Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Voretigene Neparvovec (reassessment after the deadline: inherited retinal dystrophy)

of 15 September 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore

subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient voretigene neparvovec (Luxturna) for the first time on 9 April 2019. For the resolution of 17 October 2019 made by the G-BA in this procedure, a limitation up to 31 December 2021 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 April 2022 by the resolution of the G-BA of 20 May 2021.

In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Luxturna recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 March 2022.

Voretigene neparvovec indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999. Voretigene neparvovec concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 July 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-09) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1,

numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of voretigene neparvovec.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Voretigene Neparvovec (Luxturna) according to the product information

Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Therapeutic indication of the resolution (resolution of 15 September 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of voretigene neparvovec is assessed as follows:

There is a hint for a considerable additional benefit for adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Justification:

The benefit assessment is based on the randomised, controlled, multicentre, open-label phase III marketing authorisation 301 study investigating voretigene neparvovec versus monitoring wait-and-see approach, and the non-randomised, uncontrolled, multicentre observational LTFU study investigating the long-term safety and efficacy of voretigene neparvovec in patients who previously participated in the predecessor 301 study.

The 301 study enrolled 31 patients (intervention group N = 21, control group N = 10; corresponds to the ITT population) exclusively with a confirmed diagnosis of liver congenital amaurosis (LCA) due to RPE65 gene mutations. The study envisaged the enrolment of patients aged ≥ 3 years. Patients in the intervention arm each received 1.5 x 10^{11} vector genome voretigene neparvovec as a gene therapy intervention in the form of a subretinal injection under anaesthesia; after application to the first eye (day 0A; maximum 90 days after baseline), non-simultaneous injection was given in the second eye (day 0B) within 12 ± 6 days. A change of patients from the control group to the intervention arm was possible after one year at the earliest. According to the study protocol, the observation period after injection of the test medication into the second eye was 1 to 1.5 years in both groups. The patients could be followed up for up to 15 years after the 301 study in the single-arm LTFU extension study. Patients in the 301 study were randomised 2:1 stratified by age (≥ 10 vs < 10 years) and outcome level of the mobility test for screening with the worse eye (passing at ≥ 125 vs < 125 lux). The primary endpoint of the study was the change in the multi-luminance mobility test (MLMT), measured bilaterally at year 1B (= year 1 after treatment of the second eye in the intervention group) and year 1C (= year 1 after baseline in the control group) between the treatment groups.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

In addition to the evaluations of the pivotal, comparator RCT 301, the pharmaceutical company also submitted the results of the LTFU extension study for the benefit assessment. For the benefit assessment, only the results of patients who had previously participated in the 301 study were presented. All patients who completed the 301 study participated in the extension study, with one subject per treatment group dropping out already at the start of the 301 study (original intervention group N = 20, original control group N = 9). The original intervention group received the test preparation already at the start of the 301 study, while the patients in the original control group received the test preparation at the start of the LTFU study, provided they fulfilled the inclusion or exclusion criteria. The specifications for the injections in both eyes were identical to those of the 301 study. The study duration is 15 years; the study is currently not completed. The current data cut-off from 30 June 2020 is used for the benefit assessment. The median observation period since injection into the first eye until data cut-off (30 June 2020) is approximately 6 years 10 months in the former intervention arm of the 301 study and approximately 6 years in the former control arm of the 301 study. Therefore, based on this data cut-off, results are available up to year 5 after treatment of the second eye. Although the significance of the study is limited due to the single-arm study design and methodological limitations, the descriptive results are taken into account in the benefit assessment in order to be able to make an assessment of the sustainability of the effects of voretigene neparvovec. In the LTFU study, the efficacy and safety endpoints defined in the 301 study were further raised.

The 401 registry study was part of the time limit requirements for the reassessment after the deadline of the long-term effects, in particular on safety. This is a non-interventional, open-label, single-arm observational study of adult and paediatric patients aged 3 years and above with visual loss due to inherited retinal dystrophy who have received or will receive the intervention. The median observation period from injection into the first eye to the 31 August 2021 data cut-off is 0.65 years. Due to the short observation period of the 401 study up to the current data cut-off, no statements on long-term effects can be made. Therefore, the 401 registry study is not used for the benefit assessment.

Mortality

In the 301 and LTFU studies, mortality was recorded as a safety endpoint in the assessment of adverse events. No deaths were reported during either study.

Morbidity

Functional vision using the multi-luminance mobility test (MLMT)

The multi-luminance mobility test (MLMT) is used to measure changes in functional vision, in particular the ability to orientate and move independently in an obstacle course under different lighting conditions. The test uses seven standardised illuminance levels from 1 lux to 400 lux, which are checked with calibrated light meters at five different positions on the obstacle course. The testers assessed the outcome level of the mobility test using a predefined combination of speed and precision at a given illuminance level, which could range from 1 lux to 400 lux. The decisive factor for mobility was the illuminance at which the patient could still pass the mobility test in the corresponding test setting with the eye covered/ uncovered. This lux value was then converted into a mobility test score between 6 and -1 for each test setting, with a higher score corresponding to better mobility.

The ability to orientate or visual function in different ambient lighting is considered patient-relevant. In the 301 study, analysis of the change in MLMT mobility score for both eyes (bilateral) between the treatment groups at year 1B/C compared to baseline was defined as the primary endpoint. In MLMT, there is a statistically significant advantage in favour of voretigene neparvovec over the monitoring wait-and-see approach at year 1. Under voretigene neparvovec, no patient performed worse on the test at year 1 than at baseline.

For the dossier, the SMD was calculated- *post hoc* - according to Hedges'g; for MLMT, this is completely outside the irrelevance range of -0.2 to 0.2, so that a statistically significant, clinically relevant advantage is derived for voretigene neparvovec over the monitoring wait-and-see approach.

Due to the open-label study design, the risk of bias in the subjective endpoint is considered high. Thus, knowledge of the treatment assignment may have influenced the patient's performance of the test. Regardless of this, the assessment of the test was blinded, quality assurance measures were used during the study; the test was also conducted in a standardised manner. Furthermore, uncertainties remain, among other things, with regard to the increased percentage of procedure-related deviations in test performance (intervention group). In addition, a ceiling effect could be observed due to the already high values in the mobility score at baseline. Notwithstanding the methodological limitations mentioned above, there is a statistically significant, clinically relevant advantage for voretigene neparvovec over the monitoring wait-and-see approach for the endpoint MLMT.

In the LTFU study, changes from baseline were reported for the MLMT endpoint. The purely descriptive, non-comparator data for change from baseline are of a similar magnitude for the original intervention and control groups up to year 5.

Light sensitivity by means of full-field stimulus threshold test (FST)

The full-field stimulus threshold test (FST) was used to measure full-field light sensitivity in both studies.

This is a test with the aim of recording the subjective light sensitivity of the entire visual field at which the test subject can still see. For this purpose, patients are exposed to different luminances (brightnesses) in order to record the patients' perception of the luminance of a flash of light. A whole-field electroretinogram (ERG) was used to measure the luminance of a flash of light that the subject can still see. White, red and blue light stimuli were tested individually for each eye. An algorithm identified the minimum luminance (brightness) at which the test subject reliably perceived light. The luminance was converted into a logarithmic value. For log10 (cd s/m^2), a more negative result corresponds to a lower threshold and thus improved light sensitivity, indicating improved photoreceptor function.

From a methodological point of view, it is noted that the subjective tests could be measured several times until acceptable reliability values were achieved. Criteria for reliability assessment are described in the SOP, but this procedure is viewed critically in view of the open-label study design. The decision to repeat the test was thus made at the subjective discretion of the investigator (depending on the graphical assessment of reliability). For a final assessment of the risk of bias, there is a lack of information on how often measurement repetitions took place in the respective treatment arms. The risk of bias is considered high due to the open-label study design and the lack of blinding in the evaluation of the FST. According to the pharmaceutical company, the statistical analyses were carried out using the ITT

population. The reason for the missing data in the measurement with blue and red light (for three patients in the intervention group and one patient in the control group) is unclear.

Light sensitivity is assessed as patient-relevant. For the FST, the 301 study shows statistically significant effects to the advantage of voretigene neparvovec over the monitoring wait-and-see approach for the white, blue and red light. The results are also comparable for all three light variants and remain consistent over the entire course of the study up to year 1 after baseline. The SMD according to Hedges' g calculated *post hoc* exclusively for the test measured with white light is also completely outside the irrelevance range of -0.2 to 0.2.

The LTFU extension study shows a numerical reduction in scores compared to baseline that is of a similar magnitude in both original treatment groups.

Visual acuity by means of ETDRS/HOTV eye chart

Visual acuity was assessed in the studies using either the ETDRS eye chart or the HOTV eye chart, depending on the child's cognitive ability. The ETDRS chart was used in the 301 study for 18 subjects in the intervention group and 8 subjects in the control group. The HOTV chart was used for three subjects in the intervention group and one subject in the control group.

Visual acuity is a patient-relevant endpoint. The results on the a priori defined analyses, where both eye charts (ETDRS, HOTV chart) were evaluated together, were not statistically significant between treatment groups at year 1 and are consistent throughout the study up to year 1 after baseline. It remains unclear to what extent both eye charts are interchangeable, which is why the results are limited in significance. Separate analyses for each of the eye charts were not performed. The risk of bias is considered high due to the open-label study design and the lack of blinding during the evaluation.

In addition, *post hoc* responder analyses for an improvement or deterioration by ≥ 10 or ≥ 15 letters for both eye charts combined were submitted for the 301 study in the dossier. In addition, analyses for an improvement by ≥ 10 or 15 letters were presented separately for both eye charts. Studies on the transferability of the MID from the ETDRS to the HOTV eye chart or on the investigation of an MID by ≥ 10 or ≥ 15 letters for the HOTV eye chart were not presented. For these reasons, only the responder analyses for the ETDRS eye chart are considered. An improvement by ≥ 10 letters could be derived for 29% of the participants in the intervention group and ≥ 15 letters for 19% of the participants, whereas this was not the case for any subject in the control group.

For the LTFU study, no separate responder analysis for improvement or deterioration by ≥ 10 or ≥ 15 letters for the ETDRS chart could be identified. However, the descriptive, non-comparator results mostly show a numerical reduction in scores in both original treatment groups of similar magnitude.

Visual field measured by perimetry according to Goldmann and Humphrey

Both static (according to Humphrey) and kinetic examination methods (according to Goldmann) were used to measure the visual field in the 301 study. Both perimetry methods are widely used in clinical practice to measure the visual field. Goldman perimetry captures the entire visual field, while Humphrey perimetry focuses on specific regions in the visual field. An extension of the visual field defect or visual field limitations are considered patient-relevant.

In the Humphrey static examination method used here, the stimuli are located at a fixed position in the visual field to be examined and the light intensity of the stimuli is varied. In the Goldmann kinetic examination method, in contrast, the intensity remains constant and the stimuli are mobile. They are moved from outside the visual field boundary into the suspected visual field and the location of the first perception is documented. Different stimuli were used for both perimetric methods.

From a methodological point of view, it is critically noted that specific information on the frequency of the performance of subjective tests as well as on the repeatability of the measurement at baseline is not available. Also, the statistical analysis procedure was only described post hoc in the study report or Module 4. For a final assessment of the risk of bias, there is a lack of information on how often measurement repetitions took place in the respective treatment arms. The risk of bias is considered high due to the open-label study design and the lack of blinding in the evaluation of both methods of perimetry.

Since the test medication is applied to a specific region (macula) of the eye, Humphrey perimetry examined differences in function in this region before and after application of the test medication. Since application in the fovea region should be avoided, an examination was also carried out in this region. In the dossier, the results were averaged over both eyes for the light sensitivity limit in the unit decibel for the macular and foveal area. For Humphrey's perimetry, a statistically significant result for the mean macular limit to the advantage of voretigene neparvovec was shown in the macular region. The SMD according to Hedges' g calculated *post hoc* was also completely outside the irrelevance range of -0.2 to 0.2. No statistically significant difference could be derived in the area of the fovea.

In the Goldmann perimetry, the stimuli V4e (size: 64 mm^2, luminance: 315 cd/m^2) and III4e (size: 4 mm^2, luminance: 315 cd/m^2) were used. The study planned to collect baseline data for both stimuli together. At the follow-up visits, the test was started with stimulus III4e (1/16 smaller area than stimulus V4e). If it was suitable, the test was conducted with this stimulus and stimulus V4e was not used. Due to the small number of patients (<70% each) in the intervention group (n = 11) and the control group (n = 5), the results for stimulus V4e are not presented. In the 301 study, Goldmann perimetry showed a statistically significant, clinically relevant difference to the advantage of voretigene neparvovec for the total stimulus III4e score.

Overall, statistically significant effects to the advantage of voretigene neparvovec over the monitoring wait-and-see approach were shown for both methods of perimetry in the 301 study, which are judged to be clinically relevant based on Hedges' g evaluations.

In the LTFU study, Goldmann perimetry showed a numerical increase in scores at all time points compared to baseline in both original treatment groups. Humphrey's perimetry of the fovea and macula showed higher values at all time points compared to baseline in both original treatment groups.

Quality of life

Visual function questionnaire

In the 301 and LTFU studies, health-related quality of life was assessed using the Visual Function Questionnaire. This is a tool developed in orientation to the validated disease-specific quality of life questionnaire NEI VFQ-25. Thus, the questions of the two questionnaires

differ considerably in their wording; also, answer options and the structure of the questionnaire were changed compared to the NEI VFQ-25. The pharmaceutical company submitted validation studies for the NEI VFQ-25 only. Due to the considerable differences, neither the psychometric properties nor the MID of the NEI VFQ-25 appear to be transferable to the new updated version of the *Visual Function Questionnaire*. The evaluations cannot be taken into account in the benefit assessment.

Side effects

AEs, SAEs, discontinuation due to AEs

SAEs and severe AEs occurred only in the intervention group in the 301 study. Neither the number of patients with AEs, nor the number of patients with severe AEs, SAEs and therapy discontinuations due to AEs showed statistically significant differences between treatment with voretigene neparvovec versus the monitoring wait-and-see approach in the 301 study. Overall, there are no differences between the treatment groups in the overall rates that are relevant for the benefit assessment.

In detail, a statistically significant difference to the disadvantage of the intervention was observed for the AE SOC "Blood and lymphatic system disorders" and PT "Leukocytosis".

In contrast to the control group and the usual procedure of simultaneous recording, it should be noted in the intervention group that AEs were not reported from baseline, but only from the first injection. This took place on average 34.3 days after randomisation; thus, no AEs were evaluated for this period.
The pharmaceutical company submitted observation periods from screening for the 301 study with the current dossier for both treatment groups; information on the observation periods according to the study report (intervention group from 1st injection and control group from baseline) was not submitted. In the previous procedure, an average observation period of 406.6 days from the first injection to one year after the second injection was given for the intervention group. In the control group, the average time between baseline and year 1 was 354.8 days. The difference between the two groups was thus about 50 days.

Furthermore, for AE at SOC and PT level, the information on the number of subjects with AEs differs between the final study report and dossier Module 4. In the present resolution, primarily the AE evaluations were depicted based on the observation periods according to the study report (intervention group from the 1st injection and control group from baseline).

Due to the small number of sample size, the reliability of data is limited. In addition, due to the open-label study design, the risk of bias for the safety endpoints is to be assessed as high.

In the LTFU study, according to SAP V1, all AEs should be fully monitored until year 1 after the second injection. Subsequently, the focus of the documentation should only be on specific AEs (oncological events, haematological events, neurologic events and/or autoimmune diseases). From study protocol V2 onwards, the passage for complete monitoring of AEs until year 1B is no longer included. Upon request, the pharmaceutical company explained at the oral hearing that SAEs, frequently occurring AEs and, in addition, AEs possibly or probably related to the administration of the test preparation as well as new or deteriorating AEs in one of the 4 categories (oncological events, haematological events, neurologic events and/or autoimmune diseases) were recorded from year 1 onwards. Even if the uncertainties could be largely

eliminated as part of the written statement procedure, a residual uncertainty remains overall with regard to the question of the completeness of the AE survey.

On the basis of the available data and with a high risk of bias, new AEs only occurred in subjects in the LTFU study after year 1. Overall, the significance of the safety evaluations is limited by the small sample size.

Overall assessment / conclusion

For the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells, results on mortality, morbidity, quality of life and side effects are available based on the pivotal phase III 301 RCT. There are also results from the single-arm LTFU extension study on long-term efficacy and safety effects of voretigene neparvovec up to year 5 after treatment of the second eye.

In the mortality category, no deaths occurred in the 301 and LTFU studies.

In the morbidity category, there are statistically significant, clinically relevant advantages in favour of voretigene neparvovec for the patient-relevant endpoints of MLMT (functional vision/ orientation), FST (light sensitivity) as well as perimetry (visual field) in the 301 study; a statistically significant change in visual acuity could not be shown for voretigene neparvovec compared to the monitoring wait-and-see approach. In the LTFU extension study, an improvement in the endpoints of MLMT, FST, visual acuity and perimetry was observed in the descriptive, non-comparator analyses up to year 5 in both original treatment groups compared to baseline.

For quality of life, no suitable data are available for the benefit assessment.

In the endpoint category of side effects, the 301 study did not show any differences between the treatment groups that are relevant for the benefit assessment. In the LTFU study, only a few new side effects occurred after year 1.

The analyses of the LTFU study (at the data cut-off from 30 June 2020) indicate that the positive effects achieved in the 301 study under voretigene neparvovec are maintained in their magnitude up to 5 years after administration.

Overall, the long-term data presented confirm with reasonable certainty the long-term efficacy and safety of voretigene neparvovec for at least 5 years after a single dose of gene therapy. The sustainability of the changes achieved under voretigene neparvovec cannot be determined at this point in time.

In summary, the statistically significant and clinically relevant advantages of voretigene neparvovec over the monitoring wait-and-see approach shown in the 301 study are confirmed in magnitude by the LTFU study with respect to the MLMT, FST and perimetry endpoints, and are classified as considerable overall.

Significance of the evidence

The assessment of the additional benefit is based on the randomised, controlled, multicentre, open-label, phase III 301 marketing authorisation study, which investigated the efficacy and

safety of voretigene neparvovec over the monitoring wait-and-see approach. Furthermore, the results of the ongoing single-arm LTFU extension study were taken into account.

The risk of bias is rated as high for both studies at the study level. In addition to the open-label (and single-arm in the case of the LTFU) study design, the lack of blinding in the implementation and evaluation of the endpoints may pose a risk of bias in the results, especially for subjective endpoints. The risk of bias at the endpoint level is rated as high for all endpoints collected with subjective tests. This applies in particular to the patient-relevant endpoints of light sensitivity (using FST), visual field (using perimetry) and the endpoint of visual acuity (using ETDRS/HOTV eye chart). For the FST in particular, the test was not repeated according to systematic guidelines, but subjectively at the discretion of the principal investigator. For the endpoints of FST and perimetry, considerable uncertainties remain with regard to the operationalisation, especially the repeatability of the subjective tests. Furthermore, any influence of the natural development of children and adolescents on the performance of the tests also remains unclear.

Based on the 301 study, no statement can be made about the sustainability of the effects. The significance of the LTFU extension study is limited, among other things, due to the single-arm study design and methodological limitations.

Overall, the long-term data presented confirm with reasonable certainty the long-term efficacy and safety of voretigene neparvovec for at least 5 years after a single dose of gene therapy. The sustainability of the changes achieved under voretigene neparvovec cannot be determined at this point in time.

Uncertainties also remain regarding the operationalisation of the criterion "sufficiently viable retinal cells" used in the studies.

In addition, no data are available on the safety and efficacy of voretigene neparvovec in patients aged 4 years and below.

In the overall assessment, the result is a hint for a considerable additional benefit with regard to reliability of data.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Luxturna with the active ingredient voretigene neparvovec due to the expiry of the limitation of the resolution of 17 October 2019.

The present assessment relates to the therapeutic indication "treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells".

For the benefit assessment, the pharmaceutical company submits the results of the pivotal phase III 301 RCT, which allow comparative statements for voretigene neparvovec over the monitoring wait-and-see approach. There are also results from the single-arm LTFU extension study up to year 5 after treatment of the second eye.

The 301 study showed statistically significant, clinically relevant advantages in favour of voretigene neparvovec in the morbidity category in the endpoints of MLMT (functional vision/ orientation), FST (light sensitivity) and perimetry (visual field); no statistically significant change in visual acuity was shown for voretigene neparvovec compared to the monitoring

wait-and-see approach. The LTFU study also shows a numerical improvement in scores compared to baseline in the endpoints of MLMT, FST, visual acuity and perimetry by year 5. For quality of life, no suitable data are available for the benefit assessment. In the endpoint category of side effects, no statistically significant differences between the comparator arms can be derived from the 301 study. In the LTFU study, only a few new side effects occurred after year 1.

The significance of the two studies presented is classified as limited. Among other things, this is due to the respective study design as well as the existing uncertainties with regard to the subjective tests used to record morbidity and their repeatability.

Overall, the long-term data presented confirm with reasonable certainty the long-term efficacy and safety of voretigene neparvovec for at least 5 years after a single dose of gene therapy. The sustainability of the changes achieved under voretigene neparvovec cannot be determined at this point in time.

In the overall assessment, a hint for a considerable additional benefit. of voretigene neparvovec over the monitoring wait-and-see approach is derived for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The information is based on the pharmaceutical company's data from the 2019 dossier for the initial assessment of voretigene neparvovec. The figures are based on prevalence data of patients with Leber's congenital amaurosis (LCA) and retinitis pigmentosa (RP), each with biallelic RPE65 mutations; taking into account the lowest and highest prevalence, this results in a range from the minimum and maximum percentage of 188 to 655 patients (mean 355 patients). In a next step, the minimum and maximum percentage of treatable patients is taken into account; the resulting patient population of approx. 100 to 530 patients results from the approved therapeutic indication, which is restricted to those patients with "sufficiently viable retinal cells". Overall, the calculation of the size of the target population is of a plausible order of magnitude, but is subject to uncertainties. Regardless of this, it should be noted that the uncertainties described are estimated to be lower overall compared to the uncertainties resulting from the more recent figures presented with the current dossier.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Luxturna (active ingredient: voretigene neparvovec) at the following publicly accessible link (last access: 22 August 2022):

https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf

Treatment with voretigene neparvovec should only be initiated and monitored by retinal surgeons experienced in performing macular surgery.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must provide training material for medical professionals (e.g., retinal surgeons -and pharmacists) and a patient identification card. The training material contains, in particular, instructions for preparing and performing intraocular, subretinal application of voretigene neparvovec in a surgical setting under anaesthesia. The patient card shall be provided in specific formats, including large print format and audio file.

The Risk Management Plan (RMP) details that the training material for medical professionals contains relevant information on the preparation, storage and use of voretigene neparvovec including a description of the materials as well as subretinal administration.

To minimise safety risks associated with treatment with voretigene neparvovec, the aim is to ensure that treatment facilities preparing and administering voretigene neparvovec treatment comply with the criteria approved by the EMA and to be implemented in accordance with the risk management plan. The personnel involved in the administration (i.e. vitreoretinal surgeons and pharmacists) have participated in a mandatory training programme on the use of voretigene neparvovec to ensure the correct use of voretigene neparvovec to minimise the risks associated with its administration and/or the administration procedure (increased intraocular pressure, retinal tear, macular disease, cataract, intraocular inflammation and/or infection associated with the procedure and retinal detachment, third party transmission).

The criteria for treatment facilities should include the following:

- Presence of a specialised ophthalmologist with expertise in the care and treatment of patients with inherited retinal dystrophy.
- Attendance or affiliation with a retinal surgeon experienced in subretinal surgery and competent to administer voretigene neparvovec.
- An anti-inflammatory concomitant medication should be prescribed according to the product information.
- The interval for the treatment of the second eye should be planned according to the product information.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 01 September 2022).

Luxturna is intended for single administration in one eye[2]. The medicinal product is administered after vitrectomy as a subretinal injection as a single dose of 1.5 x 10^{11} vector genomes (Vg) in each eye, treating both eyes on different days within a short time interval of at least 6 days.

[2] Inpatient application is assumed.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Voretigene neparvovec	Single dose; 1x per eye on different days	2	1	2

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Voretigene neparvovec	1.5×10^{11} vector genome (Vg)	1.5×10^{11} Vg	$1 \times 1.5 \times 10^{11}$ Vg	2	$2 \times 1.5 \times 10^{11}$ Vg

Costs:

Voretigene neparvovec is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack[2]. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

Furthermore, costs are incurred for the pre and postoperative immunomodulatory treatment with prednisone recommended according to the product information.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Voretigene neparvovec	1 PSI	€ 295,000.00	€ 56,050.00	€ 351,050.00

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Abbreviations: PSI = powder and solvent for solution for injection				

LAUER-TAXE® last revised: 01 September 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Voretigene neparvovec is administered by subretinal injection after previous vitrectomy. The procedure is currently performed inpatient in specialised study sites. The inpatient costs are given for the pars plana vitrectomy to be performed prior to the administration of voretigene neparvovec. The basis for calculation is the valuation ratio of DRG C15Z (0.68) multiplied by the federal base case value 2022 (€ 3,833.07). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of DRG C15Z (3.4 days) multiplied by the nursing fee Section 15 para. 2A KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (since July 2022: € 200) and the nursing revenue valuation ratio (0.7628).

According to the product information, pre and postoperative immunomodulatory treatment with prednisone is recommended, which is illustrated below for children and adults. Initiation of the immunomodulatory treatment schedule is recommended 3 days prior to administration of voretigene neparvovec in the first eye; this should follow the same treatment regimens for the second eye and take the place of the treatment schedule for the first eye.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, an adult's average weight of 77.0 kg is assumed for the body weight, according to the official representative statistics "Microcensus 2017"[3]. For children, this results in an average weight of 36.79 kg (<1 year to <18 years). A range of the minimum (6 days between administrations in both eyes) and maximum (>16 days between administrations in both eyes) duration of the regimen is used as the basis for the calculation, depending on the time interval between the administration of voretigene neparvovec in the first and second eye. As a result, the costs for the time-limited immunomodulatory treatment with prednisone are the same (for one pack of 50 tablets each), regardless of age and treatment regimen, taking into account the ranges mentioned.

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pre and postoperative immunomodulatory treatment with prednisone[4]	50 TAB	€ 20.87	€ 1.77	€ 0.76	€ 18.34
Abbreviations: TAB = Tablets					

LAUER-TAXE® last revised: 01 September 2022

Voretigene neparvovec application leads to further costs in the outpatient area due to the need for control examinations (e.g., optical coherence tomography (OCT)).

Costs are incurred for the diagnostic examinations and check-ups carried out. Among others, there are GOP of the EBM for optical coherence tomography (OCT) for therapy control (GOP 06338 (right eye) or GOP 06339 (left eye)). The frequency and type of examination used can vary from patient to patient. The costs incurred cannot be quantified due to the individual determination of the control intervals by the attending physician.

Calculation year	DRG	Average duration of stay	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
2022	C15Z	3.4	0.680	€ 3,833.07	0.7628	€ 200	€ 2,606.49	€ 518.70	€ 3,125.19

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient
Medicinal product to be assessed				
Voretigene neparvovec	Pars plana vitrectomy including subretinal injection[5,6] (Operation and Procedure Code (OPC): 5-158.01) + nursing revenue	2	approx. € 3,125.19	approx. € 6,250.38
	Control examinations	Varies from patient to patient	non-quantifiable	

[4] Fixed reimbursement rate
[5] The cost of subretinal injection is based on inpatient treatment and billing via DRG code C15Z, which includes pars plana vitrectomy.
[6] Shown are the costs for an inpatient procedure.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 30 March 2022, the pharmaceutical company submitted a dossier for the benefit assessment of voretigene neparvovec to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 1 July 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 June 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	3 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing
Working group Section 35a	17 August 2022 31 August 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee	6 September 2022	Concluding discussion of the draft resolution

Medicinal products		
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken