NIS PROTOCOL (SECONDARY DATA USE)

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	5.0
STUDIED MEDICINAL PRODUCT:	EVRYSDI® (RISDIPLAM)
PRODUCT REFERENCE NUMBER{S}	European Union (EU) marketing authorization number: EU/1/21/1531/001
AUTHOR:	[redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

MARKETING AUTHORIZATION HOLDER{S} (MAH) or STUDY INITIATOR:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
RESEARCH QUESTION AND OBJECTIVES:	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nusinersen and onasemnogene abeparvovec. Safety data is analyzed to allow a comparison of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec.
COUNTRIES OF STUDY POPULATION:	Germany, Austria

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PROTOCOL ACCEPTANCE FORM

-not applicable-

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PROTOCOL NUMBER:	ML44661
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STUDIED MEDICINAL PRODUCT{S}:	EVRYSDI® (RISDIPLAM)
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I agree to conduct the study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPP	Good Pharmacoepidemiological Practice
HFMSE	Hammersmith Functional Motor Scale Expanded
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities,
NBS	Newborn Screening
RULM	Revised Upper Limb Module
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMA	Spinal Muscular Atrophy
SMN 1/2	Survival Motor Neuron 1/2
SmPC	Summary of Product Characteristics
WHO	World Health Organization

2. RESEARCH TEAM

External Scientific Leader

[redacted]

Scientific Responsible

[redacted]

NIS Data Science Responsible

[redacted]

Protocol Development Responsible

[redacted]

Complementary information is given in

3. SYNOPSIS

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	5.0
DATE OF SYNOPSIS:	10.04.2026
STUDIED MEDICINAL PRODUCT	EVRYSDI® (RISDIPLAM)
MAIN AUTHOR:	[redacted]
INDICATION:	Spinal Muscular Atrophy (SMA)
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
Rationale and background	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The described study design is based on the previous exchange with the Gemeinsamer Bundesausschuss (G-BA, Federal Joint Committee) and scientific experts (1–6). Based on the previous assumptions on the specifics of the disease, the regulatory requirements and the novelty of this project, futility will be checked in the interim analysis.
Research question and objectives	The primary objectives for this study are as follows (presented by population): **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the survival motor neuron 2 (*SMN2*) gene:** • To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of adverse events (AE) leading to hospitalization over time

Symptomatic patients with a clinically diagnosed SMA type 1:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of the Revised Upper Limb Module (RULM) total score at 36 months after index date

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 36 months after index date

The secondary objectives for this study are as follows:

- To assess the oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
    - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 1
    - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

  including the following variables:
- Mortality
    - Death
- Morbidity
    - Motorfunction (assessed with age-appropriate instruments)
    - Achievement and loss of motor milestones (World Health Organization (WHO) motor development milestones)
    - Respiratory function (need for permanent ventilation)
    - Bulbar function (ability to swallow, need for non-oral nutritional support)
    - Other complications of disease (e.g. orthopedic complications)

The safety objectives for this study are as follows:

- To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
    - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 1
    - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

including the following safety variables:

- Number of adverse events (AE) leading to hospitalization over time
- Proportion of patients with a serious adverse event (SAE)
- Proportion of patients with an adverse event (AE) leading to hospitalization

Study design

Registry-based study, comparative, non-interventional, multicentric, multinational, open-label. As the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls.

Start Date of Study:

October 30th, 2024

Start of treatment with risdiplam is March 26, 2021 at the earliest. Start of treatment with nusinersen is May 30, 2017 at the earliest. Start of treatment with onasemnogene abeparvovec is May 18, 2020 at the earliest.

End of Study

All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end of study date is October 01, 2027. Data that is documented in the study database after that time point will not be taken into account.

Length of Study

Interim analyses are planned 12 (October 2025) and 24 months (October 2026) after start of the study and will be handed in to G-BA latest 18 and 30 months after the start of the study. Final analysis will take place in October 2027.

Data sources

This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria and Switzerland. Data from Germany and Austria will be used for this analysis.

Patients' data will be recorded on case report forms (CRFs). The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient files should be entered on the CRF as soon as they become available.

An electronic data capture (EDC) system will be used in this registry. Each patient will be identified in the registry by a unique patient identification code (patient number) that is assigned when the patient is registered and is retained as the primary identifier for the patient throughout entire participation in the registry and also in case the patient returns to registry participation after a temporary discontinuation.

Population

Patients must meet the following criteria for study entry:

For all populations:

- Signed informed consent form (if applicable by legal representative) to participate in the study
- Genetically confirmed 5q-autosomal recessive SMA
- Treatment according to the Summary of Product Characteristics (SmPC) with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting not earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec

Specific to the indicated populations:

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

- Pre-symptomatic diagnosis
- *SMN2* copy number is ≤ 3

Symptomatic patients with a clinically diagnosed SMA type 1:

- Not pre-symptomatic at time of diagnosis
- Onset of symptoms $\leqslant$ 6 months OR never achieved ability to sit unaided

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis
- *SMN2* copy number is ≤ 3
- Onset of symptoms > 6 months and $\leqslant$ 18 months OR never achieved ability to walk unaided

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis

- *SMN2* copy number is ≤ 3
- Onset of symptoms > 18 months
- Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from study entry:

- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen OR onasemnogene abeparvovec). Exception: Patients with initial treatment (nusinersen OR risdiplam) for less than three months followed by an alternative treatment will not be excluded but assigned to the subsequent treatment (7).
- Current treatment with therapies which effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

Variables

Primary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Number of AE leading to hospitalization over time	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	Change from baseline of RULM total score at 36 months after index date	Change from baseline of RULM total score at 36 months after index date

Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			
Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development	Time from first treatment to reaching the WHO motor development milestone of walking without support	-

standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support		
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: -Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in HFMSE total score at 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12 and 24 months after index date*** RULM total score at 36 months after index date***	Change from baseline HFMSE total score 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12 and 24 months after index date*** RULM total score at 36 months after index date***
Walking performance endpoints			
			For ambulatory patients:

			Relative change from baseline in walking distance at 12, 24 and 36 months after index date[#] Evaluation of the total walking distance at month 36 after index date[#]
Bulbary function			
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients:

Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, *** As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), #As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk

Safety Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization

Study size

In this study patients will be enrolled across the German and Austrian SMArtCARE centers (according to the SMArtCARE homepage, there are currently 49 centers in Germany and 13 centers in Austria).

The described study design is based on the previous exchange with the G-BA and scientific experts. Due to insufficient data on effect sizes and the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec, it is not possible to calculate the sample size yet. As stated in the G-BA decision the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (section 8.7.5) and considering all relevant endpoints. In addition, futility will be checked in the interim analysis, in consultation with the G-BA.

Data Analysis

All analyses are based on the full analysis set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. To adjust for differences in the confounder variables between the treatment groups,

propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation are considered according to the rules defined in the statistical analysis plan (SAP).
All primary estimands as defined in Section 8.3 will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch). Additionally, supplementary estimands with the hypothetical strategy will be investigated as well, as described in the SAP. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

Milestones

First Data Extraction:
The first data extraction is the date from which the variables used for the analysis as per protocol start to be extracted. For details, see section 5. MILESTONES

Last Data Extraction:
The last data extraction is the date from which the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) is completely available. The planned last data extraction date is October 2027.

4. AMENDMENTS AND UPDATES

1. and 2. Amendment due to G-BA requirements from April 4th, 2024 (8)

3. Amendment due to G-BA requirements from September 19th, 2024 (9)

4. Amendment due to changes specified in the Data Review Meeting from December 19th, 2025

5. MILESTONES

Milestone	Planned Date
First Data Extraction	Within 6 months after study start
Last Data Extraction	October 2027
Status report	6, 18 and 30 months after study start
Interim report	18 and 30 months after study start
Final report of study results (CSR)	Not applicable
Publication submission	April 2028

6. RATIONALE AND BACKGROUND

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and *SMN2* copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of

fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

6.1 STUDY RATIONALE

On the basis of the ongoing or completed studies on risdiplam considered for approval, the identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam with the following PICO scheme requirements.

Population:

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

Intervention:

- Risdiplam

Treatment according to the Summary of Product Characteristics (SmPC).

Comparator:

- Therapy according to physician’s choice taking into account nusinersen und onasemnogene abeparvovec.

Treatment according to the respective SmPC.

Outcome

- Mortality: Number of deaths
- Morbidity:

  Motorfunction (assessed with age-appropriate instruments)

  Achieving and loss of motor milestones (World Health Organization (WHO) motor development milestones)

Respiratory function (need for permanent ventilation)

Bulbar function (ability to swallow, need for non-oral nutritional support, ability to speak)

Other complications of the disease (e.g. orthopedic complications)

- Number of AE leading to hospitalization over time
- Adverse events:

  Proportion of patients with a SAE

  Proportion of patients with an AE leading to hospitalization

  Proportion of patients with a selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. The research questions will be addressed using registry data from the SMArtCARE registry.

Primary Objectives

The primary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of AE leading to hospitalization over time

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of Revised Upper Limb Module (RULM) total score at 36 months after index date

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 36 months after index date

Secondary objectives

The secondary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

To evaluate the time from first treatment to reaching the WHO motor development milestone of sitting without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of standing without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of walking without support

To evaluate the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to sit without support
- Loss of the ability to stand without support
- Loss of the ability to walk without support

To assess the change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after index date

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after index date

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To evaluate the time from first treatment to reaching the WHO motor development milestone of sitting without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of standing without support

To evaluate the time from first treatment to reaching the WHO motor development milestone of walking without support

To evaluate the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to sit without support
- Loss of the ability to stand without support
- Loss of the ability to walk without support

To assess the change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after index date

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after index date

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

To assess the impact of treatment on time to death or permanent ventilation

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To assess the time from first treatment to reaching the WHO motor development milestone of walking without support

To assess the time from gaining WHO motor development milestone to permanent loss of milestone ability:

- Loss of the ability to sit without support
- Loss of the ability to stand without support
- Loss of the ability to walk without support

To assess the change from baseline in HFMSE total score at 12, 24, 36 months after index date

To assess the HFMSE total score at 36 months after index date

To assess the change from baseline in RULM total score at 12 and 24 months after index date

To assess the RULM total score at 36 months after index date

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after index date

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after index date

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

  To assess the time from gaining WHO motor development milestone to permanent loss of milestone ability:

  - Loss of the ability to sit without support
  - Loss of the ability to stand without support
  - Loss of the ability to walk without support

  To assess the change from baseline HFMSE total score 12, 24, 36 months after index date

  To assess the HFMSE total score at 36 months after index date

  To assess the change from baseline in RULM total score at 12 and 24 months after index date

  To assess the RULM total score at 36 months after index date

  For ambulatory patients: to assess the relative change from baseline in walking distance at 12, 24 and 36 months after index date (As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk)

  For ambulatory patients: to evaluate the total walking distance at month 36 (As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk)

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after index date

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after index date

To assess orthopedic complications by measuring the time to first documentation of scoliosis or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of scoliosis

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To assess the number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

Safety Objectives

The safety objectives of this study are as follows:

- **To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec:**
  including the following safety variables:

  Number of AE leading to hospitalization over time

  Proportion of patients with SAE

  Proportion of patients with AE leading to hospitalization

8. RESEARCH METHODS

8.1 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2017. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol.

Start Date of Study:
October 30th, 2024

Interim Analysis:
Interim analyses are planned 12 (October 2025) and 24 months (October 2026) after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analyses, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in October 2027.

End of Study:
All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end date is October 30, 2027. Data that is documented in the study database after that time point will not be taken into account.

8.1.1 Rationale for Study Design

According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nusinersen and onasemnogene abeparvovec. Since the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls. The described study design is based on the previous exchange with the G-BA and scientific experts (1–6). Due to insufficient data on effect sizes and the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec, it is not possible to calculate the sample size yet. As stated in the G-BA Beschluss the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (Section 8.7.5) and considering all relevant endpoints. In addition, futility will be checked in the interim analyses (4).

8.1.2 Number of Patients Observed in the Study

In this study patients will be enrolled across the German and Austrian SMArtCARE centers.

The planned number of cases cannot be determined yet due to insufficient data on effect sizes and the distribution of patients (see section 8.5). Based on the interim analysis, a sample size estimate will be made for each population using the observed effect assumptions.

8.1.3 Sites

The registry collects data of patients from Germany and Austria (according to the SMArtCARE homepage, https://www.smartcare.de/).

8.2 SETTING

8.2.1 Selection Criteria

The following criteria regarding data quality as required by G-BA must be fulfilled (especially for historic data):

- Data collection according to SMArtCARE registry protocol
- Exact definition or operationalization of exposures (type and duration of exposures), drug therapy and other accompanying therapies), clinical events, endpoints and confounders
- Use of standard classifications and terminologies
- Use of validated standard survey instruments (questionnaires, scales, tests)
- Study sites trained on data collection and recording
- Implementation of an agreed disease-specific core data set
- Use of exact dates about the patient, the illness, important examinations and treatments/interventions
- Clearly defined inclusion and exclusion criteria for registry patients
- Strategies to avoid unwanted selection during patient inclusion to achieve representativeness
- Requirements to ensure the data completeness for all time points and of the data per time point
- Source data verification for 100% of patients per study site for the primary endpoint and for at least 10% of randomly selected patients of each study site for all other endpoints since the beginning of the data collection
- Ensuring scientific independence and transparency of the register

Patients must meet the following criteria for study entry:

For all populations:

- Signed informed consent form (by legal representative) to participate in the study
- Genetically confirmed 5q-autosomal recessive SMA
- Treatment according to the SmPC with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting no earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec.

Specific to the indicated populations:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  Pre-symptomatic at time of diagnosis

SMN2 copy number is ≤ 3

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

  Not pre-symptomatic at time of diagnosis

  Onset of symptoms ≤ 6 months OR never achieved ability to sit unaided

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is ≤ 3

  Onset of symptoms > 6 months and ≤ 18 months OR never achieved ability to walk unaided

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is ≤ 3

  Onset of symptoms > 18 months

  Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from the evaluation of the real world data collection for the reassessment of the additional benefit of Evrysdi®:

- Enrollment at a Swiss SMArtCARE center
- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen, or onasemnogene abeparvovec). Exception: Patients with initial treatment (nusinersen OR risdiplam) for less than three months followed by an alternative treatment will not be excluded but assigned to the subsequent treatment (7).
- Current treatment with therapies whose effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

Table 1: Operationalization of selection criteria in SMArtCARE eCRF

Inclusion criteria	Fields of SMArtCARE eCRF
For all patients • Signed informed consent form (by legal representative) • Genetically confirmed 5q-autosomal recessive SMA • Treatment according to the SmPC with	• Enrolment: Consent date • Enrolment: Consent version • Genetically confirmed 5q-autosomal recessive SMA: *Variable is not exportable. However, patients can only be registered in SMArtCARE with a genetic confirmation of the 5qSMA disease* • Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment)

Inclusion criteria	Fields of SMArtCARE eCRF
risdiplam OR nusinersen OR onasemnogene abeparvovec	
Pre-symptomatic patients Pre-symptomatic at time of diagnosis SMN2 copy number is ≤ 3	• Baseline: Was diagnosis made pre-symptomatically? • Baseline: SMN2 copy number
Patients with SMA Type 1 Not pre-symptomatic at time of diagnosis Onset of symptoms ≤ 6 months OR never achieved ability to sit unaided	• Baseline: Was diagnosis made pre-symptomatically? • Baseline: SMN2 copy number • Baseline: Age at symptoms onset • Baseline: Sitting without support
Patients with SMA Type 2 Not pre-symptomatic at time of diagnosis SMN2 copy number is ≤ 3 Onset of symptoms > 6 months and < 18 months OR never achieved ability to walk unaided	• Baseline: Was diagnosis made pre-symptomatically? • Baseline: SMN2 copy number • Baseline: Age at symptoms onset • Baseline: Walking without support
Patients with SMA Type 3 Not pre-symptomatic at time of diagnosis SMN2 copy number is ≤ 3 Onset of symptoms > 18 months Patient is able to walk unaided OR was able to walk unaided but has lost that ability	• Baseline: Was diagnosis made pre-symptomatically? • Baseline: SMN2 copy number • Baseline: Age at symptoms onset • Baseline: Walking without support
Exclusion criteria	
• Enrollment at a Swiss SMArtCARE center	• Recruitment: Country of centre
• Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen, or onasemnogene abeparvovec). *Exception: Patients with initial treatment (nusinersen OR risdiplam) for less than*	• Baseline: Has the patient previously been on any SMA-specific drug treatment? • Baseline: Name of drug • Baseline: Nusinersen: Start date | End date • Baseline: Zolgensma: Date of treatment • Baseline: Risdiplam: Start date | End date • Medical Assessment: Other medication taken on a regular basis • Medical Assessment: Name of drug = Other, Please specify • Baseline: Is the patient currently or was previously included in a clinical trial?

Inclusion criteria	Fields of SMArtCARE eCRF
three months followed by an alternative treatment will not be excluded but assigned to the subsequent treatment. • Current treatment with therapies whose effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea • Current or previous participation in clinical trials	• Medical assessment: Is the patient currently included in a clinical trial?

8.2.2 Treatment

8.2.2.1 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products are according to the respective SmPC.

Risdiplam

The recommended once daily dose of risdiplam is determined by age and body weight (see Table 2). Risdiplam is taken orally once a day after a meal at approximately the same time each day.

Table 2: Dosing regimen by age and body weight

Age* and body weight	Recommended daily dose
< 2 months of age	0.15 mg/kg
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

*based on corrected age for preterm infants

Risdiplam is taken orally once a day after a meal at approximately the same time each day, using the reusable oral syringe provided. In infants who are breastfed, risdiplam should be administered after breastfeeding. Risdiplam should not be mixed with milk or formula milk. Risdiplam should be taken immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, it should be discarded from the oral syringe and a new dose be prepared. If risdiplam spills or gets on the skin, the area should be washed with soap and water. The patient should drink water after taking risdiplam to

ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, risdiplam can be administered via the tube. The tube should be flushed with water after delivering risdiplam.

Nusinersen

The recommended dosage of nusinersen 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.

Nusinersen is for intrathecal use by lumbar puncture. Treatment should be administered by health care professionals experienced in performing lumbar punctures. Nusinersen is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid, equivalent to the volume of nusinersen to be injected, is removed prior to administration of nusinersen. Sedation may be required to administer nusinersen, 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.

Onasemnogene abeparvovec

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. Patients will receive a dose of nominal 1.1×10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.

Onasemnogene abeparvovec 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. Insertion of a secondary (‘back-up’) catheter is recommended in case of blockage in the primary catheter. Following completion of infusion, the line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection. Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen. Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature.

8.2.3 Concomitant Medication and Treatment

Concomitant medication will be allowed except for treatments defined as exclusion criterion.

Medication taken on a regular basis is documented in the SMArtCARE database.

8.3 ENDPOINTS AND ESTIMANDS

8.3.1 Primary Objectives and Corresponding Estimands

Table 3: Primary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of AE leading to hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol) Endpoint: number of AE leading to hospitalization over time Treatment (see Section 8.2.2 of the protocol):Experimental arm: Risdiplam according to SmPC Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol) Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Endpoint: Change from baseline of RULM total score at 36 months after index date Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen’s d

Primary Objective	Estimand Definition
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene (see Section 6.1 of the protocol). Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

Additional information to primary objectives:

Table 4: Operationalization of primary endpoints in SMArtCARE eCRF

Primary Endpoint	Fields of SMArtCARE eCRF
Pre-symptomatic patients Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Patients with SMA Type 1 Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Patients with SMA Type 2 Change from baseline of RULM total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
Patients with SMA Type 3 Change from baseline of RULM total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side

8.3.2 Secondary Variables

Table 5: Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation	Time to death	Time to death or permanent ventilation	Time to death or permanent ventilation

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
(two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	(two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	(two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			
Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of walking without support	-
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in HFMSE total score at 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12	Change from baseline HFMSE total score 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
		and 24 months after index date*** RULM total score at 36 months after index date***	and 24 months after index date*** RULM total score at 36 months after index date***
Walking performance endpoints			
		-	**For ambulatory patients:** Relative change from baseline in walking distance at 12, 24 and 36 months after index date[#] Evaluation of the total walking distance at month 36 after index date[#]
Bulbary function			
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and

HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, *** As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), #As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk

Table 6: Operationalization of secondary endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Secondary Variables (as applicable)	
Time to death	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN (Date of treatment) • End of data collection: Date of death
Time to permanent ventilation (two consecutive documentations of permanent ventilation of >16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to any respiratory support	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support?
Time from first treatment to reaching the WHO motor development milestone “sitting without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Sitting or higher current motor function
Time from first treatment to reaching the WHO motor development milestone “standing without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Standing without support or higher current motor function
Time from first treatment to reaching the WHO motor development milestone “walking without support”	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Walking without support
Time from gaining WHO motor development	• Medical assessment: Visit date • Medical assessment: Best current motor function • Medical assessment: Changes in motor milestones

Variable	Fields of SMArtCARE eCRF
milestone to permanent loss of milestone ability: • Loss of the ability to sit without support • Loss of the ability to stand without support • Loss of the ability to walk without support	
Change from baseline in CHOP INTEND total score at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • CHOP-INTEND: Date of evaluation CHOP-INTEND: Score
Change from baseline in HFMSE total score at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
HFMSE total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
Change from baseline in RULM total score at 12 and 24 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
RULM total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
For ambulatory patients: relative change from baseline in walking distance at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: Evaluation of the total walking distance at month 36 after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Swallowing? = With difficulties • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids.
Proportion of patients with need of non-oral nutritional	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment)

Variable	Fields of SMArtCARE eCRF
support at 12, 24, 36 months after index date	• Medical assessment: Visit date • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids
Time to first documentation of scoliosis or orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Orthopedic surgery since last visit?
Time to first documentation of scoliosis	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis?
Time to first documentation of orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Orthopedic surgery since last visit?
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Planned hospitalization since last visit (except for treatment administration)? • Medical assessment: Admission date • Nusinersen/onasemnogene abeparvovec; Care setting = Inpatient (overnight)? 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.

8.3.3 Safety Variables

In the SMArtCARE eCRF there is no specific field for the documentation of serious adverse events. Instead, there is an option to document adverse events that lead to unplanned or prolonged hospitalization. Further, seriousness can be documented in a free text field. For this study the “adverse events that lead to unplanned or prolonged hospitalization” and “adverse events which lead to death (as inferred from the free text field “cause of death “)” are used to approximately represent serious adverse events. Additional criteria for “serious adverse events” are: life-threatening adverse events, adverse events leading to permanent or serious disability or invalidity, medically significant, development of a congenital anomaly or birth defect.

Table 7: Safety Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization

Table 8: Operationalization of safety endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Proportion of patients with a SAE	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date • Adverse event: Description of adverse event • End of data collection: Is the patient deceased? | Date of death | Cause of death
Proportion of patients with an AE leading to hospitalization	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date

8.4 DATA SOURCE(S)

8.4.1 Collection of Data on the CRF

All clinical data for this project is collected in the SMArtCARE registry. Study site personnel is responsible for patient data collection and data entry into SMArtCARE. Data will be entered into electronic case report forms (eCRFs) of the SMArtCARE registry as timely as possible (see also SMArtCARE protocol (10)). SMArt CARE provides a summary of all relevant examinations in tabular form as “Recommendations for the evaluation of paediatric/ adult patients with SMA”.

At enrollment and baseline the SMA confirmation including the genetic details (*SMN2* copy numbers) are documented together with date of birth and gender. The following baseline data are documented: pre-symptomatic /age at onset of symptoms, motor function, pulmonary function, nutrition, scoliosis surgery in the past, other medical history, (previous) treatment of SMA, participation in clinical studies currently/in the past. Baseline data is documented at index date.

At each visit a detailed medical assessment will be performed and documented in the eCRF giving also details on the SMA treatment and other concomitant medication. In addition, the adverse events eCRF will be completed at each visit. The eCRF pages documenting the main inclusion criteria, and effectiveness and safety variables are given in the following table.

Special documentation is available for administration of nusinersen and onasemnogene abeparvovec.

Table 9: CRF pages documenting the main inclusion criteria and effectiveness and safety variables

Variable	eCRF page
Main inclusion criterion	
Pre-symptomatic diagnosis / no pre-symptomatic diagnosis	Baseline – Results of the genetic examination Baseline – Clinical diagnosis
Onset of symptoms ≤ 6 months Onset of symptoms > 6 months and ≤ 18 months Onset of symptoms > 18 months	Baseline – Clinical diagnosis
Never achieved ability to sit unaided Never achieved ability to walk unaided Patient is able to walk unaided OR was able to walk unaided but has lost that ability	Baseline– Clinical diagnosis
SMN2 copy number is ≤ 3	Baseline– Results of the genetic examination
Primary effectiveness variables	
AE leading to hospitalization	–Adverse events

Variable	eCRF page
Time to death or time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	Adverse events / End of data collection Medical assessment – Pulmonary function and support
RULM total score	Physiotherapeutic evaluation - RULM
Secondary effectiveness variables	
WHO motor development milestones	Medical assessment
HFMSE score	Physiotherapeutic evaluation - HFMSE
CHOP INTEND score	Physiotherapeutic evaluation - CHOP INTEND
Respiratory support	Baseline and Medical assessment– Pulmonary function and support
Swallowing function	Medical assessment - Nutrition
Non-oral nutritional support	Baseline and Medical assessment - Nutrition
Scoliosis	Medical assessment - Orthopedic symptoms
Orthopedic surgery	Baseline and Medical assessment - Orthopedic symptoms
Walking distance	Walk test - „distance_na“ (Total distance)
Hospitalizations	Medical assessment - Hospitalization
Safety variables	
Adverse events	Adverse events
Treatment of SMA	Medical assessment– Medication

8.4.2 Safety Data Collection

All adverse events and serious adverse will be collected at every visit and documented in the CRF in a specific AE section. For regular follow-up patients, adverse events include events with unplanned or prolonged hospitalization and additionally unexpected events without hospitalization.

For specific medications, selected AE will be collected, e.g. possible treatment-related medical occurrences such as lumbar puncture associated AE.

Death will be documented in the “End of data collection” CRF.

8.5 SAMPLE SIZE

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nusinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of AE leading to hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (RR ≥ 0,5), a one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 %, while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (11). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (HR ≥ 0,5), a one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with Nusinersen (11), but there is no data available for the change from baseline to month 36. At the time of submission, there is no data published showing the performance in RULM total score for onasemnogene abeparvovec. Further, the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known. It is therefore not possible to calculate the sample size yet.

Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (Cohen’s d ≤ 0.8), a one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size. The threshold was chosen with regard to Cohen’s rule of thumb for interpreting results (Large Effect = 0.8) (12).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with Nusinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for patients with SMA type 3 is the change from baseline in RULM total score. Based on the first interim analyses, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0.8), a one-sided alpha of 2.5% and a power of 80% using the observed effect size.

8.6 DATA MANAGEMENT

Following the extraction from the data source, anonymized data will be stored at Evidenze Germany GmbH (formerly Chrestos Concept GmbH & Co. KG / Chrestos GmbH). Access to the data will be restricted to members of Evidenze Germany. No personal data will be provided to Roche/Genentech.

8.6.1 Data Quality Assurance

Data used for this study is collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data are entered at the site into an eCRF as timely as possible. The clinical database is provided by OpenApp. SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. Patient data is validated by automated checks, which are specified beforehand, and manual checks by clinical monitors. Query lists are sent to the investigator who corrects data directly in the eCRF (see SMArtCARE protocol (10)). All programs which can be used to influence data or data quality are validated. The Sponsor will emphasize to investigators the importance of collecting complete data, both for outcome measures and for the confounder variables at baseline. On-site monitoring by clinical research associates will be performed at each site to improve data quality and completeness. Monitoring reports will be written for each visit and will include all findings and the expected corresponding corrections and changes.

Implausible data will further be assessed in Data Review Meetings conducted before each status report, interim analysis and final analysis. In this meeting the handling of implausible data and outliers will be discussed and documented.

8.6.2 Electronic Case Report Forms

SMArtCARE uses an electronic data capture (EDC) system. This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are

implemented. All programs which can be used to influence data or data quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

8.6.3 Source Data Documentation

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (SMArtCARE protocol).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG). In case of severe or repeated findings, measures are defined to increase data quality (e.g. re-training of sites by CSG, additional monitoring visits by CSG).

8.7 DATA ANALYSIS

All analyses are based on the Full Analysis Set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. If an initial therapy is documented for less than three months followed by an alternative therapy , the patient is allocated to the treatment of the following therapy (7).

The index date for each patient will be the date of the therapy decision. If the therapy decision was not documented, the index date will be the date of the first treatment administration (either of an initial treatment, if available, or of the treatment the patient was allocated to). Relevant confounders have been specified according to the description in Section 8.7.4. To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation is considered according to the rules defined in the statistical analysis plan (SAP).

8.7.1 Primary Objectives Analyses

All primary estimands will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch). Additionally, supplementary estimands with the hypothetical strategy will be investigated as well, as described in the SAP. Sensitivity analyses will be conducted as described in the SAP to assess the heterogeneity in the control arm and the use of prospective and retrospective enrolled patients in a pooled analysis. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the

shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

The comparison of the number of AE leading to hospitalization over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of AE leading to hospitalization as a function of treatment arm and the patient's observation time included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of AE leading to hospitalization associated with risdiplam in comparison to the control arm.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median, 25% and 75% quantiles. To quantify the treatment effect, the hazard ratio (and the 2-sided 95% confidence interval (CI) will be estimated.

For the change from baseline of RULM total score, a MMRM analysis will be performed to estimate differences in the mean changes from baseline over the whole analysis period. With the estimated means and standard errors, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The standard deviations needed for the calculation of SD_{pooled} will be derived from the standard errors in the MMRM. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

8.7.2 Safety Analyses

The analysis of safety outcomes/variables is based on all SAE and AE leading to hospitalization. The number and percentage of patients with a (serious) adverse event in each category will be summarized and compared using relative and absolute effect measures, including absolute risk reduction, odds ratio and relative risk

All SAE and AE leading to hospitalization term entered by the physician describing the event (the "verbatim term") will be assigned to a standardized term (the "preferred term") based on the most up-to-date version of Medical Dictionary for Regulatory Activities (MedDRA). Summary statistics of SAE and AE leading to hospitalization will be performed using preferred terms and their according system organ class.

Follow-up times will be evaluated in the Data Review Meeting before the final analysis to investigate if time to event analyses are more appropriate for all SAE and AE leading to hospitalization than responder analyses.

The proportion of patients with SAE and AE leading to hospitalization will be summarized according to the preferred term and their according system organ class.

The number of AE leading to hospitalization over time will be analyzed separately using negative binomial regression models.

8.7.3 Subgroups

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm as described in the SAP. Analyses will be presented for subgroups according to SGB V, using the subgroup “SMN2 Copy Number” as a measure of disease severity:

Table 10: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at treatment initiation	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	All
Geographic region	Germany, Austria	All
SMN2 Copy Number	1, 2, 3, ≥3, Other	All

8.7.4 Confounder

For the real world data collection for the reassessment of the additional benefit of risdiplam all confounders should be identified in advance through systematic research and prespecified for the analyses.

The Institute for Quality and Efficiency in Health Care (IQWiG) issued a rapid report on May 13, 2020, titled "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. This document offers guidance on how to analyze patient-specific data within the context of drug benefit assessments under § 35a SGB V. IQWiG addresses crucial elements such as the planning of studies and statistical analyses, as well as the significance of accounting for confounders in studies that are not randomized. The report stresses the need for a priori definition of confounders based on scientific literature and, where necessary, their validation by clinical experts. Accordingly, a systematic literature review (SLR) was performed to identify potential confounders for SMA, outlined in national and international guidelines, recommendations, and publications, and validated them with clinical experts, ensuring compliance with the evidence development requirements in Germany.

The results and the used methodology to identify confounder via a systematic literature review and validation by clinical experts are described in detail in the final report of the systematic confounder research (13).

Clinical experts categorized the identified confounders into three groups:
Very Important: Essential for adjusting non-randomized studies to ensure validity.
Less Important: Marginally affect outcomes but not critical to study validity.
Not Important: Irrelevant to the study due to specific characteristics.

The following rules were applied to select which potential confounders and characteristics will be used during data analysis:

- Confounders which were classified as “not important” will not be used during data analysis.
- All potential confounders which are classified as “very important” will be used for analysis. Except for “Presymptomatic/symptomatic at onset” which is already a stratification factor.
- If there is more than one “characteristic” found for one potential confounder, the most important one is used. In case there are several “characteristics” with the same level of importance the same characteristic will be used as in the protocol of onasemnogene abeparvovec.
- “Less important” will be used in case it is required by the IQWiG or it is used in the protocol of onasemnogene abeparvovec.

Table 11: Confounders

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number	Discrete	Very important	SMN2 copy number (1, 2, 3, ≥3, Other)	Genetic Test Result: SMN2 copy number	All
Age at symptom onset	Continuous	Less important	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Continuous	Very important	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec:	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3: Derived (treatment delay defined as time from symptom onset to treatment

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				MIN(Date of treatment)	initiation)
Nutrition support	Discrete	Very important	Gastric tube or nasal feeding tube (exclusive/ supplemental/ no ne) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Discrete	Very important	Duration of ventilator use (nighttime/int ermittent/ permanent (≥16h/day/no ne or only with acute illness) at treatment initiation	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) 4. Intermittent with acute illnesses AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Contractures	Discrete	Less important	Contractures limiting function (yes/no) at treatment initiation	Clinical Examination: Are any contractures present? = Yes AND Registries, Clinical Trials: Type of	SMA type 1, SMA type 2, SMA type 3

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Motoric function: Highest motor milestone (at treatment initiation)	Discrete	Very important	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support Walking without support Climb stairs	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 2, SMA type 3
Motoric Function CHOP-INTEND*	Discrete	Very important	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
Motoric Function: HFMSE score*	Discrete	Very important	Mean Hammersmith score treatment initiation	HFMSE: total AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN	SMA type 1, SMA type 2 SMA type 3

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				(Date of treatment)	

[a] Depiction of assessment from advising clinical experts and not subject to any input from Roche Pharma AG. Categorization of “less important” vs. “very important” does not influence depiction or handling of confounder in statistical analysis. * for analysis populations SMA type 1, SMA type 2 and SMA type 3, either CHOP-INTEND or HFMSE score will be used as a confounder. The confounder with the fewest missing values in the respective population will be selected. Remaining missing data will be handled as described in the SAP.

All confounder variables will be included in the propensity score model as indicated by their type (continuous, discrete), as long as the criteria regarding the amount of missing data as specified in the SAP is fulfilled.

8.7.5 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be within six months after study start (retrospective enrolled patients and, if possible, prospective enrolled patients).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be calculated using observed effect sizes and recruitment rates as assumptions. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped in consultation with G-BA due to futility in the respective population. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped in consultation with G-BA due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The Marketing Authorization Holder (MAH) must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, and documentation of Institutional Review Board/Ethics Committee (IRB/EC) and governmental approval/notification (if necessary).

Chrestos, a Contract research Organization (CRO) commissioned by MAH, shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from SMArtCARE registry to Chrestos. SMArtCARE registry will comply with the MAH procedures as written in the contract regarding content, archiving and records management of process documents.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by SMArtCARE for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the SMArtCARE. Written notification should be provided to the SMArtCARE prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

As any observational research this study is subject to a risk of bias. The data collected in this study is dependent on routine clinical practice and the level of data collected may differ between participating sites. Consequently, the data obtained in this study will be less comprehensive than data obtained from a prospective, interventional clinical study.

To minimize the bias, certain measurements will be performed (detailed description in the SAP). Missing confounder values will be addressed (complete case, multiple imputation or exclusion of variables). Propensity score weighting will be applied to adjust for differences in the confounder variables between the treatment groups. Data reporting will be conducted in a consistent way to avoid bias in the data collection process.

9. PROTECTION OF HUMAN PATIENTS

Data will be collected as part of routine clinical practice. The responsibility lies with the treating physician.

9.1 INFORMED CONSENT

The patients have explicitly agreed to any secondary use of their data.**CONFIDENTIALITY**

The SMArtCARE registry maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any SMArtCARE registry location. Only aggregated data from the registry are available and are used in this study.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, CSG monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol and relevant supporting information must be submitted to the EC, and reviewed and approved by the EC before the study is initiated.

SMArtCARE is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim analyses and in the final value dossier submission in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Study results will be published in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
STUDY NUMBER:	ML44661
VERSION NUMBER:	5.0
ROCHE COMPOUND(S):	EVRYSDI® (RISDIPLAM)
PLAN PREPARED BY:	[redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor Signature(s) and Date(s):

[redacted]

MARKETING AUTHORIZATIONHOLDER (MAH):	Roche Registration GmbH
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	10-Aug-2023	1.0, 31-Jul-2023
2	02-May-2024	2.0; 02-May-2024
3	25-June-2024	3.0; 25-Jun-2024
4	28-Oct-2024	4.0; 28-Oct-2024
5	see electronic date stamp on title page	5.0; 10-Apr-2026

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

1. and 2. Amendment due to G-BA requirements from April 4th, 2024 (1)

3. Amendment due to G-BA requirements from September 19th, 2024 (2)

4. Amendment due to changes specified in the Data Review Meeting from December 19th, 2025

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	Adverse event
AR	Autoregressive
BSID	Bayley scale of infant development
CHOP-INTEND	Children's hospital of Philadelphia infant test of neuromuscular disorders
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFMSE	Hammersmith functional motor scale expanded
HR	Hazard ratio
ICH	International Council on Harmonization
IPTW	Inverse probability of treatment weights
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MICE	Multiple imputation by chained equations
MMRM	Mixed model repeated measures
NBS	Newborn screening
RULM	Revised upper limb module
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard deviation
SDV	Source data verification
SMA	Spinal muscular atrophy
SMN 1/2	Survival motor neuron ½
SmPC	Summary of product characteristics
SOP	Standard operating procedures
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis of the data collected within the framework of study ML44661. It is based on the final study protocol, version 3.0, dated 24 Jun 2024 and follows the principles of the Guideline ICH E9. It gives all details for the statistical analysis of this study. The statistical analysis will be carried out according to Evidenze Germany standard operating procedures (SOP).

The SAP contains a more technical and detailed elaboration of the procedures described in the study protocol for conducting the statistical analyses.

This SAP was written and finalized prior to database hard lock and data analysis.

There are no changes to the planned analyses described in the protocol.

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (SMN1) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and SMN2 copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of

the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

On the basis of the ongoing or completed studies on risdiplam considered for approval, the identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

1.1.1 Primary Objectives and corresponding Estimands

Table 1: Primary Objectives / Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of adverse events (AE) leading to hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see protocol for details) Endpoint: Number of AE leading to hospitalization over time Treatment (see protocol for details): Experimental arm: Risdiplam according to Summary of Product Characteristics (SmPC) Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see protocol for details) Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)

Primary Objective	Estimand Definition
	Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see protocol for details). Endpoint: Change from baseline of RULM total score at 36 months after index date Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen's d
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see protocol for details). Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

Abbreviations; RULM = revised upper limb module

1.1.2 Secondary Objectives and Endpoints

Table 2: Secondary Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Overall Survival and event free survival			
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of	Time to death Time to permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to any respiratory support	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of	Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day) Time to death Time to permanent ventilation (two consecutive documentations of

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
permanent ventilation of > 16 hours/day) Time to any respiratory support		permanent ventilation of > 16 hours/day) Time to any respiratory support	permanent ventilation of > 16 hours/day) Time to any respiratory support
Achievement of WHO motor development milestones			
Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of sitting without support Time from first treatment to reaching the WHO motor development milestone of standing without support Time from first treatment to reaching the WHO motor development milestone of walking without support	Time from first treatment to reaching the WHO motor development milestone of walking without support	-
Sustainability of motor milestones			
Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support	Time from gaining WHO motor development milestone to permanent loss of milestone ability: - Loss of the ability to sit without support - Loss of the ability to stand without support - Loss of the ability to walk without support
Motorfunction Tests			
Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months after index date*	Change from baseline in HFMSE total score at 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12 and 24 months after index date*** RULM total score at 36 months after index date***	Change from baseline HFMSE total score 12, 24, 36 months after index date** HFMSE total score at 36 months after index date** Change from baseline in RULM total score at 12 and 24 months after index date*** RULM total score at 36 months after index date***
Walking performance endpoints			

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
		-	**For ambulatory patients:** Relative change from baseline in walking distance at 12, 24 and 36 months after index date[#] Evaluation of the total walking distance at month 36 after index date[#]
Bulbary function			
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date
Orthopedic complications			
Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery	Time to first documentation of scoliosis or orthopedic surgery Time to first documentation of scoliosis Time to first documentation of orthopedic surgery
Hospitalizations			
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded, *As part of the regular SMArtCARE guidelines the CHOP-INTEND is used for follow-up monitoring of the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit, **As part of the regular SMArtCARE guidelines the HFMSE I used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit, *** As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair (see SMArtCARE: Recommendations for the evaluation of adult patients with SMA), #As part of the regular SMArtCARE guidelines for follow-up monitoring used for the following patients: > 2 years for all patients with ability to walk

Table 3: Safety Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization	Number of AE leading to hospitalization over time Proportion of patients with a SAE Proportion of patients with an AE leading to hospitalization

Abbreviations: AE – adverse event, SAE – serious adverse event

1.2 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.

This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2018. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol (3).

Start Date of Study:

October 30th, 2024.

Interim Analyses:

Interim analyses are planned 12 (October 2025) and 24 months (October 2026) after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analyses, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in October 2027.

End of Study:

All patients in the study should generally be followed up for at least 36 months. Follow-up time can vary between patients depending on their entry date in the registry.

The planned end date is October 01, 2027. Data that is documented in the study database after that time point will not be taken into account.

1.2.1 Data Monitoring

Data used for this study is collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data is entered at the site into an electronic case report form (eCRF) as timely as possible. The clinical database is provided by OpenApp. SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. Patient data is validated by automated checks, which are specified beforehand, and manual checks by clinical monitors. Query lists are sent to the investigator who corrects data directly in the eCRF (see SMArtCARE protocol). All programs which can be used to influence data or data quality are validated. On-site monitoring by clinical research associates will be performed at each site to improve data quality and completeness. Monitoring reports will be written for each visit and will include all findings and the expected corresponding corrections and changes.

Implausible data will further be assessed in Data Review Meetings conducted before each status report, interim analysis and final analysis. In this meeting the handling of implausible data and outliers will be discussed and documented.

SMArtCARE uses an electronic data capture (EDC) system (3). This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are implemented. All programs which can be used to influence data or data quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (3).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG). In case of severe or repeated findings, measures are defined to increase data quality (e.g. re-training of sites by CSG, additional monitoring visits by CSG).

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The comparison of the number of AE leading to hospitalization over time between both arms will be performed using a negative binomial regression model. This analytic model estimates the rate ratio, λ_e / λ_c, which quantifies the risk of AE leading to hospitalization associated with risdiplam (λ_e) in comparison to nusinersen or onasemnogene abeparvovec (λ_c). Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The Wald test will be performed via the following hypothesis:

$$H_0: \text{Rate Ratio} \geq 0.5 \text{ versus } H_1: \text{Rate Ratio} < 0.5$$

Symptomatic patients with a clinically diagnosed SMA type 1:

Treatment comparison of the time to death or permanent ventilation will be based on the Cox-regression test. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The shifted null and alternative hypotheses can be phrased as:

$$H_0: \text{Hazard Ratio} \geq 0.5 \text{ versus } H_1: \text{Hazard Ratio} < 0.5$$

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

For the Change from baseline of RULM total score a mixed model repeated measures (MMRM) analysis will be performed and Cohen's d will be estimated as a measure of the effect size. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The hypothesis to be tested with a t-test is that the standardized difference (Cohen's d) in the mean change from baseline in the total RULM score at Month 36 between risdiplam and nusinersen or onasemnogene abeparvovec (δ) is:

$$H_0: \delta \leq 0.8 \text{ versus } H_1: \delta > 0.8$$

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

See SMA type 2 and up to three copies of the *SMN2* gene.

2.2 SAMPLE SIZE DETERMINATION

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nusinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making

assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of AE leading to hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analysis (see Section 4.7.1), the sample size for a shifted null hypothesis (RR ≥ 0.5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 % (4), while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (5). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived. It is therefore not possible to calculate the sample size yet.

Based on the first interim analysis (see Section 4.7.1), the sample size for a shifted null hypothesis (HR ≥ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score at month 36.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with nusinersen (6), but there is no data available for the change from baseline to month 36. At the time of submission, there is no data published showing the performance in RULM total score for onasemnogene abeparvovec. Further, the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known. It is therefore not possible to calculate the sample size yet.

Based on the first interim analysis (see Section 4.7.1), the sample size for a shifted null hypothesis (Cohen’s d ≤ 0.8), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size. The threshold was chosen with regard to Cohen’s rule of thumb for interpreting results (large effect = 0.8) (7).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with nusinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for patients with SMA type 3 is the change from baseline in RULM total score at month 36. Based on the first interim analysis, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0.8), a one-sided alpha of 2.5% and a power of 80% using the observed effect size.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 4.

Table 4: Participant Analysis Sets

Participant Analysis Set	Description
FAS	All enrolled participants; participants will be included in the analyses according to the treatment they received at enrollment. If an initial therapy is documented for less than three months followed by an alternative therapy, the patient is allocated to the treatment of the following therapy.

FAS = full analysis set

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All clinical data will be downloaded and transferred into SAS® datasets. All statistical analyses will be carried out using SAS®, version 9.4 or higher and R, version 4.3.0 or higher.

If not specified otherwise, descriptive statistics will be presented by treatment group and time point, where appropriate. For continuous data the sample size, mean, standard deviation (SD), median, range (min, max) and interquartile range (Q1, Q3) will be presented. Categorical data will be displayed by absolute and relative frequencies (percentages). Percentages will be based on all non-missing values. Missing categories might be displayed in addition (only by absolute frequencies). Exceptions to this rule are to be specified explicitly. In any case, the percent basis will be specified in a table footnote. Percentages will be rounded to one decimal place.

For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Shifted null hypotheses will generally be formulated according to section 2.1. For responder analyses reporting p-values for the relative risk, a value of 0.5 will be used in the null hypothesis in accordance with other relative effect measures like the hazard and rate ratio. For time to reaching a WHO motor development

milestone, where hazard ratios > 1 represent an advantage for the risdiplam group, the hypotheses H0: Hazard Ratio ≤ 2 versus H1: Hazard Ratio > 2 will be tested. Point estimators will be presented with 2-sided 95% confidence intervals.

For responder and change from baseline analyses planned to be conducted at a certain month after index date (e.g. at 12m, 24m, 36m), the closest assessment within a time frame of ±2 months will be used for the analysis, unless otherwise specified. This time frame considers that visits take place every four months. If there was no assessment within this time frame, the value is assumed to be missing.

The index date for each patient will be the date of the therapy decision. If the therapy decision was not documented, the index date will be the date of the first treatment administration (either of an initial treatment, if available, or of the treatment the patient was allocated to). The closest visit up to 4 months before or at the index date will be used as baseline visit. This time frame considers that visits take place every four months. If there was no assessment within this time frame, the baseline value is assumed to be missing.

Every switch between the study medications risdiplam, nusinersen and onasemnogene abeparvovec (exception: initial therapy is documented for less than three months followed by an alternative therapy) will be considered a treatment switch, including switches between nusinersen and onasemnogene abeparvovec within the control arm.

4.1.1 Confounder

Confounders have been identified in advance through systematic research, as described in the Protocol Section 8.7.4. The following confounders will be considered.

Table 5: Confounders

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number	Discrete	Very important	SMN2 copy number (1, 2, 3, ≥3, Other)	Genetic Test Result: SMN2 copy number	All
Age at symptom onset	Continuous	Less important	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Continuous	Very important	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3:

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	Derived (treatment delay defined as time from symptom onset to treatment initiation)
Nutrition support	Discrete	Very important	Gastric tube or nasal feeding tube (exclusive/ supplemental/ none) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Discrete	Very important	Duration of ventilator use (nighttime/intermittent/ permanent (≥16h/day)/none or only with acute illness) at treatment initiation	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) 4. Intermittent with acute illnesses AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Contractures	Discrete	Less important	Contractures limiting function (yes/no) at treatment initiation	Clinical Examination: Are any contractures present? = Yes AND	SMA type 1, SMA type 2, SMA type 3

Confounder	Type of variable	Clinical relevance [a]	Definition	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Type of limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Motoric function: Highest motor milestone (at treatment initiation)	Discrete	Very important	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support Walking without support Climb stairs	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 2, SMA type 3
Motoric Function CHOP-INTEND*	Discrete	Very important	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
Motoric Function: HFMSE score*	Discrete	Very important	Mean Hammersmith score treatment initiation	HFMSE: total AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2 SMA type 3

* for analysis populations SMA type 1, SMA type 2 and SMA type 3, either CHOP-INTEND or HFMSE score will be used as a confounder. The confounder with the fewest missing values in the respective population will be selected. Remaining missing data will be handled as described in section 4.1.3.

All confounder variables will be included in the propensity score model as indicated by their type (continuous, discrete), as long as the criteria regarding the amount of missing data as specified below is fulfilled.

4.1.2 Propensity Score

To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given, as detailed below.

The propensity score is the probability that a patient was assigned to a treatment conditional on the observed baseline covariates, $e(x) = \mathrm{pr}(z = 1 \mid x)$, and will be estimated using logistic regression (8).

After calculation of propensity scores for each patient, the overlap of propensity scores between the treatment groups will be evaluated. To date, there is no established criterion for sufficient overlap. Thus an overlap is considered sufficient if the overlap of propensity score distributions between the treatment groups is >50%, which is in accordance with the rules defined in the onasemnogene abeparvovec study protocol (9). If applicable guidelines are available at a later date, the criterion used might be amended. The overlap will be calculated by estimating the density for the treatment groups via kernel density estimation and calculating the area of the overlap as implemented in the R package overlapping (10). If the overlap is not sufficient for applying propensity score methods, only naïve comparisons will be performed.

In case of sufficient overlap, weights will be calculated based on the propensity scores. Two weighting methods will be considered, inverse probability of treatment weights (IPTW) and fine stratification weights (11). IPTW defines the weights for treated patients as $1/PS$ and weights for patients in the comparison arm as $1/(1 - PS)$. To avoid extreme weights, propensity scores above the 95th percentile in the control patients and below the 5th percentile in the risdiplam patients will be excluded from the analysis. For fine stratification weights, the propensity scores are used to define fine stratums (12). A fixed width of 0.1 will be used to define stratums, resulting in 10 stratums total. Weights are then calculated based on the total number of patients within each stratum, for all stratums with at least one treated and one reference patient, and are defined as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{exposed in PS stratum i}}$ / $N_{\text{total exposed}}$) for treated patients, and as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{reference in PS stratum i}}$ / $N_{\text{total reference}}$) for the comparison.

For both weighting methods, the balance between treatment groups for each confounder (13) variable will be evaluated by calculating standardized differences after weighting. The balance is sufficient for performing propensity score analyses if $abs(SMD) < 0.2$ is

given for each confounder. Otherwise, only naïve comparisons are performed. If both weighting methods show sufficient balance between the treatment groups, the weighting method with the best overall confounder balance after weighting will be used for all analyses. As an overall measure of balance, the post-weighting C statistic can be used (14).

A detailed description of the unweighted and weighted analysis population will be done using baseline characteristics (as described in section 4.6.2).

4.1.3 Handling of Missing Data

For efficacy variables, an incomplete event date will be replaced by the last day of the month, assuming the month and year are known. For safety variables, an incomplete event date will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence that the patient was event-free within that month, in which case the date the patient was last known to be event-free within that month will be used as the event date. Efforts to minimize the amount of missing dates are described in protocol section 8.6.1.

The Sponsor will emphasize to investigators the importance of collecting complete data, both for outcome measures and for the confounder variables at baseline required for the propensity score analysis described above.

In case missing dates are still present in the confounder variables, the following steps will be performed.

4.1.3.1 Descriptive Analysis of Missing Data

The patterns of missing data for the confounder variables will be summarized with upset-plots by population and treatment group. Furthermore, the number of complete cases will be summarized.

Depending on the percentage of missing data the method to deal with it will be chosen, as described below.

4.1.3.2 Dealing with Missing Data

There are different methods to deal with missing data. For this study complete case analysis and multiple imputation are considered. It is planned to align with the rules of thumb described by Jakobsen et al. (15). According to these rules missing data can be ignored, if the proportion of missing data is below 5%. On the other hand, it is not recommended to use multiple imputation, if more than 40% of the data is missing. With multiple confounder variables there are two ways to assess the proportion of missing data, at subject level and at variable level. It is planned to focus on the subject level first. If 95% or more of the subjects have no missing confounder variables the complete case analysis will be used, meaning that only patients without missing

confounder variables will be included in the analysis. Otherwise, the percentages of subjects with missing data per confounder variable will be considered. All variables with an amount of missing data below 40% percent will be included in the multiple imputation approach (described below). Variables with more than 40% of subjects with missing data are not imputed at all and are not used as confounder. The variables will still be included in the assessment of balance after implementation of the propensity score weights, as described in section 4.1.2, with equal consequences if sufficient balance can't be achieved.

4.1.3.3 Multiple Imputation

The confounder variables to be included in the multiple imputation are selected as described before. The missing variables will be imputed by non-missing baseline covariates using the multiple imputation by chained equations (MICE) algorithm (16). For numeric variables the Predictive mean matching method is used and for factorial variables the Logistic regression method (for 2 factors), the Multinomial logit model (for >2 factors) or the ordered logit model (for >2 ordered factors) is used.

1000 imputed datasets will be generated. For each dataset, propensity scores will be estimated using logistic regression, as described above. For each patient, propensity scores will be averaged across all imputed datasets, following the across-approach previously described (17–19) . Based on the averaged propensity scores, the overlap between treatment groups will be evaluated, weights will be generated if appropriate and the balance of confounder variables will be evaluated (Section 4.1.2). All statistical analyses described in Sections 4.2 - 4.5 will be conducted with the chosen weights.

4.2 PRIMARY ENDPOINT ANALYSIS

4.2.1 Definition of Primary Endpoints

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The primary endpoint is the number of AE leading to hospitalization over time. The primary estimand is defined as follows:

- Population: Presymptomatic patients with a 5q associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol)
- Endpoint: number of AE leading to hospitalization over time
- Treatment (see Section 8.2.2 of the protocol):
    - Experimental arm: Risdiplam according to SmPC
    - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:

    - Early discontinuation from study treatment: Treatment-policy strategy
    - Treatment switch: Treatment-policy strategy
- Population-level summary: Rate ratio

Symptomatic patients with a clinically diagnosed SMA type 1:

The primary endpoint is the time to death or permanent ventilation. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol)
- Endpoint: Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)
- Treatment (see Section 8.2.2 of the protocol):
    - Experimental arm: Risdiplam according to SmPC
    - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
    - Early discontinuation from study treatment: Treatment-policy strategy
    - Treatment switch: Treatment-policy strategy
- Population-level summary: hazard ratio

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 36 months after index date. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol).
- Endpoint: Change from baseline of RULM total score at 36 months after index date
- Treatment (see Section 8.2.2 of the protocol):
    - Experimental arm: Risdiplam according to SmPC
    - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
    - Early discontinuation from study treatment: Treatment-policy strategy
    - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen’s d

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 36 months after index date. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol).
- Endpoint: Change from baseline of RULM total score at 36 months after index date
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen's d

Table 6: Operationalization of primary endpoints in SMArtCARE eCRF

Primary Endpoint	Fields of SMArtCARE eCRF
Pre-symptomatic patients Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Patients with SMA Type 1 Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Patients with SMA Type 2 Change from baseline of RULM total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
Patients with SMA Type 3	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score

Primary Endpoint	Fields of SMArtCARE eCRF
Change from baseline of RULM total score at 36 months after index date	• RULM: Tested side

4.2.2 Main Analytical Approach for Primary Endpoint(s)

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of AE leading to hospitalization as a function of treatment arm and the patient's observation time included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of AE leading to hospitalization associated with risdiplam in comparison to the control arm.

Symptomatic patients with a clinically diagnosed SMA type 1:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The primary efficacy variable is time to death or permanent ventilation, defined as the time from index date to the death date or the start date of permanent ventilation (whichever occurs first). Permanent ventilation is defined as two consecutive documentations of permanent ventilation of more than 16 hours/day. Patients who have not had an event will be censored at the date they are last known to be alive and event free on or prior to the clinical cutoff date. Data for patients who are enrolled without any post baseline assessments will be censored at the date of index date plus 1 day. Patients with permanent ventilation at index date will be excluded from the analysis.

The main analysis for the primary endpoint will be performed using a Cox proportional hazards model. A Cox-regression test will be performed and the hazard ratio (and 95% confidence interval (CI)) will be estimated.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median, 25% and 75% quantiles based on the Kaplan-Meier approach.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a MMRM to estimate differences in the mean changes from baseline over the whole analysis period. The model will include the change from baseline at the visits in four-month intervals up to 36 months as response variable and will include the categorical covariates of treatment group visit, visit-by-treatment group interaction, baseline RULM Total Score (continuous), as fixed effects. For each visit, the closest assessment within a time frame of ±2 months will be used for the analysis. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an autoregressive (AR) (1) covariance structure may be fitted.

With the estimated means and standard errors, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The standard deviations needed for the calculation of SD_{pooled} will be derived from the standard errors in the MMRM ($SD = SE \times \sqrt{n}$). The estimated treatment difference in the mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

Starting at the second interim analysis, RULM assessments are only included in the analysis if the tested side corresponds to the side tested at baseline.

As part of the regular SMArtCARE guidelines for follow-up monitoring the RULM is used for follow-up monitoring of the following patients: Children > 2 years and adults: For all patients with ability to sit in a wheelchair.

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

As described above for type 2 patients.

4.2.3 Supplementary Analyses

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where for patients that switch treatments (risdiplam, nusinersen, onasemnogene abeparvovec) only AE leading to hospitalization before the treatment switch will be included in the analysis. The follow up times included into the negative binominal regression model for these patients ends with the treatment switch.

Symptomatic patients with a clinically diagnosed SMA type 1:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1).

However, all treatment switches will follow a hypothetical strategy, where the time to death or permanent ventilation will be censored at the date of treatment switch, to estimate a treatment effect in the absence of treatment switches.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event, to estimate a treatment effect in the absence of treatment switches. Data censored after treatment switches following hypothetical strategy will be implicitly imputed by the MMRM model assuming missing at random (MAR).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene:

As described above for type 2 patients.

4.2.4 Sensitivity Analyses

The primary endpoints and relevant secondary endpoints for all populations will be analyzed for heterogeneity using appropriate regression models with a treatment term and considering the data as three-arm trial.

As an additional sensitivity analysis, the primary analysis and the analysis of relevant secondary endpoints will also be conducted on the patient population with prospective enrollment to assess the adequacy of a pooled analysis for retrospective and prospective enrolled patients.

4.3 SECONDARY ENDPOINTS ANALYSES

Time to event analyses will be presented graphically using Kaplan-Meier curves. The median time and the 25% and 75% quantiles (and 95% CIs) will be presented. To quantify the treatment effect, the hazard ratio (and 95% 2-sided CI) will be estimated using a Cox proportional hazards model, p-values will be presented based on a 1-sided Cox Regression test.

Responder analyses will describe the number and percentage of patients who are classified as a responder. To compare between treatment arms, relative and absolute effect measures will be presented, including absolute risk reduction, odds ratio and relative risk with corresponding 95% CIs. Calculation of these effect measures will be model-based using a linear regression model for the absolute risk reduction, a logistic regression model for the odds ratio, and a log-binominal regression model for the relative risk. Wald p-values (1-sided) will be presented for the relative risk.

For analyses describing the change from baseline, an MMRM analysis will be performed as described in Section 4.2.2. With the estimated means and standard deviations, Cohen's d will be estimated as a measure of the effect size via $d = \frac{M_1 - M_2}{SD_{pooled}}$. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI and the p-value will be presented based on a 1-sided t-test. The values and change from baseline values will also be summarized using descriptive statistics. The mean absolute values and change from baseline values over time will be presented graphically using a line plot.

All secondary endpoint analyses will follow the treatment policy strategy for all intercurrent events. For analyses conducted at several time points (e.g. 12, 24 and 36 months after index date), the analysis with the longest observation time will be the relevant analysis and further time points will be analyzed supplementary.

4.3.1 Secondary Endpoints

Table 7: Operationalization of secondary endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Secondary Variables (as applicable)	
Time to death	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN (Date of treatment) • End of data collection: Date of death
Time to permanent ventilation (two consecutive documentations of permanent ventilation of >16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)

Variable	Fields of SMArtCARE eCRF
Time to death or permanent ventilation (two consecutive documentations of permanent ventilation of > 16 hours/day)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support? • Medical assessment: Ongoing use of ventilator? • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to any respiratory support	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient receive ventilator support?
Time from first treatment to reaching the WHO motor development milestone "sitting without support"	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Sitting or higher current motor function
Time from first treatment to reaching the WHO motor development milestone "standing without support"	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Standing without support or higher current motor function
Time from first treatment to reaching the WHO motor development milestone "walking without support"	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Best current motor function = Walking without support
Time from gaining WHO motor development milestone to permanent loss of milestone ability: • Loss of the ability to sit without support • Loss of the ability to stand without support • Loss of the ability to walk without support	• Medical assessment: Visit date • Medical assessment: Best current motor function • Medical assessment: Changes in motor milestones
Change from baseline in CHOP INTEND total score at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • CHOP-INTEND: Date of evaluation • CHOP-INTEND: Score
Change from baseline in HFMSE total score at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
HFMSE total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment

Variable	Fields of SMArtCARE eCRF
	• HFMSE: Extended Total HFMSE
Change from baseline in RULM total score at 12 and 24 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
RULM total score at 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score • RULM: Tested side
For ambulatory patients: relative change from baseline in walking distance at 12, 24 and 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: Evaluation of the total walking distance at month 36 after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Swallowing? = With difficulties • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids.
Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube • Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids
Time to first documentation of scoliosis or orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Orthopedic surgery since last visit?
Time to first documentation of scoliosis	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis?
Time to first documentation of orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Orthopedic surgery since last visit?

Variable	Fields of SMArtCARE eCRF
Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Planned hospitalization since last visit (except for treatment administration)? • Medical assessment: Admission date • Nusinersen/onasemnogene abeparvovec; Care setting = Inpatient (overnight)? 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.

4.3.1.1 Time to death

Time-to-death is defined as the time in months from the index date until the date of death from any cause. Patients with no death reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive.

4.3.1.2 Time to permanent ventilation

Time to permanent ventilation is defined as the time from index date to the first documentation of permanent ventilation. Permanent ventilation is defined as two consecutive documentations of ventilation of at least 16 hours per day. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without permanent ventilation. Patients with permanent ventilation at index date will be excluded from the analysis.

4.3.1.3 Time to death or permanent ventilation

See Section 4.2.1.

4.3.1.4 Time to any respiratory support

Time to any respiratory support is defined as the time from index date to the first documentation of any ventilator support. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without any respiratory support. Patients with ventilator support at index date will be excluded from the analysis.

4.3.1.5 Time from first treatment to reaching the WHO motor development milestone “sitting without support”

Time to reaching the WHO motor development milestone “sitting without support” is defined as the time from index date to the first documentation of reaching the WHO motor development milestone “sitting without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have

reached the motor milestone “sitting without support” at index date will be excluded from the analysis.

4.3.1.6 Time from first treatment to reaching the WHO motor development milestone “standing without support”

Time to reaching the WHO motor development milestone “standing without support” is defined as the time from index date to the first documentation of reaching the WHO motor development milestone “standing without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have reached the motor milestone “standing without support” at index date will be excluded from the analysis.

4.3.1.7 Time from first treatment to reaching the WHO motor development milestone “walking without support”

Time to reaching the WHO motor development milestone “walking without support” is defined as the time from index date to the first documentation of reaching the WHO motor development milestone “walking without support”. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not reached the motor milestone. Patients who have reached the motor milestone “walking without support” at index date will be excluded from the analysis.

4.3.1.8 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to sit without support

Time to the permanent loss of the ability to sit without support is defined as the time from the date of gaining the WHO motor development milestone “sitting without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone.

Only patients who have a documented date for gaining the motor milestone “sitting without support” will be included in the analysis.

4.3.1.9 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to stand without support

Time to the permanent loss of the ability to stand without support is defined as the time from the date of gaining the WHO motor development milestone “standing without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone.

Only patients who have a documented date for gaining the motor milestone “standing without support” will be included in the analysis.

4.3.1.10 Time from gaining WHO motor development milestone to permanent loss of milestone ability: Loss of the ability to walk without support

Time to the permanent loss of the ability to walk without support is defined as the time from the date of gaining the WHO motor development milestone “walking without support” to the first documentation of loss of the milestone ability. Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to have not lost the motor milestone.

Only patients who have a documented date for gaining the motor milestone “walking without support” will be included in the analysis.

4.3.1.11 Change from baseline in CHOP INTEND total score at 12, 24 and 36 months after index date

The change from baseline in the CHOP INTEND total score at 12, 24 and 36 months after index date will be presented.

The CHOP-INTEND consists of 16 items scored from 0 to 4, with a higher score indicating better motor skills. Both the left and right sides are scored and the maximum score is selected for the final item score. The total score is calculated by summing the item scores to give a maximum possible score of 64. If an individual item is missing or ‘Cannot Test (CNT)’ is recorded, the item score will be set to 0.

As part of the regular SMArtCARE guidelines for follow-up monitoring, the CHOP-INTEND is used for the following patients: Children: All children < 2 years of age; All patients > 2 years of age without ability to sit. Adults: For patients without ability to sit.

4.3.1.12 Change from baseline in HFMSE total score at 12, 24 and 36 months after index date

The change from baseline in the total score of HFMSE at 12, 24 and 36 months after index date will be presented.

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (20). The scale contains 33 items which score on a 3-point Likert scale (0-2) and are summed to derive the total score, with lower scores indicating greater impairment. The HFMSE was designed to assess important functional abilities, including standing, transfer, ambulation, and proximal and axial function.

For items recorded as “Not Done” for the HFMSE scale, these items are considered as missing with missing item scores.

If 6 or fewer items are missing, the missing items will be imputed to be “0” (unable to perform the task) prior to the calculation of the total score of HFMSE. If more than 6 items are missing at an assessment time point, the total score of HFMSE at this assessment time point will not be calculated.

As part of the regular SMArtCARE guidelines the HFMSE is used for follow-up monitoring of the following patients: Children > 2 years for all patients with ability to sit; If CHOP INTEND score >50: CHOP INTEND and HFMSE; If CHOP INTEND score >60: HFMSE instead of CHOP INTEND. Adults: All patients with ability to sit.

4.3.1.13 HFMSE total score at 36 months after index date

For the evaluation of the HFMSE total score at month 36 after index date, the mean total score and difference between means will be summarized using descriptive statistics.

4.3.1.14 Change from baseline in RULM total score at 12 and 24 months after index date

The change from baseline in RULM total score at 12 and 24 months after index date will be presented. See section 4.2.1.

4.3.1.15 RULM total score at 36 months after index date

For the evaluation of the RULM total score at month 36 after index date, the mean total score and difference between means will be summarized using descriptive statistics.

4.3.1.16 For ambulatory patients: relative change in walking distance from baseline at 12, 24 and 36 months after index date

For the relative change from baseline in walking distance at months 12, 24 and 36 after index date, the mean relative distance and relative change from baseline distance at each time point will be summarized using descriptive statistics and presented graphically using a line plot. The interpretation of the relevance of the results will be based on the walking distance.

Walking distance describes the distance walked in the 6 minute walking test.

As part of the regular SMArtCARE guidelines for follow-up monitoring, the test is used for the following patients: > 2 years for all patients with ability to walk.

4.3.1.17 For ambulatory patients: evaluation of the total walking distance at month 36 after index date

For the evaluation of the total walking distance at month 36 after index date, the mean total distance and difference between means will be summarized using descriptive statistics.

4.3.1.18 Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after index date

The assessed swallowing function is ordered as follows:

1. No feeding tube, swallowing = normal
2. No feeding tube, swallowing = with difficulties
3. Feeding tube (supplementary e.g. for fluids)
4. Feeding tube (exclusively fed by tube)

A shift table will present the number/percentage of patients per category at 12, 24 and 36 months after index date versus the corresponding swallowing function at baseline.

4.3.1.19 Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after index date

Non-oral nutritional support includes the use of a gastral or nasal feeding tube, either exclusively or supplementary.

The proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after index date will be presented. Patients who have needed non-oral nutritional support at least once between the start of treatment and the respective time point will be classified as responders. Patients who have no need of non-oral nutritional support, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with only missing assessments will also be classified as non-responders.

4.3.1.20 Time to first documentation of scoliosis or orthopedic surgery

Time to first documentation of severe scoliosis or orthopedic surgery is defined as the time from index date to the first documentation of scoliosis or to the first documentation of orthopedic surgery, whichever comes first. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without scoliosis or orthopedic surgery. Patients with scoliosis at index date will be excluded from the analysis.

4.3.1.21 Time to first documentation of scoliosis

Time to first documentation of scoliosis is defined as the time from index date to the first documentation of scoliosis. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without scoliosis. Patients with scoliosis at index date will be excluded from the analysis.

4.3.1.22 Time to first documentation of orthopedic surgery

Time to first documentation of orthopedic surgery is defined as the time from index date to the first documentation of orthopedic surgery. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without any orthopedic surgery.

4.3.1.23 Number of planned hospitalizations over time (including hospitalizations for SMA treatment administration)

The comparison of the number of planned hospitalization over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of planned hospitalizations as a

function of the treatment arm and the patient's observation time included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of planned hospitalization associated with risdiplam in comparison to the control arm.

4.4 SUBGROUP ANALYSES

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm. Analyses will be presented for subgroups according to SGB V, using the subgroup "SMN2 Copy Number" as a measure of disease severity:

Table 8: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at treatment initiation	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	All
Geographic region	Germany, Austria	All
SMN2 Copy Number	1, 2, 3, ≥3, Other	All

Effect estimates will be calculated for all subgroup categories (including categories like "missing" or "unknown") by including the subgroup in a BY statement in the respective SAS procedure.

Interaction tests (likelihood-ratio-tests) will be done for all subgroups by including an interaction term (treatment by subgroup) in the respective model. For responder analyses, interaction tests will be calculated for the relative risk. For calculating the interaction p-value, categories like "missing" or "unknown" will be excluded. The corresponding p-values will not be interpreted if in both arms combined there are less than 10 patients or events in one category. The significant interactions will be discussed in detail in the report. The consistency of the results across the various endpoints will be assessed, as well as the concordance of the effects in the individual subgroup categories. During the interpretation of the results, it will also be considered whether there is a medical rationale for an effect modification.

4.5 SAFETY ANALYSES

4.5.1 Adverse Events

Table 9: Operationalization of safety endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Number of AE leading to hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse events: Start date
Proportion of patients with a SAE	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date • Adverse event: Description of adverse event • End of data collection: Is the patient deceased? | Date of death | Cause of death
Proportion of patients with an AE leading to hospitalization	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Adverse events: Date recorded • Adverse events: Has there been any adverse event since the last visit? • Adverse events: Has there been unplanned or prolonged hospitalization? • Adverse event: Start date

The analysis of safety outcomes/variables is based on SAE and AE leading to hospitalization. The number and percentage of patients with a (serious) adverse event in each category will be summarized and compared using relative and absolute effect measures, including absolute risk reduction, odds ratio and relative risk. Calculation of these effect measures will be model-based, e.g. using a logistic regression model. Wald p-values (1-sided) will be presented for the relative risk.

All SAE and AE leading to hospitalization term entered by the physician describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the most up-to-date version of MedDRA. Data displays of SAE will be performed using the preferred terms and their according system organ class.

The proportion of patients with SAE and AE leading to hospitalization will be summarized using the preferred terms and their according system organ class.

The number of AE leading to hospitalization over time will be analyzed separately using negative binomial regression models.

According to the latest version of module 4 of the dossier template, which will be used to submit results to the GBA, the analysis of selected SAE is no longer required. Selected SAE will therefore not be analyzed.

All safety analyses will follow the hypothetical strategy for treatment switches. For responder analyses, only adverse events before the treatment switch will be considered. For the number of AE leading to hospitalization over time, only AE leading to hospitalization before the treatment switch will be included and the follow up times included into the negative binominal regression model for these patients end with the treatment switch. Additionally, all safety analyses will be analyzed using the treatment-policy strategy for all intercurrent events.

4.6 OTHER ANALYSES

4.6.1 Patient Disposition

All summaries will be done by treatment group and by retrospective / prospective enrolled patients.

Population details will be presented based on the total population in terms of:

- Number of patients enrolled (= FAS)
- Number of patients treated

The disposition will be summarized as the overall count and percentage of patients who completed respectively discontinued the study prematurely including the categories for the primary reason for withdrawal as specified in the CRF.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, geographic region, and baseline disease characteristics (such as history of scoliosis surgery, highest motor milestone, HFMSE score, nutrition support, ventilation support, contractures, SMN2 Copy Number, CHOP-INTEND, CMAP amplitude, time between first treatment and onset of symptoms, pre-existing illness, need for wheelchair, participation in other registries) will be summarized by treatment group and by retrospective / prospective enrolled patients using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate. Baseline data is documented at index date.

4.6.3 Concomitant medication/ Therapy interventions

Concomitant medication on regular basis (treatment names) and therapy interventions (Physiotherapy, Feeding/Speech therapy, Occupational therapy, Other) will be summarized by treatment group.

4.6.4 Extent of Exposure

The exposure (duration of treatment) to SMA-Medication (risdiplam, nusinersen,) will be summarized by treatment group. Dose and number of interruptions (> 4 weeks) for risdiplam will be summarized. The number of subjects treated with onasemnogene abeparvovec will be summarized.

The number of subjects that switched treatment will be summarized by treatment group. The exposure (duration of treatment) for the switched treatments will be summarized as well.

4.6.5 Orthoses/Devices/Wheelchair use

The use, location and type of orthoses, the use and type of devices and the use and type of wheelchairs will be summarized by treatment group and visit.

4.6.6 Observation period

The patient-related observation period will be summarized (median, min, max) by treatment group and by retrospective / prospective enrolled patients (overall and end-point specific if applicable).

4.7 INTERIM ANALYSES / STATUS REPORTS

4.7.1 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be within six months after study start (retrospective enrolled patients and, if possible, prospective enrolled patients).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be calculated using observed effect sizes and recruitment

rates as assumptions considering all relevant endpoints. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped in consultation with G-BA due to futility in the respective population. For populations without a calculated sample size at study start, the same procedure will be conducted to check for futility. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped in consultation with G-BA due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

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