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Cost-Utility Analysis of Luxturna versus the Standard of Care Treatment from a Narrow Danish Societal Perspective

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Project Description

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Preface

During the project period between February 2020 to June 2020, the Danish Medicines Council ended up recommending Luxturna as the standard treatment for adult and pediatric patients with visual impairment due to inherited retinal dystrophy with confirmed biallelic RPE65 mutation. They approved the drug on April 23, 2020. The approval of Luxturna is due to a new negotiated price of the medication for Denmark. The project group decided to continue to complete their original project of a cost-utility analysis of Luxturna because we believe our findings are still relevant.

Abstract

Introduction: Luxturna is the first gene therapy approved for the treatment of rare disease inherited retinal dystrophy (IRD) with confirmed biallelic RPE65 mutation. The disease impacts patients at a young age and eventually causes blindness. Luxturna has been recommended for treatment by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). Still, the Danish Medicines Council could not recommend the drug for these patients due to the findings from the cost analysis. The medication was too costly, and the long-term effects of Luxturna on the patients were unknown. We decided to conduct a full economic evaluation, specifically a cost-utility analysis (CUA), to determine if Luxturna was cost-effective compared to the current standard of care (SoC) treatment.

Methods: A cost-utility analysis (CUA) is done using a decision analytic model. A Markov model was created by using relevant costs and effects to estimate the incremental cost per QALY (quality-adjusted-life-year) gained from Luxturna compared with the SoC treatment from a Danish narrow societal perspective with the inclusion of productivity costs. The cost and effect data were estimated based on the assumption of a patient's lifetime, starting at 15 to death. The Markov Model data was obtained from phase III clinical trials and a U.K. Economic Evaluation on Luxturna by Viriato et al., which is based on a natural history study on RPE65-mediated IRD. The health states definitions were based on the American Medical Association Guides, and utility scores were based on Lloyd et al. 2019 study, which estimated IRD patients' utilities. The costs were estimated based on the cost analysis of Luxturna conducted by the Danish Medicines Council and AMGROS. The indirect costs were estimated using values from Denmark Statistics to calculate productivity loss.

Results: The base case incremental cost-effectiveness ratio (ICER) was 521,990.97 DKK/quality-adjusted life-year (QALY).

The deterministic sensitivity analysis results showed that the ICER was more sensitive to time horizon, discount rate, the exclusion of productivity loss, and the different assumptions of long-term treatment effect.

Probabilistic sensitivity analysis (PSA) showed Luxturna was a 25.9% chance of being cost-effective if the willingness-to-pay (WTP) threshold was set to be 325,000 DKK/QALY, and 77.9% chance of being cost-effective at 745,000 DKK/QALY.

Conclusion: Luxturna is likely to be cost-effective if the WTP threshold is 745,000 DKK/QALY (based on Swedish experience for rare diseases). Luxturna is not cost-effective if the WTP threshold is set to be 325,000 DKK/QALY (often-cited Danish WTP threshold, although there is no official threshold in Denmark).

There should be further investigation on the threshold for orphan drugs in Denmark for a decision rule.

Abbreviations

CUA: Cost-Utility Analysis

DkDRG: Danish diagnosis-related groups

DKK: Danish Krone

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

FST: Full-field light sensitivity test

GVF: Goldmann visual field

ICER: Incremental Cost-Effectiveness Ratio

IRD: Inherited Retinal Disease

MCDA: Multi-Criteria Decision Analysis

MLMT: Multi-luminance mobility test

NICE: The National Institute for Health and Care Excellence

PSA: Probabilistic Sensitivity Analysis

QALY: Quality-Adjusted-Life-Years

RCT: Randomized Control Trial

SoC: Standard of Care

U.K.: United Kingdom

U.S.: United States of America

VA: Visual Acuity

VF: Visual Field

V.N.: Voretigene Neparvovec

WTA: Willingness-to-Accept

WTP: Willingness-to-Pay

Introduction

Drug Information

Luxturna (active substance Voretigene Neparvovec, also known as V.N.) is the first gene therapy to treat a rare disease known as inherited retinal dystrophy (IRD) with RPE65 mutation (Product number EMEA/H/C/004451) [1]. The disease affects 1 in 200,000 people worldwide [2]. The National Institute for Health and Care Excellence (NICE) reported that the total costs, including indirect costs, took up to £523.3 million (4.4 billion DKK) in for 20,814 patients with IRD in the United Kingdom (U.K.) [3], 180 of them were identified with RPE65 mutations. The orphan drug gene therapy was developed by Spark Therapeutics and first entered the United States (U.S.) market in 2018. Spark Therapeutics has an agreement with Novartis to commercialize Luxturna outside the U.S. [2]. Luxturna is for patients with IRD caused by mutations on both copies of the RPE65 genes with enough remaining retina cells [4]. The medication works by enabling retinal cells to produce the missing enzyme due to biallelic RPE65 mutation [5]. Children who have biallelic mutated RPE65 genes incur vision loss at a young age, but the treatment can be used in pediatric and adult patients [6].

The first symptoms of the disease begin at an early age where the patient is unable to see in the dark, and this can happen as early as birth [7]. The vision continues to decline over time. There is significant vision loss of these patients during their teen years, and this eventually leads to blindness typically at the age of 30 [7]–[9] . The chart below displays what happens to the patients with IRD with RPE65 mutation over time [7].

Figure 1. Progression of Symptoms

The figure above shows the evolution of vision loss over time for IRD patients with RPE65 mutation.

When a patient presents with symptoms, the first step in diagnosis is administering a genetic test to confirm if the patient has a mutated RPE65 gene [4]. If a patient has the disease, then

Luxturna can be used, and a healthy copy of the RPE65 gene is injected under the retina of each eye that has viable retinal cells (sufficient retinal cells definition can be seen in ***Appendix 4***) [7]. Then Luxturna can allow the retina to produce the RPE65 protein, which can restore the visual cycle, then stop or reverse the decline of visual function [7]. Only one eye is treated at a time by a healthcare professional, and the second eye can be treated at least six days later [4]. Luxturna is recommended to be used on children and adults with sufficient viable retinal cells. The treatment is not recommended for children below the age of one because the retina is still growing, and if used, there is a chance Luxturna could be diluted [4], 10]. The optimal age for the recommended treatment of the disease is unknown. Still, the treatment is suggested when there are a sufficient number of functioning retinal cells, as defined in by Russell et al. in ***Appendix 4*** [11]. The most common adverse events include cataracts, increased eye pressure, and inflammation of the eye [12]. Luxturna is the only pharmacological treatment available for these patients impacted by IRD [7]. The other treatment solutions for patients are various vison aids or public assistance for those who are blind. The other treatments don't delay the disease; it will still progress quickly according to the study about the natural history of the disease where patients only receive SoC [13].

Clinical Trial for Luxturna

A randomized, controlled, open-label, Phase III clinical trial was conducted investigating the safety and efficacy of Luxturna in patients to deliver the gene for human RPE65 to the retinal pigment epithelium (clinical trial number: NCT00999609). The clinical trial included 31 participants between the ages of 4-44 in the U.S. The participants were divided into groups, the intervention group treated with Luxturna and a control group that had no treatment. The first data was collected for clinical trial NCT00999609, in July 2015, but the estimated completion of the trial to see the long-term effect of the medication is in July 2029.

The Phase III randomized clinical trial (RCT) for Luxturna had reported statistically significant ($p<0.001$) improvements in the outcome measures of multi-luminance mobility test (MLMT), and full-field light sensitivity test (FST) after one year. There are 62% of the intervention group passed the mobility test at the lowest light level of 1 lux in both eyes, which assessed the lighting in the poorly lit pavement at night. No one in the control group passed this test out

of all ten patients in the group (0/10). The efficacy was able to be maintained for at least three years [12]. As for the uncertainty regarding Luxturna's long term benefit, there was the longest follow-up evidence showing some participants in the clinical trial maintained the improvement up to 9 years after the year of injections [14].

There are two other clinical studies on Luxturna, which are based on phase I and phase II clinical trials. Still, they were not considered due to access barriers (cannot be searched in PubMed database and other available databases). They are mentioned in the European Medicines Agency assessment from 2018.

Approval of Luxturna by FDA and EMA

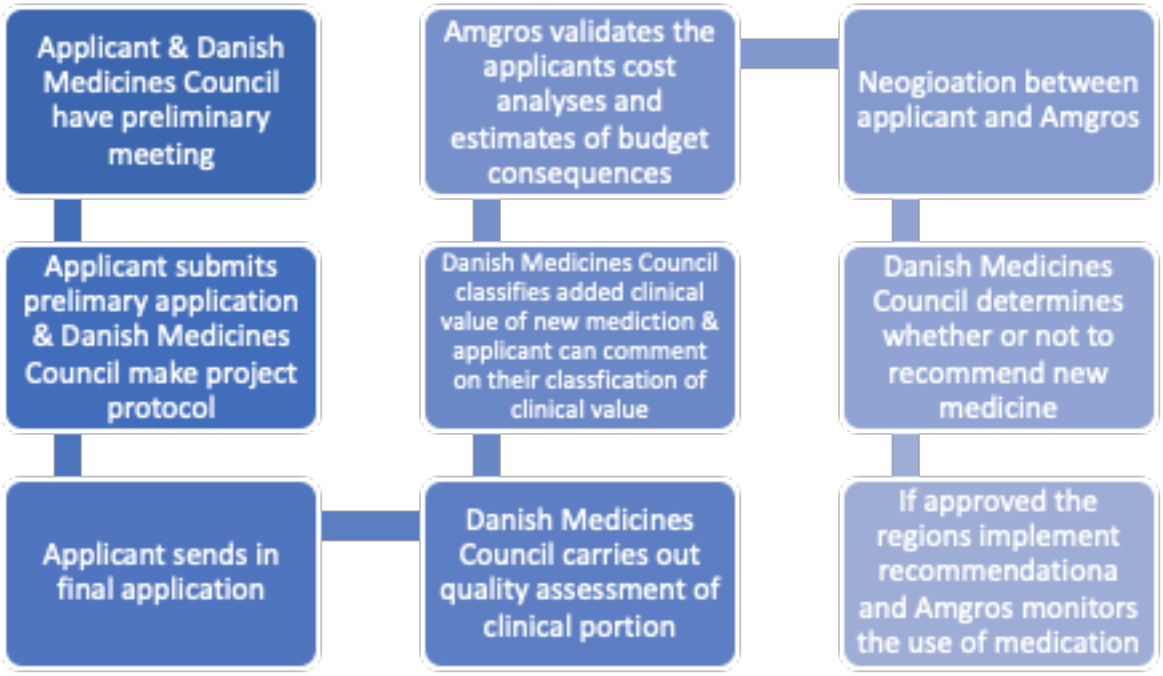
Luxturna is approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the efficacy and safety of the drug in Phase III clinical trial and data from Phase I clinical trial. The FDA approved Luxturna in December 2017, making the drug available for use in the U.S. EMA approved Luxturna for IRD patients with remaining retinal cells in November 2018 and designated as an orphan drug [1]. The approval by EMA means that the drug is available for use across the European Union, U.K., Norway, Iceland, and Lichtenstein. Still, countries do their own evaluation of the medication to determine if it is a cost-effective treatment. The individual counties handle their own drug pricing and reimbursement. Luxturna is "expected to improve quality of life and considered an important clinical benefit" and "side effects are manageable," according to the EMA assessment [15]. Despite the EMA's appraisal on Luxturna, the high list price of $850,000 (5.6 million DKK) of one-time subretinal injection to both eyes and the uncertain long-term added clinical benefits made it difficult for the decision-making in countries [16].

The National Institute for Health and Care Excellence (NICE) in the U.K. deemed Luxturna as cost-effective at list price before discount [7]. The U.K., which has a similar healthcare system to Denmark, the Beveridge model which funds the country's universal healthcare through income taxes, decided to fund Luxturna for up to 86 patients [17], [18].

Assessment Process of Luxturna in Denmark

The Danish Medicines Council is an independent council in charge of setting guidelines and recommendations for medications within the five regions of Denmark [19]. The Danish Medicines Council is in charge of the approval process for new medications to enter the Danish market based on their methods for assessing new medicines. It consists of three units: the council, the secretary, and the expert committees. The council determines recommendations for the use of new medication. The secretary assists both the council and expert committees, and the expert committee focuses on the assessment of new medicines and provides classifications of clinical added value [20].

Figure 2. Approval Process of New Medicines in Denmark



The figure above shows the general process of new medicines approval by the Danish Medicines Council found in the Process and Methods Guide for New Medicines and Indications.

The three essential processes that can be seen in the chart above, for the Danish Medicines Council to come to their decision on a new medicine are the medical assessment, economic assessment, and negotiation [20]. The medical assessment consists of a systematic evaluation of clinical value from scientific and clinical data. The clinical value is categorized from 1-6, where category 1 is high clinical value, whereas, category 6 is the non-documentable added

clinical value [20]. The expert committee assesses the clinical value of the new medication. The assessment is based on the weight of the outcomes according to the Grading of Recommendations, Assessment, Development, and Evaluation System (GRADE) approach. The GRADE approach assesses the full effect of medicine and clinically significant differences, assess relative effect measure to an inferential threshold, and critically assess the quality of evidence [20]. The AMGROS costs analysis looks at the costs per patient and how that impacts the overall budget [20]. Up until January 2020, AMGROS was the group that approved or denied economic assessments by the pharmaceutical companies, but now the Danish Medicines Council has taken over this task. AMGROS will, instead, just be in charge of negotiating the pricing of medications for the regions in Denmark [21]. The final process is the negotiation, which is used to determine if there is a reasonable relationship between the costs and clinical value of the medicine [20]. It is also recommended that health economic evaluations are included to assist decision-making processes. Still, in the case of Luxturna, a full economic evaluation was not conducted by the Danish Medicines Council, and instead, a cost-analysis is used. The guidelines of the Danish Medicines Council only call for a cost analysis to be done for new medicines being assessed.

Denial of Luxturna in Denmark

AMGROS, which did a one-year time horizon cost analysis for the Danish Medicines Council, only included cost associated with discounted medicine costs, hospital costs, and adverse events costs. The cost analysis did not include costs about standard care for IRD patients and indirect costs such as productivity loss [9]. The Danish Medicines Council denied Luxturna due to its high cost of 5 million DKK per patient, but note that the incremental cost might have been overestimated due to the exclusion of costs of SoC [19] [22]. The Danish Medicine Council's assessment on Luxturna concluded that important clinical added value under the low quality of published evidence and uncertainty about the long-term benefits and side effects without using generic quantitative measurements such as QALY. In the future, QALY will be recommended for the assessment of new health interventions starting from January 2021, according to the Danish Medicine Council news announcement [23].

There is a group of Danish patients that are impacted by the denial of Luxturna. According to the Danish eye specialist committee, 29 patients with biallelic RPE65 mutation have been identified in Denmark. Only 20 patients can qualify for treatment of Luxturna (estimated number according to the criteria of sufficient viable retinal cells, further detail see ***Appendix 4***) [19]. AMGROS estimated that 0.5 new patients would be added each year, or one patient every two years to the total number of patients in Denmark with vision loss due to IRD caused by RPE65 mutations [19].

To summarize, the denial of Luxturna was based on the previous AMGROS assessment that only focused on a biased cost-analysis, alongside with the added clinical benefits assessment that did not allow for comparison across different diseases [19]. Given that the decision had a subsequent impact on the well-being of RPE56 mediated IRD patients, more evidence should be synthesized to reflect on the decision. There are CUA of Luxturna in other countries. Zimmermann et al. reported a total incremental QALYs of 1.30 QALYs and the ICER is about 4,872,475.00 DKK/ QALY ($740,937 USD/QALY) using the U.S. healthcare perspective and 4,470,814 DKK/QALY ($679,858 USD/QALY) in the societal perspective [24]. However, Johnson et al. reported a 9.4 QALY gain for Luxturna and an ICER equal to -390,996.00 DKK/ QALY ($-59,458 USD/QALYs) which found Luxturna to be more effective and less costly in the U.S. compared to the SoC [25]. Viriato et al. reported that in the U.K., the incremental costs are 5,126,787.00 DKK (£612,404), incremental QALY of 6.4, and ICER to be 796,209.00 DKK/QALY (£95,072/QALY). The conclusion from this U.K. study was that Luxturna was likely to be cost-effective in the U.K. [7]. Halioua-Haubold et al. analyzed three cohorts of patients with the ages of 20, 45, and 60, and found the incremental QALYs to be 14.30 (age 20), 6.22 (age 45), and 1.48 (age 60) respectively in these three groups [26]. Although there have been many economic evaluation studies to provide evidence, the differences in health care background, societal preferences on quality of life, and cost of supportive care and productivity loss made these studies lack the transferability to the Danish healthcare setting. Therefore, there is still a need for further health economic evaluation that evaluates the cost-effectiveness of Luxturna using generic quantitative measurements of QALY in Denmark.

Study Aim

This project aims to synthesize more evidence and conduct a cost-utility analysis to further investigate the cost-effectiveness of Luxturna (V.N.).

The project will investigate whether Luxturna (V.N.) is cost-effective compared to the SoC treatment from a narrow societal perspective in Denmark. The extrapolation of a lifetime horizon, the inclusion of productivity costs, and the use of a generic qualitative measure like QALY will be used to reflect on the Danish Medicine Council's denial of Luxturna.

Methods

Literature Search

In order to identify all relevant data for the CUA, for instance, clinical trials outcome, costs, and cost-effectiveness analyses or other health technology assessments of Luxturna (V.N.), a systemic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. ***Figure 3*** illustrates the flow diagram by PRISMA.

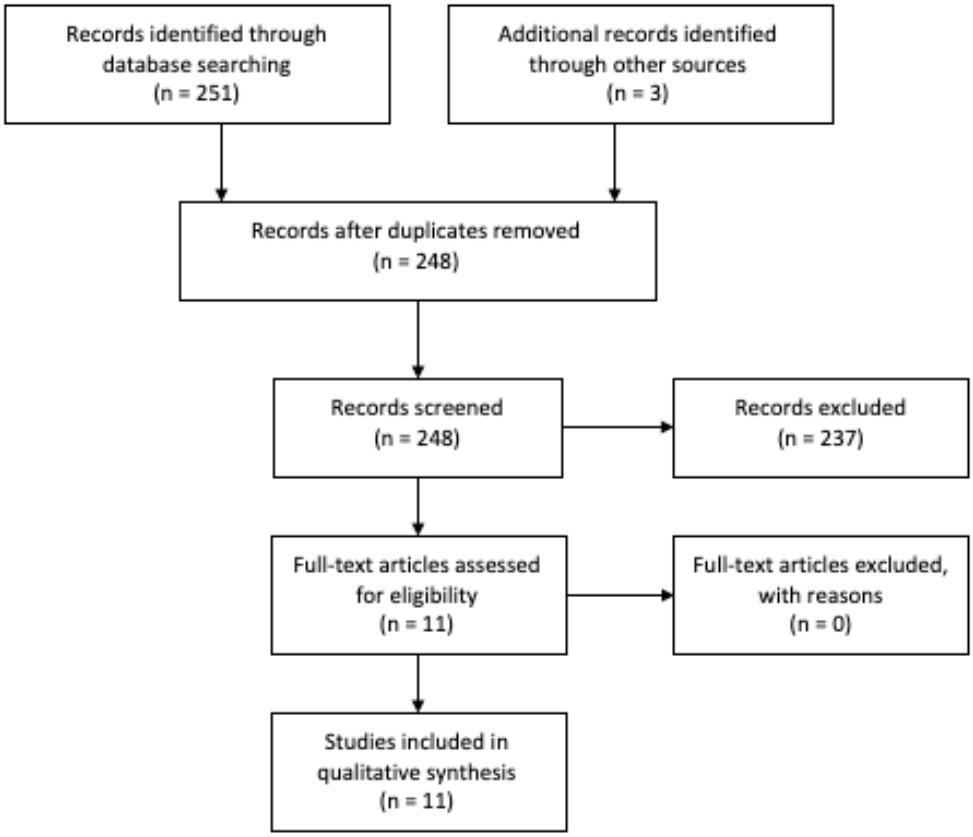


Figure 3. PRISMA Literature search flow diagram 2009.

The inclusion of studies through systematic literature mentioned above will provide the source of data that will be applied in the model as input parameters, and the existing models found will be customized to Danish healthcare settings.

The key words 'Voretigene Neparvovec or Luxturna' were searched in the PubMed database. There were 251 publications shown in the search results. The inclusion criteria are studies with clinical trial reports, health technology assessments of Luxturna, health economic evaluation of Luxturna, the economic burden of IRD, and cost analysis of Luxturna.

Through title reviewing, 8 publications were included based on the inclusion criteria. There were 243 of the search results that showed no relevance to the searched keywords, for example, they were about other gene therapy and retinal diseases. No study was excluded after abstract reading; in the end, 8 studies were included for the literature study. There were 3 studies included in from the references and searching in EMA and Danish Medicine Council websites.

Among those 8 studies, 3 economic evaluation [7], [24], [27] studies and 1 study [26] about quality of life study about V.N. were used to compare and study models for health economic evaluations. The comparisons of the methods used for assessing the cost-effectiveness in these studies were listed in ***Appendix 1***. The natural history of the RPE65-mediated IRD study was included, as referenced by (the quality of life study [26]. The assessment of Luxturna by EMA and Danish Medicine Council was also included in searching on the official website of EMA and Danish Medicine Council.

The models used in the 3 published CUA's and the one quality of life study about Luxturna varied because of their different synthesized evidence over the period of a lifetime. The 3 CUA studies base their model on phase III clinical trial, Johnson et al., and the quality of life study was based on phase I/II clinical trials (Further details in ***Appendix 1***).

Description of Phase III Clinical Trial of Luxturna (V.N.)

The phase III clinical trial of V.N. reported by Russell et al. was selected as the primary source of data for modeling the V.N. treatment effect on patients with IRD with biallelic RPE65 mutation (clinical trial number: NCT00999609) [12]. There were other clinical trial reports from phase I and phase II trials; however, they were not available in the database the project group had access to. Through the EMA's assessment report, the overall

summaries of phase I and phase II clinical outcomes were available, but not applied in the model in the end [28]. The project group decided to use a phase III clinical trial for the CUA.

There was a total of 31 subjects, which included 21 subjects in the V.N. group and 10 subjects in the control group, according to Russell et al.'s report. The primary outcome was the score changes in MLMT. Secondary endpoints were the full-field sensitivity threshold, monocular mobility testing change scores, and average change in visual acuity. The project group will explain the endpoints of the phase III clinical trial below. This is done in order to help the reader clearly understand what benefits the V.N. treatment effect brought to the observed patients, the endpoints applied in this model, and how these outcome data can be applied in our model.

Visual acuity (VA) and visual fields (VF) were the clinical endpoints chosen in our model to define health states as they are used to define health states in American Medical Association Guides to the Evaluation of Permanent Impairment. Further details will be introduced in the health state definition found further down in the methods. The rationale for choosing VA and VF was not about their ability to capture more health benefits that V.N. treatment could display, but the functional ability to define health states based on VA and VF scores. Health states can be a further link to utility scores. The project group also used VA and VF scores of both the control group and V.N. group to model initial health state distributions and after V.N. treatment.

The multi-luminance mobility test was created to quantify functional visions, which will capture visual acuity, visual field, and light sensitivity [28]. The MLMT has 12 unique and standardized approximately 1.5m by 3m obstacle courses, where there are the same number of turns, arrow, and hazards. The participants were tested under seven different lux levels or lighting conditions [12]. The MLMT test is believed to represent the V.N. treatment effect on visual acuity, visual fields, and light sensitivity, which might capture a broader aspect of treatment benefits. MLMT is not used due to the lack of studies that use MLMT scores to link to costs, utility, or mortality risks [8].

The full-field light sensitivity threshold is applied to assess participants' photoreceptor response and perception of light sensitivity at different luminance levels [29]. It is argued to be one of the most important indicators of the clinical benefits of V.N. therapy for a disease that is predominantly known by night blindness [29]. Light sensitivity is considered to demonstrate the improvement in night blindness, as it is one of the primary syndromes observed in IRD patients. The reason for not applying this outcome is the same as MLMT due to the inability to link scores to costs, utility, and mortality.

Visual acuity (VA) is evaluated using the scale adapted from Holladay [30]. VA scores are calculated for subjects who are unable to read conventional charts according to assessments of clinicians using of counting fingers or hand motions based on LogMAR measurements for adults. For young children who were instead assessing using HOTV test, which features four letters H, O, T, V. The Snellen scale, which is an eye chart to measure VA is used in HOTV can also be reversed to LogMAR:

$$LogMAR = -Log(\frac{Snellen\ numerator}{Snellen\ denominator})$$

VA is used to define health states in our model and also used to define health states in the American Medical Association Guides to the Evaluation of Permanent Impairment.

Visual Field (VF) is measured using the Goldmann visual field (GVF) perimetry test and the Humphrey computerized test, where participants were instructed to signal the investigator when the light became visible [12]. GVF was reported as the sum of total degrees. VF scores were used to define health states for initial distribution and after V.N. treatment in our model.

The phase III clinical trial report included a revised visual function questionnaire (VFQ-25). However, VFQ-25 is not validated by the creator yet; therefore, it cannot be used [12].

Markov Model

The Markov model is used as an aid to help estimate the lifetime cost-utility of V.N. for vision loss associated with biallelic RPE65-mediated inherited retinal disease is applied.

Model structure

The model structure was inspired by two studies about economic evaluations of Luxturna [7], [25]. There were similarities in these two models, including health states, the use of VA and VF scores from the phase III trial for modeling the after V.N. treatment health states and initial health state distributions, and the VA and VF scores from the natural history study used for modeling natural disease progression of patients receiving the SoC. We used the same initial health state distributions for both V.N. and SoC groups. In the V.N. group, the before and after V.N. treatment health state distributions were calculated as transition probabilities in the initial phase. Therefore, we assume the treatment effect will last for another 9 years, according to an expert report in the FDA conference [14]. After assuming 9 years of maintaining the same effect, when transition probabilities will be 0 in V.N. arm. The 10-years waning effect of V.N. treatment was assumed until the transition probabilities among health states of the V.N. group are equal to those in the SoC group (at age 34 years old). In Johnson et al.'s and Viriato et al.'s models, VA and VF scores from the natural history study were used to define health states for the natural progression of the disease, where multistate survival analyses were performed to calculate natural transition probabilities among health states in SoC group. We attempted to use Stata and the guides in their studies to reproduce a multistate survival analysis. However, given the data we had access to, we could not proceed with the calculations with the Stata 'mstate' package. The time a patient was in each state was required for 'mstate' notion, but that data was not provided in the natural history study. Therefore, we could not use multistate survival analysis. In the end, we applied the transition probabilities from Viriato et al. study [7]. The health state progression was modeled accordingly and demonstrated in the Markov chain section below in ***Figure 4*** & ***Figure 5***.

Figure 4. The model structure explained in V.N. group.

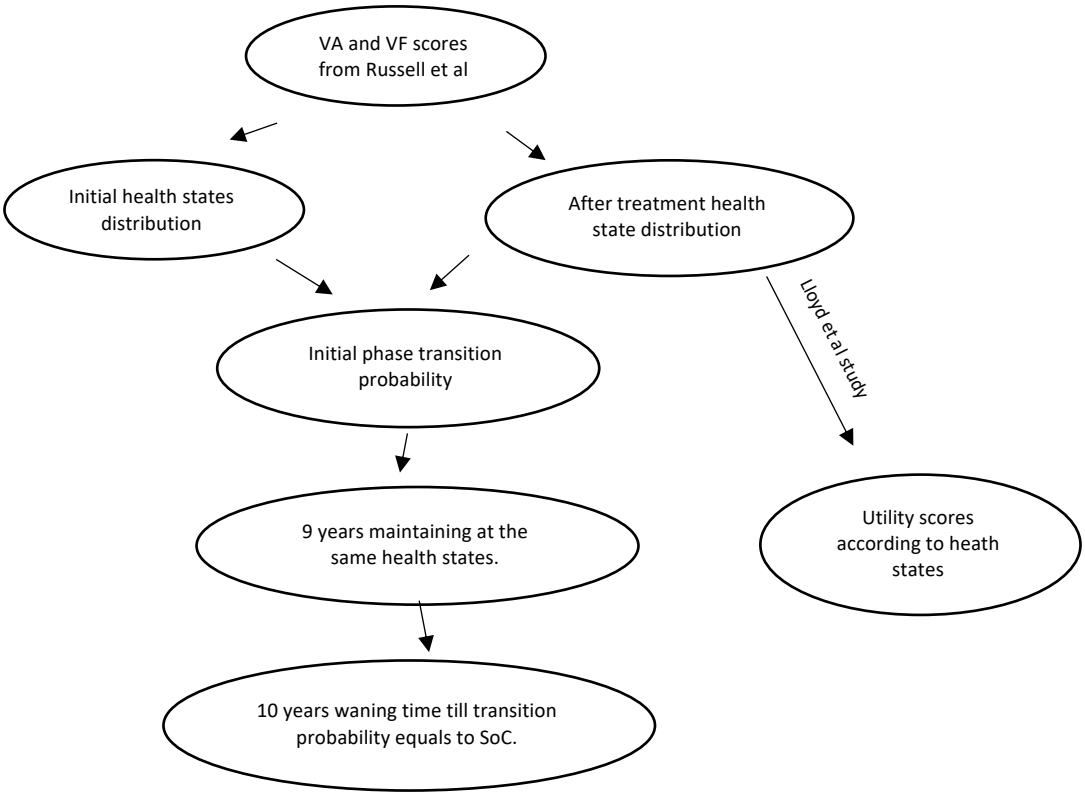
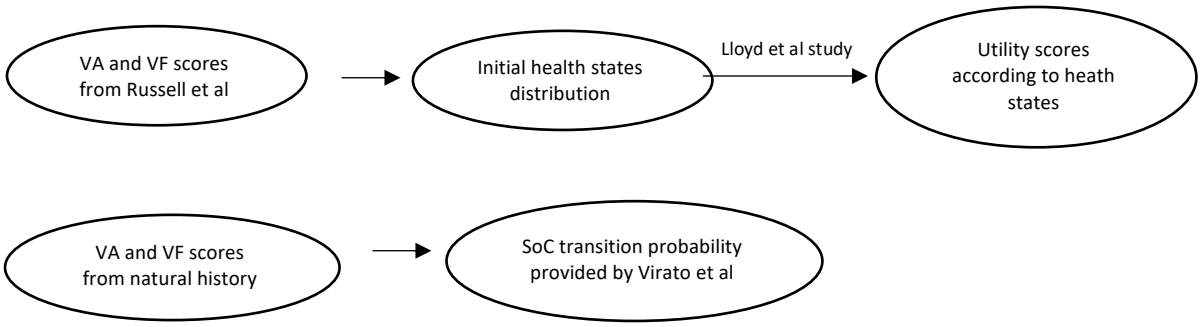


Figure 5. The model structure explained in SoC group



Heath states were then translated into utility scores using Lloyd et al.'s study that reported utility scores based on EQ-5D on health states, which is consistent with American Medical Association Guides to the Evaluation of Permanent Impairment [31]. Mortality risks were calculated using data from Statbank Denmark, with a combined health-state related hazard ratio. Cost strategies were done using a gross costing method, which involved using data from Danish diagnose-related groups (DkDRG), other relevant studies that reported cost of blindness, and officially reported costs of Luxturna [9], [32]. Further details will be explained in the cost section. An overview of the base case's resources in the Markov model can be seen below in **Table1**, and this model's assumptions can be seen in **Table 2**. Lifetime accumulations of QALYs and costs were calculated by TreeAge Pro 2019. This model was able to synthesize many available pieces of evidence specific to the RPE65-mediated IRD. We performed the Markov model in TreeAge Pro 2019 and applied the annual cycle and half-cycle correction.

Table 1. Base case references used for Markov Model input values

Treatments	Luxturna (V.N.)	SoC
Utility Scores	Lloyd et al. [31], the Danish population norm [33]	Lloyd et al. [31], the Danish population norm [33]
Initial Health States	Russell et al. [12]	Russell et al. [12]
Costs	Medicinrådet [9], the Danish Health Authority [32]	The Danish Health Authority [32]
Transition Probabilities	Russell et al. [12], Viriato et al. [7]	Viriato et al. [7]

Table 2. Key model assumptions and rationales

assumptions	rationales
treatment effect will remain the same for 8 more years	Clinician reported the longest follow-up of 9 years with no decrease in treatment effect
treatment effect will have a 10-year waning time	no evidence of longer health benefits and the uncertainty about the immuno response to carrier virus, which will affect gene expression. A clear cut-off point when the effect is suddenly gone is not realistic.
HS5 jump states equal to HS4	the participants enrolled have enough remaining cells meaning there should be also active response.
patient demography will be similar to Russell et al.	Russell et al. was a randomized clinical trial with more patients enrolled than other trials expect for the natural history study

Treatment strategies

The interventions assessed were voretigene neparvovec (V.N.), also known as Luxturna, and standard of care (SoC). The specific SoC treatment for patients in Denmark was unclear to us without the assistance of clinicians. We, therefore, assume that SoC treatment includes regular physician visits and supportive care.

Health state definitions

There are five disease-specific health states, including 'moderate,' 'severe,' 'profound,' 'count fingers,' and the last one 'hand motion, light perception or no light perception' and one absorbing state, death. The 'count fingers' was used to describe patients who can count fingers that are held up in 1m but cannot read any letters on a vision chart at the distance of 6m. The 'hand motion, light perception, and no light perception' describes when a patient cannot count fingers and are only able to see a waving hand or worse [34]. Five disease-specific health states were defined in alignment with the American Medical Association Guides to the Evaluation of Permanent Impairment. 'Moderate' or 'health state 1 (HS1)' was defined as visual impairment with VA<1 or VF>240. 'Severe' or 'HS2' was defined as visual impairment with VA≥1 and VA<1.4 or VF≤240 and VF>144. 'profound' or 'HS3' was defined as visual impairment with VA≥1.4 and VA<1.8 or VF≤144 and VF>48. 'Count fingers' or 'HS4' was defined as visual impairment with VA≥1.8 and VA<3 or VF≤48. 'Hand motion, light perception, or no light perception' or 'HS5' was defined as visual impairment with VA≥3 or indications of hand motion, light perception, or no light perception. These health states can be seen in **Table 3**. VA measurement uses the LogMAR measurement of the Holladay scale, and VF measurement is the sum of total degrees using Goldmann III-4e [35].

Table 3, Health States and Definitions [35]

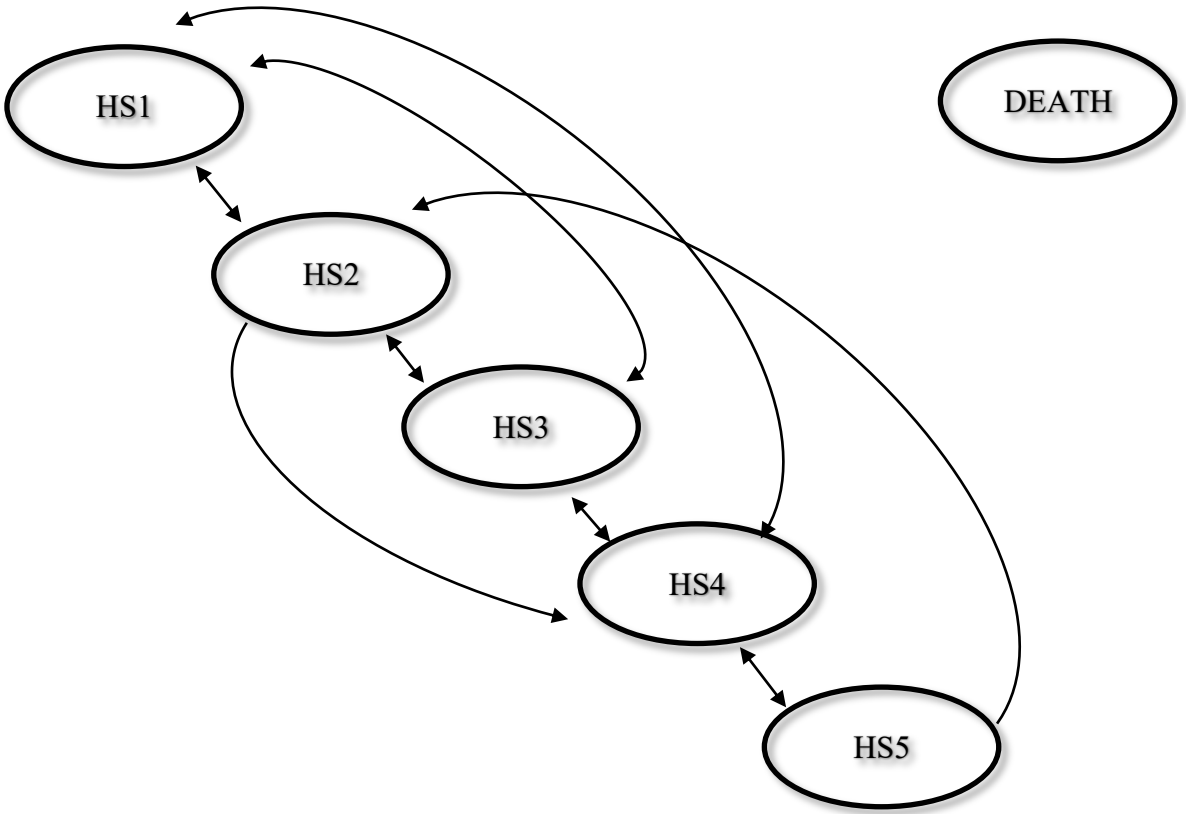
Health States	Definition
HS1: moderate VI	VA<1 or VF>240
HS2: severe VI	VA<1.4 or VF≤240 and VF>144
HS3: profound VI	VA≥1.4 and VA<1.8 or VF≤144 and VF>48
HS4: count fingers	VA≥1.8 and VA<3 or VF≤48
HS5: hand motion, light perception or no light perception	VA≥3 or indications of hand motions, light perception, no light perception

VI: visual impairment; VA: visual acuity; VF: visual field

The Markov chains and model tree

The Markov chain was made in accordance with Russell et al. and natural history study [12], [13]. For V.N. arm, patients in HS1 does not progress to any worsened state. Patients in HS2 can either move to HS1 or continue to stay. Patients in HS3 can move to HS1 or HS2. Patients in HS4 either stay or move to HS3 or HS1. Patients in HS5 can either stay or move to HS4 or HS2. In the SoC arm, the disease progression was assumed to either stay or deteriorate. According to Johnson's calculations, [25], HS1 can progress to HS2, HS3, HS4, or stay. HS2 can progress to HS3, HS4, or stay. HS3 can progress to HS4 or stay. HS4 can progress to HS5 or stay. No state was able to jump to HS5 state except for HS4 directly. For both V.N. and SoC arm, any state can transit to death. The illustration of the Markov chain is shown in ***Figure 6.***

Figure 6. The Markov Chain for V.N. and SoC



Discount Rate and Perspective

Some costs and benefits occur in the future after the study was conducted [36]. The timing is relevant since people have a time preference where present costs and effects are valued more than future costs and effects. The presence of opportunity costs can also be the reason why the value will be different in time. In cases of health intervention, opportunity costs reflect that the resources spent could have been allocated in other sectors and yield interest and return over time. In order to adjust the value of costs and benefits in a different timeline, the discounting approach was taken [37].

In Denmark, the recommended annual discount rate is 4%, according to Ehlers et al. [38]. We used the discount rate of 4% for both health outcomes and costs as many other economic evaluations in Denmark, according to the Danish Medicines Council [39]. A full societal perspective was not taken because accounting for the full effects the SoC has on the patient, their families, the public, and the overall government expenditure was not available for Denmark. The perspective taken is a narrower Danish societal perspective, which includes the indirect cost of productivity loss.

Modeled Population

The population was modeled according to the patient demography of biallelic RPE65-mediated IRD patients in Russell et al. study with the mean age of 15 years and around 40% male and 60% female, which also was close to the patient demography in the natural history study [12], [13]. The population for this analysis was not the actual characteristics of biallelic RPE65-mediated IRD patients in Denmark because the specific patient population and demographics are unreported in Denmark. There were altogether 31 patients enrolled in the randomized control trial, of which 7 were in HS1, 10 in HS2, 7 in HS3, 6 in HS4, and 1 in HS5 according to health state definitions; this can be seen in **Table 4**. Russell et al. study was used to model the baseline health state distribution for the modeled population; these values can be seen in **Table 5**. Two patients withdrew from the clinical trial, one from the V.N. group and one from the intervention group.

Table 4. The number of patients at baseline[12] [41]

	HS1	HS2	HS3	HS4	HS5
V.N.	4	6	6	4	1
SoC	3	4	1	2	0
Total	7	10	7	6	1

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception, V.N.=Voretigene Neparvovec, SoC=standard of care.

Table 5. Baseline health state distributions[12]

health states	percentage at baseline (%)
HS1	23
HS2	32
HS3	23
HS4	19
HS5	3

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception.

Treatment Effect and Transition Probability for V.N. Arm

We use the Russell et al. study for the treatment effect for the V.N. group by calculating the transition probability of health state distributions after the first year of treatment. After 1 year, we assume that the treatment effect will stay for another 9 years (based on reported longest treatment effect), and then a 10-year waning time is followed. In the 10-year waning time, we assume an approximately linear decrease in treatment effect over the period until no treatment effect is left, and the disease progression will be the same as in the SoC arm. The treatment effect in mathematical models is presented as the calculated initial phase transition probabilities in V.N. treatment leading to a different health state distribution. In the 9 years stable period, the transition probabilities will be 0, meaning cohorts staying at the same health state distribution after the initial phase. In waning-time, the transition probabilities will reappear as the health state will progress linearly until the 10th year, which equals the transition probabilities in the SoC arm. That is, health states will progress in year 1 in the waning period, but due to treatment effect, only 1/10 of that in natural health state progresses. A 10-year waning period is assumed given that there was no evidence about how long the treatment effect will last and the doubts from specialists about the immuno suppressive response, which will gradually affect the expression of active protein [40]. Therefore, it is reasonable to assume that the treatment effect might decrease gradually

instead of having a clear cut-off point. We assumed a more conservative time same as Zimmermann et al. [24].

In the Russell et al. study, there is only 1 patient out of 31 trial participants that is present in HS5 in the baseline, and this patient subsequently withdrew from the study without any follow-up data. Therefore, we used the assumption from Johnson et al. study that the patients would move the same number of health states as in HS4. That was 50% of patients in HS4 moved to HS1; under the assumption, 50% of patients in HS5 would move to HS2 [25].

In **Table 6**, the number of patients in different states 1 year after V.N. injection was listed. The number was based on the health state definitions using VA and VF from Russell et al. [12],[41]. We used the number in **Table 6** to calculate the transition probability listed in **Table 7**. The matrix should be read as, for example, in HS2, there were altogether 6 patients, of which 5 transited to HS1, and 1 remained in HS2. In **Table 7**, the matrix should be read as, for instance, patients in HS2 has an 83% chance of transitioning to HS1 and 17% chance of staying in HS2.

Table 6. Matrix of the number of patients transition to other health states 1 year after V.N. injection [12], [41]

	HS1	HS2	HS3	HS4	HS5
HS1	4	0	0	0	0
HS2	5	1	0	0	0
HS3	3	3	0	0	0
HS4	2	0	1	1	0
HS5	0	0	0	0	0

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception.

Table 7. The transition probabilities matrix, 1 year after V.N. injection [12], [41]

	HS1	HS2	HS3	HS4	HS5
HS1	1	0	0	0	0
HS2	0.83	0.17	0	0	0
HS3	0.5	0.5	0	0	0
HS4	0.5	0	0.25	0.25	0
HS5	0	0.5	0	0.25	0.25

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception.

Assumptions for this project were made according to the evidence that had the longest follow-up time of 9 years, which showed that the treatment effect is still maintained. The assumed decrease in effect was due to the uncertainties regarding the long-term gene expressions of V.N. in responses from the immune system, according to the Danish medicine council and EMA [29], [42]. We used a waning period to avoid a sudden cut-off point where the effect would immediately disappear instead of gradually fading.

The decrease was modeled as linear, meaning in age 25, which was the 10th year since injection, since the transition went from 0 to the full transition probability as in SoC arm during 10 years linear progression. The transition probability would be 1/10 of that of SoC aged 25, until in age 34, the 10th year, the transition probability would be equal to that of SoC aged 34.

An example would be:
In the nine years follow up of the treatment, the transition probability from one state to another will all be 0.

At age 26, the transition probability from HS1 to HS2 would be 0.3116 in SoC arm. In V.N. arm, the transition probability from HS1 to HS2 would be 2/10 of that in SoC arm aged 26. So, the transition probability from HS1 to HS2 for V.N. would be:

$$=0.3116 * 0.2 = 0.0623$$

The other results are listed table 1 in ***Appendix 2***.

Meaning, at the age of 26, patients in HS1 from the V.N. group have a 6.23% chance of progressing to HS2.

Disease Progression and Transition Probability for SoC Arm

We used the transition probabilities provided by the Viriato et al. study to model the disease progression in the SoC arm. The transition probabilities were not published in the article, but the covariates' efficiencies were published instead [7].We got the calculated transition

probability privately from them. The natural history study of biallelic RPE-65 mediated IRD patients is used to model the disease progression for the SoC arm patients and put in as transition probability in different health states based on the data from Viriato's estimates [13]. It was assumed that a patient could not recover and move to the previous state in the natural disease progression.

The transition probabilities for SoC are listed in table 2 in ***Appendix 2***.

Morality Risks

The risks of death by age and gender were calculated according to the data available in StatBank Denmark. We used the number of deaths by age in 2019, divided by the number of populations by age and gender in 2019 to calculate the risk of death. The overall risks of death by age were calculated according to the modeled population, where 40% were male, and 60% were female [12].

Furthermore, we used the reported hazard ratio of death associated with visual impairment by Christ et al. to adjust the mortality risk [43].

An example would be:
In 2019, there were 13 men aged 26 who died, and the population of men aged 26 that year was 33,308.

Therefore, the risk of death for men aged 26 in 2019 would be:

$$= 13 \div 33{,}308 = 0.0003903$$

In 2019, 11 women at the age of 26 died, and the population of women aged 26 that year was 31,475.

Therefore, the risk of death for women aged 26 in 2019 would be:

$$= 11 \div 31{,}475 = 0.0003495$$

Furthermore, the risk of death for our modeled population aged 26 would be:

$$= 0.0003495 \times 0.6 + 0.0003903 \times 0.4 = 0.0003658$$

Table 8.hazard ratio of death by health states according to Christ et al.[43]

	HS1	HS2	HS3	HS4	HS5
hazard ratio	1.08	1.18	1.18	1.18	1.18

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception

The risk of death, according to age for the modeled population, are listed in Table 3 in ***Appendix 2***.

Health Outcome

Health outcome was modeled as the accumulations of utility scores over life years. The utility scores were extracted from the only study from Lloyd et al. reporting the quality of life for biallelic RPE65-mediated IRD patients [31]. Utility values from this study were also aligned with the health states in this model and base on vignette descriptions of health states (which was the same with our health state definitions)and expert elicitation interviews using the EQ-5D-5L. Experts judged the impact of health states according to their experience and knowledge [31]. Expert elicitation approaches have been used for many rare diseases when the recruitment of patients in each health state was difficult [31].Unlike other serious eye conditions, for biallelic RPE65-mediated IRD patients, they suffer from deteriorating VA and VF since childhood, accompanying nyctalopia [8]. By simply using the utility scores from other visual impairment studies where visual impairment caused by, for instance, retinal complications of diabetes would not be specific enough due to the differences in the symptoms and other disease complications.

We used the utility scores from Lloyd et al. for patients younger than 20 years old [31]. After 20 years old we made an age-dependent adjustment on utility scores based on the Danish population norm [33]. The rationale for doing so was that even though the Lloyd et al. study was health-state specific, it did not have health-state-dependent and age-dependent utility scores. It is reasonable to assume that health state 5 would have a different impact on patients who were 20 years old and 70 years old [33].

The disutility of adverse events such as cataracts, retinal tear, and eye inflammation were not counted as it was reported to be mild and recovered and resolved shortly after [12]. We assumed it would not affect the utility scores, but the costs of these adverse events will be incorporated in the Luxturna treatment option.

Table 9. Utility scores published by Lloyd et al [31]

	HS1	HS2	HS3	HS4	HS5
utility scores	0.709	0.615	0.515	0.354	0.152

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception

Table 10. Danish population norm utility scores [33]

	20-29	30-39	40-49	50-59	60-69	70-79
men	0.943	0.928	0.908	0.888	0.883	0.847
women	0.919	0.903	0.881	0.858	0.839	0.818

An example of the disutility and utility score calculation would be:

Disutility Calculation

For patient aged 26 and in HS1, the disutility would be:

$$= 1 - 0.709 = 0.291$$

Utility Score Calculation

The utility score would be:

$$= 0.943 \times 0.4 + 0.919 \times 0.6 - 0.291 = 0.638$$

The other calculations would be listed in table 4 in ***Appendix 2.***

The accumulations of utility scores will be added up to be QALYs since we are doing an annual cycle, QALYs before discounting will be:

$$QALYs = (utility\ score\ at\ age\ 15 \times 1) + (utility\ score\ at\ age\ 16 \times 1) + (utility\ score\ at\ age\ 17 \times 1) + (\dots)$$

Direct Costs & Indirect Costs of Luxturna and SoC Treatment

The costs that are included in an economic evaluation are relevant costs, which are only the costs that differ between the alternatives [38]. There are two types of costs to be aware of

when performing an economic evaluation, which are direct and indirect costs. Direct costs can be easily traced to a purpose in the patient's care. Indirect costs are not easily traced to a particular purpose in the patient's treatment. Examples of these costs for Luxturna and SoC treatment can be seen in **Table 11.**

Table 11. Relevant Costs in Luxturna and SoC.

Treatments	Direct Medical Costs	Direct Non-Medical Costs	Indirect Costs
Luxturna	• Diagnostic Testing • Medication • Surgery • Medical supplies* • Physician and nurses' salaries* • Outpatient visits* • Adverse Events	• Transportation to hospital* • Care giver*	• Productivity loss
SoC Treatment	• Ophthalmologic visits* • Hospitalization* • Diagnostic Testing	• Education • Vision Aids • Support and care • Municipality cost	• Productivity loss

*The costs with * are not specifically included in this CUA due to lacking information. Diagnostic testing was considered irrelevant since there was no reason to believe it will be different for both groups. The DRG tariffs used to represent the average hospital operating costs for the specific group also take into consideration clinician salaries.*

Only some of the costs above were included in this project's economic evaluation because some information about the costs were not available to quantify in a Danish setting due to lacking information. There is a guideline provided by AMGROS for estimating unit costs for cost analysis of new medicine so that all applicants follow the same procedure when applying for a new medicine approval [44]. Medicine prices can be estimated using the tariff-based approach or a micro-costing approach. The ideal costing approach is micro-costing because it provides more details associated with the intervention, but it is harder to obtain when information is not available. Therefore, a DkDRG based costing approach is taken both by AMGROS in their cost analysis of Luxturna, and this cost-utility analysis because it was the information available [9]. The DRG costing estimates the average hospital operating charges

per DRG group [45]. The DRG codes used in the cost estimation of Luxturna are from the AMGROS published background document of the denial of Luxturna. The costs associated with the SoC treatment were from a Danish estimation of the cost of blindness in the year 2003 but was adjusted to represent the cost in 2020 using consumer price index (CPI) [32].

Cost Estimates for Luxturna

As stated above, the project group is using the narrow societal perspective with productivity costs over the health care perspective taken by the Danish Medicines Agency [38]. Therefore, the estimation of productivity loss will be included in the cost-utility analysis because it plays a significant role in these patients' lives and amounts up large production gains to the society. Patients lost their vision from a young age and were assumed to be unable to work when they were legally blind.

The cost estimates for Luxturna are based on the cost analysis accepted by AMGROS with current 2020 prices. The costs associated with Luxturna include drug costs, hospital costs, and cost of adverse events related to its use.

The medication costs associated with Luxturna include the actual drug cost and prednisone cost, which is used three days before injection and up to fifteen days after the injection [9]. The cost of Luxturna is based on the pharmacy's purchase price (PPP), which excludes VAT, and the cost of prednisone is based on the PPP. The PPP values are from medicinepriser.dk. The PPP value of prednisone dosage is based on the average patient weight from Russell et al. [19].The medication costs can be seen down between in **Table 12.**

Table 12. Cost of Medication

Medication	Strength	Package	Pharmacy Purchase Price
Luxturna	5 x 10^{12} vg/ml	1 vial with concentrate and 2 solvent vials	2,575,666.50 DKK
Prednisone	5 mg	100 tablets	56.38 DKK

The hospital costs associated with Luxturna include a large operation with general anesthesia, minor eye examination, and the use of a disposable insulator during surgery. The costs

displayed in **Table 13** below are for each operation. The costs for the large operation with general anesthesia and the minor eye examination are based on the 2020 Danish DRG tariffs. The DRG tariffs are found on the https://sundhedsdatastyrelsen.dk/
website. The DRG tariff pricing is the average cost of hospital operating expenses, and these were what was used in the AMGROS assessment of Luxturna, and this project group has done the same. The additional cost of the disposable insulator during surgery was estimated to be 18.000 DKK per operation, and this was adjusted to the 2020 price using the Consumer Price Index to measure inflation [9]. The formula below was used in the calculation:

Present Value = (old cost x new index) / old index

Table 13. Hospital Costs of Luxturna

Hospital Costs	DRG Group	DRG Rate (DKK) 2020
Large operations, retina, veins membranes and vitreous, general anesthesia	02MP07	15,452.00 DKK
Minor Eye Exam	02PR01	1,019.00 DKK
Disposable insulator	_____	18,193.74 DKK

The other costs accounted for in the cost analysis for Luxturna include those for adverse events related to the medication. The adverse events and their distributions are from the phase III, 301 study by Russell et al., and in the AMGROS assessment three treatment-related adverse events were included that had a greater than or equal incidence of 10%, and those three same adverse events were included in this assessment [9], [12]. The difference is the updated pricing of the DRG tariff to the year 2020, to their present value using the CPI, can be seen in **Table 14**.

Table 14. Cost of Adverse Events

Adverse Events	Incidence Rate	DRG group	DRG (DKK) 2020
Cataracts	15%	02MP20	9,015.00 DKK
Eye Inflammation	10%	02PR01	1,019.00 DKK
Increased Pressure in the Eye	20%	02PR01	1,019.00 DKK

The estimated cost of Luxturna for both eyes is 5,224,091.14 DKK. That is summing the expected adverse events cost, hospital costs, and medication costs and multiplying by two (patients assumed to get their eyes treated at different visits, therefore 2 visits for both eyes) but excluding PPP of prednisone (the dose is for both eyes).

Cost Estimate of Blindness

The AMGROS cost analysis did not account for any costs associated with the current standard treatment, also known as SoC. The cost of the comparator in this project will be accounted for based on the cost of blindness in Denmark with 2020 prices [32]. The cost of blindness is divided into categories, the first being support, and care. Support and care costs account for caretakers and home care. The Danish Health Authority has estimated that a total of 180 hours of caretaker assistance is needed per year for those patients who are considered blind; therefore, the present value total cost per patient is 73,434.79 DKK per year [32]. The cost of assistive devices includes aids such as a cane, tape recorder, and note devices. There are various packages for patients and vary in cost, but the average cost per patient, per year, is 23,271.59 DKK in present value for the year 2020 [32]. Guide dogs are also used by blind patients but are not as common. In 2003, there were only 219 guide dogs who were trained in Denmark. There was an assumption that only 1 in 5000 of those who are blind would receive a dog for assistance; therefore, even though it was expensive to train a guide dog, the average annual cost per year in the present value is 905.01 DKK for a guide dog. The reason to include this average cost was that there was no guideline and information on who got the guide dog, and it could be RPE65-mediated IRD patients.

The next cost is the written and audio sources available at the Danish Blind Library, which is around 5,329.19 DKK per year in the present value [32]. There are additional costs for the municipality in terms of aids for blind patients such as special lights, watches, or talking weights. The Danish Health Authority mentioned it is difficult to calculate this because there is no clear overview on how many blind patients have such aids, and estimate that it costs 12,928.66 DKK per year in present value [32]. Education includes the costs to attend courses at the Institute for the Blind and Visually Impaired in Hellerup. It is estimated to be around 51,714.64 DKK in the present value to attend per blind patient [32]. There are additional costs associated with being blind. However, they have been left out of the analysis because there is no available data on their costs and the number of used resources. There is an assumption

that patients are blind once they reach HS2, which aligns with the Danish definition of legal blindness, and the cost analysis data we used for blindness [32], therefore, they will endure these costs after they reach that health state. HS1 was assumed not to cost anything as they would not require supportive care in our definition. The estimated costs associated with SoC can be seen in **Table 15.**

Table 15. Cost of SoC

Costs	2003 (DKK)	2020 (DKK)
Support and Care	56,800.00 DKK	73,434.79 DKK
Assistive Devices	18,000.00 DKK	23,271.59 DKK
Guide Dogs	700.00 DKK	905.01 DKK
Danish Blind Library	4,122.00 DKK	5,329.19 DKK
Municipality cost	10.000,00 DKK	12.928,66 DKK
Education	40.000,00 DKK	51.714,64 DKK

The estimated cost of these resources for patient with SoC treatment is 167,583.88 DKK per patient per year.

Productivity Costs

According to the U.K. study and based on the Royal National Institute of Blind People, all patients in HS2 are considered blind, which aligns with the Danish definition of blindness [7][46]. In Denmark, the Medical Council states that patients will become completely blind at 30 years old [19]. Patient's lives are significantly impacted by their condition, which impacts their ability to participate in society. The Danish Blind Society mentions that there are around 2,500 members within the working age (15-64), but only 1 in 5 are employed on ordinary terms or in a flexible job [47]. Therefore, the project group has decided to come up with a theoretical estimation of productivity cost to the Danish society of the patients confirmed with biallelic RPE65 mutation-associated with retinal dystrophy. There is an assumption that absenteeism productivity loss for all RPE65 mediated IRD patients from the age of 15 until retirement age at 64.

Productivity costs account for the cost to a society based on morbidity and mortality in a population [38]. It is a way to estimate if a new treatment can have a monetary benefit of being introduced, and the impact it can have on the patient's lives [38]. A theoretical attempt

is made to measure the productivity costs if the standard of care treatment is used, and not with the intervention of Luxturna. There is an assumption that for patients under the age of 15, their productivity loss will be zero because the minimum legal age for working in Denmark is 15 [48].The productivity cost is estimated using the human capital approach as opposed to the friction-cost method because the project group is looking at the patient's work lifetime gross income before taxes instead of looking into a specific period of a few months [38]. Pension money was the fund that was part of the before tax salaries; therefore, it will not be added in for risks of double counting.

Assumptions of Patient Population for Calculation of Productivity Costs for V.N. and SoC

- Age 15- 64
- An unemployment rate of zero based on human capital approach
- Cannot work in HS2, HS3, HS4, or HS5
- Average of a 37-hour work week
- 30 days of vacation because of the Danish Holiday Act
- Average Annual Pre-Tax income of men and women in Denmark used because HCA calls for gross annual income which includes all the sources of how a person earns money for a year
- If they didn't have this disease, then they would be able to get a job

Luxturna is currently the only treatment available to treat these patients. The Danish Medicines Council denied it; therefore, it is important to calculate the theoretical estimate of productivity costs associated with this disease if there is no treatment available. The Danish Medicines Council found the SoC cost to be zero because the information was not available. We have decided to calculate productivity costs in this analysis, even though the Danish Medicines Council does not recommend it [38]. This disease hits at a young age and impacts their lifetime income and their ability to contribute to society by paying taxes. Some diseases hit older populations, and it makes sense not to include productivity costs because they may get the disease after they have left the workforce. The inclusion of productivity costs is relevant for the analysis of Luxturna because of the severe consequences this disease imposes on younger patients with their future productivity at stake [49].

The values that are necessary to calculate productivity costs are gross annual income before tax, depending on age and gender. The gross annual income values are from Denmark Statistics, 2018 (https://www.statbank.dk/10331). These were the most current gross annual incomes available at this time. This population is chosen because they are the ones who are in the workforce and accounted for in the human capital cost of productivity approach. Therefore, it is important for these to be included in the model. Expected productivity costs for legally blind patients are listed in Table 7 in ***Appendix 2***.

The expected productivity loss with gender distribution from age 15-64 is seen in the chart above. The gender distribution is based on study 301 Phase III, which found that 60% were female and 40% were male who were impacted by this disease [10], [12], [13]. The expected productivity loss with gender distribution in Denmark is 16,558,509.00 DKK annually without discounting.

The calculation can be seen below:

(Expected income for males x 0,40)+ (Expected income for females x 0,60) = 16,558,509 DKK.

The value above signifies the estimated productivity costs for patients between the ages of 15 and 64 with RPE65-mediated inherited retinal disease who do not receive treatment, which is the current SoC available in Denmark. The productivity costs were included in our Markov Model. However, a sensitivity analysis will be conducted on how the ICER value changes with the exclusion of productivity costs in the model. This will be displayed in the results section.

To summarize, the cost of V.N. arm will be the sum of Luxturna costs, blindness costs and productivity loss while in SoC arm, the cost will be the sum of blindness costs and productivity loss.

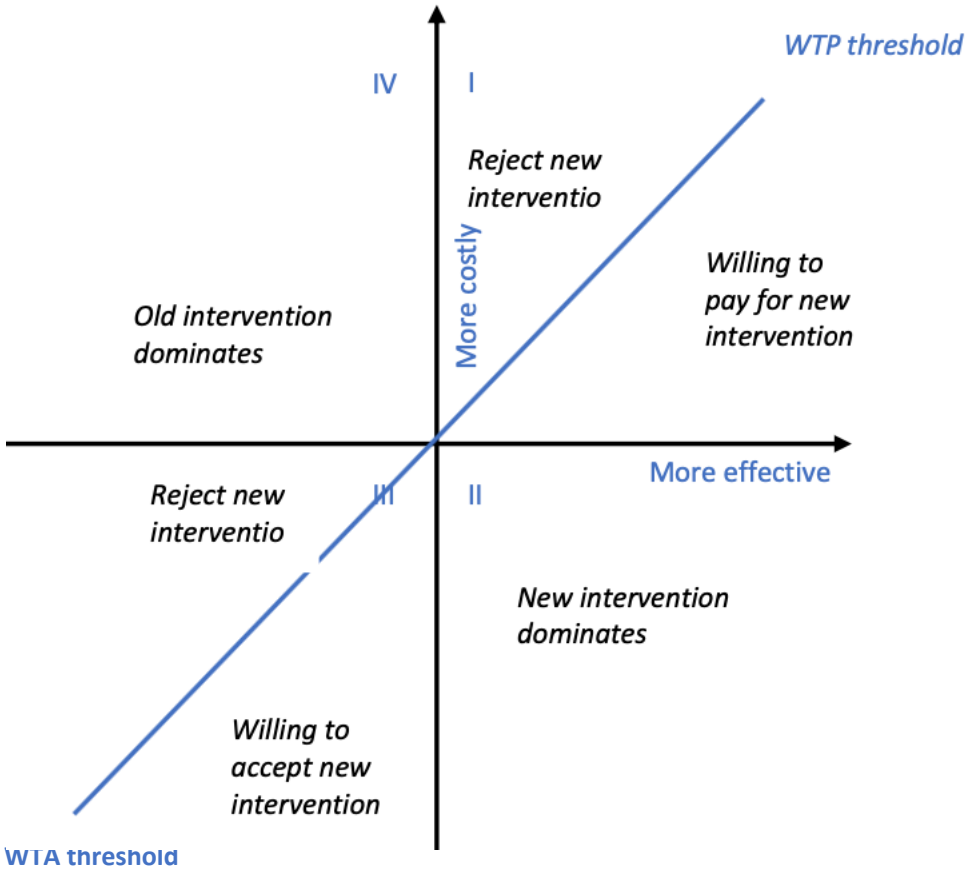
ICER Plane and Decision Rule

The result of this study will be calculated as ICER:

$$ICER = \frac{cost(VN) - cost(SoC)}{QALY(VN) - QALY(SoC)}$$

In ***Figure 7***, in ICER plane was displayed. In quadrant I, Luxturna is more costly and more effective, the society will be willing to pay for Luxturna if ICER is below the WTP threshold. In quadrant II, Luxturna is more effective and less costly, meaning Luxturna dominates over SoC. In quadrant III, Luxturna is less effective and less costly; if the ICER is placed below the WTA threshold, Luxturna will be accepted. In quadrant IV, Luxturna is more costly and less effective, meaning SoC dominates [36].

Figure 7. The ICER plane and decision rule explained



Sensitivity Analysis

To test the robustness of the results, we performed deterministic sensitivity analyses as well as probabilistic sensitivity analysis.

Deterministic Sensitivity Analyses

One-Way Sensitivity Analyses

One-way sensitivity analyses test how individual variables impact the robustness of the results while holding other variables constant. It can help to understand how sensitive the result will be to every single parameter chosen. However, it cannot indicate the overall uncertainty of the decisions. The results of one-way sensitivity analyses will be listed as in table and tornado diagram. Tornado diagram helps to visually demonstrate how the results will range when one value or scenario is changed from the lower to the upper value, and which parameters the results are most sensitive to [36].

One-way sensitivity analyses include testing the discount rate range from 0 to 5% for either cost or the effect measure of QALY. The lower bound of 0% was chosen to see how the result will change if time preference of cost or effect is not considered. The upper bound of 5% was chosen since most health economic studies applied the discount rate from 3% to 5%, according to Severens et al. [50].

Utility scores from HS1, HS2, HS3, HS4, and HS5 were included in one-way sensitivities analyses individually to see how they might alter the results. Due to the lack of upper and lower value of utility scores, we used 10% to add and minus as to define the upper and lower value of utility scores.

Productivity loss from 0, meaning not including the productivity loss to the upper limit of an additional 20%, was used to see how the result will change accordingly. Blindness associated supportive care costs were also included, due to the lack of upper and lower limits data, we used 20% to add and minus for the costs data.

The Deterministic Multi-Way Scenario Analysis

We performed scenario analyses to see how different model cases will alter the results. Scenario analysis includes the use of natural history data to distribute initial health states entry, assuming that HS5 does not transition to other health states after a V.N. injection [12]. A third scenario sensitivity analysis is completed using 5 years and 40 years of waning time. The other scenario sensitivity analyses include utility scores using only Lloyd et al., not applying a hazard ratio, and assuming treatment effect last extra 9 years without waning period, treatment effect last 20 years, 40 years (base case model in Viriato et al. to lifetime without considering the waning period. The lifetime horizon of 1 year (AMGROS report, [9]), 10 years, 20 years, and 40 years were put in for scenario analyses too.

Probabilistic Sensitivity Analysis

In order to evaluate parameter uncertainty, probabilistic sensitivity analyses (PSA) were performed. For costs, gamma distributions were used with an assumed 20% increase and decrease in upper and lower limits. The distributions were selected according to how the scatters in real life will likely shape up. For probability, beta distributions were used with an assumed 5% increase and decrease in upper and lower limits when there was no available confidence interval data. For utility, beta distributions were used with an assumed 10% increase and decrease in upper and lower limits when there was no available confidence interval data.

The inputs of natural history initial distribution are shown below in **Table 16**, and the calculation methods were same as the base case above.

Table 16. Initial health state distributions according to natural history data [28].

health states	percentage at baseline (%)
HS1	47
HS2	24
HS3	12
HS4	15
HS5	3

HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception.

TreeAge Pro 2019 is used to conduct the PSAs. In order to do a proper PSA, we contacted the TreeAge support team for instructions when dealing with table inputs.

In the end, we distributed utility scores and costs by creating distributions for each value (beta distribution for utility, gamma for cost) and then created variables with an array of those distributions. For transition probabilities, we first created the tables with transition probabilities with upper and lower values. Then a PERT distribution was created (named as dist_PERT), a reference to column 1 as mean, 2 as a minimum, and 3 as maximum, 5 for shape, which is similar to beta distribution. For instance, we created transition probability in SoC from health states 1 to 2 as table p_h12, then variable defined as p_h12[age;dist_PERT]. Further explanation is seen in the TreeAge website knowledge base [51].

Results

The results of translating VA scores and VF scores into health states were already shown in the method section, see **Table 4**, **Table 6**.

Base Case Result

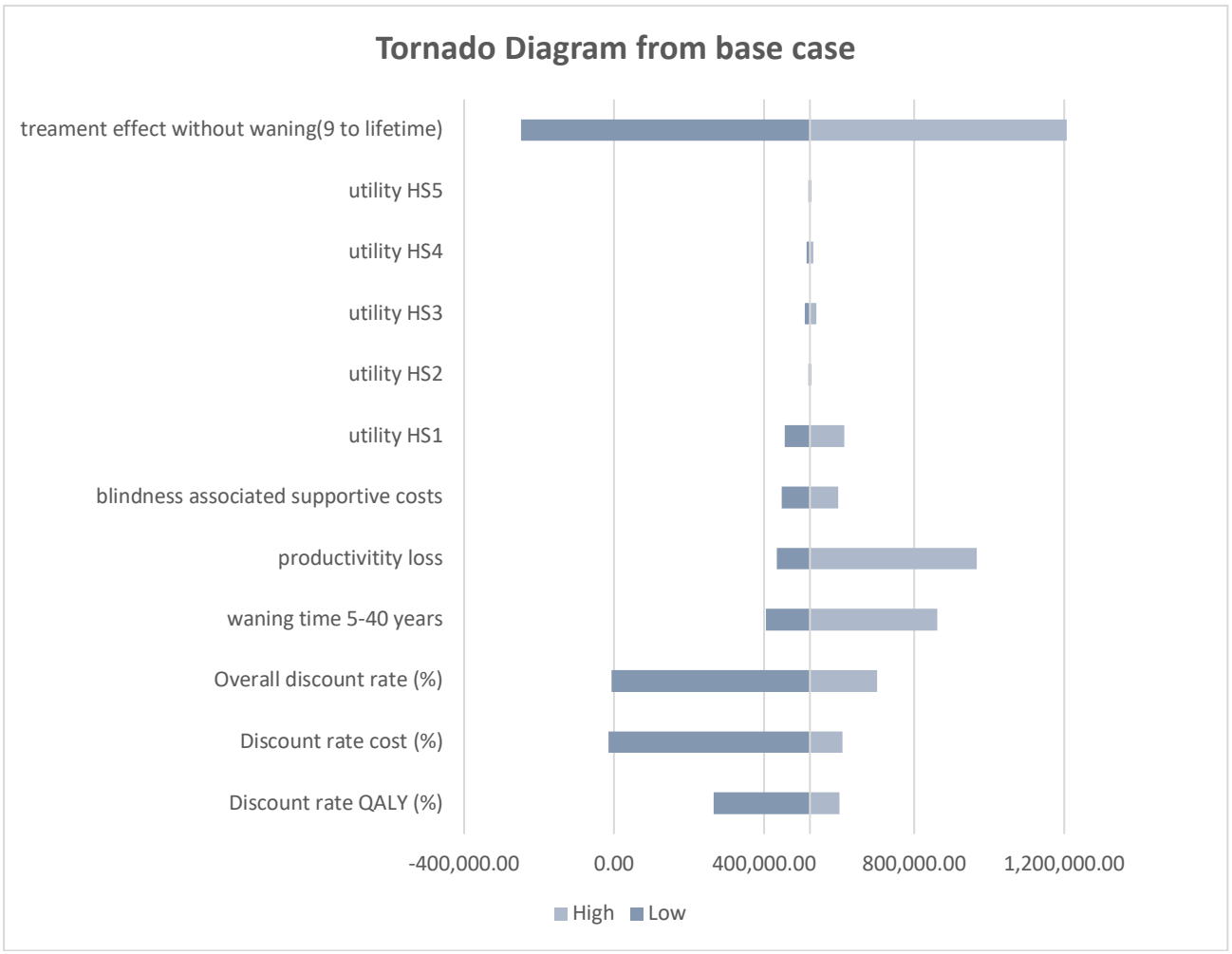
The base case lifetime stimulations in the Markov model from using TreeAge Pro showed that the accumulations of costs for SoC and V.N. are 10,072,535.85 DKK and 12,097,860.80 DKK respectively, and the accumulations of QALYs for SoC and V.N. were 6.16, 10.04 respectively, which means it would cost 1,635,151.92 DKK/QALY for SoC and 1,204,966.22 DKK/QALY for V.N.. The base case ICER comparing V.N. against SoC is 521,990.97 DKK/QALY.

In TreeAge, the Markov cohorts showed that in the SoC group, at the age of 24, all of the patients will be in the states that were defined as legally blind in Denmark, which include HS2, HS3, HS4, and HS5 [46]. However, in the V.N. group, the results differed, showing that at the age of 61 that all of the patients will be in legally blind states. The results from the model can be seen in **Table 17.**

One-Way Sensitivity Analysis Results

A tornado diagram, ***Figure 8,*** was constructed using the base case parameters from the Markov model. The purpose of the tornado diagram is to show what parameters have the most uncertainty in our model. The wider the bar is, the more significant the effect on the model. The most uncertainty lies with the treatment without waning, which is the treatment becoming less effective over time, from 9 years after treatment to the remaining years of the patient's life. The other parameters that have more uncertainty in the model are the overall discount rate, the discount rate of costs, the discount rate of QALY, and productivity costs.

Figure 8. The Tornado diagram of the base case



The horizontal axis displays ICER (DKK/QALY). The centerline value is that of base case result.

Table 17. Base case and one-way sensitivity analysis results from age 15 to death.

	Cost SoC	QALY SoC	Cost V.N.	QALY V.N.	ICER
Base case	10,072,535.85	6.16	12,097,860.80	10.04	521,990.97
	CE V.N.	1,635,151.92	**CE V.N.**	1,204,966.22	

	Cost SoC	QALY SoC	Cost V.N.	QALY V.N.	ICER
Discount: QALY 0%	10,072,535.85	9.87	12,097,860.80	17.5	265,442.33
Discount: QALY 5%	10,072,535.85	5.62	12,097,860.80	8.99	600,986.63
Discount: Cost 0%	32,793,624.25	6.16	32,737,685.99	10.04	-14,417.08
Discount: Cost 5%	8,070,427.24	6.16	10,432,765.02	10.04	608,849.94
HS1 utility scores -10%	10,072,535.85	6.12	12,097,860.80	9.42	613,734.83
HS1 utility scores +10%	10,072,535.85	6.21	12,097,860.80	10.66	455,129.20
HS2 utility scores -10%	10,072,535.85	6.02	12,097,860.80	9.87	526,058.43
HS2 utility scores +10%	10,072,535.85	6.31	12,097,860.80	10.22	517,985.92
HS3 utility scores -10%	10,072,535.85	5.93	12,097,860.80	9.92	507,600.24
HS3 utility scores +10%	10,072,535.85	6.40	12,097,860.80	10.16	538,650.25
HS4 utility scores -10%	10,072,535.85	6.01	12,097,860.80	9.96	512,740.49
HS4 utility scores +10%	10,072,535.85	6.32	12,097,860.80	10.13	531,581.35
HS5 utility scores -10%	10,072,535.85	6.12	12,097,860.80	10.03	517,985.92
HS5 utility scores +10%	10,072,535.85	6.20	12,097,860.80	10.05	526,058.43
productivity loss not included	3,765,368.88	6.16	7,516,863.94	10.04	966,880.17
productivity loss +20%	11,333,969.25	6.16	13,014,060.18	10.04	433,013.13
blindness supportive care costs -20%	9,319,462.07	6.16	11,639,283.69	10.04	597,892.17
blindness supportive care costs +20%	10,825,609.63	6.16	12,556,437.92	10.04	446,089.77

ICER= (Cost Luxturna-Cost SoC)/ (QALY Luxturna-QALY SoC), costs are all in DKK. ICER and CE scale are DKK/QALY. HS1=moderate; HS2=severe; HS3=profound; HS4=count fingers; HS5=hand motion, light perception or low light perception. CE=cost effectiveness

As seen in **Table 17,** QALY was discounted from 0% to 5%, and the ICER value changed from 265,442.33 DKK/QALY (no discount) to 600,986.63 DKK/QALY (5% discount). When the costs were discounted from 0% to 5%, the ICER moves from -14,417.08DKK/QALY (V.N. less costly, more effective) to 608,849.94 DKK/QALY.

The ICER ranged from 613,734.83 DKK/QALY to 455,129.20 DKK/QALY when HS1 utility scores had a -10% to 10% upper and lower limits. The ICER ranged from 526,058.43 DKK/QALY to 517,985.92 DKK/QALY when HS2 utility scores had a -10% to 10% upper and lower limits. The ICER ranged from 507,600.24 DKK/QALY to 538,650.25 DKK/QALY when HS3 utility scores had a -10% to 10% upper and lower limits. The ICER ranged from 512,740.49 DKK/QALY to 531,581.35 DKK/QALY when HS4 utility scores had a -10% to 10% upper and lower limits. The ICER ranged from 517,985.92 DKK/QALY to 526,058.43 DKK/QALY when HS5 utility scores had a -10% to 10% upper and lower limits.

When productivity loss was not included, the ICER changed to 966,880.17 DKK/QALY. When 20% more productivity loss was added, the ICER changed to 433,013.13 DKK/QALY.
According to the model, the productivity costs have a significant impact on the total costs of V.N. and the SoC, which impacts the ICER. The estimated value of productivity costs is important because it can determine if the treatment is cost-effective compared to the SoC and if the treatment will be accepted for use.
Blindness supportive care costs' upper 20% and lower 20% will make the ICER ranged from 597,892.17DKK/QALY to 446,089.77 DKK/QALY. Although the supportive care cost estimates have an impact on the ICER values, this parameter is not as significant as some of the other listed above.

Scenario Analyses Result

Scenario analyses are multi-way deterministic analyses that were performed to test how different scenarios impact the ICER.
When both QALY and costs are discounted at the same time from 0% to 5%, the ICER will range from -7,331.36 DKK/QALY (less costly and more effective) to 700,990.44 DKK/QALY.
The ICER value moved to 455,449.10 DKK/QALY when the natural history study was applied as the evidence for distributing initial health states for the modeled population. The ICER value ranged from 861,800.96 DKK/QALY to 404,096.75 DKK/QALY if the waning time after 9 years of staying stagnant with the V.N. treatment effect changes from 5 years to 40 years. If there was no jump state effect in HS5 for the V.N. group, which opposes the assumption made in the base case, the ICER changed to 540,086.65 DKK/QALY. The ICER changed to 636,894.64 DKK/QALY when the Lloyd et al., utility scores were used without adapting the Danish

population norm. When the hazard ratio of mortality risks was abandoned in each state, the ICER changed to 520,655.46 DKK/QALY. Treatment effect without waning period lasting an extra 9 years, lasting 20 years, lasting 40 years and lifetime will make the results changed to 1,206,164.71 DKK/QALY, 65,175.19 DKK/QALY, -183,093.00 DKK/QALY, -247,974.77 DKK/QALY respectively. The time horizon of 1 year, 10 years, 20 years, 40 years chosen changed the results to 86,191,818.33 DKK/QALY, 2,127,666.45 DKK/QALY, 851,040.45 DKK/QALY, 533,206.35 DKK/QALY respectively. Further details of all the ICER values used in the deterministic sensitivity analysis were included in **Table 17** found above, and the scenario analysis results are found in **Table 18** below.

Table 18. Scenario analysis results

	Cost SoC	QALY SoC	Cost V.N.	QALY V.N.	ICER
Discount both 0%	32,793,624.25	9.87	32,737,685.99	17.5	-7,331.36
Discount both 5%	8,070,427.24	5.62	10,432,765.02	8.99	700,990.44
Baseline distribution according to natural history study	9,918,990.71	6.61	11,608,706.87	10.32	455,449.10
assuming 5 years of waning time	10,072,535.85	6.16	12,925,097.03	9.47	861,800.96
assuming 40 years of waning time	10,072,535.85	6.16	11,979,872.52	10.88	404,096.75
assuming no jump states from health state 5	10,072,535.85	6.16	12,097,860.80	9.91	540,086.65
utility scores using only Lloyd et al	10,072,535.85	8.00	12,097,860.80	11.18	636,894.64
without applying hazard ratio for mortality risk	10,153,504.44	6.17	12,173,647.64	10.05	520,655.46
treatment effect last 9 extra year and no waning period	10,072,535.85	6.16	13,534,228.58	9.03	1,206,164.71
treatment effect last 20 years and no waning period	10,072,535.85	6.16	10,429,695.87	11.64	65,175.19
treatment effect last 40 years and no waning period	10,072,535.85	6.16	8,834,827.14	12.92	-183,093.00
treatment effect last life time	10,072,535.85	6.16	8,284,637.76	13.37	-247,974.77
time horizon 1 year	*160,437.90*	*0.53*	*5,331,947*	*0.59*	*86,191,818.33*
time horizon 10 years	*2,965,910.47*	*3.71*	*5,923,366.83*	*5.10*	*2,127,666.45*
time horizon 20 years	*4,647,306.85*	*5.29*	*7,055,751.32*	*8.12*	*851,040.45*
time horizon 40 years	*8,342,271.24*	*6.11*	*10,368,455.37*	*9.91*	*533,206.35*

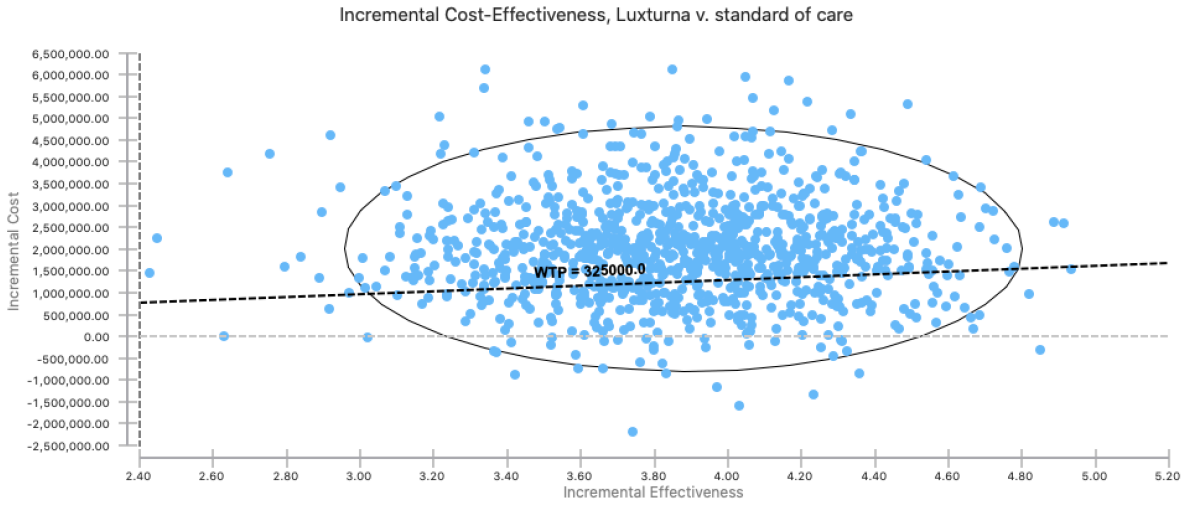
ICER= (Cost Luxturna-Cost SoC)/ (QALY Luxturna-QALY SoC), costs are all in DKK. ICER and CE scale are DKK/QALY

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis was performed by using a software program called TreeAge Pro 2019. A Monte-Carlo simulation was used to run 10,000 samples for the stimulation process to estimate the model probability of different outcomes. The relating figures found below were also generated by TreeAge Pro 2019. The figures below have a WTP threshold value of 325,000 DKK/QALY for traditional hospital mediations based on this value being used in other Danish CEA. The Swedish WTP threshold value of 745,0000 DKK/QALY for rare diseases is also used since this project is doing a CUA on an orphan drug, and it is not the same category as a standard drug.

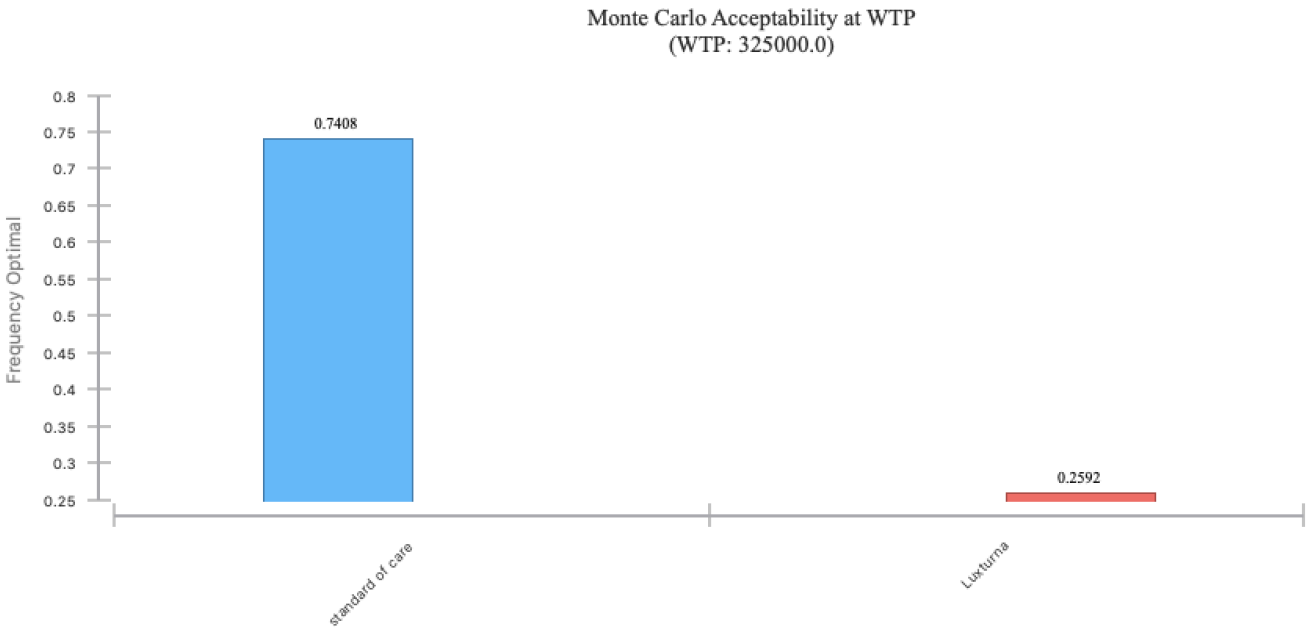
The ICER scatter plot is illustrated in ***Figure 9***, most iterations were scattered in the north-east quadrant of the ICER plane, which means Luxturna is more effective and more costly than SoC. The threshold of 325,000 DKK per QALY is used because it is often cited as the Danish willingness-to-pay threshold for medications, but it is important to note that Denmark does not have an official WTP threshold [38], [52]. The threshold value is used because it has been used for CEA when determining if a medication is cost-effective in Denmark. The scatters above the WTP threshold represent simulations that are not cost-effective, and the scatters below the WTP threshold represent the simulations that are cost-effective. The ICER scatterplot of Luxturna versus SoC with the threshold value of 325,000 DKK/ QALY can be seen below.

Figure 9. The ICER scatter plot Luxturna vs. SoC at the 325,000 DKK/QALY threshold.



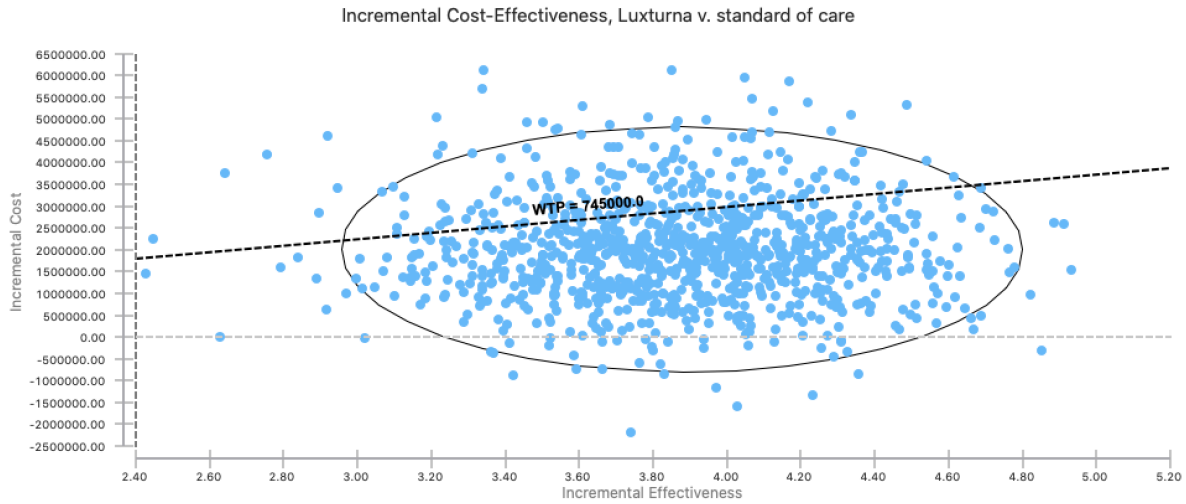
Another figure is used to show the Monte-Carlo simulation in a bar graph. ***Figure 10*** shows that when the threshold is at 325,000 DKK/QALY, the chance of Luxturna being cost-effective is 25.9%.

Figure 10. Acceptability at WTP threshold at 325,000 DKK/QALY



In ***Figure 11***, the same method was used as in figure 9 except the willingness-to-pay threshold was to set to be €100,000/QALY according to recent Swedish ultra-orphan drug experience, [53], which is equal to 745,000 DKK/QALY due to fixed exchange rate between Euros and Danish Kroner by the Danish Central Bank. This can be seen in the figure below.

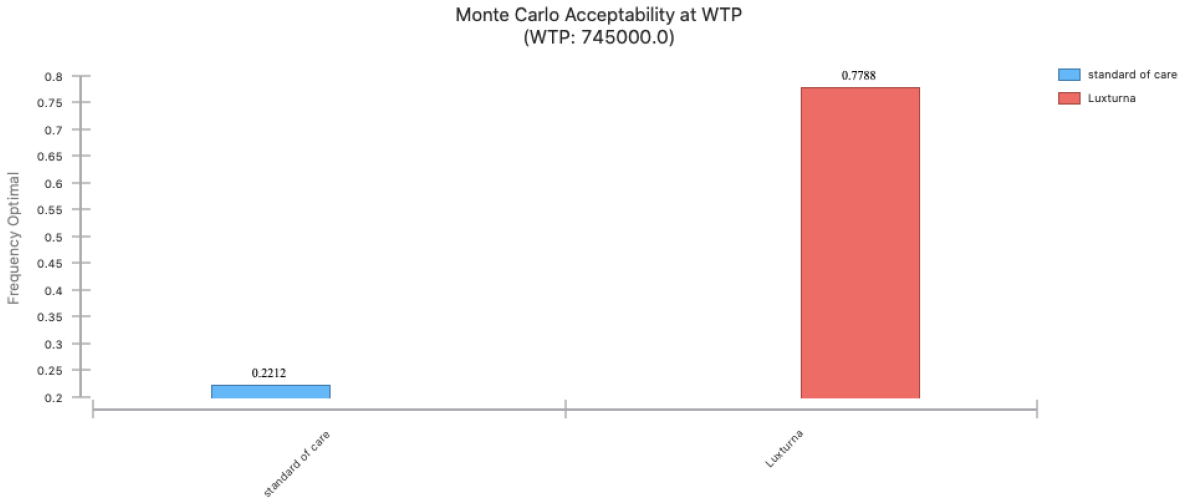
Figure 11. The ICER scatter plot Luxturna vs. SoC at the 745,000 DKK/QALY threshold



The scatters above the WTP threshold represent stimulations that are not cost-effective, and the scatters below the WTP threshold represent the stimulations that are cost-effective.

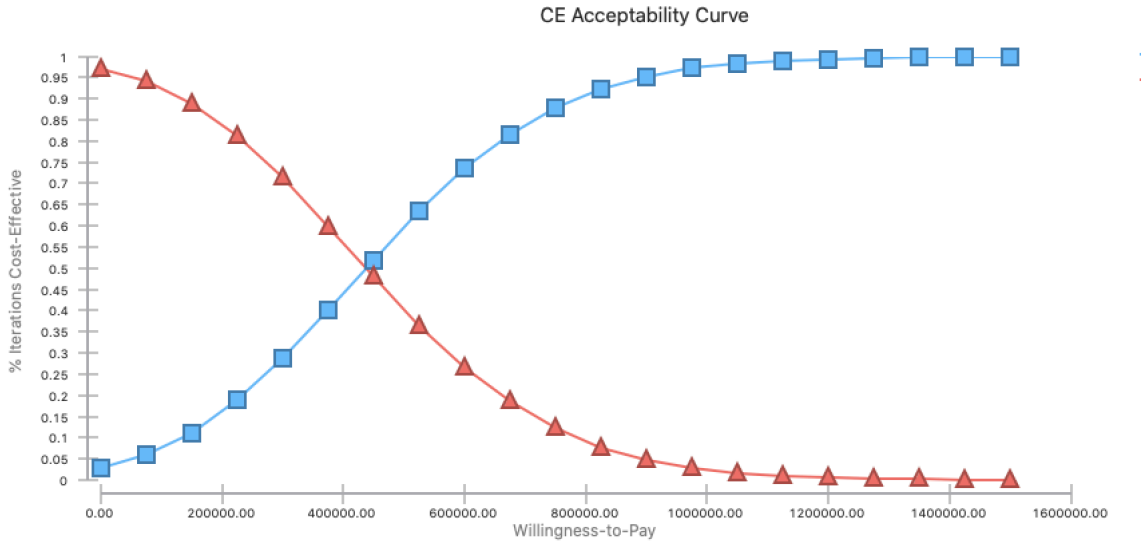
In ***Figure 12***, the chance of Luxturna being accepted as cost-effective is 77.9% if the threshold is at 745,000 DKK/QALY, which is the Swedish value used for rare diseases [53].

Figure 12. Acceptability at the WTP threshold at 745,000 DKK/QALY.



The purpose of ***Figure 13*** is to show the point in which Luxturna is cost-effective compared to the SoC. The acceptability curve shows that if the WTP threshold is increased to 1,000,000.00 DKK/QALY, then Luxturna will be almost 100% likely to be cost-effective compared to SoC.

Figure 13. Cost-Effectiveness Acceptability Curve Chart



The blue curve represents the curve for Luxturna and the red curve for SoC.

Discussion

As stated in the preface, the project group had already started conducting a CUA to determine if Luxturna is a cost-effective treatment in Denmark for IRD patients with RPE65 gene mutation. However, on April 23, 2020, the medication was approved by the Danish Medicines Council to be used on patients in hospitals. Luxturna was initially denied in September 2019 because of the extremely high cost associated with the drug. The reason behind the approval is a newly negotiated deal of how Denmark will pay for Luxturna if it has a positive effect. There was uncertainty associated with the medication because only a small number of patients were treated with the drug in the clinical trial. Therefore, a new agreement was made, which divided the payment into installments instead of all at once. The payment depends on the effect of the medication [19]. The agreement laid out in the new Background information about Luxturna published in April states that there is not a lower price of the drug, but a 4% annual discount rate over nine years. If the drug does work, it is the same as the previous offer presented by Novartis to AMGROS in 2019, which is 5.2 million DKK for the treatment of Luxturna [19]. According to the new report published by the Danish Medicines Council, the new decision did not provide any new analysis, like an economic evaluation, on Luxturna and SoC; therefore, we deemed it necessary to continue our project.

The results from CUA on Luxturna versus SoC showed that the base case ICER of Luxturna in comparison with SoC was 521,990.97 DKK/QALY. This value is higher than the often-cited Danish WTP threshold of 325,000 DKK/QALY for other usual interventions but lower than the Swedish experience in accessing ultra-orphan drugs which equals to 745,000 DKK/QALY. Luxturna is likely to be cost-effective from the narrow Danish societal perspective if the threshold is the same as the Swedish experience for an ultra-orphan drug. However, if the threshold was chosen, it has to be the same as other common interventions in Denmark, which would mean that Luxturna is not likely to be cost-effective. The applied CUA incorporating QALY did provide a quantitative estimate of how many additional QALYs that Luxturna could bring. While in the Danish Medicine Council's report, the conclusion was given about the categorical added clinical value without a numeric scale to measure. The inclusion of productivity loss made Luxturna more cost-effective (without productivity loss= 966,800.17 DKK/QALY vs. base case with productivity loss= 521,990.97 DKK/QALY). The lifetime

extrapolation from 15 of costs and effects changed the result and conclusion significantly (1-year time horizon= 86,191,818.33 DKK/QALY vs. base case lifetime horizon= 521,990.97 DKK/QALY). We also found that Luxturna could potentially delay the progression that patients are legally blind. The model estimated that with the use of Luxturna, patients become blind at an expected age of 61, and with the SoC treatment, patients will become blind at the expected age of 24.

The sensitivity analyses show that the results are susceptible to the time horizon chosen, length of treatment effect without waning period assumptions, productivity loss, the waning period length when there is treatment, and discount rate. When only Lloyd et al.'s utility scores were used, it did change the ICER, but not to the extent to change the conclusion for the 745,000 DKK/QALY threshold. The methodological changes to initial health state distributions and treatment effects in the HS5 V.N. group did not change the ICER much. The probabilistic sensitivity analyses show that most of the iterations are consistent with the conclusion of the cost-effectiveness ratio at the two thresholds. If the threshold is 1,000,000 DKK/QALY, Luxturna would be almost 100% cost-effective.

The time horizon has a considerable effect on the ICER result since Luxturna has a very high initial one-time payment cost. When Luxturna is used as a treatment, it can save society money throughout the years by reducing the costs on blindness supportive care and productivity costs by delaying the progression of patients to legally blind states because if they were not blind they could work and society could get tax-incomes from their labor. The treatment effect extrapolation assumptions are either treatment effect is going to last without a waning period, or the waning period assumptions determine the chance of the progression to legally blind states in each following year. Therefore, if the chances are lower for the progression of the disease, the ICER results are naturally lower with increased incremental QALYs and decreased incremental costs. The productivity costs took up a considerable proportion of costs for those in blind health states (H2-H5); therefore, the exclusion of those costs will make Luxturna appear less cost-effective and cost society more money. The utility scores and the different methods of applying utility scores did not affect ICER as much given that the utility scores were very close and equal to 0 in later heath states in either approach, meaning that differences are quite small. However, in HS1, the utility

scores have a more significant impact on ICER, likely due to the differences in between groups are higher, and that Luxturna arm collected more QALYs from HS1 throughout the stimulations. HS5 treatment effect did not impact the result much since, in initial distribution, the percentage (1/31) of patients in HS5 was scarce. However, if it were for another age group, the percentage of patients in HS5 would be more extensive, according to the natural history study, and Luxturna will be likely to be less cost-effective [13].

Overall, the project group found that the AMGROS report had produced a biased cost analysis against Luxturna's case by using a 1-year time horizon, excluding blindness supportive care costs and productivity costs. The Danish Medicine Council should recommend using CUA to assist in decision-making, especially when it comes to approval or denial of an orphan drug.

Our project's strength is that we determine the cost-effectiveness of Luxturna with adjustment to Danish healthcare settings, synthesizing more specific evidence in Denmark to make the conclusion more tailored to the Danish society. The adjusted parameter inputs that fit more in the Danish health background include the Danish population norm adjusted utility scores and costs data obtained from Danish databases and reports [9], [32], [33]. Combining the Danish population norm utility scores would make the QALYs adjusted to be more on the general preference for health outcomes in Denmark in different age groups, subsequently making the results closer to Danish healthcare settings. Since the healthcare costs were different in the U.K. and the U.S. compared with Denmark, collecting and applying the cost data in Denmark will produce results that more likely to reflect real-life costs. We also include the productivity loss that was fairer in the case of Luxturna. RPE65-mediated IRD is characterized by making patients went blind from a very young age and disabled patients from going to work [54]. The benefits of Luxturna include not only the health benefits but also the benefits of society by saving more workforce and reducing caregivers' burden. This monetary benefit of saving more productivity can be substantial until retirement since patients tend to lose their ability to work at a very young age in the SoC arm (1,726,170.11 DKK productivity loss saved over lifetime comparing V.N. to SoC in base case model). There might be concerns about age discrimination and discrimination to those without work, including productivity costs in a CUA. For instance, if the treatment is primarily for children or retired people, there will be productivity loss counted and subsequently make the treatment

benefit in saving cost less in comparison with other treatments that have considered productivity loss. However, it is disproportional to deny the treatment that will potentially bring society more productivity and enable people to have equal rights to work and contribute. They have equal rights to see and discover the world to make sure there is no discrimination across diseases and treatments, especially from the perspective of our study. Our perspective was a narrow societal perspective. It would be unfair not to value production gain since there is no difference between the labor costs included in the cost estimates and production gain. According to Drummond et al., including productivity loss, should depend on the perspective taken. If a societal perspective is taken, it is more reasonable to consider production gains to the community [36]. For the case of valuing Luxturna, as some of the blindness associated costs did not fall on health care, for instance, community support and special education, a societal perspective would be able to consider more aspects. We have also chosen to perform deterministic sensitivity analysis to see if Luxturna is cost-effective without the inclusion of productivity costs in response to the arbitrary inclusion. Luxturna would appear to be not cost-effective at any threshold without the inclusion of productivity loss.

As for our Markov model, one strength lies in the definitions of the health states in line with the expertise of the American Medical Association Guides, which is in accordance with the Danish definition of being legally blind (health states starting from health state 2 are considered legally blind). This information gives more validation to the model. The disutility score was based on the Lloyd et al. study [31], which was done by experts' elicitation on REP65-mediated IRD patients based on the EQ-5D questionnaire and aligned with our health state definition. Using these disutility scores enable our model to produce disease-specific QALYs that make the model closer estimate to real-life cases.

There were limitations regarding the health outcome within the model. The uncertainties of the results will be discussed in the following. A significant uncertainty of the chosen clinical trial is the lack of statistical significance of VA and VF scores. This is possible because of the small sample size in the randomized clinical trial and the difficulty for recruiting patients in the randomized clinical trial, which is typical for clinical trials for rare diseases with small prevalence. Meanwhile, due to ethical considerations, children are difficult to recruit in the

clinical trial, wherein rare diseases, many of them are associated with a genetic inheritance that emerge early in childhood [55]. It is important to note that the phase III clinical trial might not be ethically sound because there was a treatment group and a placebo group. It would seem that patients in the placebo group were left out for treatment.

The data used in the model included information from the Phase III clinical trial, which only had 31 patients with 20 treated [12]. The natural history study, which had 72 patients was also included [13]. The lack of statistical significance makes the data chosen uncertain and could affect our results significantly. We used the data from the Phase III clinical trial to model treatment effect transition probability, which will redistribute patients in different health states. When the transition probability used has great uncertainty, it could mean that in a real-life scenario, not just theoretical, there will be fewer people transitioning to HS1, making Luxturna less cost-effective, or more people transitioning to HS1, making Luxturna more cost-effective.

Moreover, in response to the lack of clinical reports of the long-term effect of V.N., we used the longest 9 years follow-up treatment effect that was reported at the FDA conference in our model [14], and assumed a 10-year waning period afterward in our base case. The real-life outcome is difficult to predict unless more evidence surfaces. Different assumptions on how the treatment effect will last and decrease did make the results varied greatly, as concluded in the scenario analyses. As for the transition probability for natural disease progression, the data was provided by Viriato et al. [7]. Viriato et al. applied a multistate survival model using data from the natural history study [28], and chose the statistic model with the most AIC and BIC test fit. Due to the statistical difficulty, we cannot do a multistate survival model to verify the results of the calculated transition probability; however, we compared the co-efficient number from Viriato et al. and Johnson et al. [27], and the results were quite similar. As for utility scores, we used Danish population norm data to adjust the age effect on utility; however, if the patients adjusted more to blindness over the year, then the utility scores might be underestimated, making Luxturna appeared to be more cost-effective comparatively.

There was uncertainty around the costs for Luxturna and SoC treatment because not much detailed information was available from Denmark; therefore, some costs were estimated based on information published for other blindness conditions. The blindness associated costs were obtained from the Danish report on Type-2 diabetes [32]. Even though the definition of blindness aligns with our health states, we must inform that the data was not specific to RPE65-mediated blindness, together with the gross-costing strategy that might increase the uncertainty of the costs. This also applies to the hospital costs and adverse events cost, which was based on DRG tariffs that averaged the costs reported from all hospitals in Denmark, based on diagnosis group. The DRG tariffs are not specific, and since it is also a gross-costing strategy, the uncertainty of how real-life costs on operation and adverse events costs might vary considerably. We assume that in real-life scenarios, the costs mentioned above might be underestimated for IRD patients. Their rationale for this assertion was considering IRD associated blindness has been reported to cost more in a socioeconomic report of IRD in the U.K. [56]. Also, there were many possible costs that we did not include, which are costs associated with psychologist visits, caregivers' loss, and others that we could not identify without the help from the municipalities and specialists. We might have significantly underestimated the cost of blindness in supportive care. If costs are missing from the model, then it could cause a downward bias. Generally, if the blindness supportive care costs were underestimated, Luxturna should have been more cost-effective comparatively.

Another cost estimation uncertainty comes from that of productivity loss estimates. We used the average salary of modeled populations, regardless of their educational status. According to Jensen et al., the completion of college decreases as VA drops in the US, and the average salaries are higher for people who complete a college education [25], [57].Moreover, according to Viriato et al., blindness only associated with a 48% additional unemployment rate in the U.K. [58]. Given the mentioned above, the productivity costs were very likely overestimated; therefore, an upward bias could be present. We did not consider presenteeism in productivity costs in HS1 because of the lack of information available, which might add more to the productivity loss. Also, we did not use the friction cost method for productivity loss. Friction costs calculate the productivity loss as the productivity loss for the time in between finding another replacing workforce, which is less than the per capita cost method. Some believe it reflected more of what society's loss was more likely to be [59]. In

general, we think that productivity loss was likely to be overestimated, making Luxturna appeared more cost-effective.

Another limitation is that most of the information included in the CUA was in Danish; therefore, we had to translate all documents in google translate. We could have misunderstood something written based off of the translation. It is essential to consider this if this CUA were to be replicated.

Zimmermann et al. concluded Luxturna as not cost-effective based off the ICER value of $643,800 /QALY, which translates to an ICER of 4.2 million DKK/QALY) [24]. Halioua-Haubold et al. made a lifetime quality of life benefit assessment of Luxturna with subgroup analyses. It has concluded that patients that are younger than 20 years old will benefit much more than other age groups [26]. However, the similar models from Johnson et al. and Viriato [7], [27] concluded differently (ICER=-$59,458 /QALY (392,678 DKK/QALY), 18.1 QALYs gain in V.N., 8.6 QALY gains in SoC in Johnson's; ICER=£95,072/QALY (795,553 DKK/QALY), threshold=£100,000/QALY (837,236.00 DKK/QALY) in Viriato, incremental QALY was 6.4). Our model assumptions were more conservative in comparison with the other two models. The differences in model assumptions and healthcare background could be the reasons for the difference in conclusions (Further details can be seen in ***Appendix 1***).

Even though we used similar models as Johnson et al. and Viriato et al., the results and conclusions are very different. The biggest reasons for the differences are the cost strategy; in Johnson's study, the SoC associated costs include fundus photography, fluorescein angiography, optical coherence tomography, depression costs, productivity loss according to patients educational level, caregiver burden, and government programs, which added up to huge amounts of costs (Further information see ***Appendix 1***). The model assumptions were less conservative compared with ours (treatment effects were modeled to last). In the Viriato et al. study, the treatment effects were assumed to last for 40 years; the productivity costs were estimated to be much less. The threshold value was set to be 837,236.00 DKK/ QALY (£100,000/QALY) for Highly Specialized Technology in the U.K.

In general, our model has more strength because it is more likely to reflect decisions in the Danish healthcare setting. In comparison with the AMGROS report, we included the

associated costs of blindness in Denmark, which was not included in the 2019 or 2020 AMGROS report. Another strength in our model compared to the AMGROS assessment is our estimation of the ICER value over a patient's lifetime, which starts at age 15 to death in our model, instead of basing it on the effect Luxturna has on patients on year after treatment [60]. However, we had limited data applied in the models in comparison with Viriato et al. and Johnson et al. reports. Our cost analyses for SoC and Luxturna are less thorough, and the productivity loss calculation method was less evidence-based in our model compared to the other reports.

Looking forward, the Danish Medicine Council will provide a methodological guide on how to implement the use of QALY for economic evaluations in 2021 [61]. However, the Danish Medicines council does not require economic evaluations to be done when deciding on whether or not to recommend a medication to be used in a Danish hospital. So far, there has not been any official guide for a cost-effectiveness threshold in the Danish healthcare setting. It will be difficult for a decision rule for CUA without an official WTP threshold. Previous economic evaluation studies applied threshold values of 300,000, 325,000, and 350,000DKK/QALY for different diseases, and in this study, 325,000 DKK/QALY is used [37], [46]. Merely applying those threshold values for an orphan drug is debatable. In the US, Neumann et al. suggested either $100,000 (657,510.00 DKK) or $150,000 (986,265.00 DKK) per QALY should be used instead of $50,000 (328,755.00 DKK) if 'to select a single threshold outside the context of an explicit resource constraint or opportunity cost' [62]. In the U.K., NICE has proposed 837,236.00 DKK/QALY (£100,000 per QALY) for Highly Specialized Technology (HST), while 167,446.00 DKK to 251,128.00 DKK (£20,000 to £30,000) were proposed for non-HST. The recent Swedish experience used WTP ranged from €30,000 to €100,000 (224,000.00 DKK to 745,000.00 DKK), which is dependent on the rarity of the disease [63]. There is so far, to our knowledge, no relative recommendations in Denmark. The application of a fixed generic threshold for an ultra-rare disease like RPE65-mediated IRD is still being debated.

The considerations often back one rationale for a higher threshold for ultra-rare diseases for making decisions according to societal preferences. There is a strong societal preference to prioritize treatments for diseases that are genetic inherited mostly, severe, and

disproportionately ill children and young patients as well as the societal preference to achieve equity to access care regardless of cost-effectiveness [64], [65].The high research and development costs and the small size of the target patient population increase the chances of not getting much return from the investment [66]. In order to ensure profits, the price of ultra-orphan drugs must be put high and often is not lower than the commonly cited cost-effectiveness threshold [65]. Using the same threshold as other medical interventions would deny the access to medicines for these disease minorities and deny the equity to care, especially when in most ultra-rare diseases, there would be no other medicines to treat [67]. As the case of RPE65-mediated IRD patients, without access to Luxturna, there would be no treatment for slowing down or reverse the deterioration of vision, but the supportive care for blindness [8]. The societal preference for equity in health for patients with the ultra-rare disease can be seen in primary regulatory policy, such as the Orphan Drug Act of 1983, which promotes orphan drug development for rare diseases by providing tax incentives and research subsidies [68]. However, without the adaptation of a higher threshold, as Drummond et al. mentioned, "it does not make much sense (in terms of efficiency) for the public system to fund or subsidize R&D on orphan drugs and later no reimburse the resulting innovations. This strategy will lead to a waste of R&D resources (if the products are finally not used) and discourage future investment in R&D on orphan drugs" [59].

The other incentive to apply a higher threshold would be rewarding the additional benefits. The market incentive for a higher profit will promote the research on rare conditions and innovations that would have been neglected due to the small population size [53].

The ethical considerations of equality require the application of universal standards to judge and value different treatments for all patients [64]. Equality can be defined as providing patients with the same health resources and benefits under this scenario. According to social welfare, the health system's primary objective is to maximize the health benefits of the entire population [69]. If the disproportional resources are spent for rare conditions when the same resources would have brought out more benefits for other patients, there will be unfair opportunity cost. The other patients that are ‘invisible’ to the economic report and decision makers will ultimately be harmed by the unfair opportunity costs [53].

Nevertheless, many countries proposed different evaluation systems for an orphan drug. Some health economists have argued that the goal of a healthcare system is not only about maximizing the health gains across all citizens but to ensure all patients get some fair chances at a meaningful health benefit, even if it is deemed cost-ineffective [70].

Hughes et al. has concluded the competing ethical interpretations of fairness well,

"A key issue around whether ... funding should support the provision of ultra-orphan drugs. This is whether the rarity and gravity of the condition represent a rational basis for applying a different value to health gain obtained by people with that condition. That ultra-orphan drugs are reimbursed at all illustrates the fact that budget impact, clinical effectiveness, and/or equity issues are given precedence over cost-effectiveness in decisions on resource allocation in some countries. The consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment" [64].

The decision making for the pricing and reimbursement process for orphan drugs is particularly challenging. As discussed above, the lack of understanding of the natural progression of the diseases [71], difficulties in clinical trial recruitment and development, and the lack of clinical endpoints to evaluate long term outcomes [72] increase the uncertainties of technology assessment. The orphan drugs have often failed to meet the often-cited thresholds for cost-effectiveness analyses due to the high list price. These uncertainties increase the financial risks for funding the treatments for rare diseases. As for a cost-effectiveness analysis, many have criticized the lack of tools used to capture the potential benefits for orphan drugs and failure to put in all stakeholders' perspectives into consideration [53], [67], [73]. Examples include the additional benefits for innovation, and the perspective of patients and their caregivers [53]. In cost-effectiveness analysis, the professionals' assessments of technology weighted more on the evaluation process, which can be misleading given the significant uncertainties.

To tackle the dilemma above, many countries have brought up supplementary orphan drug assessment systems to assist the reimbursement process—namely, the NICE Highly Specialized Technology. However, often the decisions are made following the universal

process for all medicines. The Danish Medicine Council has also addressed the methodological challenges due to uncertainties regarding Luxturna for the current evaluation system [54].
Hughes et al. proposed the Multi-criteria decision analysis (MCDA) to evaluate new orphan drugs against several criteria. Each government would decide on the attributing weights of each criterion according to the societal preference. The criteria are measurable and assessable. Each government would then be able to rank the orphan drugs according to their overall scores and allocate resources until the budget for rare diseases exhausted [28]. These criteria include: 'rarity,' 'level of research undertaken to receive marketing authorization as an orphan drug,' 'level of uncertainty of effectiveness, manufacturing complexity,' 'follow up measures' (additional benefits and associated costs), 'characteristics without direct cost impact,' 'disease severity,' 'available alternatives,' 'level of impact on the condition,' 'use in unique indication or not' [70].

The MCDA model can be further adapted and add more domains if needed. In comparison with other evaluation models, it captures more values and benefits that orphan drugs might bring. Moreover, countries can weigh different domains according to their societal preferences, making it more adjustable to different healthcare settings. However, since the decision rules are under the precondition that a particular budget is set for rare diseases, the government must reasonably make a budget for a rare disease first. In England, the budget impact threshold is £20 million (167 million DKK) per year, while €30 million (224 million DKK) and €50 million (373 million DKK) respectively in France and Germany [53]. Countries like Denmark, Sweden, and the Netherlands have not set their budget impact threshold to our knowledge.

The European Working Group has recommended member governments to follow nine principles on decision criteria, decision process, orphan drug sustainable funding systems, and European coordination [74]. It is recommended to assess the value of orphan drugs by looking at the patient level, healthcare system, and societal level, identifying the value evaluation's uncertainty, and considering the value beyond, such as budget impact, the sustainability of innovation in rare diseases, and societal preferences. In the future, there should be greater coordination of orphan drug value assessment even though most countries are handling it at the national level. The rationale for greater coordination is to include greater

consistency in the definition and assessment of clinical value, to gather more clinical specialists as well as patient data, and to reduce the duplication of effort for member countries [74]. In the case of Luxturna, the Danish Medicine Council started the price and reimbursement process from September 25, 2019, to April 23 in 2020 [54]. The decision changed from denial to approval even though there were no more new substantial pieces of evidence. If there had been European coordination for orphan drugs for a rare disease, it could have saved the number of efforts and time in the evaluation and potentially reduced the uncertainties by having more extensive patient data.

The Danish Medicines Council should consider a European cooperation organization when dealing with orphan drugs, or Nordic cooperation on the guidelines for evaluating an orphan drug. We would recommend doing a full economic evaluation to determine the cost-effectiveness of the treatment compared with an alternative. There is a lot of time and resources that go into conducting an economic evaluation. However, we find it necessary when dealing with orphan drugs because they are typically very costly but can improve the life of a patient significantly. That is why we conducted a CUA on an orphan drug because it provides transparency of what is needed to determine if the drug cost-effective compared to the other treatment.

Conclusion

A CUA was done using a narrow Danish societal perspective and the project group found that estimated ICER value for Luxturna with the inclusion of productivity costs was 521,990.97 DKK/QALY. According to this value, Luxturna is likely to be cost-effective if the WTP threshold is the same as the Swedish ultra-orphan drug experience of 745,000 DKK/QALY. It is likely not cost-effective when using often-cited Danish WTP threshold of 325,000 DKK/QALY since most of the Monte-Carlo simulations were above this threshold. The estimated ICER value with the exclusion of productivity costs the value was 966,800.17 DKK/ QALY.

The Danish Medicine Council should decide on a different threshold for ultra-orphan drugs for CUA or consider using MCDA and following the European Working Group's recommendation on assessing orphan drugs. After longer follow-up evidence from phase III, clinical trials are reported, we recommend a further CUA study should be conducted to reduce the uncertainties of clinical benefits.

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