallowing | 25.5% | 0.29 | 46% | 207 | 112 | 95 |
| GBA-A Sensi2 | | 15.0% | 0.18 | 46% | 159 | 86 | 73 |
| GBA-B | Swallowing | 41.1% | 0.66 | 69% | 884 | 275 | 609 |
| GBA-B Sensi2 | | 30.7% | 0.69 | 69% | 1 388 | 431 | 957 |
| GBA-B | Any Tube Feeding | 42.6% | 0.49 | 69% | 297 | 93 | 204 |
| GBA-B Sensi2 | | 38.8% | 0.42 | 69% | 217 | 68 | 149 |
| GBA-B | Supplemental Tube Feeding | 29.4% | 0.34 | 69% | 197 | 62 | 135 |
| GBA-B Sensi2 | | 29.4% | 0.28 | 69% | 141 | 44 | 97 |

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-B | Orthopedic surgery | 26.2% | 2.76 | 69% | 226 | 71 | 155 |
| GBA-B Sensi2 | | 11.9% | 3.03 | 69% | 384 | 120 | 264 |
| GBA-C | Standing | 76.0% | 1.53 | 27% | 471 | 344 | 127 |
| GBA-C Sensi2 | | 36.0% | 1.64 | 27% | 426 | 311 | 115 |
| GBA-D | Standing | 18.9% | 3.88 | 78% | 160 | 36 | 124 |
| GBA-D Sensi2 | | 15.6% | 4.01 | 78% | 169 | 38 | 131 |
| GBA-D | Walking | 12.8% | 3.32 | 78% | 287 | 64 | 223 |
| GBA-D Sensi2 | | 10.6% | 3.5 | 78% | 296 | 66 | 230 |
| **RESTORE** | | | | | | | |
| GBA-A | Any type tube feeding | 14.3% | 0.42 | 40% | 700 | 420 | 280 |
| GBA-A Sensi2 | | 9.5% | 0.07 | 40% | 116 | 65 | 51 |
| GBA-B | Walking | 32.7% | 2.86 | 53% | 171 | 81 | 90 |
| GBA-B Sensi2 | | 11.3% | 1.57 | 53% | 1 886 | 736 | 1 150 |
| GBA-B | Permanent ventilator support | 1.3% | 8.05 | 53% | 201 | 95 | 106 |
| GBA-B Sensi2 | Any type ventilation support | 8.0% | 2.4 | 53% | 509 | 199 | 310 |
| GBA-D | Any type tube feeding | 18.2% | 0.41 | 48% | 452 | 236 | 216 |
| GBA-D Sensi2 | | 13.6% | 0.44 | 48% | 687 | 207 | 480 |
| **SMArtCARE + RESTORE** | | | | | | | |
| GBA-A | Swallowing | 12.7% | 0.33 | 44% | 487 | 273 | 214 |
| GBA-A Sensi2 | | 7.1% | 0.15 | 44% | 241 | 135 | 106 |

| Population | Endpoint | Event rate comparator | Hazard Ratio | Patient share comparator | N total | N intervention | N comparator |
|---|---|---|---|---|---|---|---|
| GBA-B | Swallowing | 23.8% | 0.49 | 61% | 519 | 203 | 316 |
| GBA-B Sensi2 | | 17.7% | 0.46 | 61% | 547 | 214 | 333 |
| GBA-B | Tube feeding | 47.3% | 0.59 | 61% | 443 | 173 | 270 |
| GBA-B Sensi2 | | 37.9% | 0.53 | 61% | 365 | 143 | 222 |
| GBA-B | Supplemental tube feeding | 20.4% | 0.27 | 61% | 195 | 77 | 118 |
| GBA-B Sensi2 | | 19.8% | 0.21 | 61% | 141 | 55 | 86 |
| GBA-B | Invasive ventilation | 3.8% | 0.26 | 61% | 1 000 | 390 | 610 |
| GBA-B Sensi2 | | 2.3% | 0.3 | 61% | 1 889 | 737 | 1 152 |
| GBA-C | Standing | 84.6% | 1.41 | 26% | 716 | 530 | 186 |
| GBA-C Sensi2 | | 43.8% | 1.43 | 26% | 777 | 575 | 202 |
| GBA-D | Standing | 19.2% | 4.61 | 70% | 90 | 27 | 63 |
| GBA-D Sensi2 | | 16.7% | 4.61 | 70% | 97 | 29 | 68 |
| GBA-D | Walking | 13.6% | 4.24 | 70% | 141 | 43 | 98 |
| GBA-D Sensi2 | | 11.0% | 4.65 | 70% | 137 | 41 | 96 |

n.e. = not estimable
Event Rate Comparator: contains the assumed probability of an event in the control group.
Hazard Ratio: is the assumed actual hazard ratio at which power is calculated.
Patient share comparator: serves as the percentage of the total sample size that is in the control group.

Application of a shifted null hypothesis significantly increases required patient numbers compared to a scenario using a standard null-hypothesis with $\alpha = 0.01$. As described in section 1 of this addendum, interim results and patient shares are subject to uncertainties and should be seen as such when assessing feasibility. Even small changes in effect sizes and event rates can have a significant impact on required patient numbers, especially when using a shifted null hypothesis.

Especially in pre-symptomatic analysis populations (GBA-A, GBA-C), effects from interim analysis are still uncertain and based on quite small patient numbers in the

comparator arm while these populations are also characterized by significant expected increases in patient numbers until the end of data collection. Results may still change significantly, leading to fewer patients being required. Actual patient numbers available for final analysis are also to be regarded as not completely certain. In addition, the possibility of performing meta-analysis of SMArtCARE and RESTORE is dependent on the homogeneity of results and can only be assessed individually per data cut, population, and endpoint. From the current knowledge of patient numbers, it can be assumed that meta-analysis including patients from the RESTORE registry plays a significant role and has a positive impact on study feasibility.

Table A5 6: Comparison of sample size estimation and expected patient numbers per study population based on the results for the main analysis and the Sensi 2 analysis at the data cut for the second interim analysis

| Population | Endpoint | N total needed (per sample size estimation) | N total expected | Feasibility |
|---|---|---|---|---|
| **SMArtCARE** | | | | |
| GBA-A | Swallowing | 564 | 150 | Likely no |
| GBA-A Sensi2 | | 237 | | Potentially (subject to moderate changes in effect size or event rate) |
| GBA-B | Supplemental tube Feeding | 815 | 188 | Likely no |
| GBA-B Sensi2 | | 361 | | Potentially (subject to moderate changes in effect size or event rate) |
| GBA-C | Standing | n.e. | 150 | Likely no |
| GBA-C Sensi2 | | n.e. | | Likely no |
| GBA-D | Standing | 351 | 135 | Likely no |
| GBA-D Sensi2 | | 360 | | Likely not |
| **SMArtCARE + RESTORE** | | | | |
| GBA-A | Swallowing | 1 832 | 215 | Likely no |
| GBA-A Sensi2 | | 317 | | Potentially (subject to moderate changes in effect size or event rate) |

| Population | Endpoint | N total needed (per sample size estimation) | N total expected | Feasibility |
|---|---|---|---|---|
| GBA-B | Supplemental tube feeding | 466 | 356 | Potentially (subject to moderate changes in effect size or event rate) |
| GBA-B Sensi2 | | 241 | | Likely yes |
| GBA-C | Standing | n.e. | 195 | Likely no |
| GBA-C Sensi2 | | n.e. | | Likely no |
| GBA-D | Standing | 160 | 185 | Potentially (subject to moderate changes in effect size or event rate) |
| GBA-D Sensi2 | | 170 | | Likely yes |

n.e. = not estimable

As expected, the sample size calculations based on the results from the Sensi 2 (censoring at time of treatment switch) generally require smaller patient numbers. For two populations (GBA-B and GBA-D) the sample size calculations indicate clearly that the necessary numbers of patients for showing effects are achievable when addressing the bias introduced by treatment switching through censoring. While sample size estimations for the populations GBA-A and GBA-C suggest more challenging feasibility, this may change as the data for these population matures and observation times get closer to what is observed in populations GBA-B and GBA-D. The profound differences in the estimated patient numbers derived from the results of the main analyses vs. the Sensi 2 analyses (in some cases less than the half of the numbers for the main analysis) also indicate that small changes in effect estimates and event rates may lead to significant changes in the required patient numbers and thus conclusions on feasibility.

Novartis thus recommends to keep enrolling patients in all analysis populations until the planned end of data collection on December 31, 2026. The entirety of results – both from main analysis as well as sensitivity analysis – will then be subject to the benefit assessment. Additionally, it is conceivable that the existing AbD framework may be expanded in the future to include patients treated with intrathecal onasemnogene abeparvovec, for which a G-BA consultation (2025-B-054) took place on May 7, 2025.

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