Evaluation of the OCU400 treatment for patients with Retinitis Pigmentosa

S. Arunajatesan, M. Bui, J. Duijvelshof, J. Hendrickx, D. Spenkelink

Early Health Technology Assessment

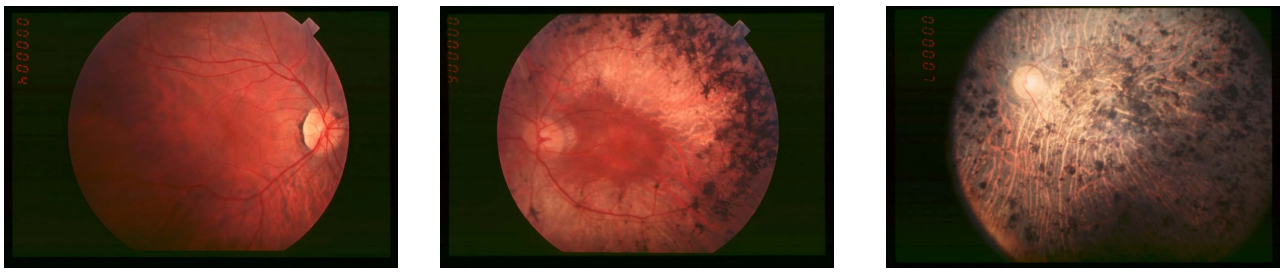
June 2021

1 Health Clinical Need

Retinitis pigmentosa (RP) is a class of disorders involving progressive degeneration of the retina that affects 1 in 3500 in the Netherlands [1]. Typical for RP is the initial degeneration of the mid periphery and advancing degeneration towards the central periphery. It presents initially as night blindness, followed by a decrease in the visual field, tunnel vision, and in the last stage as complete blindness. Symptoms of night blindness typically start in the teenage years and worsen until severe visual impairment is reached at the ages of 40 to 50 years [2].

The symptoms of RP have a major impact on patients' lives and can drastically reduce an individual's vision-related quality of life (VRQOL) [3, 4]. The VRQOL is generally measured using the National Eye Institute Visual Function Questionnaire: NEI VFQ-25 [5]. Moreover, supportive evidence for commonness of depression amongst RP patients has been found as well [6]. After all, peripheral visual field loss (PVFL) has implications for individuals' self-reliance. Substantial reductions in mobility performance due to PVFL often leads to difficulties in independent travel and daily living [7].

In the early stage of RP, patients experience night blindness as the main symptom. Night blindness can be present from birth or develop in the second decade of life. Possible peripheral visual field defects in dim light can be present in the early stage of RP. Examination of the fundus (Figure 1a), the interior surface of the eye opposite the lens, may still see normal. Midstage RP presents with obvious night blindness and difficulties to drive and walk at night. Patients become aware of the loss of peripheral vision and experience photophobia. Fundus examination (Figure 1b) shows pigment deposits in the mid-periphery. At the end stage of RP patients can no longer move autonomously due to blindness. Through the loss of peripheral vision only a few percent of visual field is left at the fixation point. Photophobia is experienced as intense and reading is difficult. Progression of the disease in this stage is still in effect as the central visual field vanishes. Leaving patients usually with only the ability to perceive light in the peripheral visual field. Fundus examination (Figure 1c) shows widespread pigment deposits [8].



(a) early stage (b) mid stage (c) end stage

Figure 1: Fundus examinations of a patient with retinitis pigmentosa during different disease stages [8].

Characteristic for RP is the progressive degeneration and death of rod photoreceptors during the early stage of the disease. Rod photoreceptors function better in lower light and are more concentrated in the outer area of the retina compared to the cone photoreceptors. Thus, clarifying the symptoms of tunnel vision and loss of night vision in the early stage of the disease. The following stage of RP is initiated when the rod photoreceptors are severely depleted. In the mid stage and end stage the cone photoreceptors undergo non-autonomous apoptosis. Resulting in loss of central vision (detail and colour perception) as these cells are concentrated in the center of the retina. A large variance in duration is observed in the time between stage progressions [9].

RP is a genetic disorder caused by the mutation of a critical gene for the visual system of the human body. The genes involved in RP vary as it is a class of disorders with shared symptoms. Genetic heterogeneity occurs in RP, as different genetic mechanisms produce the same disease phenotype. Studies are still performed to find

all the different genes that can induce RP. However, each case of RP can be by itself genetically specific. Genetic modifiers are allelic variants distinct from the disease-causing gene that can alter the disease its onset, severity and progress [10]. The genetic disorder causing RP is mainly inherited. Depending on the type and location of the mutated gene, RP can be inherited through an autosomal dominant, autosomal recessive or a X-linked pattern [2]. Table 1 gives an illustration of the large number of genes found to be associated with RP per type of genetically heritable RP.

Table 1: Summary of genes associated with RP [2].

Disease	**Total No. of Genes and Loci**	**No. of Identified Genes**
Retinitis pigmentosa, autosomal dominant	17	17
Retinitis pigmentosa, autosomal recessive	24	21
Retinitis pigmentosa, X-linked	6	2

The American-based company Ocugen [11] is one of the first to develop a potential therapy for RP. Their OCU400 novel gene therapy is a product candidate with the acclaimed potential to be effective in restoring retinal integrity and function in a subgroup of RP patients. Current methods of gene therapy are based on gene augmentation in which a functional version of a non-functional gene is transferred into a group of target cells [12]. The novel gene therapy on which OCU400 is based, uses nuclear genes instead of functional genes. Nuclear genes have the ability to modify the expression of many genes, gene-networks and reset cell homeostasis. OCU400 consists of a functional copy of the nuclear hormone receptor gene NR2E3 to be delivered to target cells in the retina using an adeno-associated viral (AAV) vector [13]. Ocugen states that by the implementation of the novel gene therapy the need for more than 150 individual products for each different gene for the treatment of RP is eliminated [14]. These 150 products are the group of genetic therapies to combat each mutated gene associated with RP, these groups do not exist at this time. The OCU400 therapy has been proven to work in mice models and regeneration of the retinas' function has been observed [10], nevertheless clinical human trials are still to be conducted. It is also unclear from the mice models study if the effect of the gene therapy is permanent or if booster therapies will be necessary.

RP induced by a mutation in the NR2E3 mutated gene account for only 1-2% of the total RP patient group [15]. In the Netherlands that would account for 50 - 100 people which could be treated with OCU400 of the approximate 5000 patients with RP. To find this patient group the diagnosis of NR2E3 induced RP has to be made. RP is diagnosed based on symptoms and fundus examination. Additional tests can be conducted, these are typically a visual field examination, an electric-retinogram or a genetic examination. To find the NR2E3 induced RP the genetic examination will be necessary [16].

At the moment there is no cure for RP in the Netherlands. Treatments implemented to cope with RP can be spectacle strength corrections or a bionic eye that functions with the still active parts of the retina [1]. The Erasmus Medical Center advises patients with RP to take additional vitamin A supplement. Due to RP there can be a break in the vitamin A cyclus, which is a critical cyclus for the production of the rhodopsine protein. Rhodopsine is used to transform light into an electric signal. Studies have shown that vitamin A supplement reduces the progression of RP over the six years that the patients have been followed [17, 18]. In the United States the same coping treatments are implemented as in the Netherlands to guide the patient with the progression of RP [19].

Although there is no cure in the Netherlands, multiple methods other than OCU400 are in development to treat RP with other genetic mutations than the NR2E3 gene. Luxturna is a gene therapy for RP caused by a mutated RPE65 gen. This therapy has shown to improve visual capabilities of test subjects and is a clinically available product for patients that are eligible for Luxturna [20]. Early-stage patients treated with Luxturna are estimated to gain 14.30 quality-adjusted life years (QALY) over standard care. For the mid-stage patients this is 6.22 QALYs and for late-stage patients 1.48 QALYs [21]. In 2020 Luxturna was not available for patients in the Netherlands as the price of the therapy is deemed too much at €650,000 for two eyes [22]. However, in 2021 the Dutch minister of Health, Welfare and Sport Tamara van Ark confirmed that Luxturna will now be covered by Dutch health insurance after price negotiations which took place at the end of 2020 [23].

The OCU410 is a novel gene therapy under development by Ocugen that works like OCU400 but delivers the RAR Related Orphan Receptor A (RORA) gene instead of the NR2E3 [24]. This therapy combats RP just like OCU400 and Luxturna, but due to the delivery of a different type of gene it is difficult to say to what extent these therapies compete with each other.

A different approach than gene therapy are the ocular implants used a coping treatment for patient in late stage RP. There are two types of devices commercially available, the Argus II from the company Second Sight and the Alpha AMS from Retina Implant AG [25, 26]. The Argus II is a subretinal implant that stimulates the bipolar cells layer at the retinal input using a photodiode array positioned in the layer of degenerated photoreceptors. This ocular implant is accompanied by glasses with a built-in camera from which visual information is sent to the implant. The Alpha AMS is an epiretinal implant that stimulates the ganglion cells of the retina. It collects and

processes visual information through a head mounted camera. The aim of these ocular implants is to restore some of the vision in end-stage RP patients who are completely blind or have light perception without light localization. All these implants replace to some extent the lost photoreceptor function with artificial vision by stimulating the remaining neurons [27].

A follow-up study in patients with the Argus II ocular implant shows that 89.3% of patients performed better in a square localization visual test than without a device. About half could identify the direction of motion of a moving bar. Quality of life impact was commonly done using Functional Low-Vision Observer Rated Assessment (FLORA), 80% reported a positive or mildly positive impact of the device after one year. After three years 65% of the patients still reported a positive impact, no patients reported a negative impact [28]. A study on the Alpha AMS reports the same type of improvements as the Argus II implant. Patients were able to locate high-contrast objects which they could not locate before the implant. However, due to a small patient cohort no absolute increase in the quality of life could be presented [29].

The alternative which the OCU400 treatment is compared to is best supportive care [22]. Best supportive care consists of rehabilitation, visits to the ophthalmologist and aids for people with visual impairment or blindness. Retinal implants are solely for very late stages of RP, whereas this is not necessarily the case for gene therapies. Zorginstituut therefore deemed the retinal implants to be inadequate for the cost-effectiveness analysis for Luxturna and chose best supportive care. For the same reason, best supportive care is chosen as the comparator in this paper.

Currently, OCU400 is in the pre-clinical trail phase with the aim of starting with phase 1/2 somewhere in 2021-2022, followed by phase 2/3b starting in 2023-2025 and potential approval in the year 2025-2026 [24]. Therefore, this report conducts research into the estimation of the cost-effectiveness and returns on investment (ROI) for the OCU400 using early health technology assessment tools. Furthermore, indication on the preferences of the end-users, including patient and professionals and the general barriers and facilitators are illustrated. These various aspects relate to a description and recommendation of the feasibility of future implementation of the OCU400 in the current Dutch healthcare system.

2 Preferences

This chapter delineates the preferences covering the patients' perspective, since RP patients would benefit directly from this technology. By understanding the patient preferences, the anticipation of the further development of OCU400 will be clarified or whether there is no need for this new technology. This will reflect to some extent the market demand and therefore designates the desirability towards this new technology and whether investments based on the preferences should be made in the OCU400 novel gene therapy. Furthermore, a statement could be made based on which aspect of the new technology has more value compared to current care (best supporting care), thus what is most important for RP patients to consider this new technology.

While literature concerning gene therapy is limited, a study on the attitude towards gene editing technology among RP patients done by Hoffman-Andrews et al. showed recurring themes and aspects describing openness with regard to gene therapy [30]. Additionally, gene modification resides on the ontology of enhancement ethics. Since the goal of the OCU400 is to restore human capabilities, rather than transcending them, it can be regarded as a treatment rather than an enhancement. This nullifies the normative concerns posed by enhancement ethicists. Therefore ethical concerns towards gene therapy are not taken into account in the patient's preference survey. The themes mentioned by Hoffman-Andrews et al. created the core for all the possible criteria used to understand the patient's preferences; intervention, economic, social and clinical aspects. Herein, the aspects were formulated as sub-criteria and grouped according to the criteria. Subsequently, the sub-criteria were specified appropriately to measurable attributes in context of interest for this study. An overview is given in the form of a value tree which can be seen in figure 2.

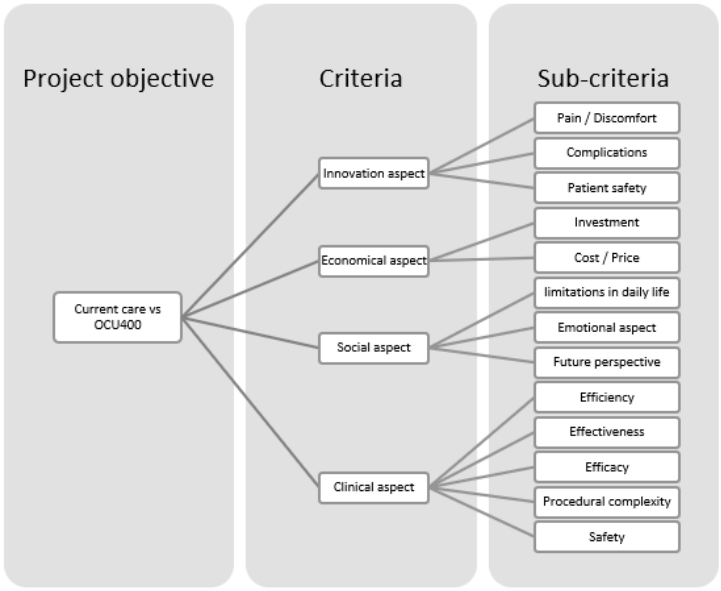


Figure 2: Value tree of criteria and sub-criteria

A Multi Criteria Decision Analysis (MCDA) is conducted to understand which of the criteria and subsequent sub-criteria are preferred from a patient's perspective. The MCDA is made for decision making when multiple criteria are to be considered, just like the sub-criteria that can be seen in the value tree of figure 2. A survey respondent has the choice between alternative treatment characteristics and chooses the preferred alternative for each paired case. For a MCDA criteria need to be stated, these are the characteristics on which a survey taker compares the treatment alternatives. In each criterion, alternatives are stated that are ranked from best to worse. As the survey respondent indicates preferences in alternatives between different criteria, a relative importance of each criteria and alternative can be calculated [31].

For the preference survey the Potentially All Pairwise Rankings of all possible Alternatives (PAPRIKA) method is used, a type of conjoint analysis. The PAPRIKA method works by making pairwise comparing alternatives that the survey respondents can indicate their preference for and thereby chooses one alternative over the other. An advantage of the PAPRIKA method is that this method does not rely on scales or ratios, which Analytic Hierarchy Process (AHP) does. Therefore precise understanding of RP is less important, which would be more critical if survey takers scale alternatives against each other. Furthermore, respondents tend to be inconsistent in AHP. Additionally, due to the given time-frame for this study, the PAPRIKA method was applicable since no large sample size is required and the method has a low analytical burden [32]. PAPRIKA is well-suited for performing benefit risk trade-offs.

In order to increase the user friendliness of the survey, overlapping sub-criteria had been combined to decrease the amount decisions that a survey taker has to make. These attributes were chosen, since they cover the sub-criteria not being targeted in table 2 as well. An example of this is the clinical aspect 'safety' and the innovation aspect 'patient safety', which were combined with 'complications'. Moreover, the sub-criteria 'investment' had been removed as this is not important from a patient perspective. The final selection of criteria which were included in the preference survey are presented in table 2.

Table 2: Criteria with corresponding attributes used in the survey.

Criteria	**Sub-criteria**	**Attributes**
Innovation aspect	Complications	Risk on side effects
	Pain / Discomfort	Discomfort during the therapy
Economic aspect	Cost / Price	Therapy price for the patient
Social aspect	Future perspective	Future perspective if therapy is implemented
Clinical aspect	Efficacy	Efficacy of the therapy
	Procedural complexity	Procedural recurrence

The patients were represented by Biomedical Engineering students, due to inability to reach out to actual RP patients or experts in the field of RP. The survey was made in the '1000 minds' [33] software and distributed through Canvas. A total of 14 participants filled in the survey. Table 3 shows the results from the survey.

Table 3: Preference values representing the relative importance or weight of the criteria and the alternatives within each criterion.

	Mean Preference Value	**Standard Deviation**
Future perspective if therapy implemented		
End-stage RP: complete blindness	0.0%	0.0%
Mid-stage RP: tunnel vision	16.7%	4.1%
Low-stage RP: night blindness	27.7%	6.9%
No visual impairment	36.6%	9.5%
Risk on side effects		
Therapy has high chance on patient harm	0.0%	0.0%
Therapy has low chance on patient harm	17.5%	5.6%
Efficacy of therapy		
Therapy has a low chance of success	0.0%	0.0%
Therapy has a high chance of success	16.9%	5.1%
Therapy price for the patient		
€500.000	0.0%	0.0%
Covered by insurance	16.4%	10%
Therapy discomfort		
Major discomfort	0.0%	0.0%
Minor discomfort	7.4%	5.0%
Procedural recurrence		
Recurring sessions of therapy necessary	0.0%	0.0%
Single session of therapy necessary	5.2%	2.2%

The survey indicates the highest mean preference value of 36.6% and a 9.5% standard deviation (SD) for complete cure of RP, followed by 27.7% with an low-stage RP of only night blindness. Notable is the approximate 10% increase in mean preference values between the stages starting from mid-stage tunnel vision up to no visual impairment. In addition to this the increase from end-stage complete blindness to mid-stage is 1.5 times moreover 15%. The risk on side effect, efficacy of the therapy and the therapy price for the patient all ranges from 16 to 18 percent. However, the reimbursement (covered by insurance) does indicate a SD of 10%. The alternatives with the lowest preference values are displayed with a mean preference value lower than 10% for therapy discomfort and procedural recurrence.

3 Expected Impact

An economic evaluation was done to assess the eventual impact of the OCU400 treatment using a model-based analysis including a headroom analysis followed by a Markov Model. A headroom analysis shows us the optimal "worth" of the technology. The Markov model makes it possible to assess the cost-effectiveness of the treatment. The outcome of both the headroom analysis and the Markov model are the costs per QALY and this value must be lower than the willingness-to-pay threshold for the treatment to be recommended for further research and development. The willingness-to-pay threshold is based on the burden of disease. RP is a disease with a burden of between 0.41-0.7, which corresponds to a threshold-to-pay of 50,000 euros [34].

3.1 Headroom analysis

The headroom analysis is used to assess the potential health benefits the technology could provide, see the potential market price and possible revenues of the treatment. The headroom is calculated from the difference in quality of life, the effectiveness gap, between patients without the treatment and with the treatment multiplied by the life years you expect to benefit from the result of the technology. The average life expectancy in the Netherlands is 82 years, measured in 2019 [35]. From the average age of diagnosis, 35.1 years, according to Tsujikawa et al., the assumption is made that patients live 42 years with RP [36]. The average quality of life of people suffering from RP at age 35 is 0.66 [37]. Hartong et al. have stated that patients with RP at age 35 are most likely to be in the stage of being legally blind [38], which corresponds to a visual acuity score (VAS) of 20/200, according to Klein et al. [39]. The OCU400 treatment is supposed to restore the QoL to a value of 0.852 [40]. This is the average Quality of Life (QoL) of an average healthy individual in the Netherlands. The calculations are then: (0.852-0.66)*47=9.024 QALYs. The headroom can be calculated as follows: Headroom: 9.024*50,000 = 451,200 euros per patient. From this an initial guess can be made about the maximal production costs for which the treatment will be cost-effective. The production costs must be lower than 451,200 euros per patient for the treatment to be cost-effective and to beneficially invest in further development. This will be taken into account when making the Markov Model and in giving an advice on whether to continue development. This analysis was done with the

following optimistic assumptions. The gene therapy is able to "fully restore" the QoL to the average QoL of an average healthy individual (in the Netherlands). Further, the maximal effects were explored here with a QoL of 0.66 for people being legally blind at age 35. However, in reality, the chance is high that people will be treated from different stage of RP. This would create a larger headroom due to a bigger difference in effects, since now the assumption is that legally blind patient with an utility value of 0.66 recover to a healthy state with an utility value of 0.852. If the headroom is calculated with a later stage of RP, for example RP1 with an utility of the 0.350, the QALYs would be larger and therefore the headroom as well. The Markov model takes into account these starting conditions as well.

To see the potential revenues this technology to the market, the return on investment is calculated. The production costs are estimated at 158,000 euros with the treatment price being 690,000 euros. This is an assumption made based on the costs of the Luxturna therapy, since there is no exact data available on the production costs of OCU400 and the Luxturna therapy is a similar technique. The estimation of the production costs for Luxturna are based on an average gross margin of 71.1% for all branded and generic drugs stated by Owermohle et al. [41]. The return on investment is the difference between the headroom and the production costs, multiplied by the number of cases per year. The number of cases per year that qualify for this treatment is between 50 and 100 people and the average is taken as the incidence. Therefore, the ROI is (451,200-158,000)*75 = 21,990,000 euros. This return on investment indicates that bringing the OCU400 technique on the market is viable.

3.2 Markov model

For the analysis of this health technology a Markov Model was used, since it is best suited for the OCU400 treatment. The Markov model takes time into account, whilst a decision tree does not. This is an important aspect to take into consideration, given the chronic nature of RP. The analysis was done with a time horizon of 65 years, calculated from the starting age of 35 years up to less that 1% of the population was still alive. Calculations showed this was at an age of 101 years. To get the realistic lifelong effect of the treatment on the QALYs and costs, this must be done [42]. The time cycle used was one year. This time cycle was chosen, since the treatment is only applied once during the first cycle and lengthening this cycle would not represent the real benefits and speed of the effects anymore. Further, the probabilities used in this paper were calculated with a time cycle of one year as well and for the use of these values the time cycle of this paper must be the same. The stages used in this paper, legally blind and RP3-RP0, were used with the purpose of having a clear comparison with the literature that states the different utility values [37]. This was necessary to be able to do the calculation in the Markov model. The stages discussed in chapter 2 are related to the stages of the Markov model in the following way; legally blind-RP3 = low-stage, RP2-RP1 = mid-stage, RP0 = end-stage. Figure 3 shows the Markov Model with and without treatment. As shown in the figure, the assumption is not made that every patient starts in the same state. This was done to show a better representation of the real-life situation, namely not everyone being diagnosed and treated in the same stage.

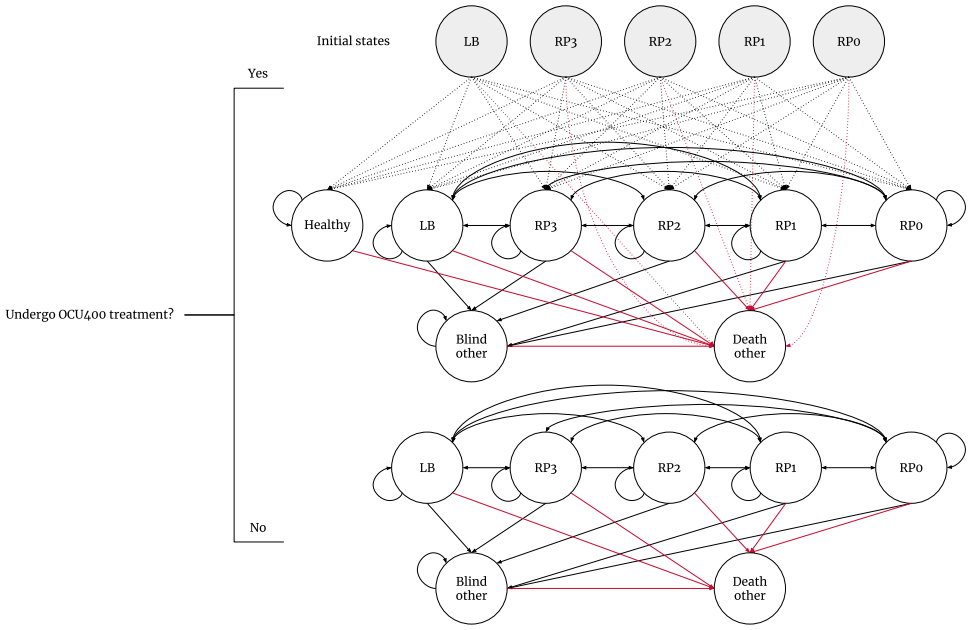


Figure 3: The upper model shows the Markov model with OCU400 treatment. The five different stages of RP are given twice in the upper model, since one can only go to the healthy state after successful treatment in the first time cycle. The lower model shows the model without OCU400 treatment, when only receiving best supportive care. All the circles are health states. The transition matrix $\mathbf{P}$ is shown in figure 4, and the cost and utility parameters are given separately in table 6.

$$\mathbf{P} = \begin{array}{r} \\ LB \\ RP3 \\ RP2 \\ RP1 \\ RP0 \\ Blind\,other \end{array} \begin{array}{c} \begin{array}{cccccc} LB & RP3 & RP2 & RP1 & RP0 & Blind\,other \end{array} \\ \left\| \begin{array}{cccccc} 0.80 & 0.05 & 0.05 & 0.05 & 0.05 & 9.260 \times 10^{-4} \\ 0.16 & 0.60 & 0.08 & 0.08 & 0.08 & 1.186 \times 10^{-4} \\ 0.08 & 0.08 & 0.60 & 0.16 & 0.16 & 1.186 \times 10^{-4} \\ 0.05 & 0.05 & 0.05 & 0.80 & 0.05 & 4.818 \times 10^{-5} \\ 0.05 & 0.05 & 0.05 & 0.05 & 0.80 & 1.519 \times 10^{-4} \\ 0 & 0 & 0 & 0 & 0 & 1 \end{array} \right\| \end{array}$$

Figure 4: Transition matrix of best supportive care.

A gene therapy by Luxturna being already tested in the Netherlands has indicated the transitions possible between the stages. The analysis uses a scale from Health State (HS) 1-5, which, based on their diagnostic meaning, is linked to the stages set in this paper. The table including the meaning of the stages in this paper and their connection to the article by Zorginstituut is in table 4. The initial distribution of the patient population was also based on the baseline distribution of the research done by the Zorginstituut.

Table 4: The fives stage of Retinitis Pigmentosa, their clinical meaning and relation to literature found (HS = health state).

Stage	Meaning (Brown et al. [37])	Relation to zorginstituut document [34]
Legally Blind	Visual Analog Scale (VAS) = 20/200	HS5
RP3	Reading letters, VAS=20/400	HS5
RP2	Counting fingers	HS4
RP1	Light perception	HS3
RP0	Blind, minimal to no light perception	HS1-2

The utility values of each health state were based on the research done by Brown et al. [37, 43]. These values were measured with a VF-14 questionnaire, but were measured in 1999. The assumption is made here that these values are still applicable. The growth in technology over the past 18 years, however, could mean that the utility is higher now due to an increase in adjustments to the lifestyle of patients with RP. The costs of the OCU400 treatment have not been stated by the company, but are based on the Luxturna gene therapy, which is 743,846

euros including the surrounding necessary costs for diagnostics and additional care [34]. The alternative which the OCU400 treatment is compared to is best supportive care. The best supportive care needed is dependent on the stage of RP and the age of the patient. The transition matrix, as depicted in figure 4 are based on previous studies on RP [21, 44]. It can be seen from the transition matrix that it is possible to improve, i.e move to a better stage, with only best supportive care. The reason for that is unclear, but due to the lack of alternative sources and the reliability of the article by the National Institute for Health and Care Excellence, these probabilities were used [44]. The assumption is made that the OCU400 treatment is 93% successful for every stage of RP. This was based on the Luxturna gene therapy, since there are no clear results available yet from the OCU400 treatment and the Luxturna therapy has quite similar purposes [45]. The remaining 7%, i.e. the patients for which the treatment is unsuccessful, receive best supportive care. The corresponding transition probabilities from the initial states, as depicted in figure 3, to all of the other RP states, correspond to the transition matrix for best supportive care (figure 4), multiplied by 0.07. The Markov model accounts for age-dependent mortality rates, which could not be visualised in the transition matrix. However, they have been implemented in the cohort simulations and are based on the mortality rates for different ages in the Netherlands as reported in [46]. In case of a successful treatment the usual health care cost, were the only yearly costs and these are based on an article from the Central Agency for Statistics [47]. Therefore, OCU400 treatment with best supportive care in case of failure is compared to only best supportive care. In addition to best supportive care these patients also receive at home care, since it was deduced that patients with visual impairment would be in need of this depending on their RP stage and age [34]. In table 6, the utilities and the costs of the OCU400 treatment and best supportive care including the at home care are visible. This data was used to create two cohort simulations, one with the implementation of the OCU400 treatment and one with only the alternative, best supportive care. The incremental cost-effectiveness was calculated by dividing the difference in costs by the difference in QALYs from the cohort simulation with the time horizon of 65 years. The results are visible in table 5. Furthermore, the health state memberships throughout the cohort simulation are shown in figure 5. In the OCU400 arm, it can be seen that health and death are the dominant health states as 93% of the patients are subjected to successful treatments, leading to a major depletion of RP health state memberships.

Table 5: The results of the cohort simulations for the base case.

Markov model	**Average QALYs per patient**	**Average costs per patient(€)**	**ICER(€/QALY)**
OCU400	38.66	1069970.58	
Best supportive care	21.24	882966.13	
			10735.10

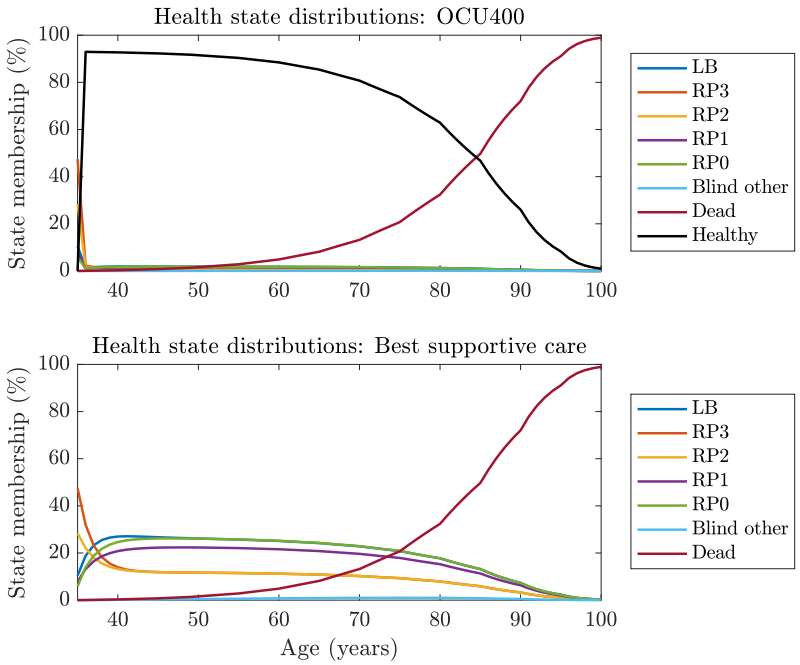


Figure 5: Overviews of the health states in the OCU400 and best supportive care arms obtained from the cohort simulations with the base case.

Table 6: Markov model cost(€) and utility parameters.

Name	Description	Value	Source
UHealthy	Utility value in cured RP patients / average healthy individuals	0.852	[40]
ULB	Utility value in RP patients who are LB	0.660	[37]
URP3	Utility value in RP3 patients	0.540	[37]
URP2	Utility value in RP2 patients	0.350	[37]
URP1	Utility value in RP1 patients	0.350	[37]
URP0	Utility value in RP0 patients	0.260	[37]
UBlindOther	Utility value in RP patients who are blind due to other causes	0.260	[37]
CTreatment	One-time OCU400 costs incurred on RP patients	743846	[34]
CHealthy	Annual healthcare costs incurred on healthy individuals	6120	[34]
CRehabilitation	One-time rehabilitation costs incurred on RP patients in best supportive care	38560	[34]
CBSCLB-1	Annual best supportive care costs incurred on RP patients who are LB (cycles 1-31)	11801	[34]
CBSCLB-2	Annual best supportive care costs incurred on RP patients who are LB (cycles 32-65)	11725	[34]
CBSCRP3-1	Annual best supportive care costs incurred on RP3 patients (cycles 1-31)	16842	[34]
CBSCRP3-2	Annual best supportive care costs incurred on RP3 patients (cycles 32-65)	16851	[34]
CBSCRP2-1	Annual best supportive care costs incurred on RP2 patients (cycles 1-31)	16842	[34]
CBSCRP2-2	Annual best supportive care costs incurred on RP2 patients (cycles 32-65)	16851	[34]
CBSCRP1-1	Annual best supportive care costs incurred on RP1 patients (cycles 1-31)	21952	[34]
CBSCRP1-2	Annual best supportive care costs incurred on RP1 patients (cycles 32-65)	21961	[34]
CBSCRP0-1	Annual best supportive care costs incurred on RP0 patients (cycles 1-31)	21952	[34]
CBSCRP0-2	Annual best supportive care costs incurred on RP0 patients (cycles 32-65)	21961	[34]
CBlindOther	Annual healthcare costs incurred on RP patients who are blind due to other causes	21450	[34]

The results show an incremental cost-effectiveness (ICER) of 10,736 euros/QALY. This must be compared to the willingness-to-pay threshold, 50,000 euros/QALY. The ICER is smaller than the willingness-to-pay threshold which indicates that the treatment would be cost-effective. From this analysis, the advice would be to further invest in this research.

4 Barriers and facilitators

Potential barriers and facilitators are tools for drafting possible future scenarios and are an essential key in improving decision-making in (early) Health Technology Assessment. These future scenarios describe thinkable pathways which might occur during the implementation of the OCU400 within the first five to ten years.
In order to obtain the key barriers and facilitators concerning the OCU400, literature review had been performed. All papers were assessed based on relevance and screened using domains of the consolidated framework of implementation research (CFIR) [48]. This eventually resulted in 10 papers describing useful barriers and facilitators. Furthermore, internal information about the OCU400 treatment within Ocugen and personal insights were used and added to the CFIR domains. When in fact certain topics were interrelated and not all domains of the CFIR were well supported, the barriers and facilitators were divided into the following domains: technical, social, clinical evidence and implementation, market and reimbursement. With the aim of prioritising the most important barriers and facilitators, internal ranking had been executed. All group members were asked to rank the barriers and facilitators independently to their importance by giving the different statements points accordingly. This was in accordance with the amount of statements. Subsequently, all results had been assessed based on the total of points

for each statement, mode and range (inter-rating) and this eventually resulted in a top ten, visible in table 7.

Table 7: Barriers and facilitators inter-rated according to importance

No. Rank	Barrier	Facilitator
1	The OCU400 therapy will not be fully reimbursed in the Netherlands	The OCU400 has timeless long-lasting effect
2	Market approval of the OCU400 in the Netherlands	Patients need for treatment[30]
3	Lack of consistent evidence including long-term effects of the OCU400 gene therapy [49, 50, 51]	Reduced psychological and social burden amongst retinitis pigmentosa patients[52]
4	The OCU400 therapy will significantly give complications [53, 54]	The OCU400 addresses a broad-spectrum (multiple genes) of retinitis pigmentosa in early and advanced stages with one genetic modifier gene[13, 55, 50, 56]
5	High costs involving implementation of the intervention	The overall process of treatment with the OCU400 is less time consuming
6	Gene testing limitations in human use [57]	By implementing the OCU400 patients are given an extra option/treatment [30]
7	Ethical considerations for long-term vision[56]	Minimal competitive pressure for implementing the OCU400 due to the unique value proposition of restoring visual function rather than merely slowing down retinal degeneration[58]
8	Patient cannot be exposed to a new genetic material a second time (immune system will reject it)	Successful outcome of the intervention might relieve burden on relatives/friends[52]
9	The strength and quality of literature among the OCU400 will remain minimal[13]	Due to the absence of effective retinitis pigmentosa treatments, full market penetration is plausible
10	Low incidence of retinitis pigmentosa in The Netherland and therefore minor patients' eligibility for OCU400 therapy	Ease in workload for clinicians

4.1 Formulation of scenarios

Scenarios were realized through internal brainstorm sessions and by including domain overlapping barriers and facilitators and were presented to the experts. The experts, consisting of Biomedical Engineering (BME) students, were asked to rank the barriers and facilitators from table 7 to their importance and rate the scenarios with their barriers and/or facilitators to their possible likelihood.

Scenario 1: What if the OCU400 therapy is not approved onto the market due to an overall lack of evidence and high costs for implementing OCU400 into clinical use. For instance, gene testing on humans remains limited and therefore influences the strength and quality of literature concerning the OCU400 and ethical considerations on long-term vision.

Scenario 2: What if the success rate of the OCU400 therapy is acceptable with low risks of complications and therefore results in reduction of patients' psychological and social burden e.g. anxiety for the risk of falling, social interaction concerns due to lack of eye contact, inability to participate in outdoor activities and relieves family and/or friends burden who care for the patient compared to the current care (coping with RP).

Scenario 3: What if another treatment is developed covering the same aspects as the OCU400 therapy within five to ten years, resulting in an increase of the outer pressure and full market penetration of the OCU400 therapy.

Scenario 4: What if the OCU400 therapy succeeds in addressing a broad-spectrum (multiple genes) of retinitis pigmentosa in early and advanced stages with one genetic modifier gene, resulting in a less time consuming process compared to current care (coping with RP) e.g. connection with healthcare and the associated adjusting care over time (mental and physical support, diagnostic tests, accidental care) and therefore creating ease in workload for clinicians.

Scenario 5: What if the OCU400 therapy will not be fully reimbursed in The Netherlands due minor patients eligibility for OCU400 therapy.

Scenario 6: What if the main reason for the limited availability of options (treatments), long-lasting effects and the overall need for treatment outweighs the fact that it is not possible to be exposed to new genetic material a

second time.
Baseline scenario: Within 5-10 years the OCU400 gene novel therapy will be the first therapy choice for people with inherited retinal disease.

4.2 Expert results

Based on the ranking results of the experts (n=9) the top three most important barriers are: the possibility that the OCU400 gives complications, high costs involved in the implementation and the chance of not being fully reimbursement. Additionally, the top three facilitators are: patients need for treatment, long-lasting effect from the OCU400 therapy and the extra given option to the patients.

The results from the rating are presented in the table 8. Herein, the lowest average is conducted from the interpretation of the experts wherein the lowest possible likelihood occurs during the implementation of the OCU400 given the time horizon of five to ten years for the given statement and thus the barrier or facilitator. Subsequently, the highest average is the highest possible likelihood wherein the statement is considered to be true within the "real world". The mean average presents the most accurate chance the statement will occur. Lastly, the median is calculated between the lowest and highest average. It can be seen that the facilitator concerning the long-lasting effects has the most possible likelihood that influences the implementation of the OCU400 within the first five to ten years, followed by relieve burden on relatives and the needs for treatment. Looking at the barriers high costs of the treatment, low incidence of retinitis pigmentosa in the Netherlands and the limitations in the number of exposure to the therapy are assumed to have the highest likelihood.

Table 8: rated barriers and facilitators by experts; numbered according to table 7

Scenario	**Barrier (B) / facilitator (F)**	**Lowest average**	**Highest average**	**Mean average**	**Median high vs low**
1 (n=10)	B - No. 6	40.4	56.3	50	50.6
	B - No. 9	37.1	52.7	42.9	44.9
	B - No.7	44.1	62.2	53.9	53.2
	B - No.2	48.9	71.8	56.6	60.3
	B - No.5	57.4	76.0	66.0	66.7
2 (n=8)	B - No. 4	40.4	53.4	48.3	46.9
	F - No. 3	44.4	77.4	60.4	60.9
	F - No. 8	52.6	84.0	67.1	68.3
3 (n=8)	F - No. 7	40.5	72.6	56.3	56.6
	F - No. 9	47.8	75.6	58.9	61.7
4 (n=7)	F - No. 4	29.6	60.0	46.6	44.8
	F - No. 5	491	75.9	65.4	62.5
	F - No. 10	46.1	69.4	57.1	57.8
5 (n=8)	B - No. 10	46.8	78.0	63.9	62.4
	B - No. 6	46.6	75.5	60.3	61.1
6 (n=8)	F - No. 6	39.8	65.3	53.8	52.5
	F - No. 1	59.1	82.3	70.4	70.7
	F - No. 2	50.3	78.9	66.9	64.6
	B - No. 8	25.8	70.6	50.3	48.2
7 (n=8)	Based on all barriers and facilitators	39.0	73.9	57.3	56.4

4.3 Scenario and sensitivity analysis

As mentioned previously, the high costs and risks for complications were amongst the top rated barriers. In terms of scenarios, this translates to inspecting unanticipated increases in treatment costs, and complication-induced decreases in the restoration utility. Apart from these scenarios, there is also an uncertainty in the treatment success rates, maximum restoration utility, and the treatment costs. Firstly, due to the lack of clinical evidence, it is rather optimistic to assume that OCU400 treatments have a success rate of 93%. Secondly, trials in mice have shown that treatment effectiveness manifested itself as a partial rescue of the outer nuclear layer count (30-80%) in the retina [13]. Hence, the assumption that all patients attain a quality of life score of 0.852 after a successful treatment might have lead to an overestimation of QALYs. Thirdly, the treatment costs are currently based on those of Luxturna, since no direct reports from ocugen are available. Given that the OCU400 therapy aims to target a multitude of gene mutations, while Luxturna only targets a single mutation, the higher gene therapy sophistication could be accompanied by higher costs. Therefore, scenarios were drafted to inspect the influence of

treatment success rates, maximum restoration utility, and OCU400 treatment costs on the cost-effectiveness. Since all three parameters estimates have a rather high uncertainty, univariate analyses would be incomplete. Hence, an additional multivariate analysis was conducted to determine how simultaneous variation would affect the ICER. The results can be seen in figure 6.

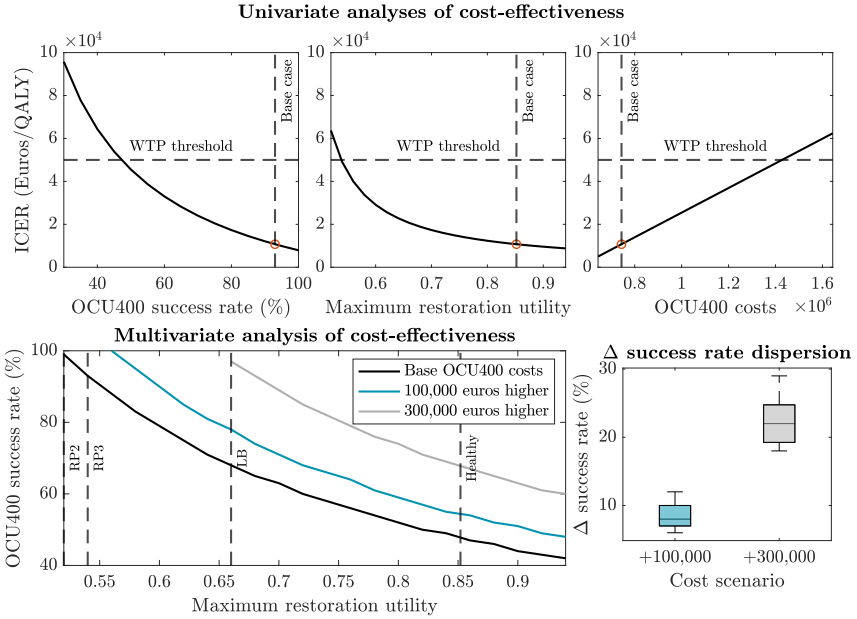


Figure 6: The upper left, middle, and right panel depict the changes in ICER upon varying the treatment success rate, maximum restoration utility, and OCU400 treatment costs respectively. The lower left panel depicts the pairs of restoration utilities and minimally required success rates for which the OCU400 is cost-effective, for three treatment cost scenarios. The lower right panel depicts the distribution of success rate differences for two cost scenarios relative to the base cost scenario.

The first univariate analysis revealed that 48% is the minimum viable success rate to attain cost-effectiveness according to the Markov model, yielding an ICER of 48684.99 euros/QALY. The second univariate analysis showed that if the OCU400 was only able to yield a quality of life of 0.54 (RP3), the gene therapy would still be cost-effective with an ICER of 49118.80 euros/QALY. The third univariate analysis suggests that the OCU400 treatment costs could rise up to 1,427,000 euros to retain cost-effectiveness with an ICER of 49951.94 euros/QALY. Overall, under univariate assumptions, the success rates, restoration utility, and OCU400 treatment costs permit absolute error margins of 45%, 0.312, and 683154 euros respectively with respect to the base case.

Furthermore, the multivariate analysis indicates that a lack of restoration utility can be compensated by higher success rates to safeguard cost-effectiveness. Moreover, it appears that the Markov model could even yield a cost-effective ICER of 49161.37 euros/QALY for a restoration utility of 0.52 (RP2), which is below the lower bound of 0.54 (RP3) as deduced from the univariate analysis. However, this would require the success rate to be increased to 99% within the base treatment cost condition, which is 6% higher than in the overall base case. Additionally, the multivariate analysis suggests that the minimum required success rate might increase substantially upon increasing the OCU400 treatment costs, as illustrated in table 9. For unanticipated increases in treatment costs of 100000 or 300000 euros, the expected increases in minimally required success rates are 8.25% and 22.27% respectively. All in all, the sensitivity analyses suggest that the ICER estimates of the Markov model are relatively robust to deviations in the aforementioned parameter estimates. Therefore, if ocugen manages to adhere to a similar cost structure as Luxturna, there should be little to no concern about achieving cost-effectiveness according to the results.

Table 9: The 95% confidence intervals of the mean increase in minimally required success rates for scenarios where the OCU400 treatment costs are 100000 and 300000 euros higher respectively.

Parameter	**Point estimate**	**Standard error**	**95% confidence interval**	**Estimation method**
μ_{100}	8.25	0.44	[7.39, 9.11]	Gaussian approximation
μ_{300}	22.27	0.91	[20.49, 24.05]	Gaussian approximation

To provide preliminary recommendations to ocugen based on the multivariate analysis, it is assumed that the success rate is the most challenging parameter to improve throughout gene therapy developments for RP. This

presupposition is based on two arguments. Firstly, RP is known to have a large number of mutations. Secondly, in 40% of the cases where RP has been diagnosed, the implicated genes are still unknown [13]. Therefore, the optimism in the success rate estimate of 93% is decreased for the preliminary advice. For a success rate of 65%, Ocugen should ensure restoration utilities between 0.68 and 0.88. This range encompasses the fluctuations in treatment costs for all three cost scenarios. Given the aforementioned results in mice, indicating a partial rescue (30-80%) of the outer nuclear layer count in the retina, while 20% is already significant, it seems plausible that the restoration utility is a viable parameter for Ocugen to further improve.

5 Discussion

5.1 Results

The patient preference survey indicates that the most important preference is the future perspective given by implementation of the OCU400 therapy. As expected patients showed a higher preference towards the outcome with no visual impairment. The results showed that the patients are most likely willing to pay for therapy discomfort and the recurrence of the procedural recurrence for an improved outcome, as these two aspects are considered the least important among all the patient preference criterion. Risk on side effect, efficacy of the OCU400 and the price for the patients, all are of second interest with no distinction between the risk on side effects and the effectiveness of the therapy. Thus overall, this indicates that the OCU400 therapy can have disliked alternatives among a few criteria, as long as the OCU400 offers a positive perspective of maximal low-stage RP symptoms.

The OCU400 technology proved to be cost-effective for treatment of Retinitis Pigmentosa. From these results, it can be said that further research and development would be beneficial. Patients mainly have a preference for a treatment that gives a high quality future perspective. Therefore it is of importance that OCU400 is a successful treatment against RP. The limitations and assumptions must be taken into account. However, a way must be found to get more certainty on these unknown parameters, such as the success rate and utility after restoration. For now, it has been assumed that improvements in success rates are the most challenging to achieve in the development of the OCU400.

The experts opinions regarding the barriers and facilitators show that the three most likely to occur facilitators are mostly in accordance with the rating to importance provided by the experts, meaning that the chance OCU400 will provide these occurrences during the first five to ten year is high and also of importance. In contrast to the barriers, only the high costs of the treatment has high importance and occurring for OCU400. Based on the multivariate sensitivity analysis, it is recommended to focus on further improving the restoration utility of the treatment. For a success rate of 65%, which is 28% lower than as assumed in the base case, the utility after the treatment should range between approximately 0.68 and 0.88. This parameter range is applicable for a treatment cost range of 743846 to 1043846 euros.

5.2 Limitations

This study was severely limited by the small amount of literature available on the OCU400 treatment. The OCU400 treatment is only in the first stages of clinical trials. It has only been tested on mice and even on that trial there is only one article available. Due to the little amount of knowledge many assumptions had to be made based on other research done on RP and another gene therapy targeting the gene deficiencies in RP.

The costs for the OCU400 treatment are solely based on the costs of the Luxturna therapy. However, it is expected that the true treatment costs will be higher due to OCU400's ability to target multiple genes, while Luxturna solely tackles a single mutation. It was assumed that the success rate is 93% and that this is equal starting from every stage of RP. This has been assumed to stop retinal degeneration and not to restore it. OCU400 is focused on restoring it and therefore the estimated success rate of OCU400 probably is lower than 93%. Trials with the mice showed a partial rescue of 30-80% and this has proved to be significant, but the 93% success rate might not be a good representative of this. Further, the implied success is assumed to be able to restore the vision completely and to increase the utility value back to that of a healthy person, 0.852. The results from the initial trial shows a partial rescue and this implies that there is also a chance that the treatment does not restore the vision completely. This would probably cause the utility value to be lower after treatment, which will decrease the cost-effectiveness. Further, the utility values will differ per person, especially the healthy state. The utility values used in this analysis were based on the paper done by Brown et al. These values might be too low however, considering that for example the value for being completely blind is 0.26. "we think this might be low seeing zero is death".

It must be argued that whilst sources show that the majority of patients with RP at the age of 35 years are legally blind, the research done by the zorginstituut shows a distribution where most patients at age 35 are in stage RP3.

Another limitation to this study was the overall time-frame in which this research had been conducted. This resulted in no large response rates for the surveys and therefore it is doubtful how reliably and truthfully the

results reflect the expert and patient opinions. In conjunction with this, the experts were Biomedical Engineering students as no response had been obtained from Ocugen nor hospitals nor RP patients. Even though background information was supplied to the survey respondents, it cannot be assumed that the results from the preference analysis are completely in line with the survey if it was conducted by experts. Concrete values for the 'risk', 'efficacy' and 'discomfort' might also alter the concluded preference values as these values are now open for the students' own perception.

5.3 Recommendations

As discussed in the previous paragraph, a lot of assumptions had to be made to perform this early Health Technology Assessment. The main recommendation therefore is to continue research of this gene therapy and see how the parameters of OCU400 differ from the assumed values. An important assumption that is not related to the OCU400 treatment, but needs to be researched is the possibility to transition to a better stage with only best supportive care. The treatment has proven to be cost-effective within the ranges given by the scenario analysis. This provides a guideline as to the boundaries that can be worked within concerning development costs, success rate etc. However, for future studies it would be more beneficial to discuss the results of the sensitivity analysis together with Ocugen. They are currently most aware of which parameters have flexible ranges of improvement, and which parameters are more rigid or possibly even bottlenecks. These insights would help in determining the most suitable and realistic parameter ranges to aim for within the results of the multivariate analysis, to safeguard cost-effectiveness. The preference analysis should be repeated on an actual RP patient group and other preference analyses can be conducted on different stakeholder groups to map their preferences from their perspective. Before these analyses are to be conducted, one has to investigate the effectiveness of the PAPRIKA method in their analysis.

6 Critical Reflection

During this course, we learned about the theoretical aspects that go into the making of an eHTA, and the implementation of this theory. The lectures provided a good base of what is the purpose of every aspect and what is part of replicating this theory. The tutorials/practicals for the modeling provided help in implementing it into our own analysis, using it as a guideline. The guest lectures served to see the day-to-day use of the teachings and brought along a comparison for our own project.

It was quite interesting to learn about the wide range of health preference elicitation methods, and how psychological aspects played a role in people's abilities to express their preferences. Prior to the lectures, the awareness on the cognitive burden of surveys was minimal. We previously operated based on the presupposition that individuals were capable of consistently ranking their preferences linearly. Hence, the cognitive rationale behind the principles of for instance decision-making provide critical insights towards our own assumptions, as well as towards future surveys we may encounter.

The actual model implementation proved to be more challenging than expected due to the limited amount of disclosed information, since the OCU400 is still in the early development stage. In absence of information, it is challenging to provide adequate initial estimates of model parameters to derive meaningful results. However, scenario and sensitivity analyses in particular provided adequate mechanisms to cope with this uncertainty. It was very insightful, also for future model-based studies, to adjust the parameters based on what-if scenarios to characterise the model's behaviour. This gives insights in whether concerns in feasibility and viability are justified, or whether they could be partially omitted based on the model outcomes. Nevertheless, in case of multivariate uncertainty, it remains challenging to provide concrete advice on what a company should focus on in particular. The interaction between the various variables further complicates the identification of the most significant cost-drivers. This further sheds light on the importance of stakeholder engagement. Rather than fully leaving the analysis and interpretation of results up to health economists, insights from experts, for instance companies, can help in coping with the uncertainty. Assumptions regarding bottlenecks can be validated with them to improve the adequacy of recommendations for future developments, as well as the overall validity of the results. The goal of doing an early assessment is seeing whether to further invest in it, but this research has shown that it might be more reliable to make a recommendation on what must be looked into and be taken into account than giving a clear answer, yes or no, for further investment.

References

[1] Oogfonds Nederland. Oogfonds: Retinitis Pigmentosa, 5 2021.

[2] Stefano Ferrari, Enzo Di Iorio, Vanessa Barbaro, Diego Ponzin, Francesco S Sorrentino, and Francesco Parmeggiani. Retinitis pigmentosa: genes and disease mechanisms. *Current genomics*, 12(4):238–249, 6 2011.

[3] Anil Vaidya, Elio Borgonovi, Rod S. Taylor, José Alain Sahel, Stanislao Rizzo, Paulo Eduardo Stanga, Amit Kukreja, and Peter Walter. The cost-effectiveness of the Argus II retinal prosthesis in Retinitis Pigmentosa patients. *BMC Ophthalmology*, 14(1), 4 2014.

[4] Shannon E Boye, Sanford L Boye, Alfred S Lewin, and William W Hauswirth. A Comprehensive Review of Retinal Gene Therapy. *Molecular Therapy*, 21(3):509–519, 2013.

[5] Carol M Mangione, Paul P Lee, Peter R Gutierrez, Karen Spritzer, Sandra Berry, Ron D Hays, and for the National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-list-item National Eye Institute Visual Function Questionnaire. *Archives of Ophthalmology*, 119(7):1050–1058, 7 2001.

[6] B-J Hahm, Y-W Shin, E-J Shim, H J Jeon, J-M Seo, H Chung, and H G Yu. Depression and the vision-related quality of life in patients with retinitis pigmentosa. *British Journal of Ophthalmology*, 92(5):650–654, 2008.

[7] Alex Black, Jan E Lovie-Kitchin, Russell L Woods, Nicole Arnold, John Byrnes, and Jane Murrish. Mobility performance with retinitis pigmentosa. *Clinical and Experimental Optometry*, 80(1):1–12, 1 1997.

[8] Christian Hamel. Retinitis pigmentosa. *Orphanet Journal of Rare Diseases*, 1(1):40, 2006.

[9] Fay Newton and Roly Megaw. Mechanisms of Photoreceptor Death in Retinitis Pigmentosa. *Genes*, 11(10), 2020.

[10] Nelly M Cruz, Yang Yuan, Barrett D Leehy, Rinku Baid, Uday Kompella, Margaret M DeAngelis, Pascal Escher, and Neena B Haider. Modifier genes as therapeutics: the nuclear hormone receptor Rev Erb alpha (Nr1d1) rescues Nr2e3 associated retinal disease. *PloS one*, 9(1):e87942–e87942, 1 2014.

[11] Ocugen. Ocugen OCU400, 2021.

[12] Giulliana Augusta Rangel Gonçalves and Raquel de Melo Alves Paiva. Gene therapy: advances, challenges and perspectives. *Einstein (Sao Paulo, Brazil)*, 15(3):369–375, 2017.

[13] Sujun Li, Shyamtanu Datta, Emily Brabbit, Zoe Love, Victoria Woytowicz, Kyle Flattery, Jessica Capri, Katie Yao, Siqi Wu, Michael Imboden, Arun Upadhyay, Rasappa Arumugham, Wallace B. Thoreson, Margaret M. DeAngelis, and Neena B. Haider. Nr2e3 is a genetic modifier that rescues retinal degeneration and promotes homeostasis in multiple models of retinitis pigmentosa. *Gene Therapy*, 2020.

[14] BioSpace. Ocugen therapy platform continues to advance towards clinic, 2020.

[15] Fiona Blanco-Kelly, María García Hoyos, Miguel Angel Lopez Martinez, Maria Isabel Lopez-Molina, Rosa Riveiro-Alvarez, Patricia Fernandez-San Jose, Almudena Avila-Fernandez, Marta Corton, Jose M Millan, Blanca García Sandoval, and Carmen Ayuso. Dominant Retinitis Pigmentosa, p.Gly56Arg Mutation in NR2E3: Phenotype in a Large Cohort of 24 Cases. *PloS one*, 11(2):e0149473–e0149473, 2 2016.

[16] Dr. V.P.T. Hoppenreijs. Oogartsen: Retinitis Pigmentosa, 2021.

[17] Erasmus MC. Patientfolder: Vitamine A therapie, 2021.

[18] Eliot L Berson, Bernard Rosner, Michael A Sandberg, K C Hayes, Britain W Nicholson, Carol Weigel-DiFranco, and Walter Willett. A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa. *Archives of Ophthalmology*, 111(6):761–772, 6 1993.

[19] Boyd Kierstan. What Is Retinitis Pigmentosa?, 9 2020.

[20] studiegroep ophthalmogenetica Medische werkgroep Retina. Gentherapie met Luxturna.

[21] Celine-Lea Halioua-Haubold, Jasleen K Jolly, James A Smith, Rafael Pinedo-Villanueva, David A Brindley, and Robert E MacLaren. Potential lifetime quality of life benefits of choroideremia gene therapy: projections from a clinically informed decision model. *Eye*, 33(8):1215–1223, 2019.

[22] Zorginstituut Nederland. Prijsafspraken nodig over gentherapie Luxturna®, 2020.

[23] Oogvereniging Nederland. Eerste gentherapie voor oogaandoening uitgevoerd in Nederland, 2021.

[24] Ocugen. Ocugen pipeline OCU410, 2021.

[25] Secondsight. Discover Argus 2, 2021.

[26] Vision Research. Retina Implant AG's Alpha IMS Wins CE Mark, 2013.

[27] Katarina Stingl, Karl Ulrich Bartz-Schmidt, Dorothea Besch, Caroline K Chee, Charles L Cottriall, Florian Gekeler, Markus Groppe, Timothy L Jackson, Robert E MacLaren, Assen Koitschev, Akos Kusnyerik, James Neffendorf, Janos Nemeth, Mohamed Adheem Naser Naeem, Tobias Peters, James D Ramsden, Helmut Sachs, Andrew Simpson, Mandeep S Singh, Barbara Wilhelm, David Wong, and Eberhart Zrenner. Subretinal Visual Implant Alpha IMS – Clinical trial interim report. *Vision Research*, 111:149–160, 2015.

[28] Avni P Finn, Dilraj S Grewal, and Lejla Vajzovic. Argus II retinal prosthesis system: a review of patient selection criteria, surgical considerations, and post-operative outcomes. *Clinical ophthalmology (Auckland, N.Z.)*, 12:1089–1097, 6 2018.

[29] Thomas L Edwards, Charles L Cottriall, Kanmin Xue, Matthew P Simunovic, James D Ramsden, Eberhart Zrenner, and Robert E MacLaren. Assessment of the Electronic Retinal Implant Alpha AMS in Restoring Vision to Blind Patients with End-Stage Retinitis Pigmentosa. *Ophthalmology*, 125(3):432–443, 3 2018.

[30] Lily Hoffman-Andrews, Ronit Mazzoni, Michelle Pacione, Rosemarie Garland-Thomson, and Kelly E. Ormond. Attitudes of people with inherited retinal conditions toward gene editing technology. *Molecular Genetics and Genomic Medicine*, 7(7), 7 2019.

[31] 1000minds. Multi-Criteria Decision-Making (MCDM), 2021.

[32] 1000minds. PAPRIKA Method, 2021.

[33] 1000minds. 1000minds survey software, 2021.

[34] Zorginstituut Nederland. Pakketadvies voretigene neparvovec (Luxturna®). Technical report.

[35] The World Bank. Life expectancy at birth, total (years) - Netherlands.

[36] Motokazu Tsujikawa, Yuko Wada, Marie Sukegawa, Miki Sawa, Fumi Gomi, Kohji Nishida, and Yasuo Tano. Age at Onset Curves of Retinitis Pigmentosa. Technical Report 3, 2008.

[37] Melissa M. Brown, Gary C. Brown, Sanjay Sharma, and Jennifer Landy. Health care economic analyses and value-based medicine. *Survey of Ophthalmology*, 48(2):204–223, 2003.

[38] Dyonne T Hartong, Eliot L Berson, and Thaddeus P Dryja. Retinitis pigmentosa Prevalence and inheritance patterns. Technical report, 2006.

[39] Ronald Klein, Barbara E.K. Klein, and Scot E. Moss. Visual Impairment in Diabetes. *Ophthalmology*, 91(1):1–9, 1984.

[40] X. Pouwels. Lecture Headroom Analysis, 2021.

[41] Sarah Owermohle and S&P Global. High profit margins along drug supply chain raise cost questions in report, 7 2017.

[42] X. Pouwels. Feedback session on project progress, 5 2021.

[43] Gary C Brown. Vision and Quality of Life. *Transactions of the American Ophthalmological Society*, 1999.

[44] Pre-meeting briefing. Technical report, 2018.

[45] Spark Therapeutics. Spark Therapeutics Announces New Positive Data from Continuation of Phase 3 Trial of Voretigene Neparvovec, 2016.

[46] CBS Doodsoorzakenstatistiek. Relatieve sterfte naar leeftijd en geslacht, 2019.

[47] Centraal Bureau voor de Statistiek. Zorguitgaven stegen in 2019 met 5,2 procent, 2019.

[48] Laura J. Damschroder, David C. Aron, Rosalind E. Keith, Susan R. Kirsh, Jeffery A. Alexander, and Julie C. Lowery. Fostering implementation of health services research findings into practice: A consolidated framework for advancing implementation science. *Implementation Science*, 4(1):1–15, 8 2009.

[49] Xandra García-González, Teresa Cabaleiro, María José Herrero, Howard McLeod, and Luis A. López-Fernández. Clinical implementation of pharmacogenetics. *Drug Metabolism and Personalized Therapy*, 31(1):9–16, 3 2016.

[50] Luk H Vandenberghe. What Is Next for Retinal Gene Therapy? *cold spring harbor laboratory press*, 2015.

[51] John P A Ioannidis and Muin J Khoury. Evidence-based medicine and big genomic data. *Human Molecular Genetics*, 27:R2–R7, 2018.

[52] Andrew Lloyd, Natalia Piglowska, Thomas Ciulla, Sarah Pitluck, Scott Johnson, Marric Buessing, Thomas O'connell, and Acaster Lloyd. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol*, 103:1610–1614, 2019.

[53] Federico Mingozzi and Katherine A. High. Immune responses to AAV vectors: Overcoming barriers to successful gene therapy. *Blood*, 122(1):23–36, 7 2013.

[54] April R. Giles, Lakshmanan Govindasamy, Suryanarayan Somanathan, and James M. Wilson. Mapping an Adeno-associated Virus 9-Specific Neutralizing Epitope To Develop Next-Generation Gene Delivery Vectors. *Journal of Virology*, 92(20), 8 2018.

[55] Ocugen. Forward Looking Statement.

[56] Fathema Uddin, Charles M. Rudin, and Triparna Sen. CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future. *Frontiers in Oncology*, 10:1–17, 8 2020.

[57] Michael Hudecek, Zsuzsanna Izsvák, Sandra Johnen, Matthias Renner, Gabriele Thumann, and Zoltán Ivics. Going non-viral: the Sleeping Beauty transposon system breaks on through to the clinical side. *Critical reviews in biochemistry and molecular biology*, 52(4):355–380, 2017.

[58] GHMB van Rens, HL Vreeken, and RMA van Nispen. Richtlijn. Technical report, 2019.