NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

The following documents are made available to the consultees and commentators:

1. **Pre-Meeting Briefing (PMB)**

   Final Scope and Final Matrix of Consultees and Commentators

2. **Company submission** from Novartis Pharmaceuticals (UK) Ltd.

3. **Company submission addendum** from Novartis Pharmaceuticals (UK) Ltd.

4. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company responses to NICE's request for clarification

5. **Consultee submissions** from:
   - Fight for Sight
   - Retina UK - endorsed by Patient expert T Houlihan
   - Royal College of Ophthalmologists – endorsed by clinical expert Professor A Webster
   - NHS England

6. **Expert personal perspectives** from:
   - Professor Robert MacLaren – clinical expert, nominated by Novartis Pharmaceuticals UK Limited
   - Robert Johnson – patient expert, nominated by Fight for Sight.

7. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG).

8. **Evidence Review Group report – factual accuracy check**

9. **Evidence Review Group report – erratum**

10. **Evidence Review Group Addendum 1**

11. **Evidence Review Group Addendum 2**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Voretigene neparvovec for treating inherited retinal dystrophies caused by *RPE65* gene mutations [ID1054]

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key abbreviations

AAV	adeno-associated virus	**LRAT**	lecithin retinol acyltransferase
AE	adverse event	**mITT**	modified intention to treat
BCVA	best-corrected visual acuity	**MLMT**	multi-luminance mobility test
BSC	best supportive care	**NHx**	natural history
CI	confidence interval	**MLMT**	multi-luminance mobility test
CMO	cystoid macular oedema	**NR**	not reported
CS	company submission	**OCT**	optical coherence tomography
EMA	European Medicines Agency	**PAS**	patient access scheme
EOSRD	early-onset severe retinal dystrophy	**PLR**	pupillary light reflex test
ERG	Evidence Review Group	**QALY**	quality-adjusted life year
FST	full-field light sensitivity	**RCT**	randomised controlled trial
HR	hazard ratio	**RP**	retinitis pigmentosa
HRQoL	health-related quality of life	***RPE65***	retinal pigment epithelium-specific 65 kDa protein
HS	health state	**SAE**	serious adverse event
HST	highly specialised technology	**SECORD**	severe early childhood onset retinal dystrophy
ICER	incremental cost-effectiveness ratio	**TP**	transition probability
IRBP	interphotoreceptor retinoid-binding protein	**VA**	visual acuity
IRD	inherited retinal disease	**VF**	visual function
ITT	intention to treat	**VFQ**	Visual Function Questionnaire
LCA	leber’s congenital amaurosis	**VI**	visual impairment

Key issues for consideration

- Clinical effectiveness

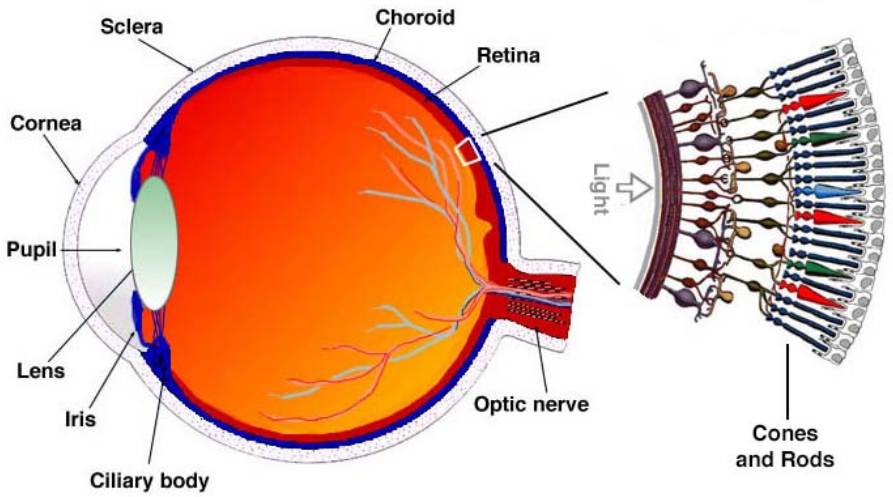
- **Study 301/302 recruited patients diagnosed with LCA and those with sufficient viable retinal cells:**
  - How would sufficient viable retinal cells be defined in clinical practice?
  - What population would be considered for treatment with VN?
  - Is the evidence generalisable to clinical practice in the UK?

- **What is the committee's view on:**
  - The imbalances in baseline characteristics and measures between VN and BSC arms in study 301/302 and the impact of that on treatment effect?
  - The clinically meaningful changes defined by the company for VA, VF, FST and MLMT?
  - The effect of VN in the short, and long term (biological plausibility)?

- **Does the committee consider the clinical trials capture:**
  - Outcomes/benefits that are important to patients?
  - Different aspects of the disease?

Disease background

- **Inherited retinal dystrophies (IRD):** a group of rare genetic eye diseases, which can be caused by germline mutations in more than 260 genes, including the *RPE65* gene
  - Mutations in the *RPE65* gene result in an insufficient supply of rhodopsin (a photosensitive protein that converts light into an electrical signal) and leads to cell apoptosis
  - Rhodopsin is found in rod cells which are responsible for vision at low light levels
- ***RPE65*-mediated IRD:** including 2 main disorders, Retinitis pigmentosa (RP), and Leber's congenital amaurosis (LCA)
  - LCA and RP are typically differentiated by clinical presentation and family history
  - LCA is less common, presenting earlier and having a more aggressive prognosis
  - According to a natural history study (Chung et al. 2018) conducted among people with RPE65-mediated IRD of 24 different diagnoses (Nhx65, n=70), 47% were diagnosed with LCA and 8% with RP



SOURCE:http://www.blueconemonochromacy.org/how-the-eye-functions/

Disease background: *RPE65*-mediated IRD

RPE65-mediated IRD presents at a range of ages between infancy and adolescence:

- **Diagnosis:** involves an assessment of medical history, clinical symptoms, and analysis of family history prior to genetic screening
  - LCA: typically diagnosed shortly after birth
  - RP: late childhood or early adulthood
- **Early symptoms:** nyctalopia (night blindness), oculo-digital sign (eye poking) and nystagmus (involuntary eye movement)
- **Progressive deterioration:** in visual field (range of sight), light sensitivity, and visual acuity (clarity of vision)
- **Blindness**: RPE65-mediated IRD can lead to complete blindness. The company note that a study of people with RP found patients lose around 50% of their remaining vison every 5 years. No evidence specific to RPE65-mediated IRD
- **Complications:** of IRD mainly include cataracts and cystoid macular oedema

Incidence/Prevalence

- **Incidence:** newly diagnosed cases estimated to be around 0.6–1.6 per 100,000 people per year
- **Prevalence:** of LCA and RP is estimated at around 12.3–28.8 per 100,000 people
  - In England, It is estimated that there are 57–564 people with *RPE65*-mediated IRD; about 86 will be eligible for treatment with voretigene neparvovec (VN)

Current treatment options

No standard clinical pathway or licensed treatment available

- Management focuses on monitoring, psychological support, mobility training and visual rehabilitation including visual aids such as glasses, magnifiers and telescopes
- Children with visual impairment are eligible for learning support, whilst adults receive supportive care from clinicians, employers and social services
- Genetic counselling is provided via medical genetic services to affected families

Related NICE guidance:

- Insertion of a subretinal prosthesis system for retinitis pigmentosa (2015) NICE interventional procedures guidance 537
  - to be used only in the context of research
- Insertion of an epiretinal prosthesis for retinitis pigmentosa (2015) NICE interventional procedures guidance 519
  - to be used only in the context of research

Patient support group comments (I): *survey of people (n=916) affected by inherited sight loss*

Overall quality of life (QoL)

- More than 50% of respondents said that their sight loss had a severe or very severe impact on their overall QoL, 36% said that there was a moderate impact on their QOL

Mental health

- 92% of respondents said their sight loss had an impact on their mental health:
  - 75% had experienced anxiety; 62% stress; 41% depression; 33% loneliness
- Progressive nature of the condition leads to a continual series of losses, requiring patients and carers to constantly adapt to increasing disability

"*There's no cure for what I have. I'm just trying to adjust. I'm 21. Can't drive. Can't see in low light or night, faces turn to shadows… This sucks, I don't want to go blind. It's very scary."*

Social integrations

- **Social life**: the majority of respondents said that their condition affected their day-to-day routines, relationships and family life:
  - **Mobility:** 97% said that their sight loss affected their mobility; 95% their condition impacted on their leisure time and hobbies
- **Education and employment**: more than 50% said their condition impacted on their education, and more than 75% felt that their career / job was affected

"Access to work: unfortunately the service does not work very well. This service has caused me too much stress and anxiety therefore I am no longer using it, even though I do need it"

Patient support group comments (II):

Unmet need

- There is currently no treatment that slows or stops the progression of sight loss
- Over 50% of survey respondents had not accessed genetic testing

"I have had very little support from the NHS in my area, therefore I have had to turn to private healthcare."

"I have seen a different doctor every single time I've had an appointment with ophthalmology. Feels like there is no continuity of care."

"I would like support and feel very lost, like I'm falling through the cracks."

Impact on parents and carers: (as noted by another patient support group)

- 'Condition has an effect on parents who had no idea that there was a history of this condition within their family'
- 'Patient has to rely heavily on her husband with tasks such as cooking, or even knowing when lights are on or off in their home'

Benefits of new treatment:

- It is noted that the ability to **navigate in the dark** will be of huge benefit to patients living with RPE65-mediated IRD
- Having "functional" sight could improve patients quality of life

Patient expert comments (I)

IRD can cause **severe visual impairment or blindness at an early age** → difficult ensuring the correct support is in place for children

> "Much of my eleven years in mainstream education was marked by frequent battles with the Local Education Authority (LEA) and schools, to ensure that my needs were recognised, relevant support provided"

Patients can be highly constrained by their condition, impacting on many aspects of their daily lives including attending **school, work and social situations**

> "**Almost every aspect of my life** that I can think of is impacted by my sight, from the place I choose to live so as to be close to public transport, to the people I socialise with, the places I go, and the confidence with which I live my life"
>
> "The uncertainty about my future sight, and its impact on my **ability to live and work** as I want to weighs heavily on my mind"
>
> "Life as a disabled student could at times be difficult – my **mobility, particularly after dark**, was poor and I relied heavily on my peers. **Perceived deterioration in my sight** at this time also made it impossible to keep up with the reading for my course"

As noted, IRD has a substantial **effect on patients, parents and carers** → patients can require extensive support and parents worry and feel guilt about passing the gene to family

> "My mother has admitted that, had she not already been pregnant with my sister she would not have sought to have another child, in case they too were disabled"
>
> "A combination of the pressure of **continually adapting to meet expectations**, and of poor support, has previously contributed to **periods of depressio**n"

Patient expert comments (II)

High unmet need

"there is still no treatment available on the NHS, and neither I nor others in the same position can realistically expect a sustained pause in or reversal of our visual degeneration"

New treatments **should address night blindness, VA, VF and stabilizing or reversing the visual deterioration of school age or younger children**

"**Night blindness** is far more than a simple inability to see clearly between dusk and dawn.. It affects patients at any point of transition between levels of light, such as on entering a dimly lit meeting room, or walking from a brightly lit station platform into an interior corridor. I find myself disorientated, confused, sometimes scared.

A change in the level of night blindness experienced could help patients to navigate more safely, confidently and independently at night, but also to approach all mobility tasks with confidence about the consistency of their visual reaction and indirectly assist the mental wellbeing of some patients"

"Despite this it is my reducing **visual acuity and field of vision** which **has arguably had the greatest impact on my effectiveness at work and my perspective on the future**"

"Growing up with a visual impairment, places a heavy burden on children, potentially preventing them from fulfilling their potential in the classroom or of participating in sport or social activities alongside their peers. **Relieving them of the stress of the constant adaptation** which is, in my experience, the hallmark of living with a degenerative eye condition, would allow them to focus their energy on becoming independent, informed adults equipped to achieve their ambitions"

Testimonies from patients/experts/carers involved in company's clinical trial

Benefits after treatment

Colour and clearer vision

Patient : *"I no longer lived in fear…I was once again able to see such things as the faces of family and friends… and the beautiful colors of a sunset over Lake Erie."*

Patient: *"Within days of the first surgery, I could see vibrant colors again… I can walk confidently in dimly lit settings"*

Independence

Patient: *"I may not have gained normal vision, but I gained all of my independence. This was significant in the way that I live and plan my life. I no longer had the fear of what the next year would take away from me… I finally can live my life the way I want to."*

Parent: *"Since the treatment, her social world has expanded"*

Benefit of small changes in vision

Parent: *"being able to detect small differences has made a huge difference in her life. Let me be plain here. This has been a tremendous, life-altering success"*

Clinical expert: *"For those who live with this condition, an improvement by even one light level would still make a difference in their quality of life. This treatment has changed my daughter's life. Before couldn't distinguish where stairs stopped or ended or the curb on a sidewalk, but not anymore. She can now function independently"*

Comments from clinical experts and the Royal College of Ophthalmologists (RCOphth)

Condition

All clinicians agreed:

- *RPE65*-mediated IRD is a rare, progressive, disease which leads to severe vision loss
- The condition often has a profound effect on patients, families and friends
- There is a huge unmet need for people living with RPE65

New technology

All clinicians agreed:

- VN is the 1st treatment option - aim of stabilising vision and preventing further visual loss
- VN offers hope for people living with IRD
- Limited impact of the surgery as treatment is one time, relatively quick and will only be given to a small number of patients (about 30-50 in the UK)
- Surgeons already adept at the required surgery

Outcomes

- RCOphth:
  - **The most important outcome is gain of navigation,** significant effect on the independence of patients
  - **Preventing deterioration will also be key** to affected patients
- Clinical expert: **the aim of treatment was to improve vision**, both in terms of **visual acuity (VA) and low light sensitivity**

Subgroups of RPE65-mediated IRD

- RCOphth: there is a dominant allele giving rise to a different phenotype (*Hull et al.* 2016), but these patients would not be covered by the MA

NHS England comments

Pathway of care

- Currently there are no specific genetic treatments available in England
- Management for affected patients is supportive and involves ensuring good liaison between clinical and educational care
- Low visual aids are provided for adults and supportive care is provided between clinical care, employers and social services
- Low visual aids are provided for adults
- Genetic counselling is provided via medical genetic services to affected families.

Commissioning

- NHS England directly commissions specialised ophthalmology services for ocular genetic disorders
- Patient selection based on a molecular diagnosis
- The treatment can be implemented using the current clinical services

Voretigene neparvovec [VN] (Novartis, *LUXTURNA)*

Marketing authorisation	Granted on 22nd November 2018 for "the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells"
Mechanism of action	VN is an AAV vector-based gene therapy which introduces a healthy copy of the defective RPE65 gene into retinal cells
Administration and dosage	• One-time treatment (1.5 x 10^{11} vector genomes each eye) • Subretinal injection in each eye performed on separate days, no fewer than 6 days apart • An immunomodulatory regimen initiated prior to administration
List price	£613,410 per patient for both eyes Simple discount PAS approved

Abbreviations: AAV, Adeno-associated virus; PAS, patient access scheme, VN, voretigene neparvovec

Decision problem

	NICE scope	Company deviations	ERG
Population	People with inherited retinal dystrophies caused by *RPE65* gene mutations	Narrower than scope: Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by *confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells*	Population change matches MA Population included in the evidence base reflects the population most likely to be treated with VN
Intervention	Voretigene neparvovec with BSC		Current treatment: visual rehabilitation, but BSC not clearly defined
Comparator	BSC		
Outcomes	• Visual acuity (VA) • Visual field (VF) • Contrast sensitivity • Photosensitivity • Cataract surgery • AEs • HRQoL	As in NICE scope • MLMT considered relevant	No data on some outcomes of clinical relevance reported, including • HRQoL • need for cataract surgery

Abbreviations: AEs, adverse events; BSC, best supportive care; HRQoL, health related quality of life; IRD, inherited retinal dystrophies; MLMT, Multi-luminance mobility test**;** VN, voretigene neparvovec

Clinical effectiveness evidence

Completed and ongoing clinical trials

Clinical effectiveness - Source

Evidence	Population	Used in clinical effectiveness	Used in cost effectiveness
Study 101/102 Single arm, dose-escalating study	Patients with molecular diagnosis of LCA due to RPE65 mutations (aged 8+) [n=12]	Yes	No
Study 301/302 phase 3, open-label RCT and cross over extension study	Patients with molecular diagnosis of LCA due to RPE65 mutations Sufficient viable retinal cells [n=31] (age range: 4-44, ≤18 n=20 [65%])	Yes	Yes
RPE65 NHx Multicentre, retrospective chart review, natural history study (NHx65)	Patients with IRD and confirmed biallelic mutations in RPE65 gene [n=70] (Longitudinal ocular history and VF testing data extracted)	No	Yes

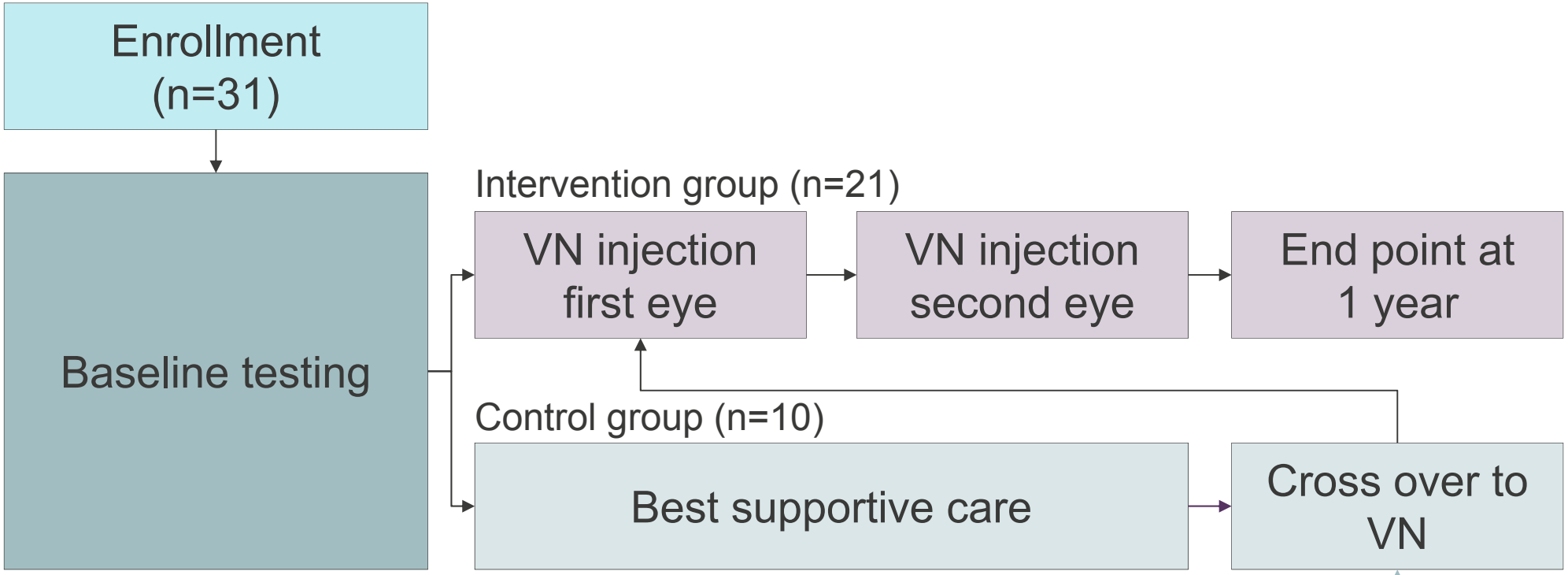
Abbreviations: IRD, inherited retinal dystrophies, LCA, Leber's congenital amaurosis; NHx, natural history; RCT, randomized control trial; VF, visual field

Company's main evidence of clinical effectiveness

	Study 101/102	Study 301/302
Design	**Study 101:** 2 year, phase 1 open-label, single arm, dose-escalating, multicentre **Study 102: f**ollow-on, open-label safety study to evaluate re-administration of VN to other eye	**Study 301:** 1 year, phase 3, open-label randomised controlled trial **Study 302:** Crossover phase, after 1 year control patients eligible to receive VN with follow-up extension study
Duration of study	**Primary endpoint:** 1 year 15 years follow up (currently 7.5 years)	**Primary endpoint:** 1 year Annual visits for 15yrs (currently 3/4 yrs)
Population	Patients with molecular diagnosis of LCA due to RPE65 mutations (aged 8+)	Patients with molecular diagnosis of LCA due to RPE65 mutations (aged 3+) Sufficient viable retinal cells
Sample size (n)	n=12 (original intervention) n=11 (re-administration to other eye)	VN: n=21 (original intervention) Control: n=10 → delayed intervention: n=9
Key outcomes	**Primary end point:** AEs **Secondary end points:** VA, VF, pupillary light response, mobility testing	**Primary trial end point (1 year):** MLMT change score to baseline **Secondary end points (1 year):** FST testing (av. both eyes), MLMT score change (first eye), BCVA (av. both eyes)

Abbreviations: AEs, adverse events; BCVA, best corrected visual acuity; FST, full-field light sensitivity; MLMT, multi-luminance mobility test; VA, visual acuity; VF, visual field; yrs, years

Study 301/302 trial - summary



Key inclusion criteria:

- Adults and children (3+ years old)
- LCA, molecular diagnosis of biallelic RPE65 mutations
- BCVA worse than 20/60 and/or VF less than 20º (both eyes)
- Sufficient viable retinal cells (OCT showing >100 µm thickness, ≥ 3 disc areas without atrophy of pigmentary degeneration within the posterior pole; or remaining visual field within 30º of fixation)

Baseline characteristics Study 301 (ITT)

Category		VN (n=21)	BSC (n=10)	Total (n=31)
Age	Mean (SD)	14.7 (11.8)	15.9 (9.5)	15.1 (10.9)
	Range (min, max)	4 - 44	4 - 31	4 - 44
Sex	Male, n (%)	9 (43%)	4 (40%)	13 (42%)
Race, n (%)	White	14 (67%)	7 (70%)	21 (68%)
	Asian	3 (14%)	2 (20%)	5 (16%)
	Black/African American	2 (10%)	0 (0%)	2 (6%)
Country, n (%)	United States	17 (81%)	6 (60%)	23 (74%)
	Other*	4 (19%)	4 (40%)	8 (26%)
Baseline visual outcomes	VA (Mean [SD])	[redacted]	[redacted]	n/a
	VF (Mean [SD])	[redacted]	[redacted]	n/a
	MLMT (Mean [SD])	[redacted]	[redacted]	n/a
	FST (Mean [SD])	[redacted]	[redacted]	n/a

Abbreviations: BSC, best supportive care; FST, full-field light sensitivity; MLMT, multi-luminance mobility test; SD, standard deviation; VA, visual acuity; VF, visual field; VN, voretigene neparvovec

Interpretation of baseline measures: VA, smaller values indicate better acuity; VF, higher values represent larger fields of vision; MLMT, lower light levels are associated with higher scores; FST, smaller values indicate better sensitivity

Baseline characteristics Study 101/102

Category	Study 101				Study 102
	Low Dose	Middle Dose	High Dose	Total (N=12)	Total (N=11)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG:

[redacted]

Age may impact on the treatment effect. Treatment at a younger age may be more beneficial

Baseline characteristics for RPE65 NHx (natural history study)

Parameter/Category/Statistic		RPE65 NHx (n=70)
Clinical diagnosis, n% *n=76	Early onset severe retinal dystrophies	4 (5.3)
	LCA	42 (55.3)
	Retinitis Pigmentosa	6 (7.9)
	Other	32 (42.1)
Age	Mean (SD)	15 (11.8)
	Range (min, max)	1 – 43
Sex, n (%)	Male	28 (40%)
Race, n (%)	White	47 (67%)
	Asian	2 (3%)
	Black/African American	14 (20%)
Ethnicity, n (%)	Not Hispanic or Latino	58 (83%)
	Hispanic or Latino	9 (13%)

ERG's comments on clinical evidence

Population	• Small evidence base, trials only recruited patients with LCA who may have a worse prognosis Unclear if evidence is generalisable to UK clinical practice
Quality of Evidence	• 101/102 dose escalating study, under-powered to evaluate clinical efficacy outcomes • RCT 301/302: subject to high risk of bias due to small population size
Baseline characteristics study 301/302	• Limited baseline characteristics reported –clinical diagnosis of patients not included • Differences in baseline characteristics (including age) – impact on treatment outcomes is yet not understood; not considered to demonstrate a clear bias • Baseline differences in MLMT, VA and VF between arms; more patients in the VN arm (19%) able to pass MLMT at 4 lux than the BSC arm (10%), but improved VA and VF in control arm • Company unable to adjust for baseline visual performance due to sample size – uncertainty in the true treatment effect
Outcomes	**Primary endpoint:** • MLMT change scores are capped at the lowest light setting, may underestimate mean change • Uncertainty in the threshold for a clinically meaningful change (1 lux) • Change in light level may be less sensitive than the change in the time to complete the test for assessing functional vision **Secondary endpoints:** • VA, VF and contrast sensitivity are relevant outcomes but have limitations and considered unreliable due to inter-test variability. • Do not capture characteristic features of the condition (night blindness) • Adapted VFQ removed items related to HRQoL, not an appropriate measure of HRQoL. No HRQoL or PRO data available for carers **Variations in timepoints reported for outcomes**: no clear reason for longer follow-up data for VA, MLMT, and VF (301/302) and FST (101/102)

Abbreviations: HRQoL, health related quality of life; LCA, Leber's congenital amaurosis; MLMT, multi-luminance mobility test; PRO, ; RCT, randomized controlled trial; VA, visual acuity; VF, visual field; VQF, Visual Function Questionnaire

Measurement of study outcomes (1)

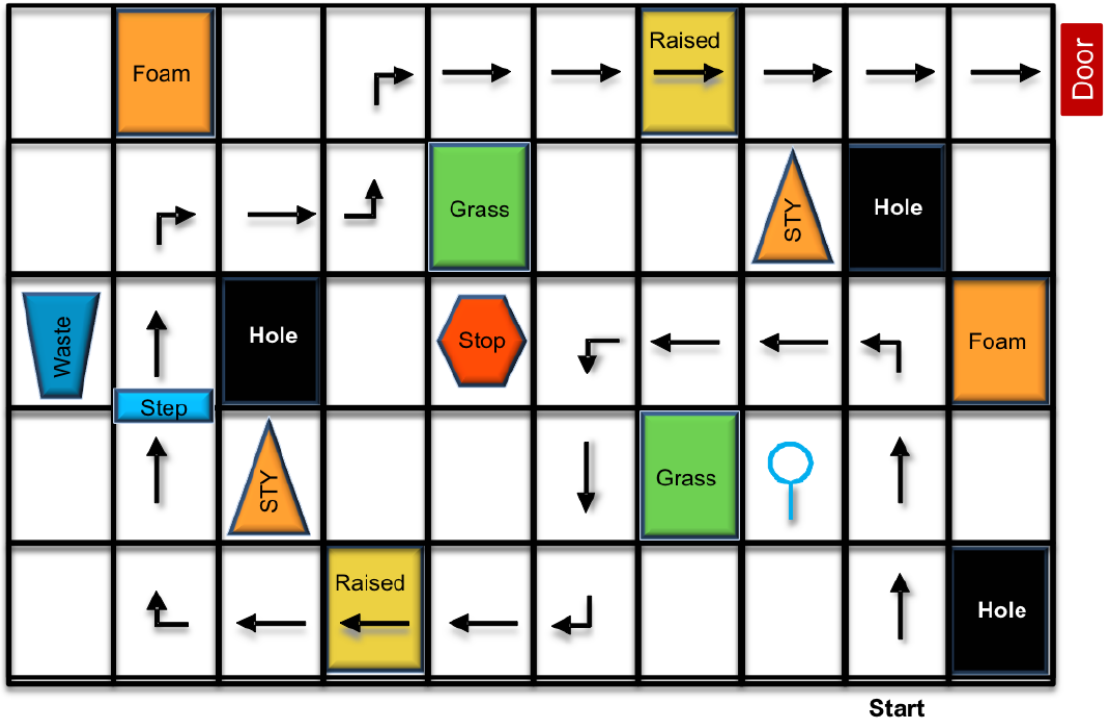
Multi-luminance mobility test (primary endpoint)

Procedure

- MLMT measures functional vision at specified light levels:

Lux	Examples
1	Moonless summer night
4	Outdoor parking lot at night
10	Bus stop at night
50	Inside of illuminated office stairwell
125	Interior of shopping centre at night
250	Interior of a lift, or office hallway
400	Office environment or food court

- Patients get a score for the minimum light level they can pass
- Patients are tested at 2 or more lighting conditions for each eye and then with both eyes open
- Lower light levels are associated with higher scores



Clinical significance

- The test relates to visual field (area that can be seen when the eye is directed forward, including peripheral vision) and light sensitivity
- The company notes that 'MLMT bypasses surrogate markers of vision and directly demonstrates clinical benefit'

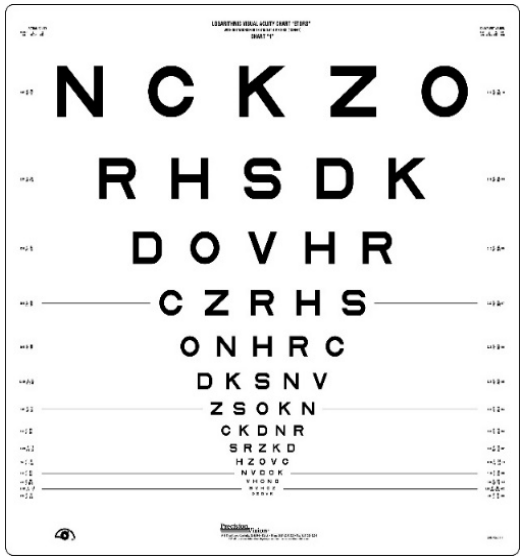
Measurement of study outcomes (2)

Full-field light sensitivity threshold (FST) testing (secondary endpoint)

- Measures light sensitivity of the entire visual field to assess the effect of treatment on nyctolpia (night blindness)
- Test calculates the minimum luminance at which the patient reliably perceives light
- More negative Log10(cd.s/m2) values indicate better sensitivity
- Clinically meaningful change: 10 dB or 1 log

Visual acuity (secondary endpoint)

- Measures sharpness or clarity of vision
- Assessed using the ETDRS test or the HOTV test (young children) measured in LogMAR units
- If a patients requires letters that are twice as large or twice as close as standard, the visual acuity is said to be ½
- Clinically meaningful change: change of LogMAR ≥0.3



Visual field (exploratory endpoint)

- Measures the area that can be seen when the eye is directed forward, including peripheral vision and how sensitive your vision is within this area
- Patients indicate when they detect light moving from the periphery to the centre
- Goldmann kinetic perimetry testing considered most relevant for RPE65-mediated IRD
- Higher values represent larger fields of vision
- Clinically meaningful change: 20% change from baseline score

Clinical effectiveness – results

Clinical effectiveness: MLMT

Study 301 and 101, year 1, ITT population; change score of ≥1 considered clinically meaningful)

Study 301		VN [n=21] (mean change from baseline MLMT score)	BSC [n=10] (mean change from baseline MLMT score)	Difference (95% CI)
1 year	Both eyes	1.8	0.2	1.6 (0.72 - 2.41; p=0.0013)
	1st (worst) eye	1.9	0.2	1.7 (0.89 - 2.52; p=0.0005)
	2nd eye	2.1	0.1	2.0 (1.14 - 2.85; p=0.0001)

Abbreviations: BSC, best supportive care; CI, confidence interval; MLMT, multi-luminance mobility test; VN, voretigene neparvovec

Study 301

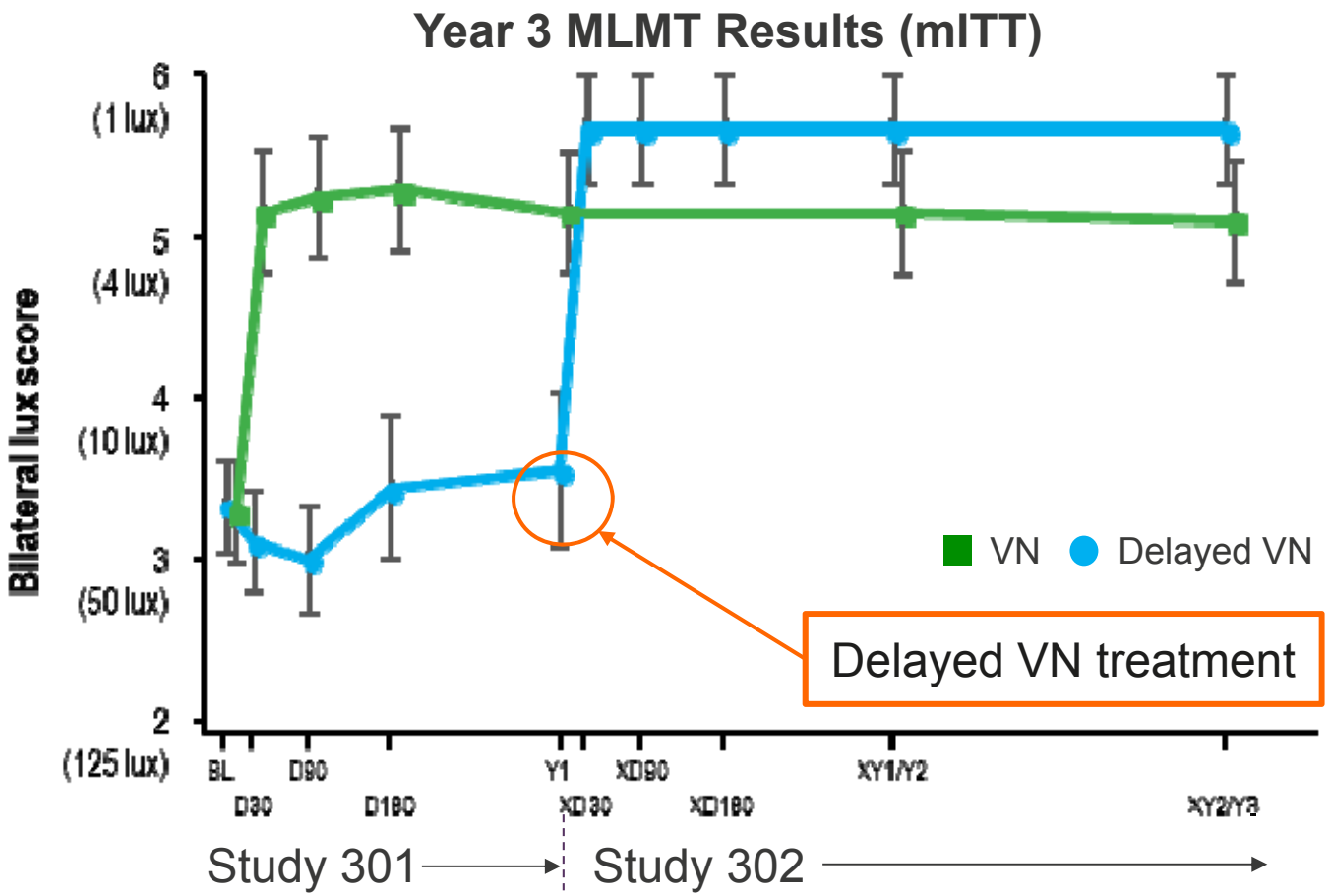
At 1 year, none of the patients in the BSC arm (0/10) were able to pass the MLMT test at 1 lux compared to 63.2% in the VN arm

Study 101/102

73% patients were evaluated using a mobility test (became MLMT)
Mean change in MLMT score at 1 year was 2.6 (SD 0.56) and 2.4 (SD 0.46) - 100% (8/8) patients demonstrated a clinically significant improvement of ≥1 light level
Maintained at follow-up at 4 years

Clinical effectiveness: MLMT scores over time

Study 302 (baseline to year 4, mITT, meaningful change ≥1 light level)



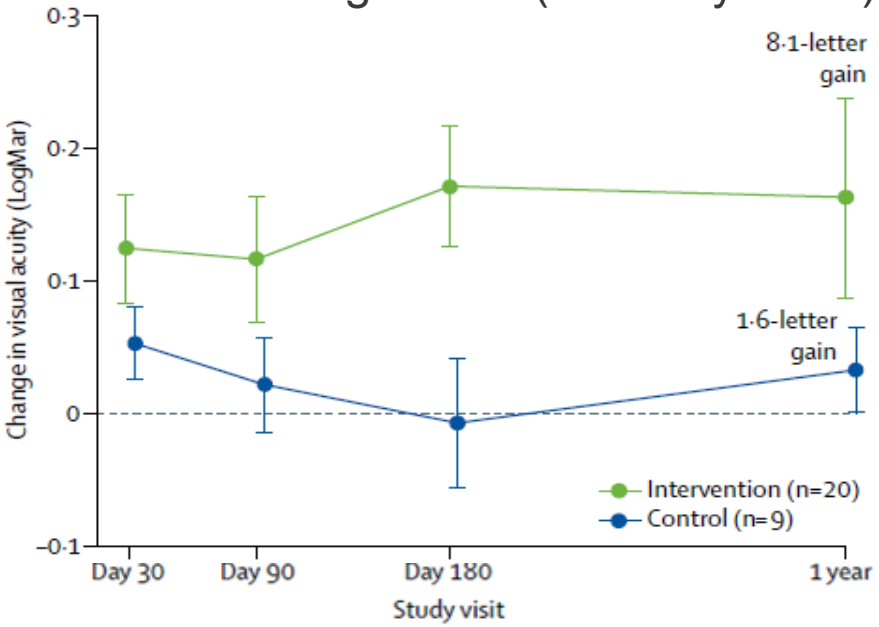
- Statistically significant rapid improvement in MLMT following VN treatment in both original and delayed arms (p=0.0013)
- Clinically meaningful improvement (change ≥1 light level)
- By year 3 60% original VN (12/20) able to pass MLMT at the lowest light level and 89% (8/9) delayed VN
- [redacted]

Year of follow up		Original VN (n=20)	Delayed VN (n=9)
Mean change from baseline (SD)	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	4	[redacted]	[redacted]

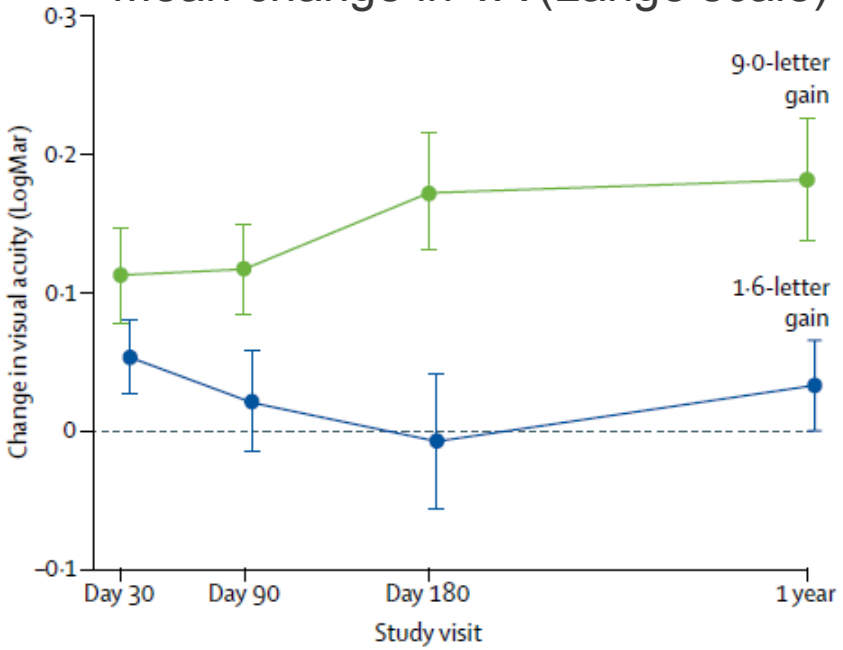
Clinical effectiveness: Visual acuity (VA)

Study 301 (1 year results, mITT, meaningful change LogMAR ≥0.3)

Mean change in VA (Holladay scale)



Mean change in VA (Lange scale)



Holladay scale

- Small improvement in VA in the VN arm compared to BSC at 1 year of 0.16 LogMAR (95%CI -0.41, 0.08; p=0.17) in the ITT population
- Not statistically significant
- Results comparable to mITT population

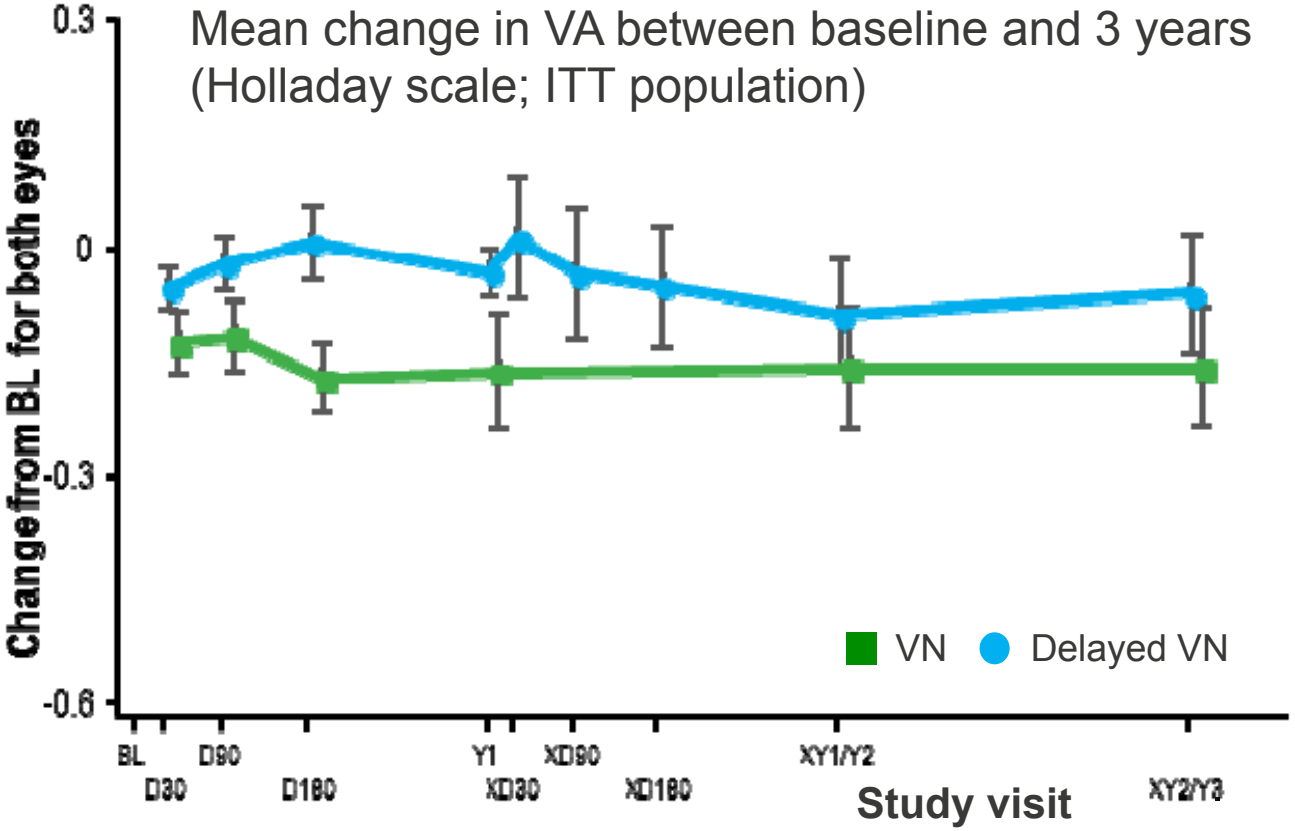
Lange scale

- Post-hoc analysis which reduced variability as a result of smaller off-chart changes
- Mean difference of -0.15 was reported (95%CI -0.29, 0.00; p=0.047) in ITT population
- Did not meet the company's definition of a clinically meaningful change (LogMAR ≥0.3)

Study 101: no statistically significant difference in change of VA between injected (-0.4233) and uninjected (-0.1525) eyes from baseline to one year (p=0.10)

Clinical effectiveness: visual acuity (VA)

Study 302 (baseline to year 4, mITT, meaningful change LogMAR ≥0.3)

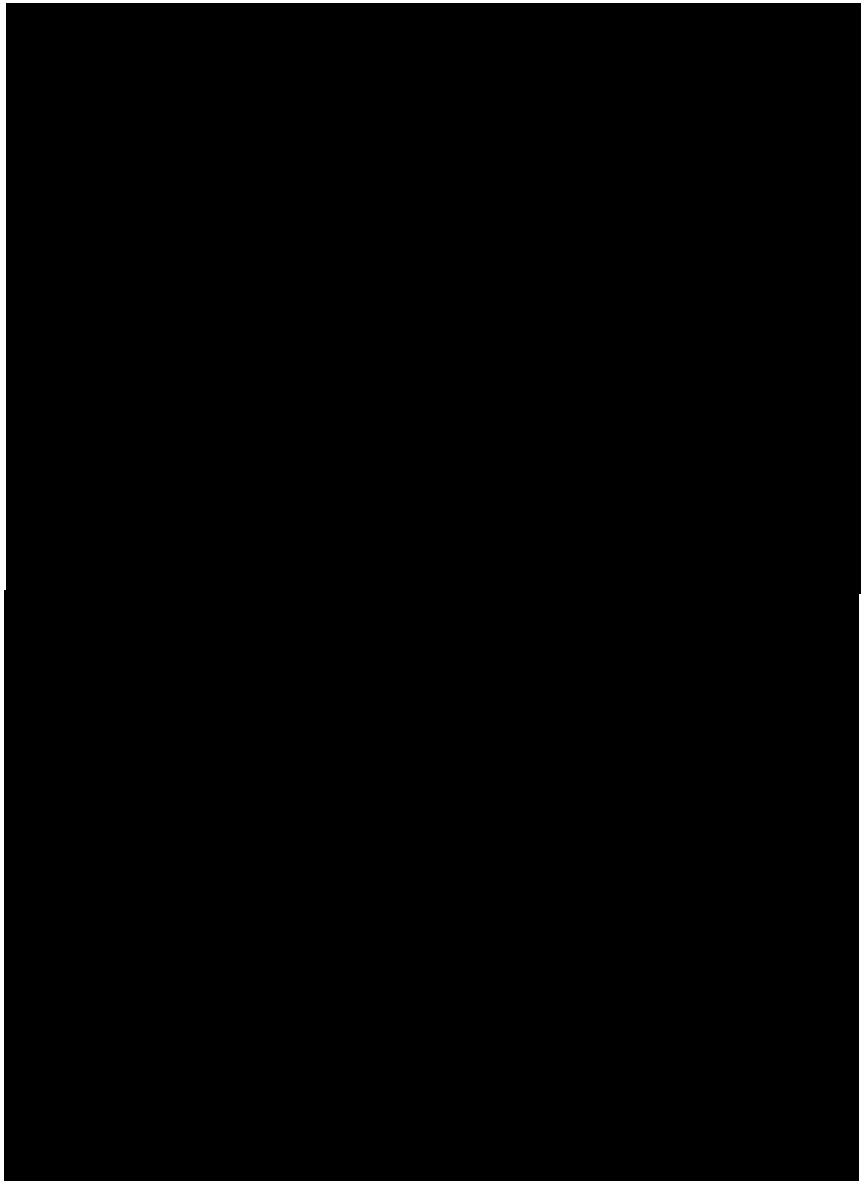


- [redacted]
- [redacted]

Year of follow up		Original VN (n=20)	Delayed VN (n=9)
Mean change from baseline (SD) using Holladay scale [mITT population]	1	-0.16 (0.34)	-0.09 (0.22)
	2	-0.16 (0.36)	-0.06 (0.23)
	3	[redacted]	[redacted]
	4	[redacted]	[redacted]

Clinical effectiveness: visual field (VF)

Study 301 (1 year results, ITT, meaningful change: 20% change from baseline score)



Goldmann visual field III4e

- Patients in the VN arm demonstrated an improvement in VF (mean change 302.1º) whilst patients in the control arm experienced a reduction in VF (mean change -76.7º)
- Statistically significant difference in improvement (378.7º) for VN compared to the control group (p=0.0059)
- Clinically meaningful change

Humphrey VF

- Statistically significant difference in macular sensitivity threshold between VN and BSC at 1 year - mean difference of 7.9 dB (95%CI 3.5, 12.2, p=0.0005)
- Improvements in Humphrey VF in the VN arm were demonstrated by 30 days, and sustained until 1 year

Clinical effectiveness: visual field (VF)

Study 302 (baseline to year 4, mITT, meaningful change: 20% change from baseline score)

- [redacted]
- [redacted]
- Improvement in VF also seen after delayed VN treatment

Clinical effectiveness: Photosensitivity

Study 301/302 (1-3 years, meaningful change 10 dB or 1 log)

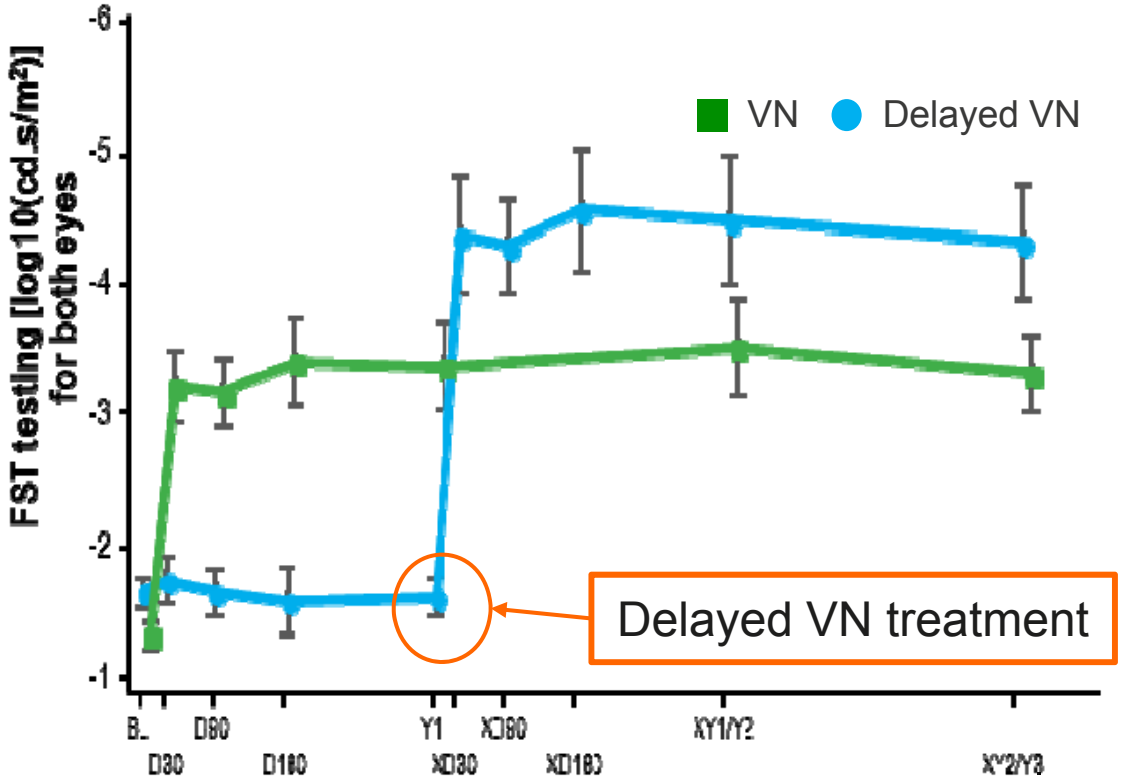
Study 301

- 2-log unit improvement was observed in mean full-field light sensitivity (FST) by Day 30
- Statistically significant difference in FST at 1 year (-2.11 log units; 95%CI -3.91, -1.04; p=0.0004) for the ITT population

Study 302

- At 3-years, the effect of VN on FST was maintained
- Improvement was above the company's defined threshold for clinical significance (≥1 log unit)

	VN (n=19)	Delayed VN (n=9)
Mean change in white light FST from baseline at Y3 (SD)	-2.04 (1.43)	-2.69 (1.41)



Study 101: Not all patients assessed for FST, but company report 57% of patients exhibited a clinically meaningful improvement in FST. FST remains stable until final follow-up at 7.5 years

Clinical effectiveness: contrast sensitivity

Study 301 (1 year, ITT, meaningful change 0.3 log units)

- [redacted]
- [redacted]
- [redacted]

NICE

Clinical effectiveness: visual function questionnaire

- No data was collected for patient or carers HRQoL using a validated measure (EQ-5D)
- Study 301/302 used a customised visual function questionnaire (VFQ)
- VFQ: higher scores indicate a reduction in the perceived difficulty of daily living activities
- [redacted]

- Change of scores from baseline to Year 1 for VN and the control group were statistically significant for patients [redacted] p=0.001) and parents [redacted] p=0.002)

ERG: Adapted VFQ removed items related to HRQoL [redacted]

Patients adaptation to their surroundings could also contribute to their change scores but the [redacted]

ERGs comments on clinical effectiveness

MLMT	• Treatment with VN was associated with a statistically significant improvement in MLMT score (patients able to navigate at lower light levels) • All patients who received VN had a clinically meaningful change in MLMT score shown to be maintained throughout follow-up to 4 years • Uncertainty around the meaningful change threshold set by the company • VN associated with clinically meaningful improvements in functional vision • Clinical advisors noted that MLMT outcome better suited to evaluating visual impairments in this patient group compared to other measures of visual performance • [redacted] leads to uncertainty in the true size of effect
Visual Acuity	• VA (and VF) can be unreliable due to natural variations in visual function between tests • Changes in VA following treatment not clinically meaningful • [redacted] • [redacted]
Visual Field	• Clinically meaningful impact of VN on VF [redacted] • Changes would be clinically significant in improving mobility and navigational vision • [redacted] • [redacted] leads to uncertainty on VN's long-term effect on VF and VA
Cataract surgery	• Outcome include in NICE scope but not reported in CS • 15% (3/20) of patients reported experiencing cataracts • Risk of cataract appears higher in VN arm compared to BSC • Insufficient evidence to determine if VN increases the risk for cataract surgery

Abbreviation: CS, company submission; BSC, best supportive care; MLMT, multi-luminance mobility test; VA, visual acuity; VF, visual field

Adverse events (AEs)

No deaths and no patients withdrew from any trials due to AEs

Treatment-emergent AEs: any AE occurring following administration of treatment, irrespective of the frequency or whether this was deemed to be related to the study drug

Study 301: TEAEs were reported in 13/20 (65%) of patients in the VN arm in comparison with 1/9 (11.1%) experiencing photopsia in the BSC arm

Study 302: The proportion of TEAEs reported was similar between patients in the Original (13/20; 65%) and Delayed VN (6/9; 67%) arms

Study 101/102 [redacted]

Non-serious TEAEs experienced by ≥10% ppts	VN / original intervention		Control / delayed intervention	
	n/N (%)	# Events	n/N (%)	# Events
Study 301 (from baseline to 1 year)				
Cataract	3/20 (15.0%)	4	0/9 (0.0%)	0
Elevated intraocular pressure	4/20 (20.0%)	5	0/9 (0.0%)	0
Retinal tear	2/20 (10.0%)	2	0/9 (0.0%)	0
Eye inflammation	2/20 (10.0%)	6	0/9 (0.0%)	0
Study 301/302 (administration related TEAEs from baseline to follow-up)				
[redacted]				

Serious adverse events (SAEs)

Study 301: [redacted]
Study 302: [redacted]
[redacted]
[redacted]
Study 101: [redacted]
Study 102: [redacted]

Serious adverse events	VN (n/N, %)	Control (n/N, %)
Study 301 (from baseline to 1 year)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Study 301/302 SAEs from baseline to data cut-off (mITT population)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ERG:
VN is associated with an acceptable safety profile
No AEs were thought to be related to VN itself. However, the administration is associated with a high risk of AEs

Cost effectiveness – evidence

Key issues for consideration

- *cost effectiveness (I)*

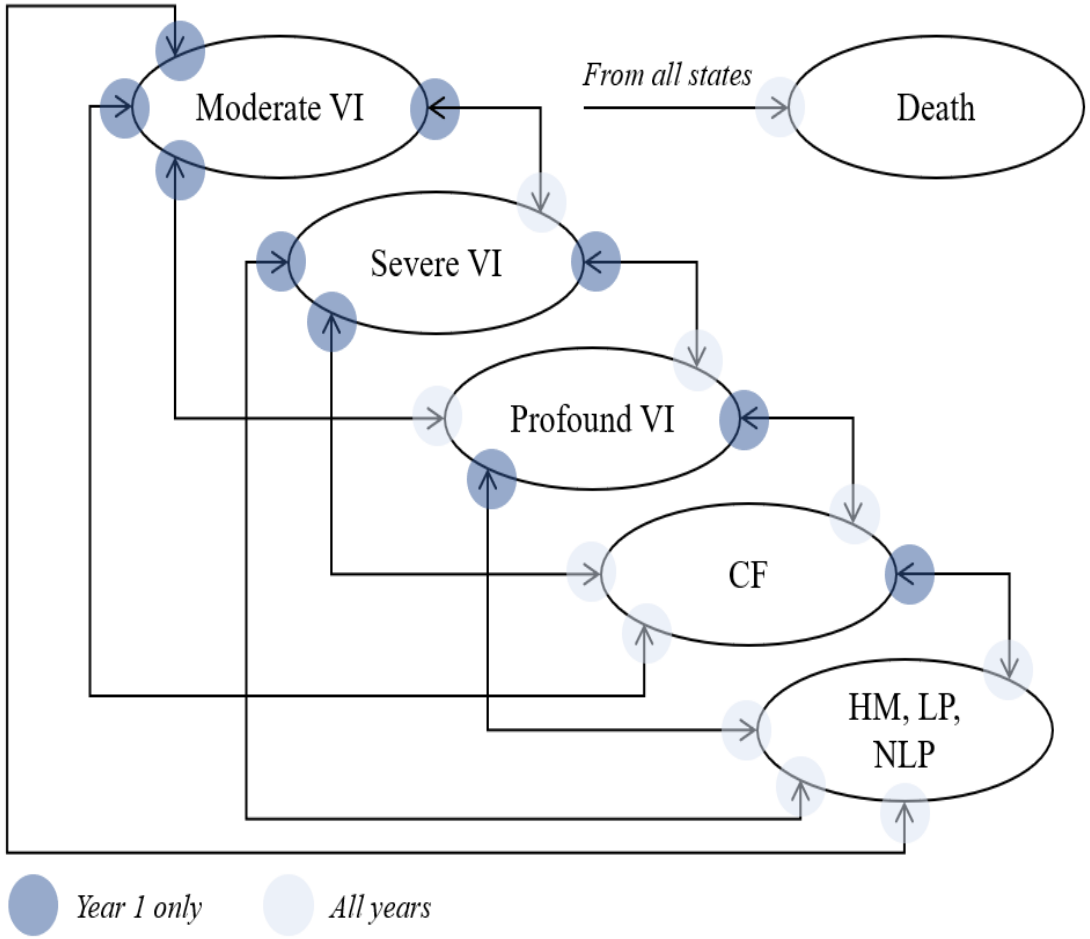
- **Model structure**
  - The primary outcome (MLMT) of study 301/302 is not included in the model, and health states are defined by VA and VF, are outcomes of importance for people living with the condition captured in the model?
  - Health states in the model are categorised according to AMA 2007 guideline (US). What is the committee view on the appropriateness of using this guideline to classify health states for people with RPE65 mediated IRD?
- **Population: baseline health states distribution**
  - What is the most suitable source of data from which to apply baseline characteristics and health state distribution? Study 301/302 alone or pooled with NHx65 natural history study?
- **Long-term treatment effect of VN, what assumptions are considered appropriate regarding:**
  - The duration of treatment effect; and
  - The waning of treatment effect?
- **HRQoL data for people living with RPE-65 IRD and elicitation methods for utility values**:
  - What is the committee's view on the company's elicitation methods for valuation of health states utilities? Does the committee consider that the HRQoL of people living with RPE65 mediated IRD appropriately captured?

Key issues for consideration

- *cost effectiveness (II)*

- **Natural history of RPE65-mediated IRD, what is the committee's view on;**
  - the long-term outcomes for patients living with the condition (treated with either VN or BSC)?
  - the generalizability of the natural history study RPE65 NHx to patients living with RPE65-mediated IRD in the UK?
- **Children and young people:**
  - Population contains children and young people, any additional considerations required?
- **Equality:**
  - Should any further adjustment be made to the process or methods taking into account RPE65-mediated IRD as a disability?
- **Implementation:**
  - With the roll-out of genetic testing across the country, what considerations should be taken into account in terms of service provision/specification should VN be recommended?

Company's modelling approach



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; MLMT, Multi-luminance mobility test; NLP, no light perception; PPS, Personal Social Services; VA, visual acuity; VF, visual field; VI, visual impairment

Model structure	Markov state transition Split into **initial stage** (1 year) and **long-term phase**
Health states	Average vision based on VA and VF; the worst of either VA or VF in each state
Discounting	3.5%
Perspective	NHS / PSS
Cycle length	One year
Time horizon	Lifetime (85 years)

ERG:

- Use of average vision is appropriate
- Improvement in VA or VF not primary outcome (MLMT) of clinical trial
- Large number of health states for a small sample size with limited number of transitions (less robust estimation of transitions)

Evidence sources and assumptions

	Assumption and adjustments
Population	• Reflects the ITT population of study 301 (mean age 15.1 years, 43% male) • Health state distribution based on year 1 trial data - original intervention arm
Health states	• 5 alive" & 1 "absorbing - death" states • Defined on 2007 American Medical Association guideline (worst of VA or VF)
Initial phase	• Transitions based on Study 301 (original intervention arm only) • Patients may move to either better or worse health states
Long-term phase (MSM)	• After year 1, model allows for progressive only transitions • Parametric multi-state model (MSM) models risk of moving between health states varying over time • VN arm: Duration of the treatment effect persists for 40 years (transitions to death only) 10-year waning period (41-51 years) implemented → long-term efficacy of VN decreases from 100% to 25% (patients follow the natural history model projections) • BSC arm: data from the natural history study (RPE65 NHx) are fitted to the MSM model
HRQoL	• Patients: derived via an expert elicitation exercise (Lloyd et al 2019) • Carer: disutility (0.08) applied from *Wittenberg et al. 2013* to HS2-5 for <18, half 18+
Adverse events	• Disutilities for 3 AEs applied as one-off QALY loss at the time of VN from NICE NG82 Age-related macular degeneration
Resource use & costs	• Administration of VN (including surgery and immunomodulatory regime) • Long-term resource use (hospitalisation, vision rehabilitation, residential care)
Mortality	• Visual impairment is associated with increased risk of mortality • HR from *Christ et al. 2013* applied to background mortality estimates (ONS)

Population: baseline distribution

Study 301/302 used to inform the baseline characteristics (mean age 15.1 years, 42% male) and distribution of patients at baseline by health state

Company ***scenario analysis*** uses baseline health state distributions from RPE65 NHx (*Chung et al. 2018*)

	Study 301/302			RPE65 NHx
Health state	**BSC (n=10)**	**VN (n=21)**	**ITT (n=31)**	**(n=68)**
HS1 (Moderate VI)	30% (3)	19% (4)	23% (7)	57% (39)
HS2 (Severe VI)	40% (4)	29% (6)	32% (10)	29% (20)
HS3 (Profound VI)	10% (1)	29% (6)	23% (7)	6% (4)
HS4 (CF)	10% (1)	24% (5)	19% (6)	4% (3)
HS5 (HM, LP, NLP)	10% (1)	0% (0)	3% (1)	3% (2)

Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment; VN

Company base-case

Company scenario

ERG base-case pooled ITT and NHx

ERG: Only patients with LCA included in clinical effectiveness

- LCA and RP grouped for cost-effectiveness, fits the MA population and is appropriate
- Less severe population in RPE65 NHx: (87% in HS1 or HS2 vs. 55% in the ITT population of Study 301/302)
- Difference in mean age between treatment arm (14.8 in VN vs. 15.9 in BSC) may have an effect on treatment outcomes and adds to uncertainty of VN treatment effect
- ERG prefer to use a ***pooled average*** of patient characteristics from Study 301/302 and the RPE65 NHx study to increase sample size and generalizability (mean age 15.0, 41% male)

Health states in the model: VA and VF

The model comprises 2 phases:

Initial phase: (from baseline to Year 1)

- Model transitions derived from Study 301/302

Long-term phase: (from Year 1 onwards)

- Model transitions based on data from the natural history study (RPE65 NHx, Chung 2018)

Health state	Description	Worst of	
		VA (LogMAR)	VF (degrees, º)
HS1	Moderate visual impairment	VA >1.0	240 < VF ≤ 360
HS2	Severe visual impairment	1.0 ≤ VA < 1.4	144 < VF ≤ 240
HS3	Profound visual impairment	1.4 ≤ VA < 1.8	48 < VF ≤ 144
HS4	Counting fingers	1.8 ≤ VA ≤ 3.0	0 < VF ≤ 48
HS5	HM, LP, NLP	VA < 3.0 or HM, LP, orNLP	-

RNIB: all patients classified as blind

Abbreviations: HM, hand motion; HS, health state; LP, light perception; NLP, no light perception; RNIB, UK Royal National Institute of Blind People; VA, visual acuity; VF, visual field

- Cut-off points between health states were derived using 2007 American Medical Association (AMA) guidelines
- AMA chosen over RNIB as they provide clear numerical cut-offs which avoids ambiguity

Health states in the model: MLMT and FST

Company's model reports the average MLMT and FST scores by health state to provide an illustration of how the score changed over the modelled time horizon
The company assumed:

- All observations were used for patients who had received VN in study 301/302
- All observations were used for patients who had not had VN (including baseline data) for study 301

Clinical outcome	Trial arm	HS1	HS2	HS3	HS4	HS5
MLMT	BSC	3.91	2.84	3.29	1.86	-1.00
	VN	5.92	5.08	4.62	-0.29	-1.00
FST	BSC	-1.61	-1.67	-1.42	-1.26	-1.19
	VN	-4.15	-3.20	-2.56	-1.34	-1.19

ERG:

- BSC are based on relatively earlier observations (as capped at year 1)
- The observations for the VN arm may be lower than those for the BSC arm
- No adjustments made to account for repeated measures within patient groups

Transition in the model: initial phase

Transitions: calculated based on data from Study 301 at baseline and 1-year follow-up

No patients in HS5 at baseline. When patients are in health states with no transition data:

1) *Base case:* Patients move the same number of health states as those patients in the next least severe health state
2) *Sensitivity analysis:* Patients remain in the same state at Year 1

worsening vision
improving vision

		VN						BSC					
		To						To					
From		HS1	HS2	HS3	HS4	HS5	From	HS1	HS2	HS3	HS4	HS5
	HS1	100%	0%	0%	0%	0%		HS1	100%	0%	0%	0%	0%
	HS2	83%	17%	0%	0%	0%		HS2	25%	50%	0%	25%	0%
	HS3	50%	50%	0%	0%	0%		HS3	0%	0%	100%	0%	0%
	HS4	50%	0%	25%	25%	0%		HS4	0%	0%	100%	0%	0%
	HS5	0%	50%	0%	25%	25%		HS5	0%	0%	0%	100%	0%

Some transitions are associated with 0% but are possible in clinical practice

The company considered two alternative approaches to account for these in scenario analyses: adjusted TP (state-dependent)' and 'adjusted TP (state-independent)

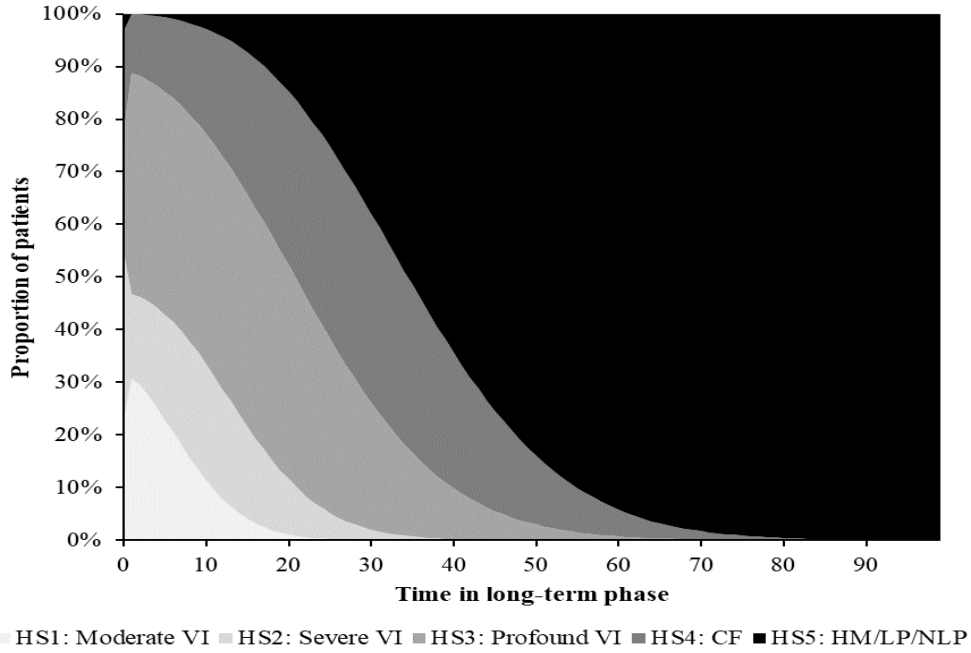
ERG:

- Using data from the original and delayed intervention could have increased sample size, informing more transitions
- Unnecessary to adjust outcomes at 1 year (twelfth-cycle correction) as data available at day 30
- Some transient transitions after the first year in study 302, ERG satisfied these were temporary

Transitions in the model: long-term phase

- Transitions after Year 1 based on parametric multi-state model (MSM)
- MSM fitted to data from the RPE65 NHx study (n= 70)
- MSM specified as 'progressive only' (patients not allowed to 'improve' health states)
- Transitions to 'dead' health state not captured by the MSM
- Five state Markov MSM fitted based on exponential, Weibull, Gompertz, log-logistic, and log-normal distributions
- Markov MSM assumption: the probability of movement to another state is dependent on the time since model entry
- Weibull MSM selected as base case on visual inspection and statistical fit
- Transition rates converted to probabilities using matrix algebra logic by *Jones et al 2017*

Long-term projections for the BSC arm removing the impact of mortality



ERG:

- Study 101/102 shows longer-term changes in VA/VF, but no criteria for sufficient retinal cells, not all patients received licensed dose
- Limitations associated with the RPE65 NHx study but use of the data is appropriate
- Small number of patients (n=2) omitted from RPE65 NHx study without explanation
- High number of transitions for small sample size; MSM is overly complex and may 'over fit' data

ERG's comments on the MSM

- MSM implemented correctly but projection of longer-term outcomes remains a key limitation of the company's model
- Cox-Snell residual plots do not provide clear evidence of the best fitting model
- Markov assumption may not hold – but small sample size limits the ability to validate assumption
- Extrapolations have not been validated and appear to conflict with the company's statements on long-term natural history outcomes;
    - "RPE65-mediated [IRDs] cause progressive vision loss, leading to near-total blindness as early as preschool years or as late as the third decade of life."
- Using the company's MSM model:
    - Patients remain in the less severe health states beyond the age of 30
    - After 15 years 10% of patients in HS1 have not progressed to HS2 or beyond
    - Substantial proportion of patients do not experience "near-total blindness" by 30

Long-term treatment effect

The effect of VN modelling in four key time points following treatment:

- **1 month:** the effect of VN is assumed to fully apply
- **1 year:** full effect of VN as measured in Study 301/302
- **41 years:** full effect of VN ceases to apply, treatment effect starts to wane
- **51 years:** 'waning' period ends, residual treatment effect applied henceforth

Company: 40-year treatment effect represents a reasonable midpoint between the absolute minimum (7.5 years of follow-up data with no loss of efficacy) and potential maximum (lifetime treatment effect of around 70 years)

ERG:

- Long-term effect plausible and aligned with the current evidence available for VN but uncertain
- Not possible to know if treatment effect will persist over the lifetime of patients
- 10-year treatment waning period from 100% to 25% not based on any biological rationale
- 25% residual treatment effect is arbitrary

Mortality

- Mortality data taken from general population life tables for England and Wales (ONS)
- The probability of death was based on the mean baseline characteristics (age and sex), and an applied health state-specific mortality effect (in the form of a hazard ratio [HR]) from *Christ et al 2014*
- Mortality multipliers (HRs):
  - HS1 – 1.08
  - HS2, HS3, HS4, HS5 – 1.18
- Limitations to *Christ et al 2014* include:
  - based on a population aged 65 to 84 years, conducted between 1993 and 2003
  - HRs are based on a comparison to a population with perfect vision
  - not possible to distinguish between health states

ERG:

- Agree that mortality should be captured separately to the transitions between living health states
- Disagrees that the model health states are associated with an increased risk of death
- No deaths occurred in any study included in the evidence base
- *Christ et al* includes a population substantially different to the scope of this appraisal

HRQoL: company's utility values

- No data were collected regarding patient or carer HRQoL and no further data identified
- No mapping function or validation for the amended VFQ completed in Study 301/302
- 6 clinicians assessed a series of vignettes to produce a proxy valuation in terms of their impact on standard generic HRQL instruments (HUI3 and EQ-5D) for each of the health states described in the model
- EQ-5D known to have poor convergent validity when used in visual disorders but HUI3 contains a vision component

Utility values from company's elicitation exercise (*Lloyd et al 2019*)		
Health state	**HUI3 mean (SD)**	**EQ-5D-5l mean (SD)**
HS1	0.52(0.16)	0.71 (0.09)
HS2	0.36 (0.11)	0.62 (0.04)
HS3	0.22 (0.10)	0.52 (0.07)
HS4	0.14 (0.09)	0.35 (0.06)
HS5	-0.04 (0.07)	0.15 (0.11)

Company base case

ERG: Lack of patient-reported values for patients treated with VN is a key limitation

- Severe methodological issues with proxy elicitation:
  - Limited number of respondents
  - Clinicians may only focus on issues related to vision loss
  - Completing 'best health state' first may lead to potential capping of utilities
- Lack of validity: values given do not match patient experience described by ERGs clinical advisors and negative utility value for HS5 unlikely as patients adapt to deteriorating vision
- Utility values for vision loss in previous NICE submissions:
  - Lowest: between 0.26 and 0.548
  - Alternative definitions of blindness would include several of the company's health states

HRQoL: valuation of modelled health states based on Rentz et al. 2014

ERG:

- Values used in previous NICE submissions from *Brown et al 2000* and *Brown et al 1999* showed worst health state to be positive and higher than company's HUI3 values
- Notes that the utility values should not reflect only VA

ERG base case

Health state	Rentz et al. 2014 (n=607)	Rentz et al. (UK only, n=152)	HS5 matched to penultimate worse health state (n=607)
HS1	0.717	0.687	0.717
HS2	0.624	0.581	0.638
HS3	0.530	0.476	0.560
HS4	0.437	0.370	0.481
HS5	0.343	0.264	0.402

- *Rentz et al. 2014* identified by the ERG
- 607 members of the general public (international) were asked to perform time-trade-off for 8 health states with varying degrees of vision problems
- ERG compared descriptions of health states given by the company to those used in the time-trade-off exercise
- HS5 assumed to be equivalent to the worst health in the *Rentz et al 2014* study
- Results are imperfect but are described via functional vision problems not just linked to VA

NICE

Adverse event dis-utilities

- Dis-utilities for AEs applied as one-off QALY loss at the time of VN treatment
- QALY loss for each AE:

  utility decrement *x* the duration *x* proportion of patients in Study 301/302
- Adverse event dis-utilities from NICE Guideline 82 - Age-related macular degeneration
  * increased intraocular pressure assumed to be the same as uncontrolled/severe glaucoma
- Company scenario: additional disutility of 0.1 applied to all patients for 1 month to account for discomfort or inconvenience associated with the administration procedure

Event in original intervention arm	Utility decrement	Duration (months)	Proportion of patients
Cataract	0.14	1.0	15%
Eye inflammation	0.30	3.6	10%
Increased intraocular pressure*	0.10	1.0	20%

ERG:
- Company's approach broadly acceptable
- Disutility for eye inflammation appears large, considering the relatively low health-state utilities

Carer disutility

- *Wittenberg et al. 2013* (systematic review original source *Kuhlthau et al. 2010*) found parents of children with activity limitations have a 0.08 lower EQ-5D score than parents of children without activity limitations
- Applied as a carer disutility to individuals in the four most severe health states up to the age of 18
- Disutility for carers of adults with RPE65-mediated IRD is half that of carers of children

Health state	Carer disutility		
	School age (<18)	Working age (18-65)	Retirement age (>65)
HS1	0	0	0
HS2	0.08	0.04	0.04
HS3	0.08	0.04	0.04
HS4	0.08	0.04	0.04
HS5	0.08	0.04	0.04

ERG:

- School age child would typically have more than one caregiver, multiplied by 1.78 (the mean number of parents in a household)
- Updated review included a UK study (*Al-Janabi et al. 2016*) presenting a matched-pair analysis of caregiver utilities versus non caregivers
- Disutility of 0.041 from *Al-Janabi et al. 2016* applied in ERG's preferred base case
- Carer disutility applied in all modelled health states in ERG's preferred base case

Resources and costs – one-off costs

Costs in the model fall into two categories:

- One-time costs (first model cycle), or;
- Long-term resource utilisation

One-time costs

Prior to treatment genetic testing is required to identify patients with an affected RPE65 gene, as well as the retinal cell assessment to ensure patients have sufficient retinal cells

If treatment is appropriate administration costs include the cost of two surgeries for children (65%) and adults (35%)

One-time event	Cost
VN acquisition (list price)	£613,410
Administration	
Surgery	£2,269.80
Immunomodulation	£173.37
Eligibility testing	£120.48
Monitoring	£457.83
Adverse events	£160.50

An immunomodulatory regimen (prednisone) is required prior to surgery. Cost are based on the average patient weight and number of days between surgeries from Study 301/302

Following VN treatment 4 monitoring outpatient visits including optimal coherence tomography (OCT) are required

The cost of resolution of adverse events (cataracts, eye inflammation and increased intraocular pressure) is also included in the first model cycle

Resources and costs – long-term costs

Long-term resource utilisation
Based on the resource utilisation of patients who are blind according to RNIB guidelines (HS2-HS5). Patients in HS1 are assumed to accrue half of the costs for the other health states (as an unknown proportion are not considered blind)

Patients are divided to three distinct age groups consisting of school-age (< 18 years old), working-age (between age 18 and 65 years) and retirement-age (>65 years)

Healthcare resource utilisation	Annual cost					
	School age (<18)		Working age (18-65)		Retirement age (>65)	
	HS1	HS2-5	HS1	HS2-5	HS1	HS2-5
Hospitalisation	£16	£32	£16	£32	£16	£32
Low vision rehabilitation	£7	£13	£7	£13	£7	£13
Low vision aids	£31	£61	£31	£61	£31	£61
Depression	£245	£490	£245	£490	£490	£979
Residential care	-	-	-	-	£6,880	£13,759
Community care	-	-	-	-	£273	£546

ERG: costs associated with depression removed from ERG base case as unlikely to be reflective of a population who are legally blind from an early age compared with other visual conditions

ERG's comments on resources and costs

Overall		ERG agrees with the company's approach to including costs
One-time costs	Administration	• Company did not account for the cost of 'very complex procedures' in adults, when included gives a (reduced) cost per administration of £1,960 • Study 301/302 may not be entirely representative of the UK population so immunomodulatory costs may be underestimated. However, immunomodulatory costs do not have a large impact on the ICER
	Eligibility testing	• Genetic testing is expected to become standard in NHS practice • Appointment should be consultant-led (increased cost)
	Monitoring	• Monitoring visits would be expected to be performed in an outpatient setting (company uses overall currency code)
	Adverse events (AE)	• ERG agrees with application of AEs • AEs costs may be underestimated but the total cost of resolving adverse events is small, and so increasing the costs would have a negligible effect on the ICER
Long-term costs		• Estimates are based on assumption as the identification of medical resource utilisation for patients with RPE65-mediated inherited retinal dystrophies is difficult • Cost adjustments should not be included in the model

Discount rate

Base case

3.5% discount rate for costs and outcomes (QALYs)

Scenario

1.5% discount rate for costs and outcomes (QALYs)

NICE guidance states a 1.5% discount rate can be considered if:

- *treatment restores people who would otherwise die or have a very severely impaired life to full or near full health*
- *treatment effect is sustained over a very long period (normally at least 30 years)*
- *the technology does not commit the NHS to significant irrecoverable costs*

ERG:

Discount rates of 1.5% may be appropriate to consider:

- Clinical evidence suggests benefits may extend beyond 30 years, however this remains unproven
- VN requires the NHS to commit significant, irrecoverable costs as a 'one-off' gene therapy

Cost effectiveness – results

Company base-case (with PAS)

	Total			Incremental			ICER
	Costs	LYGs	QALYs	Costs	LYGs	QALYs	
Deterministic company base-case							
BSC	£46,473	25.46	3.6	-	-	-	-
VN	[redacted]	25.50	10.7	[redacted]	0.04	7.1	[redacted]

Abbreviations: LYG, life years gained, QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Probabilistic company updated base-case		Costs	QALYs	ICER
VN vs BSC	10,000 simulations	[redacted]	6.8	[redacted]

At clarification stage, the company noted an error in their original MSM analysis
Company provided updated cost-effectiveness results and an updated cost-effectiveness model

Costs by health state per patient (including PAS)

- Difference is driven primarily by VN costs
- In BSC arm, the majority of total costs relate to healthcare resource utilisation
- Greatest proportion of costs are incurred in HS5 (worse health state)

Resource use	Cost (£) (BSC)	Cost (£) (VN)	Incremental costs (£)	Absolute cost increment	% Absolute increment
Acquisition, administration and monitoring	£0	[redacted]	[redacted]	[redacted]	[redacted]
AEs	£0	£146	£146	£146	[redacted]
Total healthcare resource use	£46,473	£39,648	-£6,824	£6,824	[redacted]
HS1: Moderate VI	£661	£7,810	£7,149	-	-
HS2: Severe VI	£1,804	£12,686	£10,882	-	-
HS3: Profound VI	£5,248	£10,032	£4,785	-	-
HS4: CF	£5,715	£6,712	£997	-	-
HS5: HM, LP, NLP	£33,046	£2,408	-£30,638	-	-
Total	£46,300	[redacted]	[redacted]	[redacted]	100%

Abbreviations: AE, adverse events; BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment

Company's uni-variate deterministic sensitivity analyses (with PAS)

Abbreviations: ICER, incremental cost effectiveness ratio; HS, health state; VA, visual acuity; VF, visual field

Many of the influential parameters are associated with the long-term multi-state survival model; result should be treated with caution as highly correlated parameters

Company's scenario analyses (with PAS)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	7.06	[redacted]	0%
1.5% discount rate for costs and outcomes	[redacted]	12.32	[redacted]	-43%
Health states based on best-seeing eye	[redacted]	7.17	[redacted]	-2%
Health states based on VF only	[redacted]	6.14	[redacted]	15%
Baseline characteristics from natural history	[redacted]	6.99	[redacted]	1%
Adjusted TP (state dependent)	[redacted]	6.91	[redacted]	2%
Adjusted TP (state independent)	[redacted]	7.41	[redacted]	-5%
Health states w/no data: remain in same state	[redacted]	6.95	[redacted]	2%
Use cross-over data in VN arm	[redacted]	6.58	[redacted]	8%
Duration of treatment effect: 20 years	[redacted]	5.70	[redacted]	25%
Duration of treatment effect: 30 years	[redacted]	6.54	[redacted]	9%
Duration of treatment effect: 50 years	[redacted]	7.35	[redacted]	-5%
Waning period: 5 years	[redacted]	7.17	[redacted]	-2%
Waning period: 20 years	[redacted]	6.14	[redacted]	15%
Log-normal multistate model distribution	[redacted]	6.61	[redacted]	6%
No mortality effect	[redacted]	7.10	[redacted]	-1%
Utility values: Acaster Lloyd (EQ-5D-5L)	[redacted]	6.45	[redacted]	9%
Utility values: Brown et al	[redacted]	5.09	[redacted]	38%
Carer disutility excluded	[redacted]	6.46	[redacted]	9%
No healthcare resource use in HS1	[redacted]	7.06	[redacted]	-2%

Company cost-effectiveness curve (with PAS)

Probability of VN being cost-effective is [redacted]

Summary of the ERG's preferred base case (I)

Category	Company's base case	ERG's base case	Reason for change
Baseline health state occupancy	• ITT population of Study 301/302	• Pooled populations of Study 301/302 and *RPE65* NHx	• Largest possible sample size • No reason why values would differ substantially
Transitions	• Original intervention (VN) arm only ("no crossover")	• Original intervention and delayed intervention arms ("crossover")	• Largest possible sample size • Informs otherwise "unobserved" transitions • No clear rationale for difference in treatment effect for original intervention and delayed intervention patients
Duration of treatment effect	• Duration of treatment effect (40 years) • Waning period (10 years) • Residual effect (25%)	• Duration of treatment effect (40 years) • Remove waning period and residual effect	• Treatment effect is unnecessarily complex • No clear evidence for why company's approach is more appropriate than a simple duration
Utility values	• HUI3 values based on vignette study by Acaster and Lloyd	• Based on published study by Rentz (2014)	• Company values lack validity • Issues with the study design • Does not meet the NICE reference case

Summary of the ERG's preferred base case (II)

Category	Company's base case	ERG's base case	Reason for change
Cost of resolving AEs	• GP appointment for eye inflammation and increased IOP	• Outpatient ophthalmologist	• Given specialist nature and high cost of therapy, added to potential risks
Medical resource use costs	• For missing values, assume 50% for children or working age adults, and assume 50% for HS1	• Remove depression costs • Set HS1 costs to be the same as HS2 to HS5	• Depression costs are based on sight loss in later life, as opposed to lifelong sight loss • No clear rationale for why HS1 costs lower thatn HS2 to HS5
Mortality	• Apply mortality multipliers for HS2 to HS5 based on Christ (2014)	• Remove mortality multipliers	• Mortality multipliers derived based on a substantially dissimilar population • No deaths in Study 301/302 or *RPE65* NHx study
Carer disutility	• Disutility from Kuhlthau (2010) • Assumes 1 carer per patient	• Disutility from Al Janabi (2016) • Average number of carers per child (1.78) • Remove carer disutility for adults • Applied for all patients in HS1	• Amended source reflects UK population • Adjusts disutility to account for multiple carers per child

ERG's cost-effectiveness results (I)

- Analyses include PAS discount for VN
- Each change varied independently

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Error corrections						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Change application of medical resource use (remove depression, equal by health states)						
BSC	£33,608	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Remove mortality multipliers						
BSC	£48,699	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]

ERG's cost-effectiveness results (II)

- Analyses include PAS discount for VN
- Each change varied independently

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Amend application of carer disutilities						
BSC	£46,473	4.5				
VN	[redacted]	10.9	[redacted]	6.5	[redacted]	[redacted]
Pooled baseline health state occupancy						
BSC	£46,034	4.5				
VN	[redacted]	11.5	[redacted]	7.0	[redacted]	[redacted]
Use of crossover transition probabilities						
BSC	£46,473	3.6				
VN	[redacted]	10.2	[redacted]	6.6	[redacted]	[redacted]
Removal of waning period and residual treatment effect						
BSC	£46,473	3.6				
VN	[redacted]	10.5	[redacted]	6.9	[redacted]	[redacted]
Alternative utility values						
BSC	£46,473	11.5				
VN	[redacted]	16.5	[redacted]	5.0	[redacted]	[redacted]

ERG's preferred base case (with PAS)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Company base-case					
BSC	£46,473	3.6	-	-	-
VN	[redacted]	10.7	[redacted]	7.1	[redacted]
ERG preferred base-case (all changes combined)					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]

LYG: life years gained, QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio

- ERG's preferred base-case, with all changes combined gives an increased ICER
- Change associated with the largest impact on the ICER is use of alternative utility values

ERG exploratory analyses

The ERG conducted a number of exploratory and sensitivity analyses to establish the impact of alternative assumptions and settings on the cost-effectiveness results:

Duration of treatment effect

1. Threshold analysis to determine the relationship between the duration of treatment effect for VN and the ICER
2. Institute for Clinical and Economic Review (ICER) duration of treatment effect settings - 10 years treatment effect and 10 years waning period

Medical resource use

3. Remove all healthcare resource use costs
4. Using the company base case resource use

Utility values

5. Use UK utility values (based on Rentz et al. 2014)
6. Use higher utility values (based on Rentz et al whole population)

Baseline characteristics

7. ITT population from Study 301/302 (n=31)
8. RPE65 NHx population (n=68)

ERG exploratory analysis: threshold analysis on the duration of treatment effect

Threshold analysis varying the duration of treatment effect (including PAS)

- [redacted]

ERG's exploratory analyses (with PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£35,731	12.9			
VN	[redacted]	15.0	[redacted]	2.1	[redacted]
Remove all healthcare resource use costs					
BSC	£0	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Use company-preferred healthcare resource use costs					
BSC	£48,254	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
UK utility values (based on Rentz et al. 2014)					
BSC	£35,731	11.4			
VN	[redacted]	15.9	[redacted]	4.5	[redacted]
Alternative (higher) utility values (based on Rentz et al. 2014)					
BSC	£35,731	13.8			
VN	[redacted]	17.1	[redacted]	3.3	[redacted]
Baseline characteristics derived from Study 301/302					
BSC	£35,667	12.4			
VN	[redacted]	16.5	[redacted]	4.1	[redacted]
Baseline characteristics derived from RPE65 NHx					
BSC	£35,773	13.1			
VN	[redacted]	17.0	[redacted]	3.9	[redacted]

ERG Summary

Several areas of uncertainty remain:

Long-term treatment effect of VN

- The treatment effect of VN has limited follow-up of 7.5 years, the effect of VN beyond this period is unknown
- 40-year duration of treatment effect is assumed in the company base case. This assumption is maintained in the ERG's base case due to the lack of a more plausible estimate.

Health-related quality of life

- No patient-reported values available for VN treatment
- Considerable uncertainty around the impact of treatment on patient
- ERG believes the values used in the company submission are unsuitable but unclear on the most suitable values to use in the economic evaluation

Natural history of RPE65-mediated IRD

- Use of the natural history study to inform the long-term outcomes for patients with *RPE65*-mediated IRD receiving BSC is appropriate
- MSM requires the estimation of 11 parameters for n=35 transitions observed for n=68 patients. It is overly complex and likely "over fits" the available data

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incremental QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr.)
Greater than or equal to 30	3

QALY weighting

To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains:

Deterministic analyses	Incremental QALY gains - undiscounted	Incremental QALY gains - discounted	ICER with PAS (per QALY gained)
Company base case	20.3	7.1	[redacted]
ERG preferred base case	12.1	4.0	[redacted]

Company base case incremental undiscounted QALYs: **20.3**

ERG preferred base case incremental undiscounted QALYs: **12.1**

ERG most optimistic scenario incremental undiscounted QALYS (using UK utility values from Rentz et al. 2014): **13.6**

ERG most pessimistic scenario incremental undiscounted QALYS (assuming duration of treatment effect as 10 years from the ICER analysis): **4.4**

Budget impact analysis (with PAS)

Company estimated market share

Year	% of existing patients treated per year
Year 1	3%
Year 2	29%
Year 3	29%
Year 4	29%
Year 5	10%

	Year 1	Year 2	Year 3	Year 4	Year 5
Annual budget (without VN)	£41,938	£42,587	£44,343	£46,173	£48,067
Annual budget (with VN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG:

- The company BIA assumes a large number of existing patients would wait several years before being treated as their vision would deteriorate substantially within this time
- Higher numbers of patients treated earlier on would cause VN to exceed £20 million of sales in its first year of availability; at the PAS price this would be [redacted] patients per year.

Impact of the technology beyond direct health benefits

Costs to patients and carers

Home adaptations, additional educational costs due to vision impairment, and time taken to care for patients, these are not captured in the economic modelling

Government costs

Social security benefits included in the model as:

- School age costs £8,938.73, consisting of education cost, carer's allowance, and Personal Independence Payment
- Working age costs £2,026.95 – no education costs, employment and support allowance, universal credit added, blind person's tax allowance added
- Retirement age £1,956.40 - no employment and support allowance, but universal credit, and blind person's tax allowance, addition of attendance allowance and pension credit

Productivity loss

- Caregiver productivity losses: mean 11.9 hours per week ~ £7,000 per year
- Patient productivity losses (for patients 18-65 years) – using data from the RNIB - 50% reduction in the employment - £13,000 in Health States 2 to 5 (half HS1) – linked to the UK average weekly earnings

ERG:

Scenario analysis of governmental perspective reduced the ICER by [redacted] per QALY

Equality

- Population: protected characteristic of disability under the Equality Act 2010
  - Disability: a person is disabled if they have a physical or mental impairment which has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities
- Non-uniform distribution of RPE65 mutations between different ethnic groups with prevalence highest in South Asian population
- High unmet need as no treatment available

Innovation

The company considers VN an innovative treatment because:

- First licensed medicine for the treatment of RPE65-mediated IRD
- First randomised Phase 3 gene therapy trial for a genetic disease
- Potential to advance the broader field of gene therapy

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Voretigene neparvovec for treating inherited retinal dystrophies caused by *RPE65* gene mutations

Specification for company submission of evidence

February 2019

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to

complete the clinical evidence section with ‘see appendix X’. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

List of tables and figures

Glossary of terms

Term	Definition
AAV	Adeno-associated virus
AE	Adverse event
AIC	Akaike information criterion
AMA	American Medical Association
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
BIC	Bayesian information criterion
BL	Baseline
BSC	Best supportive care
CC	Comorbidity and complication
$cd.s/m^2$	Candela second per meter squared
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CF	Counting fingers
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical study report
dB	Decibels
df	Degrees of freedom
DI	Delayed intervention
DVLA	Driver and Vehicle Licensing Agency
ELISPOT	Enzyme-linked ImmunoSpot
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
FST	Full-field light sensitivity threshold
GP	General practitioner
HCHS	Hospital and Community Health Services
HM	Hand motion
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HS	Health state
HST	Highly Specialised Technologies
HSUV	Health state utility value
HTA	Health Technology Assessment

HUI3	Health Utilitites Index Mark 3
IADL	Instrumental activities of daily living
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IOP	Intraocular pressure
IQR	Interquartile range
IRBP	Interphotoreceptor retinoid-binding protein
IRD	Inherited retinal dystrophies
ITT	Intention-to-treat
IU	International Unit
LCA	Leber congenital amaurosis
ll	Log-likelihood
LogMAR	Logarithm of the minimum angle of resolution
LP	Light perception
LP-CF	Light perception to counting fingers
LRAT	Lecithin retinol acyltransferase
LY	Life year
LYG	Life years gained
MA	Marketing authorisation
MAA	Managed Access Arrangement
MDT	Multidisciplinary team
mITT	Modified intention-to-treat
MLMT	Multi-luminance mobility test
MT	Mobility test
NEI	National Eye Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLP	No light perception
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OCT	Optical coherence tomography
OI	Original intervention
ONS	Office for National Statistics
OR	Odds ratio
Paed.	Paediatric
PAS	Patient access scheme
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PLR	Pupillary light response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Pts.	Patients
QALY	Quality-adjusted life year
qPCR	Quantitative polymerase chain reaction
QTVI	Qualified teacher of learners with vision impairment
RDH5/8	Retinol dehydrogenase 5/8
RMP	Risk Minimisation Program
RNIB	Royal National Institute of Blind People
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
RPE65	Retinal pigment epithelium 65 kDa protein
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SMC	Scottish Medicines Consortium
SOC	System organ class
SoC	Standard of care
SPC	Summary of product characteristics
SR	Systematic review
TEAE	Treatment-emergent adverse event
TP	Transition probability
TTO	Time trade off
UK	United Kingdom
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VF	Visual field
VFQ	Visual function questionnaire
vg	Vector genomes
VI	Visual impairment
VN	Voretigene neparvovec
VR	Vitreoretinal
VRQoL	Vision-related quality of life

Executive Summary

The technology

- Voretigene neparvovec is a one-time gene therapy for the treatment of adults and paediatric patients with vision loss due to inherited retinal dystrophy (IRD) caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells. No pharmacological treatment options are currently available for this condition.
- Subretinal injection of voretigene neparvovec is administered to each eye on separate days (but no fewer than six days apart), introducing a healthy copy of the defective *RPE65* gene into retinal cells, improving visual function (the performance of the eyes at the organ level) and functional vision (the ability to perform activities of daily living that are dependent on vision).
- Voretigene neparvovec is the first gene therapy to be approved for a retinal disease [1]. It is the first pharmacologic treatment for an IRD, and the Phase 3 trial was the first randomised, controlled Phase 3 gene therapy trial for an inherited disease.

Nature of the condition

- Patient burden is very high in this severe, progressive and extremely rare disease, with patients inexorably progressing to near-total blindness as early as the preschool years or as late as the third decade of life.
- The first symptom of the disease is nyctalopia (night blindness). This is followed by progressive deterioration of visual field (range of sight), light sensitivity and visual acuity (clarity of vision), ultimately leading to complete blindness.
- The disease has a profound impact on the quality of life of patients, carers and families, with affected individuals often requiring full-time

support. In the absence of treatment options, a diagnosis is purely scientific and the inexorable progression towards complete blindness means that the effects are life-changing and lifelong.

Impact of the new technology

- Voretigene neparvovec is a transformative therapy that offers patients with RPE65 genetic mutations hope for the first time, with potential for a sustained long-term improvement in vision. These improvements in functional vision give young patients the freedom to live independent lives, and also significantly alleviate caregivers' psychological and physical burden.

- Clinical trial results demonstrate clinically and statistically significant improvements in key efficacy endpoints related to functional vision after 1 year (navigation ability as assessed by MLMT [p = 0.0013], light sensitivity as assessed by FST [p = 0.0004], visual field as assessed by Goldmann perimetry [p = 0.0059], and visual acuity [post-hoc p = 0.047]).

- The latest follow-up data (four years in the Phase 3 trial and 7.5 years in the Phase 1 trial) show that improvements in functional vision and visual function have been maintained. Combined with evidence from pre-clinical studies, this suggests that the restoration of sight is long-lasting. Treatment with voretigene neparvovec offers the hope that there is a clinically meaningful lifetime improvement in vision for patients which is the ultimate aim of treatment with gene therapy.

- A single bilateral administration of voretigene neparvovec via subretinal injection demonstrated a safety profile consistent with vitrectomy and subretinal injection. Adverse events related to the procedure were mostly transient, mild in nature, or treatable.

Value for money

- Voretigene neparvovec is a cost-effective therapy in England and Wales, with an ICER of [redacted] per QALY gained, at the proposed confidential simple discount patient access scheme (PAS) price.
- Voretigene neparvovec is associated with significant QALY gains (20 undiscounted QALYs gained versus BSC), and therefore qualifies for additional weighting. The ICERs at list price and PAS price are significantly below the weighted threshold of £200,000 per QALY.
- The budget impact associated with the introduction of voretigene neparvovec is manageable and predictable, with 78 patients in England estimated to be suitable for treatment. It is anticipated that this therapy will fit a specialised centre model, with diagnosis, counselling, treatment and follow-up performed at no more than a few centres nationally.
- Assuming the PAS price for voretigene neparvovec, the net budget impact is estimated to be [redacted] in Year 1, [redacted] in each of Years 2 to 4, and [redacted] in Year 5. This does not exceed the budget impact threshold of £20 m in any of the first three years.

The technology

Voretigene neparvovec (VN; brand name LUXTURNA™) is an adeno-associated virus (AAV) vector-based gene therapy for use as a one-time treatment for biallelic *RPE65* mutation-associated inherited retinal dystrophy (IRD). Marketing Authorisation (MA) was granted by the European Commission on 22nd November 2018 [2]. The licensed indication is for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells [3] (see Section 3).

Subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells of patients with *RPE65*-mediated inherited retinal

dystrophies (IRD), improving visual function (the performance of the eyes at the organ level) and functional vision (the ability to perform activities of daily living that are dependent on vision) (see Section 2).

The pharmaceutical formulation is a concentrate and solvent for solution for injection. Each single-dose 2 mL vial contains 0.5 extractable mL of concentrate (5×10^{12} vector genomes [vg] per mL of concentrate) which requires a 1:10 dilution prior to administration. A single dose of 1.5×10^{11} vg is administered to each eye on separate days between 6 and 18 days apart[1] (see Section 2).

Nature of the condition

RPE65-mediated inherited retinal dystrophies cause progressive vision loss, leading to near-total blindness as early as preschool years or as late as the third decade of life. The first symptom of the disease is nyctalopia (night blindness). This is followed by progressive deterioration of visual field (range of sight), light sensitivity and visual acuity (clarity of vision), ultimately leading to complete blindness (Section 6).

The symptoms of the disease have a profound impact on the quality of life of patients, families and carers. [redacted] Diagnosis severely impacts job opportunities, social activities and relationships with friends and family.

Visual impairment disrupts children's participation in education, social and leisure activities. Adults with vision loss are more likely to require assistance with daily activities, and are less likely to be in paid employment than the general population. Individuals with visual impairment also report reduced wellbeing, and are more likely to suffer from depressive symptoms (see Section 7).

[1] The SmPC stipulates that the individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart [3]. In the Phase 3 trial the second injection was administered no later than 18 days after the first [4].

Patients often require full-time support – caring for blind individuals is associated with increased risk of depression and has a wider societal impact in terms of reduced productivity (see Section 7).

The most pressing issue relating to current clinical practice is the lack of treatments. Approaches to maximise remaining vison do not address the underlying condition and fail to slow or prevent the deterioration of vision. Additionally, surgical implant approaches (Section 8.1) are only indicated for patients > 25 years old and with profound vision loss. Voretigene neparvovec is among the first treatments of its kind. It is the first pharmacologic treatment for an IRD, and the pivotal Phase 3 clinical trial (Study 301/302) was the first randomised, controlled Phase 3 gene therapy trial for an inherited disease [5] (see Section 8).

Impact of the new technology

The key source of evidence on the efficacy and safety of VN for treating *RPE65*-mediated IRD is the Phase 3 clinical trial (Study 301/302). Twenty patients received bilateral treatment in the Original Intervention arm, while nine patients in the Control/Delayed Intervention arm served as a control group for the first year of the study before being eligible to receive treatment. The mean age of patients in Study 301/302 was 15.1 years, reflecting the early onset of symptoms in this progressive disease (see Section 9.3).

The primary endpoint of Study 301/302 was binocular performance on the multi-luminance mobility test (MLMT), a novel obstacle course that measures functional vision in a quantitative and standardised manner under a range of lighting levels. The MLMT was designed with input from the FDA to address the need for a clinically meaningful endpoint (see Section 9.4).

Subretinal injection of VN led to clinically meaningful and statistically significant improvements in ability to navigate independently in low-to-moderate light conditions, as shown by change in MLMT score. Improvements in both navigational abilities and light sensitivity were evident within the first 30 days after subretinal delivery and remained stable for one year. Approximately two-

thirds of patients treated with VN achieved the maximum MLMT improvement possible – the ability to pass at the lowest light level (see Section 9.6).

Improvements in visual field, visual acuity and contrast sensitivity were also apparent soon after treatment, and a visual function questionnaire (VFQ) completed by patients or parents/guardians of paediatric patients demonstrated significant reductions in the perceived ability to perform daily living activities. Improvements in all of these outcomes persisted throughout the one-year follow-up (see Section 9.6).

Patients in the Phase 1 and Phase 3 trials continue to be followed for assessment of long-term efficacy and safety. Four years of data are available from the Phase 3 trial and 7.5 years from the Phase 1 trial. These latest data demonstrate that the improvements in vision have been maintained (see Section 9.6).

As a one-time treatment, treatment continuation rules are not applicable.

Value for money

The list price of VN is £613,410 per patient. A confidential simple discount patient access scheme (PAS) has been proposed ([redacted] per patient) and is currently under review by the Department of Health.

The incremental cost-effectiveness ratio (ICER) is [redacted] per QALY gained, based on the proposed PAS price; this is lower than the standard HST threshold of £100,000 per QALY gained, and substantially lower than the weighted HST threshold of £200,000 per QALY gained (based on a gain of 20 undiscounted QALYs versus BSC). Voretigene neparvovec is therefore expected to be a cost-effective therapy in England and Wales.

Assuming the PAS price (list price) for VN, the net budget impact is estimated to be [redacted] in Year 1, [redacted] in each of Years 2 to 4, and [redacted] in Year 5. This does not exceed the budget impact threshold of £20 m in any of the first three years.

Impact of the technology beyond direct health benefits

Voretigene neparvovec is associated with improved vision, and therefore a reduction in the substantial costs and detrimental effects associated with visual impairment and blindness.

Costs associated with visual impairment and blindness incurred by government departments other than the NHS include those for education and social security. Patients themselves incur out-of-pocket costs including those for transport to eye appointments, home modifications, vision aids, and loss of earnings. Friends and family members who care for affected individuals may be expected to experience a loss of earnings, and to incur out-of-pocket expenses themselves (Section 14).

The methodology and results of the Phase 3 trial (Study 301) provide support for gene-based approaches to treating rare genetic diseases. The manufacturing techniques used might potentially be applied to the treatment of IRD with different genetic causes, and to genetic diseases involving other organ systems.

Voretigene neparvovec therefore not only has potential to improve the lives of patients with *RPE65*-mediated IRD, but also to advance the broader field of gene therapy.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table 1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with inherited retinal dystrophies caused by *RPE65* gene mutations	• Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells	• As per the licensed indication
Intervention	Voretigene neparvovec	None	N/A
Comparator(s)	Best supportive care	None	N/A
Outcomes	The outcome measures to be considered include: • Best corrected visual acuity (both eyes) • Visual field • Contrast sensitivity • Photosensitivity • Need for cataract surgery • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• The multi-luminance mobility test (MLMT) is also considered as an outcome measure	• MLMT is the primary endpoint of the pivotal clinical trial (Section 9.4.1.1.1)
Subgroups to be considered	None	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	N/A
Clinical effectiveness	• Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	• Treatment continuation rules are not considered, as VN is a one-time treatment • No subgroups will be presented in the evidence submission	• Voretigene neparvovec is a one-time treatment (Section 2) • No subgroups were prespecified in Study 301/302 (Section 9.4.4)
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable	None	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	the new technology to be used		
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. • Cost effectiveness analysis should include consideration	• Health states defined based on the average of the two eyes	• Established symmetry between the eyes for IRDs (Section 6.1.3 and Section 12.4.1) • The difference in results between modelling the average eye and the best-

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	of the benefit in the best and worst seeing eye† • Guidance will take into account any Managed Access Arrangements.		seeing eye is negligible (Section 12.5.11)‡

Abbreviations: MLMT, multi-luminance mobility test; NHS, National Health Service; PSS, Personal Social Services; RPE65, retinal pigment epithelium 65 kDa protein.

† One-eye treatment has been considered in some previous NICE appraisals [6-8]; this is not considered appropriate in the assessment of VN on the basis that the development and progression of *RPE65*-mediated IRD is symmetrical across both eyes, and there is no clear best or worst seeing eye. There is broad consensus on the importance of bilateral treatment from UK clinical experts [9].

‡ Since the average eye is calculated as the average of the best-seeing eye and the worst-seeing eye, the difference in results between modelling the average eye and the worst-seeing eye would also be negligible.

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: LUXTURNA™

Approved name: Voretigene neparvovec

Therapeutic class: Adeno-associated virus gene therapy vector

2.2 What is the principal mechanism of action of the technology?

Voretigene neparvovec, an AAV vector-based gene therapy, is a one-time treatment for biallelic *RPE65* mutation-associated inherited retinal dystrophies (IRD). The condition causes vision loss – often during childhood or adolescence – ultimately leading to near-total blindness as early as the preschool years or as late as the third decade of life [4]. No pharmacological treatments are currently available [1].

RPE65 is an enzyme critical for the visual cycle, in which light energy is converted to electrical signals in the retina at the back of the eye. *RPE65* gene mutations reduce or eliminate RPE65 activity, blocking the cycle and causing vision loss. Despite the absence of functional RPE65, photoreceptors degenerate slowly, so phenotypic recovery is possible through restoration of the enzyme [4].

Subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells. This enables patients to produce functional RPE65 protein, resulting in improved functional vision (the ability to perform activities of daily living that are dependent on vision) and visual function (the performance of the eyes at the organ level).

In order to benefit from treatment, patients must have confirmed biallelic *RPE65* mutations and sufficient viable retinal cells into which healthy copies of the *RPE65* gene can be introduced [3].

2.3 Please complete the table below.

Table 2: Dosing Information of technology being evaluated

Pharmaceutical formulation	Concentrate and solvent for solution for injection
Method of administration	Subretinal injection
Doses	A single dose of 1.5 x 10^{11} vector genomes in each eye, delivered into the subretinal space in a total volume of 0.3 mL. An immunomodulatory regimen should be initiated, starting 3 days prior to administration and lasting between 18 and 30 days, depending on the timing of administration to the second eye (see Section 8.7).
Dosing frequency	Once per lifetime (a single dose in each eye)
Average length of a course of treatment	One-time treatment
Anticipated average interval between courses of treatments	The individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart (in the Phase 3 trial the mean time between treatments was 8.8 days).
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	None

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing Authorisation for VN was granted by the European Commission on 22nd November 2018 [2]. The licensed indication is for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells [3].

Prior to the identification of causative genes, clinical diagnoses including Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) were assigned, but it is now considered more appropriate to categorise this group of disorders by the disease-causing gene. *RPE65* mutations are only associated with LCA and RP, and not with other clinical diagnoses [10].

Orphan status was maintained at the time of marketing authorisation [11]. The Committee for Orphan Medicinal Products acknowledged that a given mutation may give rise to more than one clinical phenotype, so the two previous orphan designations (for treatment of LCA [EU/3/12/981] [12] and for treatment of RP [EU/3/15/1518] [13]) were merged. Both original designations remain on the Community Register of Orphan Medicinal Products, with the indication wording updated to “for treatment of inherited retinal dystrophies”.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that UK stock of VN will be available in [redacted]

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The MA granted by the European Commission approves VN for use in the 27 other EU member states, in addition to Iceland, Liechtenstein and Norway. In addition, VN received Food and Drug Administration (FDA) approval on 19th December 2017 as a one-time gene therapy to restore functional vision in children and adult patients with biallelic mutations of the *RPE65* gene.

3.4 If the technology has been launched in the UK provide information on the use in England.

Not applicable.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Two clinical trials provide evidence on the efficacy and safety of VN in the treatment of *RPE65*-mediated IRD:

- **Study 101/102 (Phase 1):** Dose-escalation safety study, in which 12 patients received treatment in one eye[2] only in the dose-escalation phase (Study 101) [14, 16]. Eleven of these patients then received the Phase 3 dose in the contralateral eye in a follow-on phase (Study 102) [17, 18].

- **Study 301/302 (Phase 3):** Randomised controlled trial, with an Original Intervention (OI) arm in which 20 patients received bilateral treatment, and a best supportive care (BSC) Control/Delayed Intervention (DI) arm consisting of nine patients (Study 301) [4, 19]. Patients in the DI arm served as a control group for the first year of the study, before being eligible to receive bilateral treatment in the subsequent stage (Study 302) [20].

In total, VN was administered to 81 eyes in 41 patients:

- Study 101: 12 patients (12 eyes)

- Study 102: 11 patients from Study 101[3] (11 eyes)

- Study 301/302: 29 patients (58 eyes)

All trial patients will be followed for analysis of long-term safety and efficacy for 15 years following treatment. Details of these studies are provided in Table 3.

[2] The eye chosen was the subject's eye with worse function, if this worse function was determined to be due to disease-related factors or other variables which would not confound data acquisition or interpretation (e.g., glaucoma). Otherwise, the study eye was assigned randomly [14]. However due to the symmetrical nature of disease progression the difference between the best and worst-seeing eye is not expected to be significant [15].
[3] One patient treated in one eye in Study 101 did not receive treatment in the contralateral eye in Study 102 – see Section 9.4.6.

Although Study 101/102 is essentially a single clinical trial with a dose-escalation phase and a continuation phase, Study 101 and Study 102 are presented separately throughout this document due to differences in methodology, such as dose administered and eye treated.

Table 3: Completed and ongoing studies

Study ID	Study 101	Study 102	Study 301/302
NCT ID	NCT00516477	NCT01208389	NCT00999609
Level of evidence	Supportive	Supportive	Pivotal
Study design	Phase 1, open label dose-escalation safety study	Phase 1, open label safety study (follow-on to Study 101)	Phase 3, open label, randomised safety and efficacy study with crossover continuation phase
Patients enrolled	12	11 (one patient from Study 101 did not receive treatment in the contralateral eye in Study 102 – see Section 9.4.6)	31 (two patients withdrew prior to knowledge of treatment allocation – see Section 9.4.6)
Study population	Adults and children ≥ 8 years old with a molecular diagnosis of LCA† due to *RPE65* mutations	Patients from Study 101	Adults and children ≥ 3 years old with a molecular diagnosis of LCA† due to *RPE65* mutations
Intervention	Subretinal injection of VN into one eye: • low dose (1.5 x 10^{10} vg in 150 µl) • middle dose (4.8 x 10^{10} vg in 150 µl) or • high dose (1.5 x 10^{11} vg in 300 µl)	Subretinal injection of 1.5 x 10^{11} vg VN in a volume of 300 µl into the previously uninjected eye	Subretinal injection of 1.5 x 10^{11} vg VN in a volume of 300 µl into each eye
Comparator	N/A	N/A	BSC
Primary endpoint	Not defined. The primary objective of this study was to determine the safety and tolerability of subretinal administration.	Not defined. The primary objective of this study was to determine the safety and tolerability of subretinal administration.	Performance on the mobility test*, as measured by a change score one year following vector administration as compared to patients' pre-administration mobility test performance

Study ID	Study 101	Study 102	Study 301/302
Secondary outcomes	To assess the objective clinical measures of efficacy in human subjects	Secondary outcome measures included changes in visual function as measured by subjective, psychophysical tests and by objective, physiologic tests	One year change from baseline in FST, monocular MLMT performance and VA.
Study status	Primary objective complete. Ongoing safety and efficacy follow-up.	Primary objective complete. Ongoing safety and efficacy follow-up.	Primary objective complete. Ongoing safety and efficacy follow-up.
Source	Study 101 CSR [14] Maguire 2009 [16]	Study 102 CSR [18] Bennett 2016 [17]	Study 301 CSR [19] Russell 2017 [4] Novartis data on file [20]

Abbreviations: BCVA, best-corrected visual acuity; CSR, clinical study report; FDA, Food and Drug Administration; FST, full-field light sensitivity threshold; LCA, Leber Congenital Amaurosis; MLMT, multi-luminance mobility test; NCT ID, National Clinical Trial identifier; RPE65, retinal pigment epithelium 65kDa protein; VA, visual acuity; vg, vector genomes; VN, voretigene neparvovec

† The phenotype is driven by the underlying genetic mutation regardless of clinical diagnosis (Section 6.1).

* The MLMT (multi-luminance mobility test) is an obstacle course designed to test patients' ability to navigate at different light levels. It was developed in conjunction with the FDA to address the requirement for a relevant, reliable and clinically meaningful measure of functional vision in low-vision patients with nyctalopia (night blindness) [21].

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

A submission to the Scottish Medicines Consortium (SMC) is planned for April 2019.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

In addition to being currently untreatable, visual impairment that results from *RPE65* mutation is a legally recognised disability, as stated in the Equality Act 2010. The patient population addressed in this submission is a protected group under this act [22].

There is a non-uniform distribution of *RPE65* mutations between different ethnic groups – prevalence is higher in the South Asian population worldwide [23], and UK clinicians have confirmed the mutation is more prevalent in South Asian populations in the UK due to consanguinity [9]. Access to genetic testing in regions of the UK is variable in the context of limited budgets and no treatment options being available to date [9].

5.2 How will the submission address these issues and any equality issues raised in the scope?

A positive recommendation will ensure access to the only licensed treatment for patients with a currently untreatable rare genetic disease who have or will have a level of vision loss that is a legally recognised disability.

In addition to providing patients with their only chance of treatment, availability of VN may also help to accelerate the push towards more standardised access to genetic testing. In October 2018, a national network for genomic testing was established, comprising seven Genomic Laboratory Hubs, each responsible for coordinating services in a particular part of the country [24]. Working alongside these seven hubs are 25 partner trusts [25]. Three sites (Manchester, Great Ormond Street Hospital and Oxford) will perform ophthalmologic genetic testing, which includes screening for mutations in genes such as *RPE65* that are associated with retinal dystrophies. These sites will cover patients in England and Wales, and the new structure is expected to be in place from March 2019 [9].

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

- Patient burden is very high in this severe, progressive and extremely rare disease for which no treatments are currently available.
- Progressive vision loss leads to near-total blindness as early as preschool years or as late as the third decade of life.
- The first symptom of the disease is nyctalopia (night blindness). This is followed by progressive deterioration of visual field (range of sight), light sensitivity and visual acuity (clarity of vision), ultimately leading to complete blindness.
- Vision loss can begin as early as in the first few months of life, or during childhood or adolescence.
- Administration of VN introduces healthy copies of *RPE65* into retinal cells, providing the potential to restore visual function in this group of patients for the first time.

Inherited retinal dystrophies are a heterogenous group of rare genetic diseases that cause progressive vision loss leading to complete blindness in almost all patients [4]. These conditions can be caused by mutations in more than 260 genes, including the *RPE65* gene [26].

Prior to the identification of causative genes, clinicians assigned clinical diagnoses (including retinitis pigmentosa [RP] and Leber congenital amaurosis

[LCA]) to patients with IRDs based on medical history and physical examination, age, and inheritance patterns. There is considerable overlap in clinical symptoms for the diagnoses of RP and LCA, and there is no standardised method for assigning one diagnosis or the other.

As mutations in a gene are more directly linked to the underlying molecular pathogenesis, it is now considered more appropriate to categorise this group of disorders by the individual disease-causing gene, so RP and LCA caused by *RPE65* mutations are considered to be the same disease (*RPE65*-mediated IRD) rather than separate conditions.

The mechanism of action for VN is not dependent on the clinical diagnosis, but on the confirmed genetic diagnosis.

6.1.1 Epidemiology

6.1.1.1 Approach

The practice of assigning a molecular diagnosis is a recent development [27], so the available epidemiology data distinguish between clinical diagnoses of RP and LCA. A systematic literature review was conducted to identify sources reporting epidemiology data for these clinical diagnoses.

To obtain a prevalence estimate for *RPE65*-mediated IRD, the upper and lower bounds of prevalence estimates for LCA and RP were summed. *RPE65* mutations are only associated with LCA and RP [10] so these data can be used to estimate the total number of patients with *RPE65*-mediated IRD. In a natural history study, 9/70 subjects (13%) had received diagnoses of both LCA and RP over the course of their lives [28], so this approach may result in an overestimate of total patient numbers.

6.1.1.2 Prevalence

LCA and RP have a combined prevalence of around 12.3–28.8 per 100,000 people [29-41]. Mutations in the *RPE65* gene account for 0.8%–1.9% (median: 1.1%) of RP cases [42-44] and 1.0%–22.2% (median: 6.4%) of LCA cases [23,

42, 45-67]. It is estimated that the prevalence of *RPE65*-mediated IRD in England is 57–564.

6.1.1.3 Incidence

Three studies reported the incidence of RP [32, 37, 68]. The incidence of newly diagnosed cases was estimated to be around 0.6–1.6 per 100,000 people per year. No studies were found reporting the incidence of LCA.

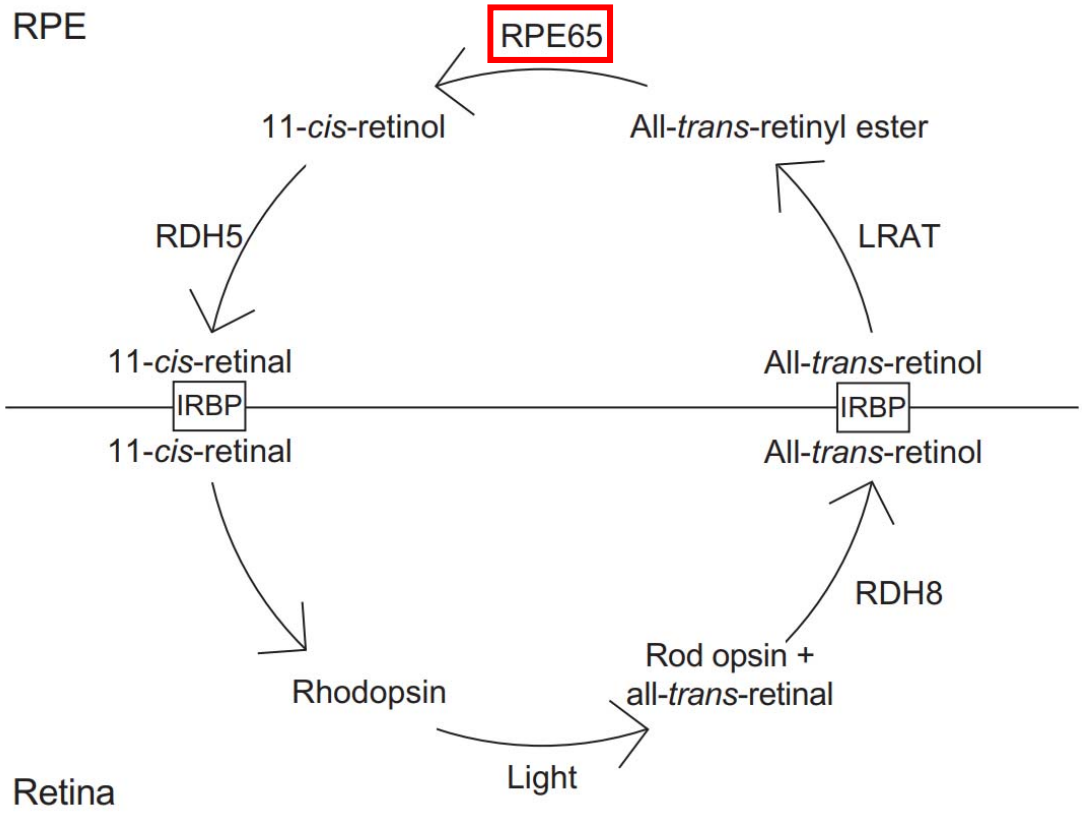
6.1.2 Pathogenesis

RPE65 is an enzyme critical for the visual cycle (Figure 1), a process essential for vision. The visual cycle occurs in light-sensitive photoreceptor cells in the retina and the underlying retinal pigment epithelium (RPE) at the back of the eye [69].

When light strikes rhodopsin (a pigment composed of the light-sensitive compound 11-*cis*-retinal and a signalling protein), 11-*cis*-retinal is converted to all-*trans*-retinal and the protein undergoes a conformational change, triggering the generation of an electrical signal that ultimately reaches the brain. For vision to be maintained, the supply of 11-*cis*-retinal must be constantly replenished [70].

Mutations in the *RPE65* gene result in the production of faulty RPE65, arresting this cycle. This causes a severe deficiency of functional rhodopsin, and apoptosis (death) of photoreceptor cells through accumulation of toxic all-*trans*-retinyl esters [71]. Patients (of whom a large proportion are young children) experience progressive vision loss that ultimately leads to complete blindness.

Figure 1: Biochemistry of the visual cycle



Source: Wright 2015 [69]
Abbreviations: IRBP, interphotoreceptor retinoid-binding protein; LRAT, lecithin retinol acyltransferase; RDH5, retinol dehydrogenase 5; RDH8, retinol dehydrogenase 8; RPE, retinal pigment epithelium; RPE65, retinal pigment epithelium 65kDa protein.

6.1.3 Symptoms

Visual impairment in individuals with *RPE65*-mediated IRD can present at a range of ages, from infancy to adolescence [4], leading to an inexorable progression towards near-total blindness as early as preschool years or as late as the third decade of life. Vision loss in patients with IRD is bilaterally symmetrical, with similar rates of deterioration in both eyes [15].

The first symptom of the disease is nyctalopia (night blindness), resulting in difficulty seeing in dim light, such as at dusk or at night [72]. Whereas people with normal night vision can almost fully adapt to dim light in 15 to 30 minutes, patients with *RPE65*-mediated IRD take much longer or are unable to adapt at all [73].

The progressive nature of the condition is well documented, with deterioration over time in both VF and VA [28, 74, 75]. There is no evidence of spontaneous

sustained improvement in either measurement in any individual [28, 76]. Retinal sensitivity also declines with age, as demonstrated in a cross-section of patients aged 9–23 [77], with patients ultimately losing the ability to detect light of any intensity [4].

Vision loss due to *RPE65*-mediated IRD involves the whole retina, and without stereoscopic vision patients' ability to navigate is impacted. Progressive VF loss causes affected individuals to miss objects and people in their vicinity and to have difficulty navigating around obstacles [78]. Patients tend to lose around 50% of their remaining VF every five years [79]. Peripheral blind spots merge to produce tunnel vision, and loss of central vision in the advanced stages of the disease leads to complete blindness [72, 78, 80].

Some individuals experience severe visual impairment or blindness in early infancy, frequently before six months of age [72, 81-83]. Visual acuity is usually no higher than 20/400 [82], with one third of affected infants having no perception of light at all [82]. Oscillations of the eyes (nystagmus) and absence of fixation are key signs noted by parents of affected infants [84].

Affected infants commonly present with the 'oculo-digital sign', also known as 'eye poking', in which the child repeatedly pokes, rubs or presses their eye with a knuckle or finger [83, 85]. This leads to intense pain and can itself result in permanent visual loss or total blindness [86]. This behaviour may contribute to deep-set eyes and keratoconus (an abnormally thin, cone-shaped cornea) in affected children [83]. In addition to the direct harm caused, it is distressing to witness and therefore adds to the burden on caregivers [86].

In a natural history study, 92.9% of subjects had documentation of a clinical diagnosis or onset of symptoms by the age of 18. By this age, more than half of patients had a VA lower than 6/60 in one eye.[28, 76]. This degree of VA loss places these individuals in the "sight impaired" (partially sighted) and "severely sight impaired" (blind) categories under UK RNIB guidelines, depending on the extent of VF loss [87].

Both of these categories reflect severe vision loss – having VA lower than 6/60 means that individuals are only able to see at 6 metres what someone with standard vision can see 60 metres away.

6.1.4 Complications of IRDs

Cataracts and cystoid macular oedema are common complications of inherited retinal dystrophies [72]. Cataracts may be removed through surgery to improve vision, but in severe cases of retinal degeneration there is a risk of making vision worse. Macular oedema results from leakage of blood vessels into the retina and may arise spontaneously or following cataract surgery. Treatment options depend on the cause of cataract formation. Patients may benefit from carbonic anhydrase inhibitors, although not all patients can tolerate these [72, 88]. Other treatment options available include oral, topical, intravitreal and periocular steroids, topical non-steroidal anti-inflammatory medications, photocoagulation, and intravitreal anti-VEGF injections [89].

6.1.5 Current standard of care

No treatments are currently available for *RPE65*-mediated IRD – support is limited to measures allowing the management of the diseases such as low-vision aids [1] and prostheses (NICE only recommends these in the context of research (Section 8.1).

Children with visual impairment are entitled to learning support from birth by a qualified teacher of learners with vision impairment (QTVI). Key services offered in early childhood by QTVIs include supporting early development and learning through play and, in liaison with health professionals, assessing functional vision and advising on the range of available low vision devices. In the school and further education setting, QTVIs teach specialist skills such as reading Braille, advise on access arrangements for exams, and support the transition into adulthood by teaching independent living and learning skills [90].

About 2% of children with vision impairment attend schools specifically for blind and partially sighted pupils, and another 32% attend other types of special schools. Approximately 64% are educated in mainstream schools, which may

have a resource base for pupils with visual impairment, or may put adaptations in place to assist visually impaired pupils [91].

Low vision aids and other devices assist with daily living, but do not prevent the inevitable deterioration of vision and progression to complete blindness [72]. If a diagnosis is confirmed by genetic testing, counselling is usually advised to help patients understand the prognosis and the risks of passing the condition on to their children [92].

6.1.6 Needs addressed by voretigene neparvovec

Voretigene neparvovec transduces retinal pigment epithelium cells with healthy copies of the *RPE65* gene, providing the potential to restore the visual cycle. In a randomised controlled Phase 3 clinical trial, in which 42% of patients were under 10 years of age, VN treatment resulted in improvements in several endpoints of relevance to patients' daily lives, including ability to navigate, light sensitivity, visual acuity and visual field (see Section 9.6).

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

As discussed in Section 6.1.1, a systematic literature review was conducted to identify published sources of epidemiology data for RP and LCA[4], and data for the proportion of cases caused by *RPE65* mutations.

All identified data sources were reviewed for suitability for inclusion in the calculation of patient numbers in England, and selected on the following basis:

- Where one or more sources of UK data were available, the mean of these data points was taken.

[4] RPE65 mutations are only associated with LCA and RP, and not with other clinical diagnoses such as cone-rod dystrophies [5]. Therefore, LCA and RP prevalence data can be used to estimate the total number of patients with RPE65-mediated IRD.

- Otherwise, the average of all available data points from Western Europe and North America was taken.

The number of diagnosed patients with *RPE65* mutations and sufficient viable retinal cells is estimated to be 86 (see Table 4); however, a small number of these patients are expected to be ineligible for treatment with VN due to participation in the MeiraGTx trial. 15 patients have enrolled in the MeiraGTx trial across sites in the UK and the US [93]; assuming an even distribution between UK and US sites, 7-8 UK patients are expected to be ineligible for treatment with VN, giving a total eligible population of 78 patients.

Table 4: Eligible population data

Parameter	%	N
Population of England in 2019†	-	56,512,870
Population of England in 2017 [94]	-	*55,619,400*
Annual population growth in England [94]	-	*0.8%*
Prevalence of *RPE65*-mediated IRD‡	0.0003%	180
Prevalence of RP [36]	*0.02%*	*11,402*
% of RP that is RPE65-mediated [42-44]	*1.3%*	*144*
Prevalence of LCA [29, 40]	*0.002%*	*1,001*
% of LCA that is RPE65-mediated [60]	*3.4%*	*34*
% of patients with sufficient viable retinal cells [9]	95%	171
% of patients who are diagnosed¶	50%	86

Abbreviations: LCA, Leber congenital amaurosis; RP, retinitis pigmentosa.
† Calculated as (2017 population size) x (1 + annual population growth)^2
‡ Calculated as (prevalence of RP x % of RP that is *RPE65*-mediated) + (prevalence of LCA x % of LCA that is *RPE65*-mediated)
¶ Clinical experts estimated that between 33% and 50% of patients have been diagnosed with an *RPE65* mutation; given that diagnosis rates may be expected to increase following the availability of voretigene neparvovec, the upper end of this range was used.

The annual incidence of RP is estimated to be 0.70 per 100,000 per year [32, 37]. In the absence of data on the incidence of LCA, it is assumed that the ratio of RP to LCA is the same in incident patients as in existing patients, giving an incidence of eligible patients (i.e. individuals with a confirmed diagnosis of *RPE65*-mediated IRD and sufficient viable retinal cells) of three per year.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

The disease mechanism itself is not fatal, but reduced VA is associated with increased mortality. A prospective longitudinal study of adults aged 65–84 evaluated the effects of VA loss on mortality risk through functional status changes in instrumental activities of daily living (IADL). Functional status was measured using standardised validated questionnaires. Lower VA levels at baseline were associated with increased mortality risk (HR 1.16 [95% CI: 1.04, 1.28]; $p < 0.01$) through their effect on baseline lower IADL levels. Declining VA over time was also associated with increased mortality risk (HR 1.78 [95% CI: 1.27, 2.51]; $p < 0.01$) through decreasing IADL levels over time. [95].

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

- The symptoms of *RPE65* mutation-associated inherited retinal dystrophies appear early in life and have a profound impact on the quality of life of patients, families and carers.
- The inexorable progression towards complete blindness means that the effects are life-changing and lifelong.
- Visual impairment disrupts children's participation in education, social and leisure activities, and impacts negatively on educational outcomes.
- Adults with vision loss are more likely to require assistance with daily activities, and are less likely to be in paid employment than the general population.
- Individuals with visual impairment report reduced wellbeing, and are more likely to suffer from depressive symptoms.
- Patients often require full time support – caring for blind individuals is associated with increased risk of depression and has a wider societal impact in terms of reduced productivity.

Inherited retinal dystrophies usually manifest in children and young people, and have a profound impact on the quality of life of patients and their families. The inexorable progression towards complete blindness means that the effects are life-changing and lifelong [4, 28]. Individuals with visual impairment and

blindness rate their quality of life similarly to those with severe systemic diseases [96].

[redacted]

Key quality of life issues caused by the disease are discussed below.

7.1.1 Early life and education

Children who are affected by early-onset disease experience severe visual impairment or blindness early in life, often by six months of age [72, 81-83], with visual acuity so poor that most meet the criteria for certification as severely sight impaired (blind) (see Section 6.1.3) [82, 87].

This has a significant impact on children's development, including detrimental effects on emotional bonding, personality and social interactive skills [98]). Severe visual impairment in children often leads to social isolation through difficulty in participating in activities [99].

In education, the attainment of learners with visual impairment (VI) is lower than that of learners without special educational needs or disabilities, at all key stages. According to the Millennium Cohort Survey, at the age of 11 children with VI are more likely to feel tired at school and are less likely to feel they can do things as well as other children. Poor mobility and reduced independence becomes an increasing problem as young adults progress into further and higher education, and visual impairment affects long term prospects with affected children being more likely to experience social and economic disadvantage [100].

7.1.2 Employment and productivity

The younger visually impaired individuals are, the greater the impact of their sight loss on productivity [101]. Visually impaired people are significantly less likely to be in paid employment than the general population or other disabled people (25% versus 75%), and the proportion in employment fell in the decade between 2005–2015 [102]. Across members of the 1958 British birth cohort study, impaired vision-related quality of life (VRQoL) was strongly associated with being unable to work owing to a permanent illness, and having low socioeconomic status [103].

Individuals with sight loss who are in employment are less likely to be high earners and more likely to be on a low income – they are twice as likely as the general population to be living in a household with an income of less than £300 per week [102].

7.1.3 Mobility

Night blindness (nyctalopia) – a defining feature of *RPE65*-mediated IRD – has a large impact on patients' quality of life [9]. Under circumstances of low light, individuals with nyctalopia have reduced mobility and experience a greater number of mobility-related incidents [104-106]. One study found that subjects with a clinical diagnosis of RP were five times more likely to have a mobility incident under reduced illumination than normal-sighted subjects [105]. These difficulties can be particularly exacerbated during the winter months when

reduced daylight hours in many countries, including the UK, mean that people travel to and from work in the dark.

7.1.4 Poorer mental health

Patients with severe visual impairment are more likely to suffer from depression, anxiety and emotional distress [107-111]. A French study of 148 patients with a clinical diagnosis of RP found that 36.5% and 15.5% had mental health scores suggestive of anxiety and depression respectively, compared to reported values of 9% and 2% in healthy controls. A significant correlation existed between residual visual field and quality of life scores assessed using the NEI VFQ-25 [111]. In a survey conducted on 22,486 individuals aged over 50 years old across 10 European countries, lower vision was associated with a highly significant, negative impact on all measured aspects of wellbeing. The worse the eyesight, the higher percentage of respondents reporting depressive symptoms [110].

7.1.5 Sleep

Visual impairment is also associated with an increased risk of sleep disorders [109, 112-115], including increased occurrence of sleep/wake disorders and involuntary daily naps [115]. Amongst children, Leger et al found that 17.4% reported sleeping less than seven hours per night on weekdays compared with 2.6% of controls, with blind children waking much earlier. Blind children also had more sleep complaints and daily episodes of involuntary sleepiness [114].

7.1.6 Economic and health burden on caregivers

Patients with the condition often require full time support [9]. Adults with severe visual impairment are more likely to require assistance with activities of daily living, including shopping, climbing steps, paperwork, travel, housework, preparing meals and taking medications [116, 117].

The number of hours spent caring for visually impaired individuals increases with severity of impairment [118, 119]. A large proportion of the patient population are young children, placing an emotional and economic burden on

families and carers. Parents can feel the emotional and economic burden of providing care, whilst normal-sighted siblings may feel left out or not valued [120].

Caregivers experience an increased risk of depression [121, 122], and spouses of older individuals with vision loss have an increased risk of poorer physical and emotional wellbeing [123]. A study conducted in the USA found that the risk of depression increased with vision loss from 6.9% in carers of individuals with BCVA 20/200–10/200 to 17.9% in carers of individuals with no light perception. Carers providing ≥ 2.5 hours of care per day were 5.33 times more likely to suffer depression than those who provided < 2.5 hours per day [121].

This also creates a significant economic burden due to reductions in productivity, employment rates and income [124]. Brézin et al [117] found that elderly individuals with greater vision loss required more building adaptations. Equipping the home with adaptations not covered by local authorities may further exacerbate the financial impact of the condition on affected individuals and their families.

7.1.7 Driving

Concerns about the ability to drive are another common issue in affected adults [72]. The key symptoms of the condition – night blindness, nystagmus, reduced VA, and VF defects – are notifiable to the Driver and Vehicle Licensing Agency (DVLA) [125], after which vision is assessed regularly to determine if it meets the required standards of vision for driving [78]. Certification as sight impaired or severely sight impaired would result in revocation of the driver's license [126]. Having a driving license revoked because of poor vision can affect patients' ability to work, see family and friends, and to maintain independence, as described by a patient diagnosed in adulthood:

"I noticed as my eyes started to deteriorate, that unfortunately the [building] work was starting to deteriorate… When I was diagnosed with RP, it was a big, big shock, and the biggest thing probably was losing my driving licence… I was quite down and depressed for the first two months, I'd say, after the

diagnosis, just thinking – 'What am I going to do? I can't drive, I can't really carry on with the building work." [73]

7.1.8 Impact of current standard of care on QoL

Current SoC does not prevent the inexorable deterioration to complete blindness [4]. As *RPE65*-mediated IRD is a progressive condition with no chance of improvement in vision, there is a need to constantly adapt as vision deteriorates [78]. Poorer vision is associated with reduced independence and greater dependence on carers [118], poorer mental wellbeing [110, 111], and increasing difficulty in performing activities of daily living [119].

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Given the inexorable progression towards complete blindness currently experienced by patients due to the lack of treatments [4], any improvement or preservation of visual function and functional vision is expected to have a large impact on patients' wellbeing and that of their families and carers. Utility values for visual impairment are dramatically lower in individuals with complete loss of light perception, demonstrating that preservation of even small amounts of vision is critically important to quality of life (73).

Poorer vision is associated with reduced social interactive skills in children [98], poorer mental health [107-111], problems with sleeping [109, 112-115], and reduced employment and productivity in adults [101, 103]. It is anticipated that improvements in functional vision following VN administration will greatly impact on patients' sense of wellbeing and independence. For some patients, including children, the improvement in functional vision may allow them to lead normal/near-normal lives.

7.2.1 Impact on patients in clinical trials

One of the exploratory endpoints in the Phase 3 trial for VN (Study 301/302) was a Visual Function Questionnaire (VFQ), results of which were compared at baseline and year 1 post-administration.

The questionnaire is similar to the NEI VFQ-25, and contains 25 questions pertaining to activities of daily living that are dependent upon vision or have a vision component (see Appendix 7). Subjects (and parents of subjects under 18) rated the perceived difficulty of these activities on a 0 to 10 scale (0 being the most difficult), with the output being an average score from all 25 questions.

VFQ scores of patients who received treatment increased significantly following administration, indicating a reduction in the perceived difficulty of daily living activities which was sustained through follow-up. Detailed results are provided in Section 9.6.1.1.8 and Section 10.3.

7.2.2 Impact on families and carers

In addition to providing direct clinical benefits, VN treatment is anticipated to benefit families and carers by improving wellbeing and reducing time spent caring, potentially leading to productivity gains. A reduction in the length and intensity of caring may also reduce the risk of mental health problems and family difficulties.

7.2.3 Wider benefits to society

The clinical benefits of VN would be expected to reduce the indirect costs associated with impaired vision, such those associated with reduced employment and productivity, and the provision of specialist support, including in education. In the UK, the total indirect cost attributable to sight loss and blindness was estimated to be £5.65 billion in 2013 [127]. These costs were attributed to factors including reduced productivity, absenteeism, the costs of informal carers and the cost of visual aids and modifications.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are two NICE interventional procedures guidance reports on the use of subretinal [128] and epiretinal [129] prostheses for RP, each recommending that the devices are only used in the context of research. There are no other NICE or NHS England guidelines for the treatment of *RPE65*-mediated IRD, and very few national or expert guidelines exist owing to the lack of current treatment options and the rare nature of the condition.

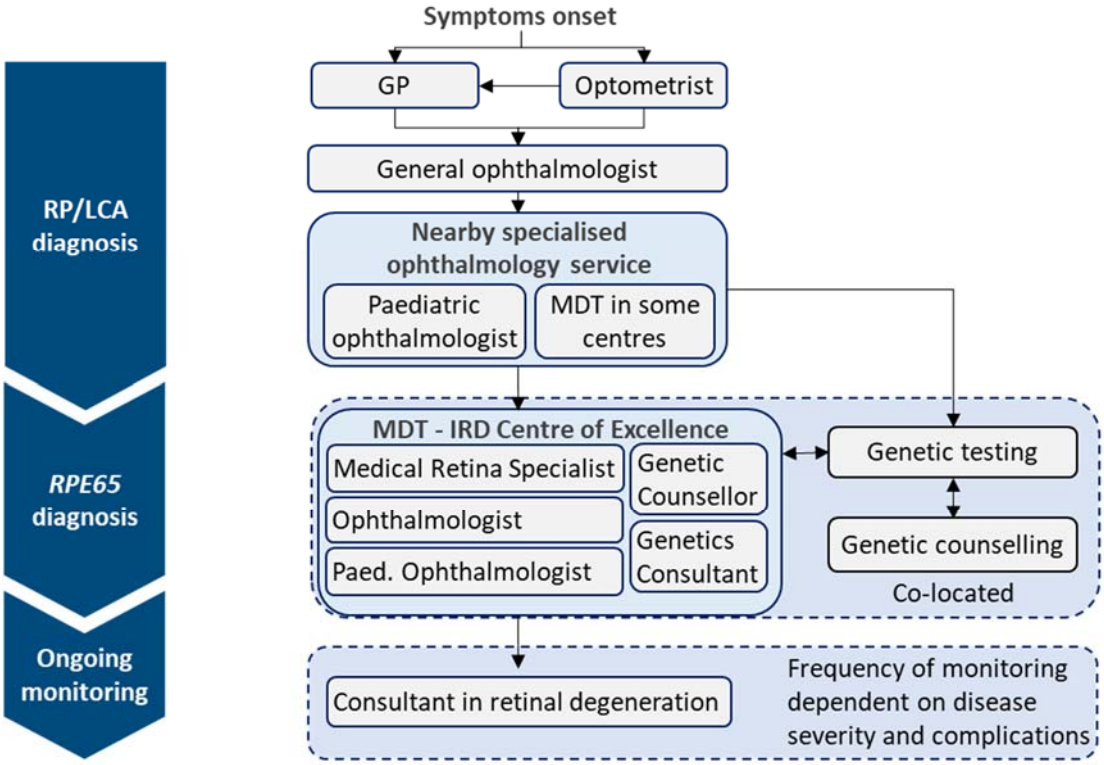
British Medical Journal guidelines [72] state that in the absence of treatment, the key priority should be to optimise remaining vision with the help of visual aids such as glasses, magnifiers and telescopes. Adjuncts to these approaches include vitamin A supplements and fish oils, with the aim of slowing retinal degeneration. However, vitamin A supplements are not suitable for all patients, and a therapeutic benefit of fish oils has yet to be demonstrated in clinical trials. Surgery and carbonic anhydrase inhibitors are recommended for treating posterior subcapsular cataracts and cystoid macular oedema, respectively, which are common complications [72].

Whilst aiming to maximise remaining vision, none of these approaches treat *RPE65*-mediated IRD or prevent the inevitable decline to complete blindness. There is a significant unmet need for treatments in this area.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Figure 2 illustrates the UK clinical pathway of care for *RPE65*-mediated IRD.

Figure 2: UK patient and provider pathway



Abbreviations: GP, general practitioner; IRD, inherited retinal dystrophies; LCA, Leber congenital amaurosis; MDT, multidisciplinary team; Paed., paediatric; Pts. patients; RP, retinitis pigmentosa; RPE65, retinal pigment epithelium 65 kDa protein.

8.2.1 RP/LCA diagnosis

Patients with problems seeing in dim light or at night typically visit their optometrist or GP in the first instance. Symptoms in babies and young children, including nystagmus, light-seeking behaviours and eye rubbing, are often noticed by parents. If IRD is suspected, patients are referred from primary care to a hospital outpatient ophthalmology service [78]. To minimise patient travel, the point of first referral is usually a nearby specialised paediatric ophthalmology centre. These are commissioned nationally by NHS England.

8.2.2 *RPE65* diagnosis

Genetic testing is also commissioned nationally by NHS England, although access varies by region (See Section 5.2). Between 30–50% of RP/LCA patients are believed to have undergone genetic testing [130]. This proportion is expected to increase as the provision of genetic testing improves and treatment options become available. Most patients are diagnosed in childhood,

although some are not diagnosed until their twenties or thirties [9]. For the reasons described above it is expected that the average age at diagnosis will fall to under 15 years.

Upon confirmation of diagnosis patients should be referred to a low-vision consultant (an ophthalmologist or optometrist) who can help them to obtain visual aids [72]. The BMJ guidelines recommend that patients with suspected IRD should be seen by a consultant, given the severe implications of the diagnosis.

The number of tests used between different treatment centres varies but all patients should have VF tests and an ERG performed [72].

8.2.3 Ongoing monitoring

Patients should be followed up by a consultant in retinal degeneration every one to two years to monitor changes in vision and to address concerns [72]. However, expert clinical input [9] suggested monitoring may take place every 3–6 months if patients have more severe disease or complications (e.g. macular oedema). Regular testing is a legal requirement for those who drive, as the DVLA will review patients' vision to ensure that it meets their standards (see Section 7.1.7) [78].

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

8.3.1 Lack of treatments

The most pressing issue relating to current clinical practice is the lack of treatments. Approaches to maximise remaining vison do not address the underlying condition and fail to slow or prevent the deterioration of vision.

8.3.2 Genetic testing

Eligibility for VN treatment would depend on confirmed genetic diagnosis of biallelic *RPE65* mutations (see clinical pathway of care in Figure 3). One issue

relating to current clinical practice is the regional variability in access to genetic testing services, discussed in Section 5.2.

Another issue is that the benefits of knowing the gene responsible for the condition (such as increasing the precision of prognoses and facilitating informed decision making by couples planning to have children) must be balanced against the issues that can arise as a result of this knowledge (such as anxiety caused by the prognosis and the lack of treatment options).

The availability of a VN as the first treatment option for patients affected by this disease would alter this risk-benefit ratio, offering hope to those with confirmed biallelic *RPE65* mutations.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

8.4.1 Diagnosis

The licensed indication is for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells [3].

Therefore genetic testing will be required to determine eligibility, and Optical Coherence Tomography (OCT) will be required to determine the presence of sufficient viable retinal cells. These are required to support transduction of the vector to enable production of the RPE65 protein, restoring the visual cycle and improving functional vision.

In the clinical trials, patients were deemed to have sufficient viable retinal cells if they had an area of retina within the posterior pole of > 100 micron thickness, as estimated by OCT. In clinical practice, OCT examinations are likely to be more qualitative, and supplemented by tests of VA and VF.

8.4.2 Treatment

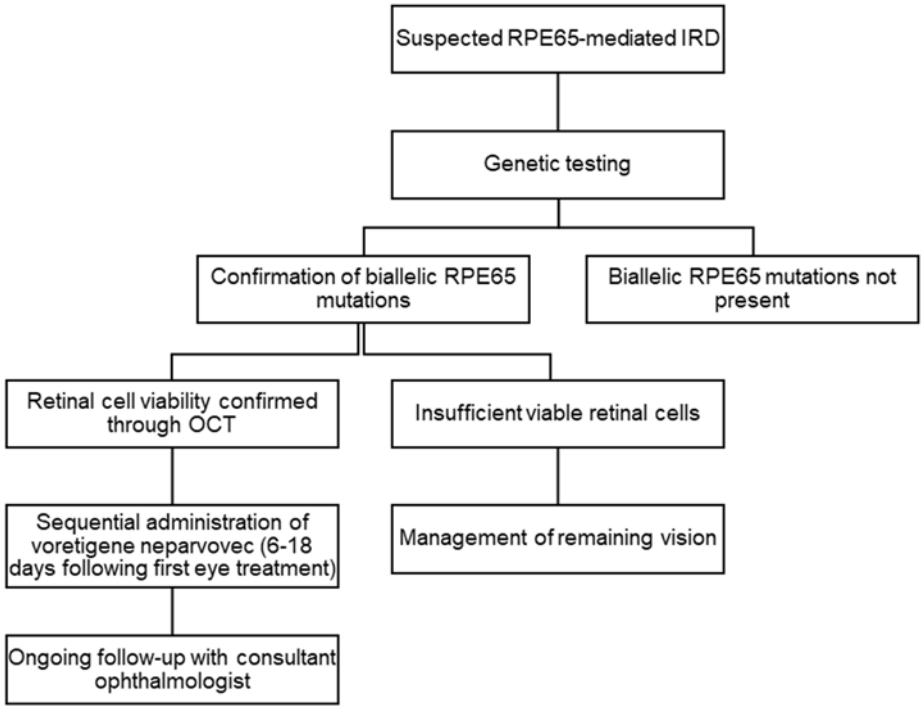
In eligible patients, bilateral treatment with VN will be the first-line (and only) treatment option. Treatment will be initiated by a consultant in retinal degeneration and administered by a retinal surgeon experienced in performing macular surgery. A single dose will be administered to each eye within a close interval between 6-18 days apart [3].

In the Phase 3 trial the 18 day upper limit on the interval between doses was introduced to reduce the potential for an immunological boosting effect [19]. A clinical expert consulted for this submission also highlighted this point, and described the ability to use only one course of steroids in the immunomodulatory regimen as an additional benefit of having a narrow treatment window (Section 8.7.2) [9].

Patients who are not eligible for treatment will be managed according to the current pathway of care described above (Figure 2).

The proposed pathway of care incorporating VN is presented in Figure 3.

Figure 3: Proposed pathway of care incorporating voretigene neparvovec



Abbreviations: IRD, inherited retinal dystrophies; OCT, optical coherence tomography; RPE65, retinal pigment epithelium 65 kDa protein.

8.4.3 Monitoring

As described in Section 8.2, patients not suffering from complications will currently be followed up every one to two years (23). Patients treated with VN will require more frequent monitoring, which may include FST testing. This would take place every 3–6 months following administration and then annually once the patient is stable. Other than increased frequency, it is not anticipated that monitoring requirements will change.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

8.5.1 First treatment for *RPE65*-mediated IRD

Voretigene neparvovec represents a step-change in the management of *RPE65*-mediated IRD, a condition which currently lacks any form of treatment. Current approaches aim to maximise existing vision through the use of mobility and visual aids, but fail to address the underlying condition, which involves progressive deterioration to complete blindness.

Voretigene neparvovec has demonstrated sustained improvement from baseline compared with BSC in outcomes including functional vision, light sensitivity, visual acuity and visual field in clinical trials (see Section 9.6).

8.5.2 Potential to advance the wider field of gene therapy

The methodology and results of the Phase 3 trial (Study 301) provide support for gene-based approaches to treating rare genetic diseases. The manufacturing techniques used might potentially be applied to the treatment of IRD with different genetic causes, and to genetic diseases involving other organ systems.

Voretigene neparvovec therefore not only has potential to improve the lives of patients with *RPE65*-mediated IRD, but also to advance the broader field of gene therapy.

8.5.3 Innovation

Voretigene neparvovec is the first gene therapy to be approved for a retinal disease [1]. It is the first pharmacologic treatment for an IRD, and Study 301/302 was the first randomised, controlled Phase 3 gene therapy trial for an inherited disease [5].

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

It is anticipated that VN gene therapy will fit a specialised centre model, with diagnosis, counselling, treatment and follow-up performed at a few centres nationally. An example of this in current practice is management of ocular melanoma, which occurs at three designated specialised centres in the UK [131].

Treatment centres will need to meet the following EMA risk management plan criteria:

- Presence of a specialist ophthalmologist with expertise in care and treatment of patients with IRD;
- Presence of or affiliation with a retinal surgeon experienced in sub-retinal surgery and capable of administrating VN;
- Presence of a clinical pharmacy capable of handling and preparing AAV vector-based gene therapy products; and
- Have undertaken mandatory surgical and pharmacy educational programs (Section 8.7.1) and commit to ongoing training of new and future staff [3].

In order to be eligible for treatment, patients will need to have confirmed biallelic *RPE65* mutations, so genetic testing and counselling [92] will need to be available to patients who might benefit from treatment.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Additional tests or investigations for selecting or monitoring patients will not be required, however as discussed above, genetic testing would need to be initiated, and monitoring will need to be performed more regularly following treatment until a patient has stabilised.

Treatment will be initiated and administered by retinal surgeons experienced in performing macular surgery [3].

8.7.1 Education of surgeons and pharmacists

Pharmacists and vitreoretinal (VR) surgeons involved in the preparation and administration of VN will be required to participate in a mandatory educational program as per the EMA Risk Minimisation Program (RMP) [3].

Surgeons will be required to attend a 4–5 hour session (including an anaesthetised animal wet-lab) at a preclinical clinical research organisation in Denmark or France, and pharmacists a 2–3 hour on-site session. This program will be paid for by Novartis.

The purpose of these sessions will be to provide education on the RMP, safety data from the clinical trials, and the specific surgical and pharmacy handling techniques described in the SmPC. Retinal surgeons embarking on the program must be experienced in performing subretinal surgery.

8.7.2 Immunomodulatory regimen

To reduce the risk of an immune response an immunomodulatory regimen using prednisone (or equivalent) should be initiated, starting 3 days prior to

administration and lasting between 18 and 30 days. One course of prednisone (or equivalent) treatment will be sufficient to cover the fellow eye administration as this is expected to be planned between 6-18[5] days following the first eye administration (Table 5) [3].

Table 5: Pre- and post-operative immunomodulatory regimen

Period	Duration	Treatment
Pre-operative	3 days prior to VN administration	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of administration)	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
	Followed by up to 5 days, or until the beginning of second eye regimen, for the first eye or 5 days for the second eye	Prednisone (or equivalent) 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day for the first eye only	Prednisone (or equivalent) 0.5 mg/kg every other day (maximum of 20mg/day)

Abbreviations: VN, voretigene neparvovec.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Facilities will be required by the pharmacy handling the product to keep it at the required storage temperature (≤ -65 ºC) and quarantine level. Pharmacies will require a Class II Laminar Flow Cabinet for the preparation of the syringes for subretinal injection.

[5] The SmPC stipulates that the individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart [3]. In the Phase 3 trial the second injection was administered no later than 18 days after the first [4].

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is anticipated that all of those in current practice will still be required. However, for individual patients, the requirement for visual and mobility aids may reduce following treatment with VN.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A systematic review was conducted to retrieve clinical and safety data relevant to VN in *RPE65*-mediated IRD. The searches were run on 8th March 2018, and were updated on 11th January 2019.

Details of search strings, databases searched, and inclusion/exclusion criteria are provided in Appendix 1.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Details of hand searching are provided in Appendix 1.

9.2 Study selection

Published studies

9.2.1 Complete Table 6 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Selection criteria used to identify relevant studies from the published and unpublished literature are presented in Table 6.

Table 6: Selection criteria used for published and unpublished studies

Inclusion criteria	
Population	Patients with inherited retinal dystrophies caused by *RPE65* gene mutations
Interventions	Voretigene neparvovec
Outcomes	Clinical efficacy: • Multi-luminance mobility test • Full-field light sensitivity threshold • Visual acuity • Visual field Safety†: • Treatment emergent adverse events (TEAEs) • Serious adverse events • Administration-related TEAEs
Study design	• Randomised controlled trials • Phase 1/2 studies
Language restrictions	English
Search dates	From inception of database to 8th March 2018 (original search) and to 11th January 2019 (updated search)
Exclusion criteria	
Population	Patients with inherited retinal dystrophies caused by gene mutations other than *RPE65*
Interventions	• Gene therapy using other vectors (e.g. rAAV2-CBSB-hRPE65, tgAAG76, rAAV2-CB-hRPE65, rAAV2/4.hRPE65, rAAV2-hRPE65) • Other oral preventive drugs (e.g. QLT091001, oral synthetic cis-retinoid)
Outcomes	None
Study design	• Reviews • Editorials

	• Notes • Opinions • Case reports
Language restrictions	None
Search dates	None

†These outcomes were included to capture studies relevant to Section 9.7.1 on adverse events.
Abbreviations: RPE65, retinal pigment epithelium 65 kDa protein; TEAE, treatment emergent adverse event.

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

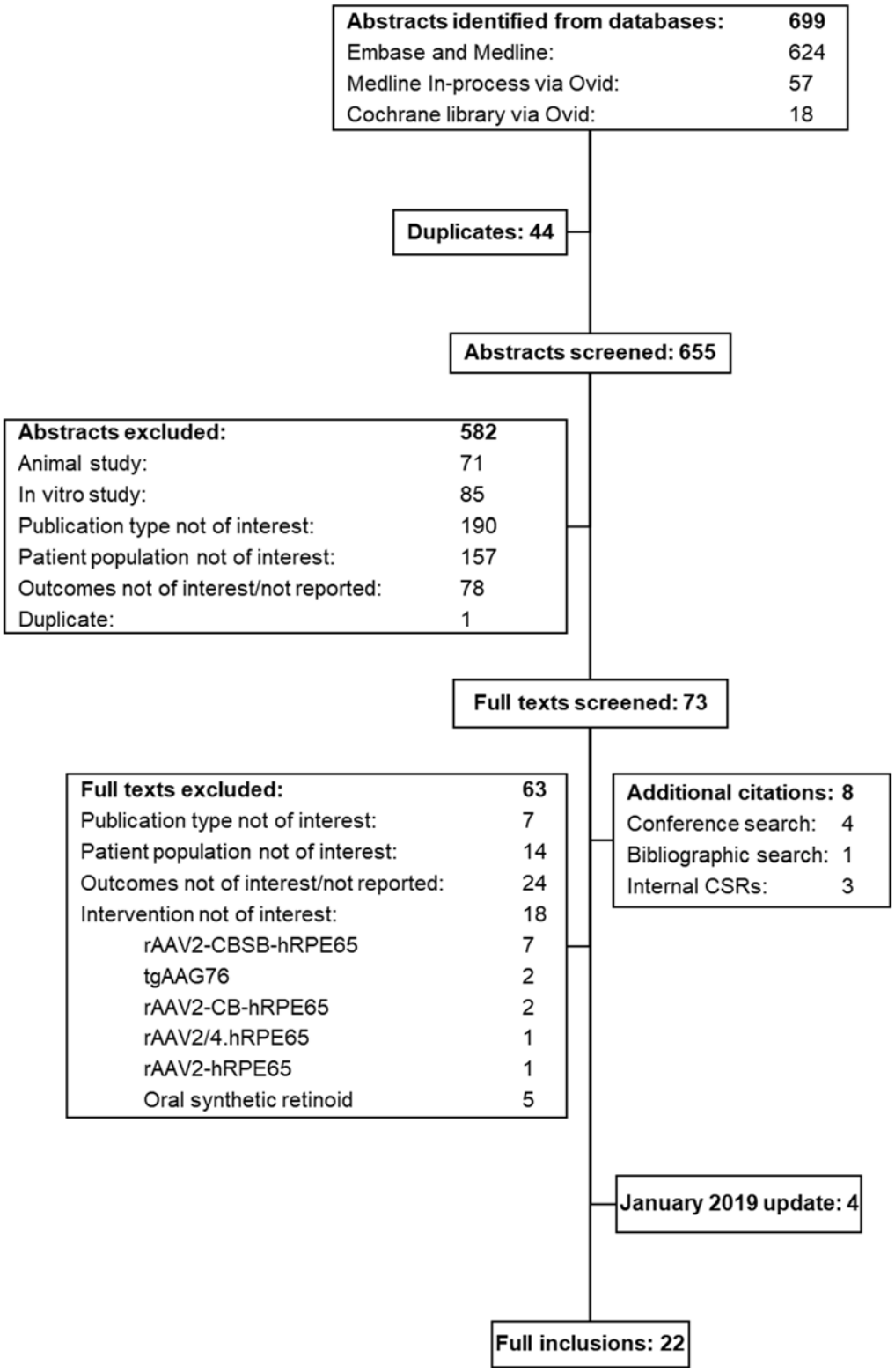
In the original search, 699 papers were identified through the electronic searches. Upon the removal of duplicate papers, 655 titles and abstracts were reviewed. A total of 73 papers were potentially relevant and were ordered for full paper review. At this stage, a further 63 papers were excluded. Hand searching yielded eight additional relevant papers, resulting in a total of 18 papers for final inclusion in the original review.

In the January 2019 update, 124 papers were identified through the electronic searches. Upon the removal of duplicate papers, 80 titles and abstracts were reviewed. A total of 22 papers were potentially relevant and were ordered for full paper review. At this stage, a further 22 papers were excluded. Hand searching yielded four additional relevant papers, resulting in a total of four papers for final inclusion in the updated review.

Across the original review and the January 2019 update, a total of 22 studies were identified for final inclusion in the review.

The flow of studies through the review is reported in the PRISMA flow diagram in Figure 4. Separate PRISMA diagrams for the original and updated reviews are presented in Appendix 1.

Figure 4: PRISMA flow diagram for published and unpublished studies in clinical evidence SLR



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The inclusion and exclusion criteria used to select studies from the unpublished literature are those described in Table 6.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

The PRISMA flow diagram in Figure 4 and the accompanying text refer to both published and unpublished studies.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in Table 7 and Table 8.

The initial and updated SLRs identified a total of ten published records and 12 unpublished records.

Details of published and unpublished studies are provided in Table 7 and Table 8, respectively, and summarised below.

9.3.1.1 Published studies

The pivotal trial is Study 301/302, which compared VN with BSC, in line with the decision problem (Table 1):

- One primary reference and five secondary references.

The other published study is a Phase 1 safety study (Study 101/102) which did not include a comparator arm:

- Study 101 – one primary reference and five secondary references.
- Study 102 – one primary reference and four secondary references.

9.3.1.2 Unpublished studies

Results of the continuation phase of Study 301/302, in which control patients crossed over to the intervention arm, are not yet published. Five references were identified which provide data from this study.

Table 7: List of relevant published studies

Study name (NCT ID)	Primary study reference	Secondary study references	Population	Intervention	Comparator
Study 301 (NCT00999609)	Russell et al 2017 [4] *Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial*	[19, 132-135]	Patients with a molecular diagnosis (or confirmation of diagnosis) of biallelic RPE65 mutations	Bilateral subretinal injection of VN	BSC†
Study 102 (NCT01208389)	Bennett et al 2016 [17] *Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial*	[18, 136-138]		Subretinal injection of VN in the contralateral eye previously untreated in Study 101	N/A
Study 101 (NCT00516477)	Maguire 2009 [16] *Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial*	[14, 139-142]		Unilateral subretinal injection of VN	N/A

Abbreviations: BSC, best supportive care; NCT ID, National Clinical Trial identifier; RPE65, retinal pigment epithelium 65 kDa protein; VN, voretigene neparvovec.

†After Year 1 patients in the control (BSC) arm switched over to receive voretigene neparvovec. This unpublished continuation phase is known as Study 302 – details are provided in Table 8.

Table 8: List of relevant unpublished studies

Study name	Data sources	Population	Intervention	Comparator
Study 302 (continuation phase of Study 301)	Maguire 2017 [143] *Phase 3 trial update of voretigene neparvovec in biallelic RPE65 mutation-associated inherited retinal disease*	Patients with a molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations	Bilateral subretinal injection of VN	N/A[†]
	Russell 2017 [144] *Two-Year Results for a Phase 3 Trial of Voretigene Neparvovec in Biallelic RPE65-mediated Inherited Retinal Disease*			
	Russell 2018 [145] *Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation–associated inherited retinal disease*			
	Leroy 2018 [146] *Year 3 Results and Age-Stratified Analyses for a Phase 3 Trial of Voretigene Neparvovec in RPE65 Mutation–Associated Inherited*			
	Maguire 2018 [147] *PA074 Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial*			

Abbreviations: RPE65, retinal pigment epithelium 65 kDa protein; VN, voretigene neparvovec.
[†]Study 302 is the continuation phase of Study 301/302 in which patients from the control arm switched over to receive VN.

9.3.2 State the rationale behind excluding any of the published studies listed in Table 7 and Table 8.

No studies listed in Table 7 and Table 8 were excluded.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies. A separate table should be completed for each study.

9.4.1.1 Study 301/302 (Phase 3) methodology

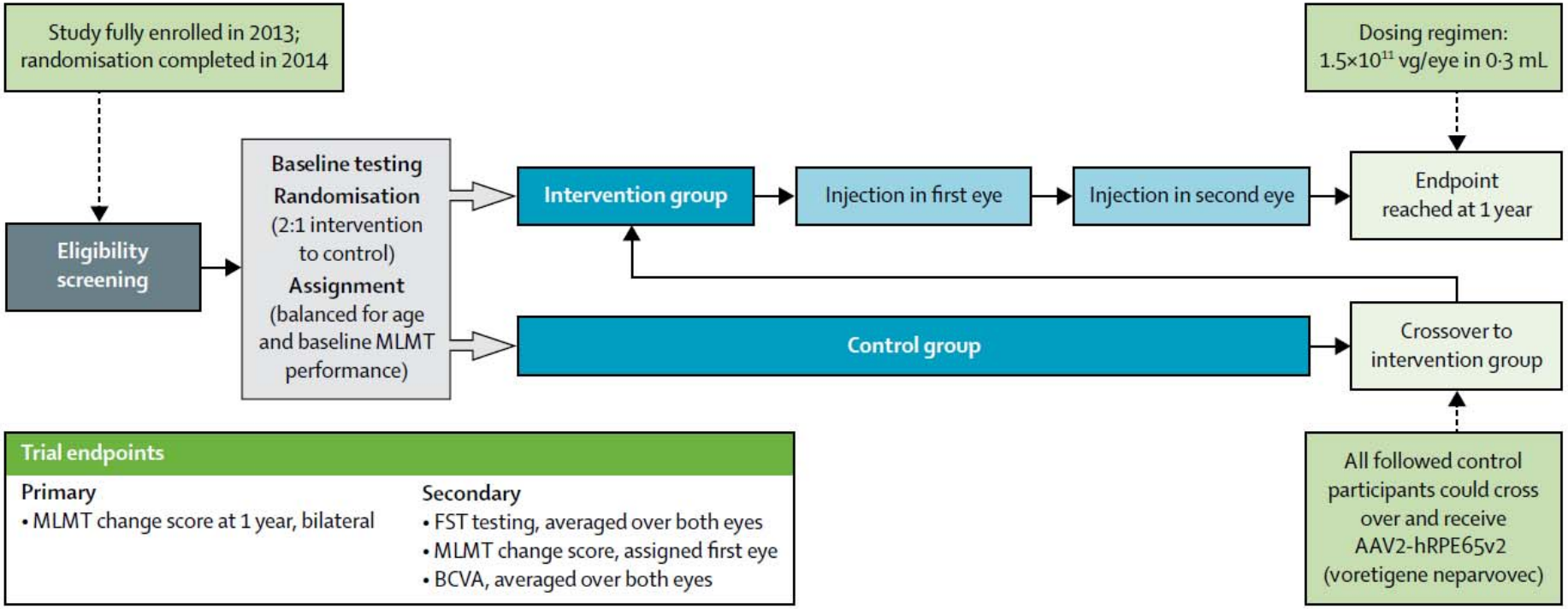
Study 301/302 was a Phase 3 randomised controlled trial assessing the safety and efficacy of sequential bilateral administration of VN versus BSC [4]. The two arms of the trial were:

- Original Intervention arm – these patients received sequential bilateral treatment with VN at the start of the study.
- Control/Delayed Intervention arm – these patients served as a control group for the first year of the study, before crossing over to receive treatment.

The continuation phase in which Control/Delayed Intervention patients were treated is referred to as Study 302.

Figure 5Figure 5: summarises the design of Study 301/302. Table 9 summarises the trial methodology and is followed by a discussion on the selection of endpoints for the trial.

Figure 5: Design of Study 301/302



Abbreviations: BCVA, best-corrected visual acuity; FST, full-field light sensitivity threshold; MLMT, multi-luminance mobility test; vg, vector genomes.
Source: Russell 2017 [4]

Table 9: Summary of methodology for Study 301/302

Study name	A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)
Objectives	**Primary objective:** to determine whether non-simultaneous, bilateral subretinal administration of AAV2-hRPE65v2 improved the ability to navigate (as measured by mobility testing) in adults and children, three years of age or older, with LCA† due to *RPE65* mutations **Secondary objective:** to continue to assess the safety and tolerability of AAV2-hRPE65v2 administrations
Location	The Children's Hospital of Philadelphia, Philadelphia and University of Iowa Hospitals and Clinics, Iowa City
Design	Phase 3, open-label randomised controlled trial
Duration of study	1 year (primary endpoint); 15 year follow-up for long-term safety and efficacy
Sample size	31
Power	The simulated power to detect a clinically meaningful difference was greater than 99%, based on a type I error rate of 0.05.
Sample size calculation	Power calculations were based on randomisation of 24 patients (16 in intervention group and 8 in control group). Greater than 50% of intervention patients were expected to demonstrate improvement in navigational ability as assessed by mobility testing. The control group was assumed to have a mean change of zero because of the potential for a learning effect despite the degenerative nature of the condition. A change score of 1 was considered a clinically meaningful change between baseline and Year 1. Assuming 16 intervention patients and 8 controls with no change, the simulated power to detect a clinically meaningful difference using a Wilcoxon rank sum test is nearly 100%.
Inclusion criteria	• Molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations • Three years of age or older • BCVA worse than 20/60 (both eyes) **and/or** visual field less than 20º in any meridian (both eyes) • Sufficient viable retinal cells as defined by: o an area of retina within the posterior pole of > 100 µm thickness as shown on OCT; o ≥ 3 disc areas of retina without atrophy of pigmentary degeneration within the posterior pole based on ophthalmoscopy; **or** o remaining visual field within 30º of fixation.

	• Ability to perform mobility testing (primary efficacy endpoint) at Screening within the luminance range evaluated in the study: o by receiving an accuracy score of ≤ 1 at 400 lux (maximum light level); **and** o by being unable to pass mobility testing at 1 lux (minimum light level).
Exclusion criteria	• Prior participation in a study in which a gene therapy vector was administered • Use of high-dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months • Prior intraocular surgery within six months • Sensitivity to medications planned for use in the peri-operative period • Pre-existing eye conditions or complicating systemic diseases (in which the disease itself or treatment of it could alter ocular function) that would preclude the planned surgery or interfere with study interpretations • Pregnancy or unwillingness to use effective contraception for four months following vector administration • Inability to perform mobility testing (primary efficacy endpoint) for reasons other than poor vision, including physical and attentional limitations • Any other condition that would not allow the patient to complete follow-up examinations or, in the opinion of the investigator, makes the patient unsuitable for the study
Method of randomisation	Patients were stratified by age (≥ 10 years vs < 10 years) and Screening mobility testing passing level (pass at ≥ 125 lux vs < 125 lux) and randomised (2:1) to the Intervention or Control group. Within each age and mobility testing stratum, randomised blocks (block size 3) governed the allocation to treatment group.
Method of masking	The study was open-label because the use of sham surgery for the control group was not considered ethical. Mobility testing, home orientation and mobility assessments were graded by independent assessors masked to treatment assignment and test sequence.
Intervention (N = 21)	Subretinal injection of 1.5 x 10^{11} vg AAV2-hRPE65v2 (voretigene neparvovec) in each eye.
Comparator (N = 10)	Untreated for at least one year from baseline. After one year control patients were eligible to receive the intervention.
Baseline differences	Patient demographics were well-matched across the two groups (see Section 9.4.3). At baseline patients completed the mobility test. [redacted] patients in the intervention group passed the test at 4 lux compared to [redacted] in the control

	group. Details of patient demography and baseline MLMT performance are provided in Appendix 6.
Duration of follow-up, lost to follow-up information	Patients were followed up for the primary endpoint for one year post-administration (intervention) or post-baseline (control). Retinal and visual function analysis, including mobility testing, was performed at 30 days, 90 days, 180 days and 1 year. No patients were lost to follow-up however two patients withdrew prior to knowledge of treatment allocation. Annual visits will be conducted for 15 years post-administration to assess long-term safety and therapeutic effects.
Statistical tests	The ITT populations were used for statistical analyses. The ITT populations included all patients who were allocated to intervention or control, including the two patients (one from each group) who withdrew prior to knowledge of treatment allocation. • Primary endpoint o Non-parametric permutation test based on a Wilcoxon rank-sum o Tested at a two-side Type I error rate of 0.05 o Two-sided confidence intervals • Secondary endpoints o For monocular mobility testing the same method was used as for the primary endpoint o For FST and VA analysis was performed based on longitudinal models that provided estimates of the difference between baseline and Year 1. The secondary outcomes were only to be formally tested statistically if the primary outcome was statistically significant. Statistical significance of the secondary outcomes was performed in a hierarchical manner to maintain control of Type I error rate: 1. If the primary outcome was statistically significant, FST was to be tested. 2. If FST was statistically significant, monocular mobility change score was to be tested. 3. If monocular mobility change score was statistically significant, VA was to be tested. All secondary endpoints were tested at a two-sided Type I error rate of 0.05
Primary outcomes (including scoring methods and timings of assessments)	**Change in bilateral mobility test performance at Year 1 relative to baseline** • Patients were assigned scores based on the minimum light level at which they were able to pass the test. The change score was calculated as the difference in score between baseline and Year 1. • Tests were videotaped and performance was assessed by independent trained assessors who were masked to treatment allocation and sequence

	(e.g. whether a video was from a baseline visit or follow-up visit). Patients passed the test if they completed the course in three minutes or less with fewer than four errors. Assessments were performed at baseline and one year post-administration to second eye.
Secondary outcomes (including scoring methods and timings of assessments)	**Change in white light FST averaged over both eyes at Year 1 relative to baseline** • Full-field light sensitivity threshold testing determines the minimum luminance at which patients reliably perceive light. The test is performed separately for each eye (with the other patched) and the average score from both eyes is calculated. • The unit of measurement, dB, was converted to Log10(cd.s/m^2). More negative Log10(cd.s/m^2) values indicated better sensitivity. Assessments were performed at baseline, Day 30, Day 90, Day 180 and Year 1 post-administration.
	Change in assigned first eye MLMT performance at Year 1 relative to baseline • Scoring and timing of assessments were the same as the primary endpoint.
	Change in BCVA averaged over both eyes at Year 1 relative to baseline • BCVA was measured using age-adapted tests, such as ETDRS and HOTV testing to document changes in central vision, determined by the ability to resolve standard optotypes/letters corresponding to different visual angles. • Results are presented in LogMAR units. A 0.1 improvement in LogMAR corresponds to a 5-letter improvement on a standard eye chart. Assessments were performed at baseline, Day 30, Day 90, Day 180 and Year 1 post-administration.

† Although LCA is mentioned, patients were eligible if they had molecular diagnosis (or confirmation of diagnosis) of biallelic RPE65 mutations i.e. regardless of clinical diagnosis.
Abbreviations: BCVA, best-corrected visual acuity; dB, decibels; cd.s/m^2, candela seconds per meter squared; ETDRS, Early Treatment Diabetic Retinopathy Study; FST, full-field light sensitivity threshold; ITT, intention-to-treat; LCA, Leber congenital amaurosis; LogMAR, logarithm of the minimum angle of resolution; MLMT, multi-luminance mobility testing; OCT, optical coherence tomography; RPE, retinal pigment epithelium; RPE65, retinal pigment epithelium 65 kDa protein; VA, visual acuity; vg, vector genomes.
Source: Russell 2017 [4]; Study 301 CSR [19].

9.4.1.1.1. Requirement for a novel primary efficacy endpoint (MLMT)

The primary and secondary endpoints used in Study 301/302 were selected to enable evaluation of change in visual function and functional vision (defined as the ability to conduct visually dependent activities of daily living independently).

No treatments are currently available for *RPE65*-mediated IRD [1], so no precedents exist for endpoints to assess the therapeutic benefits of products for this unique group of diseases.

Traditional endpoints such as VA and VF are challenging to measure in this population because baseline visual function is poor (and can only deteriorate further), and they do not capture characteristic features of the condition such as night blindness (nyctalopia), reduced light sensitivity and nystagmus. There is potential for important benefit following treatment with respect to activities of daily living through improvements in these symptoms, however previously used obstacle courses that assess functional vision [148, 149] would be unable to capture this as they do not implement variable lighting. For example, a patient with nyctalopia may be able to complete a well-lit obstacle course but this would not identify their inability to navigate under low-light conditions or a change in this ability following treatment.

Another requirement for a novel efficacy endpoint to capture these benefits was that it could be performed in a paediatric population, as the symptoms of *RPE65*-mediated IRD appear in the first few months of life in some patients (see Section 6.1.3). The youngest patient in Study 301/302 was four years old [4].

In the context of these condition-specific features and the need for a clinically meaningful endpoint, the MLMT instrument was designed, with input from the FDA, and validated in a validation study [21]. The MLMT integrates aspects of light sensitivity, VF and VA, and measures functional vision in a quantitative and standardised manner at specified light levels. Change in MLMT performance from baseline to Year 1 was the primary endpoint of the study.

Use of the MLMT in the Phase 1 studies supports its use as an outcome measure, and the validation study confirmed its ability to identify a range of vision in low-vision patients, to distinguish them from normal-vision patients, and to track changes in functional vision over time. The test was scored by graders masked to treatment allocation and sequence (i.e. they were not told if a video showed a baseline test or a test performed one year post-

administration). Inter-grader agreement was 97.9%, demonstrating strong reliability. The test reflects aspects of VA and VF, as MLMT performance declined markedly below particular VA and VF thresholds [21].

Separate outcome measures for VA, VF and light sensitivity assessed visual function, and a visual function questionnaire (VFQ) assessed patients' perspective of their ability to perform vision-related tasks.

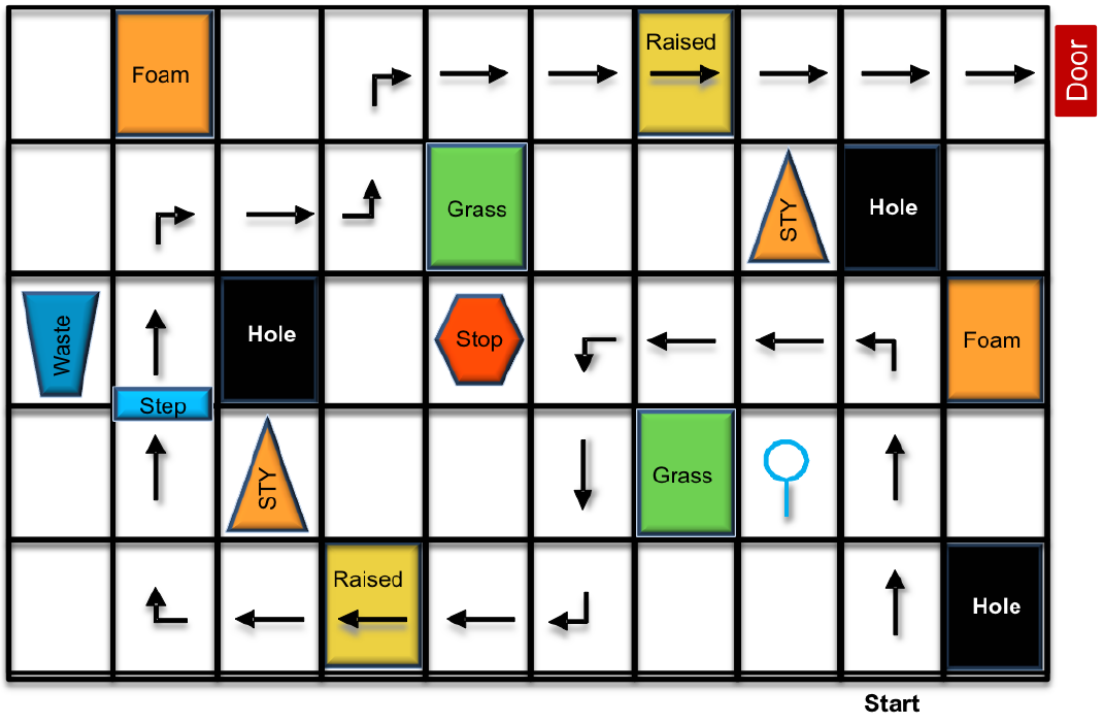
9.4.1.1.2. Bilateral MLMT change score (primary endpoint)

9.4.1.1.2.1. Procedure

The primary endpoint of Study 301/302 was performance on the multi-luminance mobility test (MLMT), measured by a change score one year following vector administration relative to patients' pre-administration MLMT performance. The MLMT measures functional vision in a quantitative and standardised manner at specified light levels. It was designed, with input from the FDA, to evaluate the ability of a subject to navigate a marked path, while avoiding obstacles, and relying on vision rather than kinaesthetic input.

Patients are asked to follow arrows on the floor whilst avoiding obstacles, traversing steps and identifying a door at the end of the course. Twelve course configurations of equal difficulty exist to reduce the risk of a learning effect when a patient repeats the test. One of these configurations is shown in Figure 6.

Figure 6: MLMT course layout (1 of 12 configurations†)



† The figure presents the layout of 1 of the 12 possible configurations. Obstacles include two raised steps with arrows (2 inches high), two grass tiles, three black tiles representing holes, two elevated foam blocks (4.5 inches high), two Styrofoam (STY) cones, one stop sign (adjustable from 40 inches to 72 inches high), one step-over obstacle (9 inches high), one waist-high obstacle (represented by the blue tree, 27 inches high), and one waste basket (13 inches high) [21].
Source: Chung 2018 [21]

The test is conducted at seven light levels, ranging from 1 to 400 lux. It was important to include varying light levels, as patients with *RPE65*-mediated IRD experience progressive loss of night vision, in addition to loss of VF and VA.

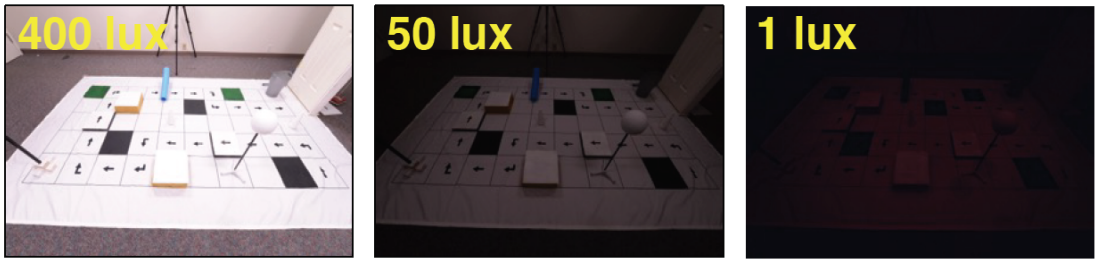
This reflects the range of light levels that might be experienced in day to day life in different environments (see Table 10 and Figure 7). Improvements in functional vision at lower light levels may indicate the potential to gain the ability to perform additional activities of daily living, thus improving quality of life and independence.

Table 10: Light levels and associated scores in the MLMT

Light level (lux)	Score	Examples
1	6	• Moonless summer night • Indoor night-light
4	5	• Cloudless summer night with half-moon • Outdoor parking lot at night • Inside a plane on a night flight
10	4	• 60 minutes after sunset in a city setting • Bus stop at night
50	3	• Outdoor train station at night • Inside of illuminated office stairwell
125	2	• 30 minutes before sunrise • Interior of a shopping centre, train, or bus at night
250	1	• Interior of a lift, library or office hallway
400	0	• Office environment or food court
> 400	-1	-

Abbreviations: MLMT, multi-luminance mobility test.

Figure 7: Example MLMT lighting conditions



Abbreviations: MLMT, multi-luminance mobility test.
Source: Chung 2017 [133]

Patients are dark-adapted for 40 minutes, and tested under at least two lighting conditions for each eye and then with both eyes open, to determine the minimum light level at which they can pass the test. The course is reconfigured between each run to minimise the impact of potential learning effect [19].

Patients are assigned a score corresponding to the minimum light level they are able to pass the test at – lower light levels are associated with higher scores.

Success or failure on the course is determined by independent graders masked to treatment allocation. Tests are filmed and anonymised, and graders determine the number of collisions and time to complete the test to assign scores for speed and accuracy.

In order to pass, patients must complete the course in < 180 seconds, and with an accuracy score of ≤ 0.25 (the accuracy score being determined by dividing the number of collisions by the total number of obstacles).

The MLMT test was performed at baseline (to identify the minimum lighting level at which a patient could pass), and on Days 30, 90, 180, and Year 1 post-administration to the second eye. The change in bilateral MLMT score between baseline and Year 1 was used to calculate primary endpoint results. The change score for the first-treated eye was reported as a secondary endpoint.

9.4.1.1.2.2. Clinical significance

An improvement in ability to ambulate is *prima facie* clinically meaningful; the use of mobility testing as the primary efficacy endpoint bypasses surrogate markers of useful vision and directly demonstrates clinical benefit [19].

The ability to navigate at different levels of environmental illumination relates to the patients' extent of VF and to light sensitivity, both functions specifically affected in patients with *RPE65*-mediated IRD. The MLMT integrates aspects of VA and VF, as test performance declined markedly below particular VA and VF thresholds in a validation study [21].

9.4.1.1.3. Full-field light sensitivity threshold (FST) testing (secondary endpoint)

To assess the effect of treatment on nyctalopia, which is experienced by the vast majority of patients (see Section 6.1.3), FST testing formed one of the secondary endpoints of the study. The test measures the threshold of light brightness that can be seen, with lower thresholds equating to higher sensitivity reflective of increased photoreceptor function.

This test determines the light sensitivity of the entire visual field by recording the luminance at which a patient reports seeing the dimmer flash. Patients are seated in front of a Ganzfeld dome in which light flashes are generated. A sound is generated at the time of the flash, and the patient indicates whether or not they saw the flash using buttons. Flashes of varying luminance are presented

in a random order allowing the algorithm to calculate the minimum luminance at which the patient reliably perceives light.

Average FST score calculated following separate testing for each eye (with the other patched) formed the secondary endpoint, with individual eye FST as supportive analyses. More negative Log10(cd.s/m^2) values indicate better sensitivity.

9.4.1.1.4. Monocular mobility testing change score (secondary endpoint)

The same method was used as for the primary endpoint. Patients wore a patch over the second assigned eye (i.e. the second eye to receive treatment with VN) to assess performance using the first assigned eye.

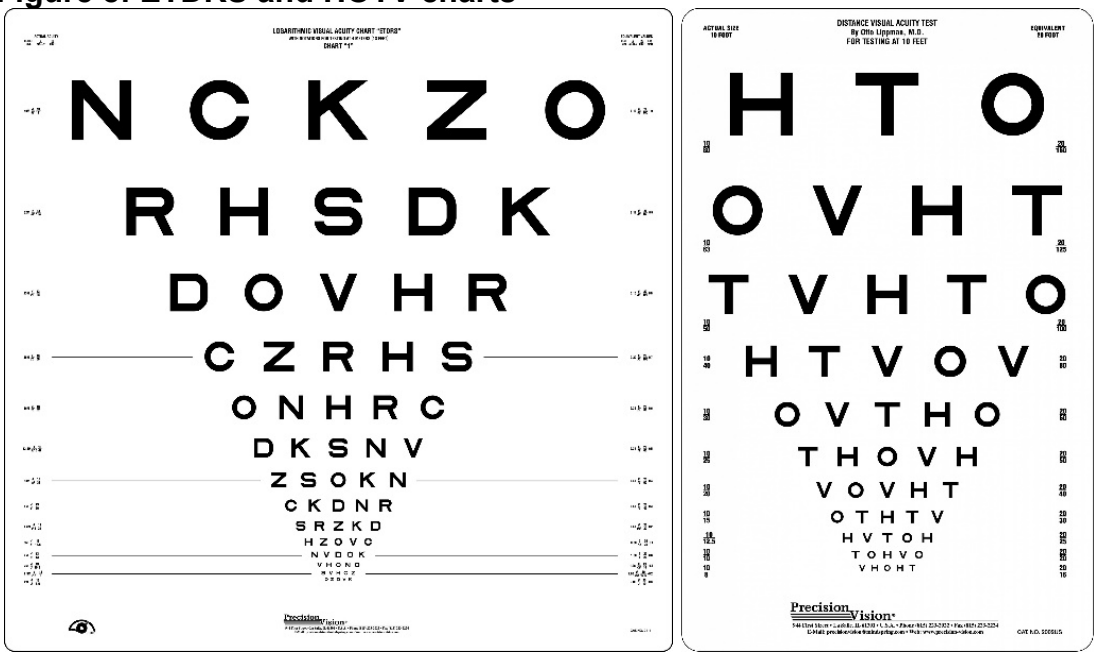
9.4.1.1.5. Visual acuity (secondary endpoint)

Visual acuity is defined as the reciprocal of the ratio between the letter size that can be recognised by a patient, relative to the size recognised by the standard eye – if a patients requires letters that are twice as large or twice as close, the visual acuity is said to be 1/2.

Visual acuity in adults was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) test, which measures VA in LogMAR units. However, it is not suitable for young children [150], who were instead assessed using the HOTV test, featuring four letters (H, O, T & V) centring around a vertical axis – this is useful as young children may reverse the appearance of objects [19]. The Snellen scale used in HOTV testing was converted to the LogMAR scale to enable comparison. The following equation can be used to determine the LogMAR equivalent of a given Snellen score (for example a Snellen score of 6/60 is equivalent to a LogMAR of 1):

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

Figure 8: ETDRS and HOTV charts



Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study.
Source: www.precision-vision.com

For comparison purposes the results of these tests were converted to logarithm of the minimum angle of resolution (LogMAR) units. Smaller values indicate better visual acuity. A 0.1 improvement in LogMAR corresponds to a 5-letter improvement (equivalent to one line) on a standard eye chart (see Figure 8:). The reference value above which people are considered to have normal visual acuity is called 20/20 vision (LogMAR 0) (i.e. at a distance of 20 feet they are able to separate contours that are 1.75 mm apart).

Off-chart measurements were performed for patients who were unable to read any letters on the chart. The scale adapted from Holladay was used to determine visual acuities for the ability to count fingers and hand motion [151]:

- Patients able to count fingers at 20 feet have approximately 20/200 vision (LogMAR -1.00)
- Patients able to detect hand motion are regarded as having 10 times (1 log-unit) worse visual acuity than someone who can count fingers at the same distance (20/2000 vision, equivalent to a LogMAR of -2.00)

- An alternative scale described by Lange et al [152] reduces the step between count fingers and hand motion to 0.3 log-units. This scale was used in a post-hoc analysis (see Section 9.6.1.1.4).

Average VA based on the VA of each eye formed the secondary endpoint. Supportive analyses used the VA of individual eyes, and a post-hoc analysis used the Lange scale (described above) as requested by the EMA and the study's Data and Safety Monitoring Board (Section 9.6.1.1.4).

9.4.1.1.6. Visual field (exploratory endpoint)

Visual field testing was performed to evaluate the effect of treatment with VN on the function of different regions of the retina. This endpoint is of relevance to the decision problem (Table 1) and visual field loss is one of the key symptoms of the condition (see Section 6.1.3). Visual field testing was not chosen as a primary or secondary endpoint due to the unique attributes of the study population, including nystagmus, which can lead to indeterminate results. However, the effect of treatment on VF is captured in the primary and secondary endpoints through MLMT and FST testing.

Analyses were performed using Goldmann kinetic perimetry testing (which evaluates the extent to which a patient can see from a central point of fixation) and Humphrey static VF analysis (which assesses function of specific domains within the visual field).

Goldmann kinetic perimetry testing is considered more relevant for *RPE65*-mediated IRD, which primarily affects rod photoreceptors that facilitate peripheral and low-light vision. Humphrey VF macula threshold testing targets the central 4 degrees of field, while foveal sensitivity testing targets the most central, cone-enriched region of the macula.

In Goldmann kinetic perimetry testing a dome-shaped white screen is positioned in front of the patient. Each eye is tested individually. The patient indicates when light moving from the periphery to the centre is detected in the visual field. The test can be conducted using different stimulus sizes and

intensities. The III4e stimulus is more sensitive than V4e, being 1/16th smaller in total area and 1/4 the diameter.

Humphrey VF static perimetry testing is performed using an automated analyser. Fixed light sources serve as a visual stimulus, which vary in luminance. A computer algorithm varies the luminance to determine the field of vision.

Results of Goldmann testing are presented as sum total degrees, with higher values representing larger fields of vision. Humphrey testing results are presented in decibels (dB) with a higher dB value representing more sensitive (better) vision in that location of the retina.

9.4.1.1.7. Contrast sensitivity (exploratory endpoint)

Contrast sensitivity defines the threshold between the “visible” and the “invisible” [153]. In Study 301/302 testing was performed using the Pelli-Robson chart, which displays horizontal lines of capital letters with decreasing contrast. The test was not performed for children unable to recognise letters of the alphabet.

9.4.1.1.8. Visual function questionnaire (exploratory endpoint)

This visual function questionnaire (VFQ) was prepared to serve as a patient-reported outcome (PRO) that evaluates the activities of daily living that are dependent on vision, or have a vision element. The questionnaire was modified to accommodate both individuals with extremely poor vision and a paediatric population.

The VFQ was completed by the patients (or by the parents/guardians of paediatric patients) at baseline, days 30, 90 and 180, and year 1. 25 questions (Appendix 7) were included requiring numerical answers ranging from 0 (worst vision) to 10 (best vision).

A retrospective validation exercise was performed to assess the psychometric validity of the questionnaire [154]. The questionnaire was shown to have good construct validity and to be sensitive to change over time, providing evidence

of improvements in patient and caregiver/patient reported functional vision scores following treatment.

9.4.1.2 Study 101/102 methodology

9.4.1.2.1. Study 101 methodology

Study 101 was a Phase 1 dose escalation safety study, in which patients received one of three doses of VN to one eye [16].

Table 11: Summary of methodology for Study 101

Study name	A Phase 1 Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE)
Objective	**Primary objective:** To determine the safety and tolerability of subretinal administration of voretigene neparvovec to patients with LCA† due to *RPE65* mutations **Secondary objective:** To assess the objective clinical measures of efficacy in human patients
Location	The Children's Hospital of Philadelphia, Philadelphia (administration site) and Second University of Naples, Department of Ophthalmology, Naples, Italy (referral/follow-up site for five patients from September 2007 through June 2011)
Design	Open-label dose-escalation safety study
Duration of study	2 years
Patient population	Adults and children with inherited retinal degeneration with a molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations
Sample size	12
Sample size determination	The sample size was based on the principle that the number of patients exposed to potential risks in a Phase 1 study should be minimised. Three patients per dose cohort is a typical design for early phase gene transfer protocols, however three additional patients were added to the middle dose group after preliminary evaluation of the first six patients injected.
Inclusion criteria	• Willingness to adhere to protocol and companion protocol for long-term follow-up as evidenced by written informed consent or parental permission and patient assent. • Adults and children diagnosed with LCA. • Molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations by a Clinical Laboratory Improvement Amendments of 1988 (CLIA)-certified laboratory.

	• Age eight years old or older at the time of administration. • Visual acuity ≤ 20/160 or visual field less than 20° in the eye to be injected.
Exclusion criteria	• Participation in a clinical study with an investigational drug in the past six months • Pre-existing eye conditions that would preclude the planned surgery or interfere with interpretation of study endpoints • Lack of sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy: o If indirect ophthalmoscopy reveals less than one disc area of retina which is not involved in complete retinal degeneration, these eyes will be excluded o In eyes where OCT scans of sufficient quality can be obtained, areas of retina with thickness measurements < 100 µm, or absence of neural retina will not be targeted for delivery of AAV2-hRPE65v2 • Complicating systemic diseases or clinically significant abnormal baseline laboratory values. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. • Prior intraocular surgery within six months • Sensitivity to medications planned for use in the peri-operative period • Pregnancy or unwillingness to use effective contraception for the duration of the study • Any other condition that would not allow the patient to complete follow-up examinations or, in the opinion of the investigator, makes the patient unsuitable for the study • Presence of neutralising antibodies to AAV2 above 1:1000
Intervention(s) (N = 12) and comparator(s) (N = 0)	**Intervention:** subretinal injection of 1.5 x 10^{10} vg (low dose), 4.8 x 10^{10} vg (middle dose) or 1.5 x 10^{11} vg (high dose) of AAV2-hRPE65v2 into one eye. Comparator: N/A
Baseline differences	N/A (single arm)
How were patients followed-up (for example, through pro-active follow-	Patients were pro-actively followed up. Scheduled study visits included: screening visit, two baseline visits, administration visit (Day 0), and follow-up visits on Days 1, 2, 3, (and 7 if ocular inflammation was present at day 3), 14, 30, 60, 90, 180, 270, 365 and Years 1.5 and 2 to 5.

up or passively). Duration of follow-up, patients lost to follow-up	
Statistical tests	• Descriptive statistics (mean, SD, median, minimum and maximum values) were tabulated for the study population. • Number and percentage by dose cohort for categorical data, mean, median, range, SD and N for continuous data were presented for each of the evaluable parameters for change from baseline and value at each time point. • AEs and SAEs were summarised by dose cohort, and clinical laboratory values were summarised by time point, patient and dose cohort. • Values and changes from baseline at each time point were tabulated.
Primary outcomes (including scoring methods and timings of assessments)	**Determination of safety and tolerability of treatment through:** • Physical examination with vital signs • AE recording • Concomitant medications • Serum chemistries and haematology • Serum for AAV and RPE65-specific neutralising antibodies and antigen-specific reactivities • Peripheral blood and tear qPCR to detect vector spread • Serial ophthalmic exams • Direct and indirect ophthalmoscopy Assessments were performed at the two baseline visits, administration visit (Day 0), and follow-up visits on Days 1, 2, 3, 14, 30, 60, 90, 180, 270, 365 and Years 1.5 and 2 to 5. Not all assessments were performed at each visit.
Secondary outcomes (including scoring methods and timings of assessments)	**Change in visual function as measured by subjective, psychophysical tests and objective, physiologic tests:** • VA testing • VF testing (Goldmann perimetry) • ERG • Contrast sensitivity • Colour vision testing • Pupil function testing • Mobility testing • Ocular motility measurements Assessments were performed at the two baseline visits, administration visit (Day 0), and follow-up visits on Days 1, 2, 3,

	14, 30, 60, 90, 180, 270, 365 and Years 1.5 and 2 to 5. Not all assessments were performed at each visit.

† Although LCA is mentioned, patients were eligible if they had molecular diagnosis (or confirmation of diagnosis) of biallelic RPE65 mutations i.e. regardless of clinical diagnosis.
Abbreviations: AAV, adeno-associated virus type 2; AE, adverse event; ERG, electroretinogram; LCA, Leber congenital amaurosis; OCT, optical coherence tomography; qPCR, quantitative polymerase chain reaction; RPE65, retinal pigment epithelium 65 kDa protein; SAE, serious adverse event; SD, standard deviation; VA, visual acuity; VF, visual field; vg, vector genomes.
Source: Maguire 2009 [16]; Study 101 CSR [14].

9.4.1.2.2. Study 102 methodology

Study 102 was a follow-on study to the Phase 1 dose-escalation study. Patients received injections in the eye that was not treated in Study 101 [17].

Table 12: Summary of methodology for Study 102

Study name	A Follow-On Study to Evaluate the Safety of Readministration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects with Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study
Objective	**Primary objective:** To assess the safety and tolerability of non-simultaneous, bilateral subretinal administration of voretigene neparvovec **Secondary objective:** To evaluate the efficacy of contralateral eye administration of voretigene neparvovec, using pre-injection measurements of the eye to be injected as a control
Location	The Children's Hospital of Philadelphia, Philadelphia
Design	Open-label safety study
Duration of study	1 year
Patient population	Patients who had participated in Study 101 and met eligibility criteria for this trial.
Sample size	11
Sample size determination	The sample size was chosen based on the initial Phase 1 study (Study 101). 12 patients received the intervention in Study 101 and all of them were considered for inclusion in this study. One patient was not eligible (see Section 9.4.6).
Inclusion criteria	• Prior participation in the initial Phase 1 study (Study 101) • Visual acuity equal to or greater than light perception • Sufficient viable retinal cells in the contralateral, previously uninjected eye, as determined by non-invasive means such as OCT and/or ophthalmoscopy. Must have:

	○ an area of retina within the posterior pole of > 100 µm thickness as shown on OCT; ○ ≥ 3 disc areas of retina without atrophy of pigmentary degeneration within the posterior pole; **or** ○ remaining visual field within 50º of fixation. • Willingness to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and patient assent (where applicable)
Exclusion criteria	• Participation in a clinical study with an investigational drug in the past six months • Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme (individuals who discontinue use of these compounds for 18 months may become eligible) • Prior intraocular surgery within six months • Sensitivity to medications planned for use in the peri-operative period • Pre-existing eye conditions, such as glaucoma, or complicating systemic diseases that would preclude the planned surgery or could interfere with the interpretation of the study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. • Pregnancy or unwillingness to use effective contraception for four months following vector administration • Any other condition that would not allow the patient to complete follow-up examinations or, in the opinion of the investigator, makes the patient unsuitable for the study
Intervention(s) (N = 11) and comparator(s) (N = 0)	**Intervention:** subretinal injection of 1.5 x 10^{11} vg of AAV2-hRPE65v2 into the previously uninjected, contralateral eye Control: N/A
Baseline differences	N/A (single arm)
How were patients followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, patients lost to follow-up	Patients were pro-actively followed-up, although the timing of follow-up depended on which part of the study they were enrolled in. Part 1 involved three eligible patients with a minimum eight week interval between vector administrations. These patients were followed at least weekly through this time period, with particular attention paid to ocular toxicities and immunological responses. All Part 1 patients were evaluated through Week 8 before proceeding to Part 2. Part 2 involved up to nine eligible patients remaining from Study 101.

	The visit schedule for Part 1 patients was as follows: Day 1, Day 2, Day 3, Week 1, Weeks 2–8, Day 90, Day 180, and Year 1. The visit schedule for Part 2 patients was as for Part 1, but without visits at Weeks 3 and Weeks 5–8.
Statistical tests	• Descriptive statistics (mean, SD, median, minimum and maximum values) were tabulated for the study population. • Number and percentage by dose cohort for categorical data, mean, median, range, SD and N for continuous data were presented for each of the evaluable parameters for change from baseline and value at each time point. • AEs and SAEs were summarised by dose cohort, and clinical laboratory values were summarised by time point, patient and dose cohort. • Values and changes from baseline at each time point were tabulated.
Primary outcomes (including scoring methods and timings of assessments)	**Determination of safety and tolerability of the study drug through:** • Recording all AEs and concomitant medications • Physical examinations including vital signs • Pre and post-administration serum chemistry including liver function and renal function panels and urinalysis • Immunology studies for AAV antibodies and antibodies for *RPE65* • PBMCs using ELISPOT assay for cell-mediated immune response • Serial ophthalmic examinations • Peripheral blood and tear PCR Assessments were performed at the two baseline visits, administration day, Days 1–3, Weeks 1–8, Days 90 and 180 and Year 1. Not all assessments were performed at each visit.
Secondary outcomes (including scoring methods and timings of assessments)	**Evaluation of the efficacy of the study drug by assessing change in visual/retinal function through subjective, psychophysical and objective, physiological tests:** • Mobility testing • PLR • FST testing • VA testing • VF testing (Goldmann perimetry) • Contrast sensitivity Assessments were performed at the two baseline visits, administration day, Days 1–3, Weeks 1–8, Days 90 and 180 and Year 1. Not all assessments were performed at each visit.

Abbreviations: AAV, adeno-associated virus type 2; AE, adverse event; ELISPOT, enzyme-linked ImmunoSpot; FST, full-field light sensitivity threshold; OCT, optical coherence

tomography; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PLR, pupillary light response; RPE65, retinal pigment epithelium 65 kDa protein; SAE, serious adverse event; SD, standard deviation; VA, visual acuity; VF, visual field; vg, vector genomes.
Source: Bennett 2016 [17]; Study 102 CSR [18].

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Sources of data used for each study are provided in Table 13. The primary sources of data used in this submission are the primary study publications, supplemented with additional detail from the CSRs.

The continuation phase of Study 301/302 and follow-up data for Study 101/102 are unpublished – the results presented below are from conference abstracts and unpublished data.

Study 302 is the continuation phase of Study 301, in which patients from the Control/Delayed Intervention group received the intervention one year post-baseline. Study 102 is a follow-on to Study 101, in which patients were injected with VN in the contralateral eye.

Table 13: Sources of data used

Study name	Source (reference)	Type
Study 101	Maguire 2009 [16] Study 101 CSR [14] Chung 2019 [155]	Primary study publication Clinical study report Conference abstract
Study 102 (follow-on to Study 101)	Bennett 2016 [17] Study 102 CSR [18] Maguire 2017 [138]	Primary study publication Clinical study report Conference presentation
Study 301	Russell 2017 [4] Study 301 CSR [19]	Primary study publication Clinical study report
Study 302 (follow-on to Study 301)	Maguire 2017 [143] Drack 2019 [156]	Conference presentation Conference presentation

Abbreviations: CSR, clinical study report.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Patient populations and eligibility criteria were very similar between clinical trials. Key inclusion criteria for Studies 101 and 301/302 were a molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations, VA < 20/60, and/or VF < 20 º in the eye(s) to be injected. To be eligible for enrolment in Study 102 (the follow-on study to Study 101), patients were required to have visual acuity equal to or greater than light perception – i.e. if visual acuity had deteriorated below light perception since Study 101 they were not eligible for this follow-on trial.

More stringent criteria were introduced for determining the number of viable retinal cells in Studies 102 and 301/302. In Study 101 patients were eligible if they had ≥ 1 disc area of retina which was not involved in complete retinal degeneration, but in Studies 102 and 301/302 eligible patients were required to have ≥ 3 disc areas of retina without atrophy or pigmentary degeneration.

Study 301/302 introduced MLMT performance as an eligibility criterion as this formed the primary endpoint of the study. Patients were required to be able to perform the MLMT within the luminance range evaluated, but unable to pass at 1 lux, the lowest luminance level tested. Those able to pass at 1 lux at screening were considered too close to normal function with respect to ability to navigate in dim light, and those unable to perform the course at screening with an accuracy score ≤ 1 at the highest illumination (400 lux) were considered to have extensive disease progression such that they are less likely to achieve measurable, clinically meaningful benefit [19]. Details of baseline MLMT performance are provided in Appendix 6.

Details of patient demography for each trial are presented in Appendix 6. A large proportion of Study 301/302 trial patients were young children – 64% of randomised patients were under 18, and 42% were under 10 years old [19]. The mean ages of patients were 20.8 (Study 101), 22.8 (Study 102) and 15.1 years (Study 301/302). Study 101 enrolled patients who were ≥ 8 years old (and

these went on to become the Study 102 population), whereas Study 301/302 was open to patients who were ≥ 3 years old.

The proportion of males in the studies was 58% (Study 101), 55% (Study 102) and 42% (Study 301/302). [redacted], whereas in Study 301/302 68% were white, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were black or African American.

Patients in all studies received subretinal injection of VN. The highest dose given in the Study 101 dose escalation study (1.5×10^{11} vg) was used in Studies 102 and 301/302.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

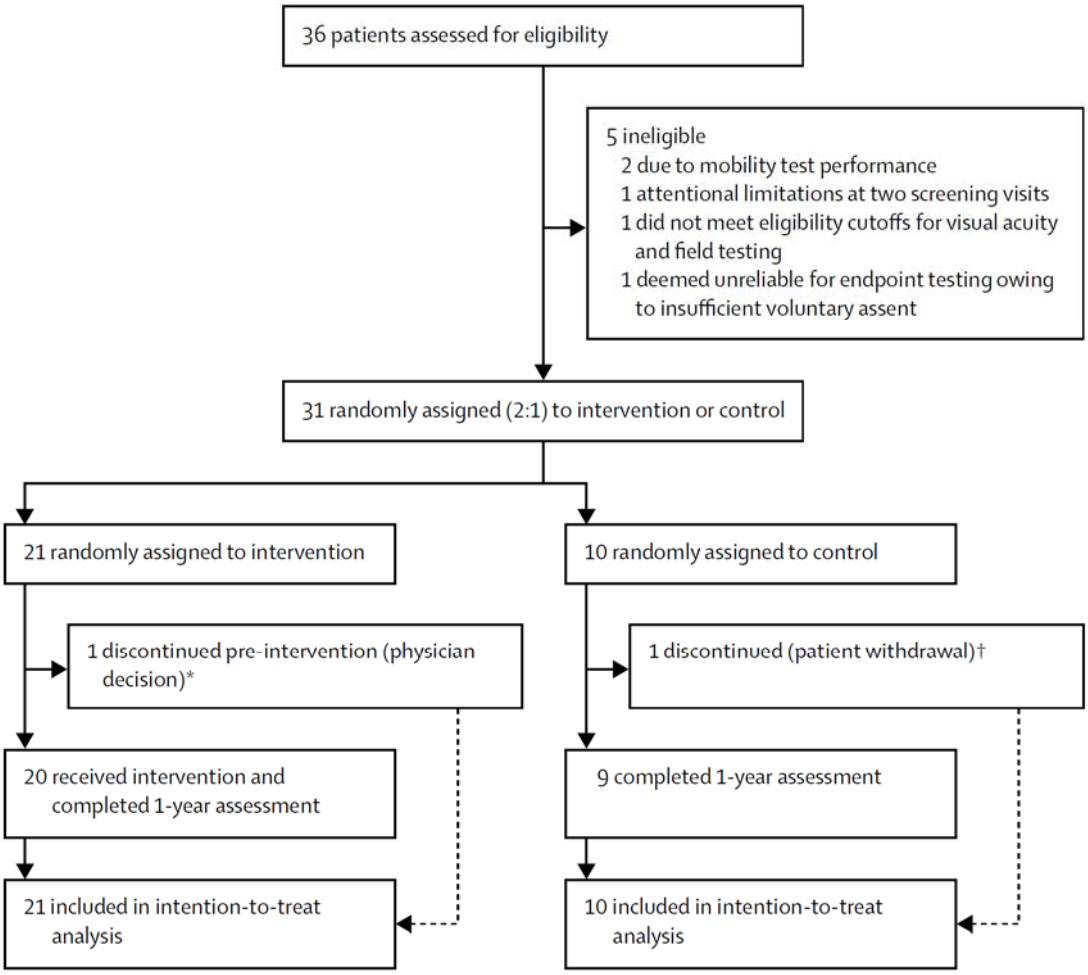
Subgroup analyses were not performed on the basis that performing a subgroup analysis in such a small sample (29 subjects) could lead to misinterpretation of results. No subgroup analyses were prespecified in Study 301/302.

Nevertheless, an exploratory age-stratified analysis (< or ≥ 10 years at time of injection) found that improvements in ambulatory navigation, light sensitivity, visual field and visual acuity did not differ significantly between age groups one year post-treatment (post-hoc; P=0.54, 0.98, 0.94 and 0.084, respectively) [146].

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

A CONSORT flow chart for Study 301/302 is presented in Figure 9.

Figure 9: CONSORT flowchart for Study 301/302



Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ITT, intention-to-treat.
*Baseline optical coherence tomography findings included severe retinal atrophy or degeneration, with an almost complete absence of the photoreceptor layer in the macular area. The discontinuation decision was made before either the participant or the physician had been informed of the treatment assignment.
†The participant discontinued due to personal reasons, and this decision was made before either the participant or the physician had been informed of the treatment assignment.
Source: Russell 2017 [4]

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

No patients were lost to follow-up in any of the clinical trials.

In Study 301/302 one patient withdrew from each arm prior to either the patient or the physician being informed of the treatment assignment. In the intervention group one patient was withdrawn by the physician based on a baseline OCT finding of severe retinal atrophy or degeneration, with an almost complete

absence of the photoreceptor layer in the macular area. One patient in the control arm discontinued for personal reasons.

The ITT population in Study 301/302 includes these two patients (21 in the intervention group and 10 in the control group). The mITT and safety populations were the same, excluding these two patients (20 in the intervention group and 9 in the control group).

One patient from Study 101 was not eligible for Study 102 due to the presence of glaucomatous changes in the eye to be treated [18].

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in Table 14.

Results of the quality assessment for Study 301/302 are presented in Table 14.

Table 14: Critical appraisal of Study 301/302

Study name	A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)	
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	A randomisation list was generated under the direction of the independent party biostatistician using a permuted block design, stratified by age (<10 years and ≥10 years) and baseline mobility testing passing level
Was the concealment of treatment allocation adequate?	No	The use of sham injections in the control group was considered unethical, so participants and investigators were aware of study group assignment
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	The groups were similar in age and sex at screening; baseline MLMT passing level was not completely balanced between the two groups due to the small number of participants

Were the care providers, patients and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Partial	• Open label allocation • Graders assessing primary outcome were affiliated with an independent reading centre, and were masked to treatment group by providing video files to them as coded files that did not reference date or assignment group • Orientation and mobility assessors were also masked to treatment group
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	• Analyses for primary and secondary efficacy endpoints included prespecified summaries on the full ITT and mITT populations • Adverse event summaries used mITT population
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes mentioned in the protocol are reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	• Analyses for primary and secondary efficacy endpoints included prespecified summaries on the full ITT and mITT populations • Adverse event summaries used mITT population
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Abbreviations: ITT, intention to treat; mITT, modified intention to treat; MLMT, multi-luminance mobility test.

9.6 Results of the relevant studies

Study 301/302 (Phase 3)

- Subretinal injection of VN led to clinically meaningful and statistically significant improvements in primary and secondary trial endpoints.
- The ability of patients to navigate independently in low-to-moderate light conditions improved significantly, as shown by change in MLMT

score (primary endpoint) in the intervention group compared with controls at Year 1 (1.8 vs 0.2, respectively; p=0.0013).

- Approximately two-thirds of patients treated with VN achieved the maximum MLMT improvement possible at Year 1, but no patients in the control group achieved this. A consequence of this ceiling effect is that the extent to which clinical benefit can be translated into MLMT change score is limited, resulting in possible underestimation of the treatment effect.

- Light sensitivity (measured by FST testing [secondary endpoint]) improved by more than two log units in the treated group, with no meaningful change in the control group (p = 0.0004).

- Clinically and statistically significant improvements in both navigational abilities and light sensitivity manifested rapidly (within the first 30 days after subretinal delivery) and were maintained through to the most recent time points (Year 4 for MLMT and Year 3 for FST).

- Improvements in Goldmann visual field (mean difference between arms 378.7 degrees; post-hoc p=0.0059) and visual acuity (mean difference between arms 0.17 LogMAR; p=0.17) were also apparent soon after treatment, and persisted throughout the one year follow-up.

- Similar statistically significant and clinically meaningful improvements were also observed in the Control/Delayed Intervention group following bilateral administration of VN.

Study 101/102 (Phase 1)

- Voretigene neparvovec was well tolerated and all patients showed sustained improvement in subjective and objective measurements of vision.

- No adverse events related to the AAV2 vector were reported, and those related to the procedure were mostly mild.

- Improvements in efficacy outcomes were observed in most patients without significant immunogenicity.
- All eight patients who participated in mobility testing improved by at least one light level following treatment. Five patients passed the MLMT at the lowest possible light level.
- Follow-up results demonstrate significant and sustained improvements in navigational mobility (mean MLMT improvement relative to baseline was 2.4 ± 0.46 at Year 4, compared to 2.6 ± 0.56 at Year 1) and light sensitivity (improvements sustained through to Year 7.5).

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

Results of the studies are provided below in table format and supplemented with text and figures where appropriate.

9.6.1.1 Study 301/302

The pivotal trial is Study 301/302, a Phase 3 open-label randomised controlled trial, with a continuation phase (Study 302) in which patients in the Control/Delayed Intervention group were eligible to receive the intervention.

As the symptoms of *RPE65*-mediated IRD appear very early in life in some patients (see Section 6.1.3) it was partly a paediatric trial – 42% of randomised patients were under 10 years old, and 65% of randomised patients were under 18 years old.

Endpoints and statistical analyses from Study 301/302 are summarised in Table 15, with additional data and results below the table. Graphs for each endpoint represent the most recent data available. Graphs presenting data through to Year 1 only are presented in Appendix 11.

Table 15: Outcomes and analyses from Study 301/302

Study name	A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)
Size of study groups	21 – intervention group (voretigene neparvovec) 10 – control group (best supportive care)
Study duration	1 year (primary endpoint); 15 year follow-up for long-term safety and efficacy
Type of analysis	ITT (all results in this table use the ITT population but the mITT population is used in some of the following figures; see Section 9.6.2 for more details)
Primary endpoint: Bilateral MLMT change score A significant difference was observed in mean bilateral MLMT change score in the intervention group compared to the control group. The majority of intervention patients (13/20, 65% [mITT population]) passed the test at the lowest level (1 lux) at Year 1 demonstrating maximum possible improvement. No control patients passed at 1 lux. When results from the continuation phase were included, 93% of patients in the Original Intervention and Control/Delayed Intervention groups demonstrated a ≥ 1 light level improvement over one year.	
Unit	MLMT change score (difference between MLMT score at baseline and Year 1)
Effect size	1.6 (95% CI: 0.72, 2.41)
p-value	0.001
Statistical test	• The primary endpoint was tested at a two-sided Type I error rate of 0.05, using a non-parametric permutation test based on Wilcoxon rank-sum as the observed test statistic and an exact method for the corresponding p-value. • The planned approach was to randomize the allocation of treatment label to patient and, for a large number of replications, to calculate the test statistic from the Wilcoxon rank-sum test. The p-value from the permutation test was to be the proportion of p-values that were smaller than the value observed in the actual dataset. • The Wilcoxon rank-sum test statistic was to use the average rank when observations had the same value (i.e., were tied). The permutation test used the set of all possible permutations.
Secondary endpoint: FST (white light averaged over both eyes)† A rapid 2-log unit improvement was observed in mean FST by Day 30 in the intervention group, an effect that was maintained over one year. No meaningful change was observed in the control group.	
Unit	log10(cd.s/m^2)
Effect size	-2.11 (95% CI: -3.19, -1.04)
p-value	< 0.001

Statistical test	• Analysis of FST was based on longitudinal models that provided estimates of the difference between baseline and Year 1. • A linear contrast from a repeated measures general linear model assessing change in response was used to estimate the magnitude of these effects. The model included study month as a fixed effect. • The estimated mean change from baseline to Year 1 and its 95% CI was calculated from the model.
Secondary endpoint: Monocular MT change score (first-treated eye) As with bilateral MLMT score, there was a significant improvement in monocular MLMT score.	
Unit	MLMT score
Effect size	1.7 (95% CI: 0.89, 2.52)
p-value	0.001
Statistical test	This analysis used models analogous to the model described for the primary outcome.
Secondary endpoint: BCVA (averaged over both eyes)† A numerical improvement was observed in VA averaged over both eyes (based on the scale adapted by Holladay [151]) between the intervention (mean gain of 8 letters) and control group (mean gain of 1.6 letters) at Year 1, however this was not statistically significant. A post-hoc analysis requested by the EMA found this difference to be significant (see 'Comments' box below).	
Unit	LogMAR
Effect size	-0.16 (95% CI: -0.41, 0.08)
p-value	0.17
Statistical test	Statistical analysis was performed as described for the FST outcome
Comments	
Visual field There was a statistically significant difference (378.7º) in improvement in Goldmann VF (III4e) between the intervention group (mean change +302.1º) and the control group (mean change -76.7º) at Year 1 relative to baseline (95% CI: 145.5, 612.0; post-hoc p = 0.0059). Macular sensitivity threshold, measured using Humphrey VF testing, increased from a mean of 16.1 dB to 24.0 dB. No meaningful change was observed in the control group. This difference (7.9 dB) was statistically significant (95% CI: 3.5, 12.2; post-hoc p = 0.0005). No significant difference was observed with Humphrey foveal sensitivity threshold. **Visual acuity (Lange scale)** A post-hoc analysis using the Lange scale for off-chart measurements [152], rather than the Holladay scale that was used for the secondary endpoint [151], showed a statistically significant (p = 0.047) mean (95% CI) treatment different of -0.15 (-0.29, -0.00), corresponding to a 7.5-letter improvement on the eye chart.	

Abbreviations: FST, full-field light sensitivity threshold; LogMAR, logarithm of the minimum angle of resolution; MT, mobility testing.

Source: Russell 2017 [4]; Study 301 CSR [19].
†Specified in decision problem (Table 1).

9.6.1.1.1. Bilateral MLMT change score (primary endpoint)

Patients were assigned MLMT scores based on the minimum light level at which they were able to pass the test. Higher MLMT score indicates better vision. The change score was calculated as the difference in score between baseline and Year 1.

At one year, the mean bilateral MLMT change score was 1.8 in the intervention group compared to 0.2 in the control group. This difference in MLMT change score between the intervention and control arms was highly statistically significant (Table 16).

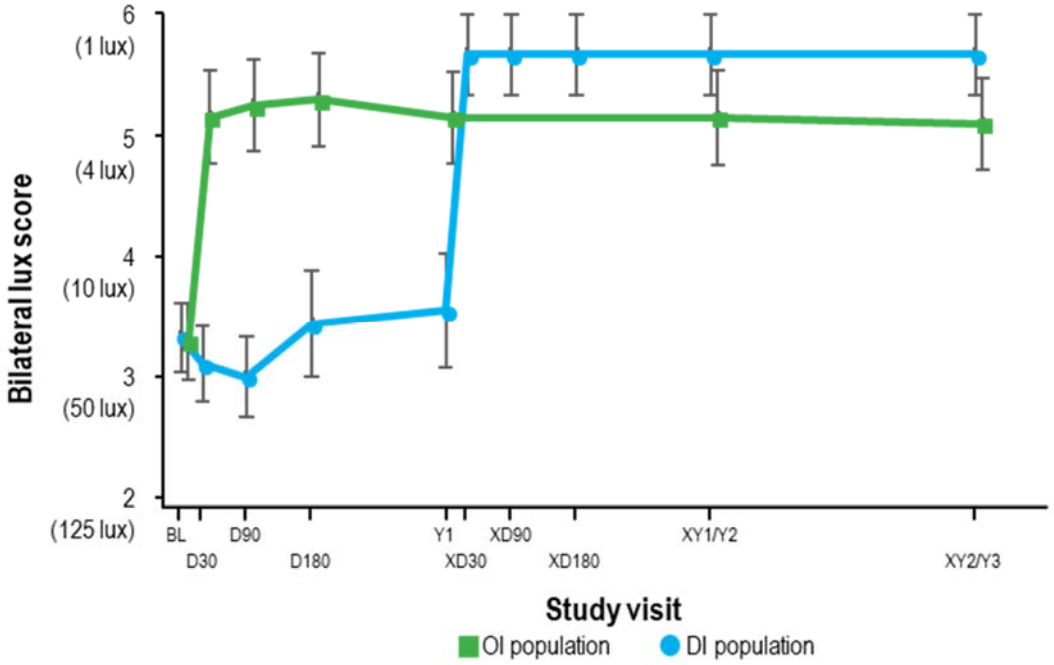
Table 16: MLMT change scores at Year 1 compared to baseline (ITT)

	Intervention	Control	Difference (95% CI)	Permutation test p value
Both eyes				
Mean (SD)	1.8 (1.1)	0.2 (1.0)	1.6 (0.72 to 2.41)	0.0013
Range	0 to 4	-1 to 2	-	
Median (IQR)	2 (1 to 3)	0 (-1 to 1)	-	
First eye				
Mean (SD)	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52)	0.0005
Range	0 to 4	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-
Second eye				
Mean (SD)	2.1 (1.2)	0.1 (0.7)	2.0 (1.14 to 2.85)	0.0001
Range	0 to 5	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-

Abbreviations: CI, confidence interval; IQR, interquartile range; ITT, intention to treat; MLMT, multi-luminance mobility test; SD, standard deviation.
Source: Russell 2017 [4].

There was a rapid and sustained improvement in mean bilateral MLMT score following treatment with VN, whilst no change was observed in the control group. At Year 1 of Study 301, patients in the Control/Delayed Intervention arm were eligible to receive treatment, and similar improvements were observed (Figure 10).

Figure 10: Year 3 MLMT results (Study 301/302)



Abbreviations: DI, delayed intervention; OI, original intervention.
Source: Maguire 2017 [143]
Error bars represent standard errors.

Recently data became available for four years of follow-up for the Original Intervention group and three years of follow-up for the Control/Delayed Intervention group [156]. Patients maintained their improvements in MLMT – the mean bilateral MLMT change score for the Original Intervention group was 1.7 at Year 4, and 2.4 at Year 3 for the Control/Delayed Intervention group [156].

At the Year 1 visit, 13 patients (65% of mITT population) in the intervention group passed the MLMT at 1 lux – the lowest luminance level tested (see Table 10) – demonstrating maximum possible improvement. By contrast no patients in the control group passed the MLMT at this light level (Figure 11). By Year 3, 69% of all patients and 89% of Control/Delayed Intervention patients were able to pass the MLMT at the lowest light level [143].

Figure 11: Bilateral MLMT scores at baseline and Year 1, by individual (ITT)

[redacted]

Only one patient treated with VN failed to improve on the MLMT. This participant had severely reduced baseline visual acuity and was one of only two patients with off-chart BCVA measurements after the immediate postoperative period.

The maximum possible improvement by the majority of patients in the intervention group highlights a ceiling effect as a limitation of the MLMT. A consequence of this ceiling effect is that the extent to which clinical benefit can be translated into MLMT change score was limited, possibly underestimating the treatment effect.

As the disease is characterised by inexorable progression towards complete blindness [4], an improvement of one light level on the MLMT was considered clinically significant. In the validation study, no patients (out of 28) improved on the MLMT – 20 had a change score of 0, and 8 had a change score of -1 or -2 [21].

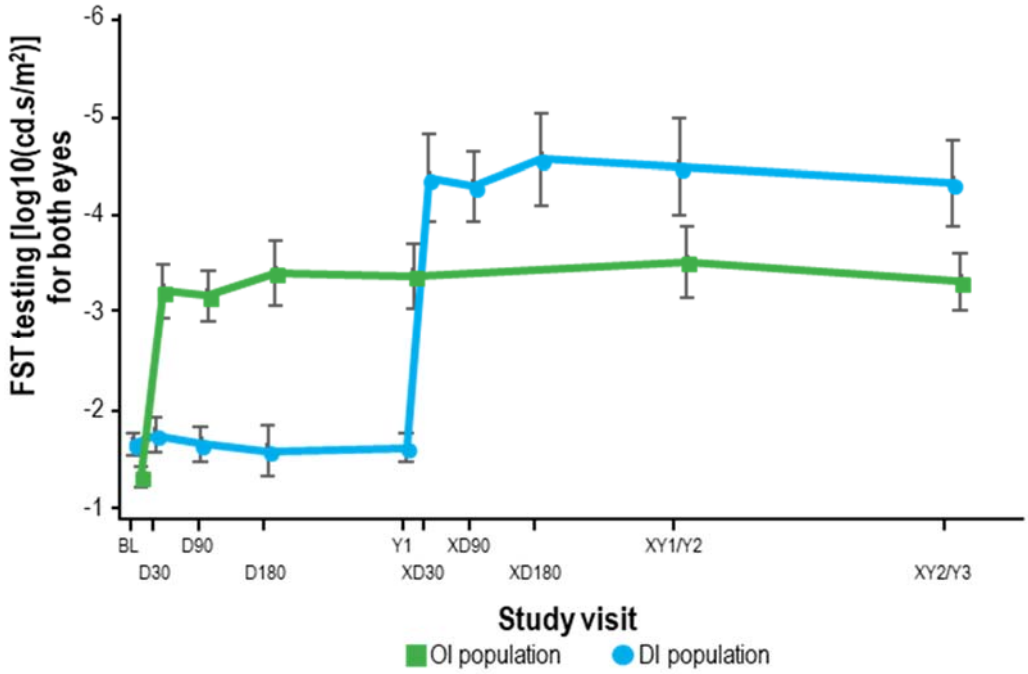
9.6.1.1.2. Full-field light sensitivity threshold testing (secondary endpoint)

As with MLMT, an improvement in FST was observed rapidly after the first post-baseline visit at Day 30, and was sustained for the duration of follow-up. Figure 12 shows the mean white light FST for the mITT population at baseline and each of the follow-up visits through to the Year 3 visit.

The group treated with VN experienced a greater than two log units improvement in light sensitivity whereas no meaningful change was observed in the control group during the first year when they remained untreated. The difference of -2.11 between arms (95% CI: -3.91, -1.04; ITT population) was highly statistically significant (p = 0.0004).

By year 3 the mean (SD) change in white light FST averaged over both eyes was -2.04 (1.43) for Original Intervention patients (N = 19) and -2.69 (1.41) for Control/Delayed Intervention patients (N = 9) (Figure 12) [143].

Figure 12: Year 3 FST results (Study 301/302)



Abbreviations: DI, delayed intervention; OI, original intervention.
Source: Maguire 2017 [143].
Error bars represent standard errors.

Generally, patients with improvements in MLMT also showed improvements in FST – 12 MLMT responders (those who improved their MLMT score) demonstrated a > 1 log improvement in FST between baseline and Year 1 [4].

9.6.1.1.3. Monocular mobility testing (secondary endpoint)

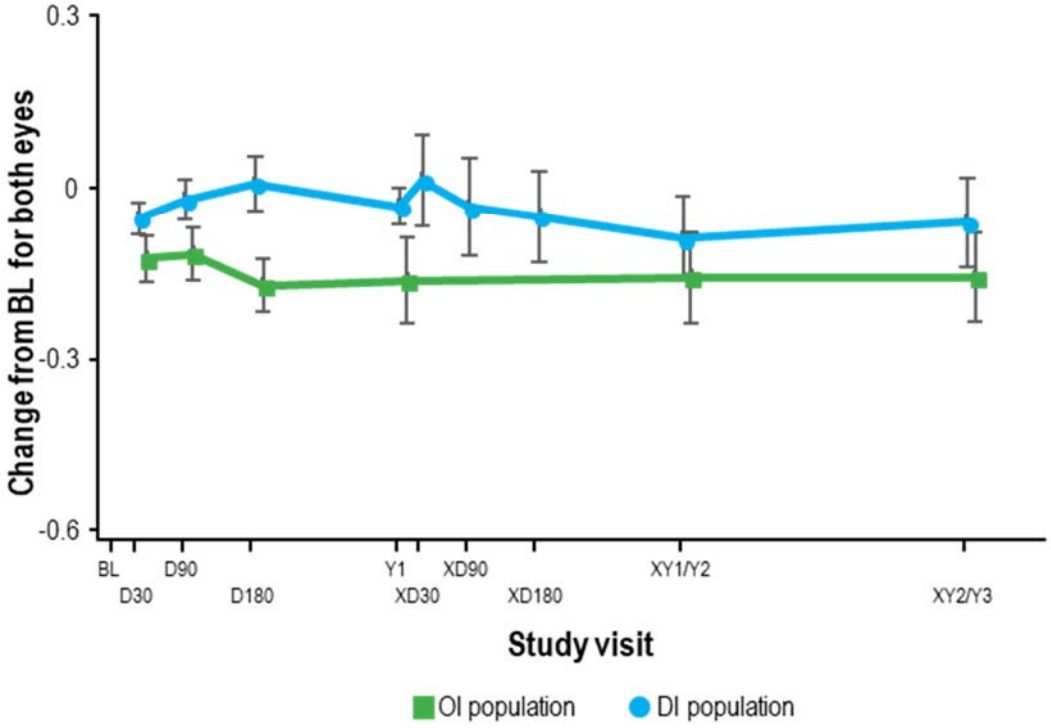
Monocular MLMT change score for the first injected eye was very similar to the bilateral results which formed the primary endpoint. The mean (SE) change from baseline to Year 1 was 1.9 (1.2) for the intervention group and 0.2 (0.6) for the control group (ITT population), with a statistically significant mean difference of 1.7 (95% CI: 0.89, 2.52; p = 0.001).

9.6.1.1.4. Visual acuity (secondary endpoint)

By Year 1, in the intervention group there was a modelled mean change of -0.16 LogMAR units, with minimal change in the control group (+0.01) (ITT population). This treatment difference of -0.16 (95% CI: -0.41, 0.08; p = 0.17) was not statistically significant despite a numerical improvement in BCVA.

In the mITT population the mean change in the intervention group was -0.16 compared to -0.03 in the control group (95% CI: -0.37, 0.11; p = 0.27) [19] which is equivalent to gains of 8.1 letters and 1.6 letters in each group, respectively. By Year 3, little change was observed in VA for either arm following treatment (Figure 13).

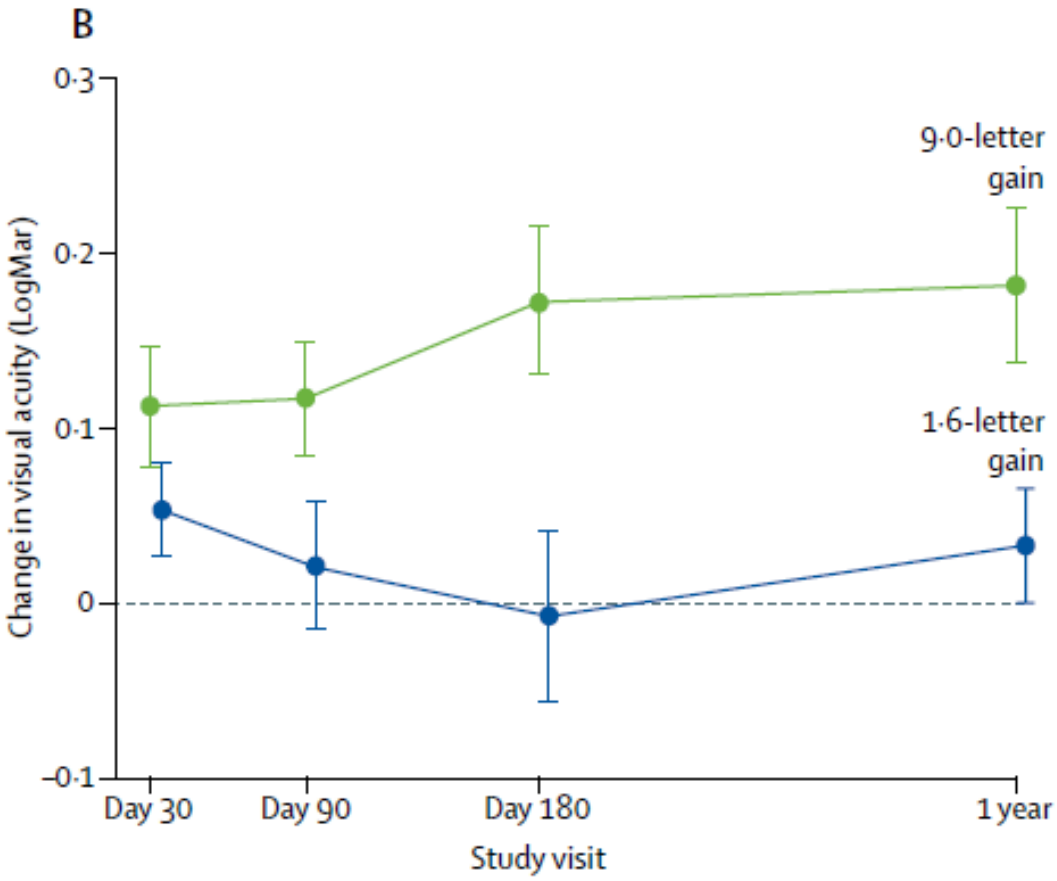
Figure 13: Mean change in VA (Holladay scale) – Year 3



Abbreviations: BL, baseline; DI, delayed intervention; OI, original intervention; VA, visual acuity.
Source: Maguire 2017 [143]
Error bars represent standard errors.

The Holladay scale assumes a 10-fold (1-log-unit) difference in VA between counting fingers and hand motion. The EMA and the study's Data and Safety Monitoring Board expressed the opinion that this scale could present a biased estimate of treatment effect for patients with off-chart measurements at baseline; therefore a post-hoc analysis was performed using an alternative scale for off-chart measurements described by Lange et al [152], in which the difference between counting fingers and hand motion perception is reduced to a 0.3 log-unit step. Results are shown in Figure 14.

Figure 14: Mean change in BCVA (mITT population) – Lange scale



Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; mITT, modified intention-to-treat.
Source: Russell 2017 [4]
Error bars represent standard errors.

Using this scale, intervention patients had a mean improvement of 9 letters compared to a 1.6 letter improvement in the control group (mITT population). This represented a statistically significant difference (95% CI: 0.1, 14.6; p = 0.0469). The difference in statistical significance using the different scales is likely due to reduced variability using the Lange scale as a consequence of a smaller off-chart step change for the two patients who had baseline and follow-up VA assessments in the off-chart range.

9.6.1.1.5. Summary of secondary endpoints

Results of the secondary endpoints for the ITT population are presented in Table 17. Secondary endpoints were tested in a hierarchical manner for statistical significance.

Table 17: FST, MT First Eye, and VA, Modelled Estimates (ITT)

Outcome	Intervention (N = 21)			Control (N = 10)			Difference (95% CI) (Intervention-Control)	*p*-value
	Baseline	Year 1	Change	Baseline	Year 1	Change		
Full-field light sensitivity testing: white light [Log10(cd.s/m^2)]								
N	20	20	19	9	9	9	-	-
Mean (SE)	-1.29 (0.09)	-3.36 (0.28)	-2.08 (0.29)	-1.65 (0.14)	-1.61 (0.42)	0.04 (0.44)	-2.11 (-3.19, -1.04)	<0.001
First eye: lux score[b]								
N	21	21	21	10	10	10	-	-
Mean (SD)	2.2 (1.8)	4.1 (2.7)	1.9 (1.2)	2.4 (1.5)	2.6 (1.7)	0.2 (0.6)	1.7 (0.89, 2.52)	0.001
Visual acuity (LogMAR)[a]								
N	21	20	20	10	9	9	-	-
Mean (SE)	1.18 (0.14)	1.03 (0.17)	-0.16 (0.07)	1.29 (0.21)	1.30 (0.25)	0.01 (0.10)	-0.16 (-0.41, 0.08)	0.17

Abbreviations: CI, confidence interval; FST, full-field light sensitivity threshold; ITT, intention-to-treat; LogMAR, logarithm of the minimum angle of resolution; MT, mobility test; SD, standard deviation; SE, standard error; VA, visual acuity.
Source: Table 11.17, Study 301 CSR [19].
a. All measures are averaged over both eyes and then analysed. Changes, 95% confidence intervals, and *p*-values were estimated using a repeated measures model with time, treatment, and time by treatment interaction as specified in the SAP.
b. Baseline and Year 1 present means of the lowest passing lux levels for the first eye. The *p*-value is from a permutation test.

9.6.1.1.6. Visual field (exploratory endpoint)

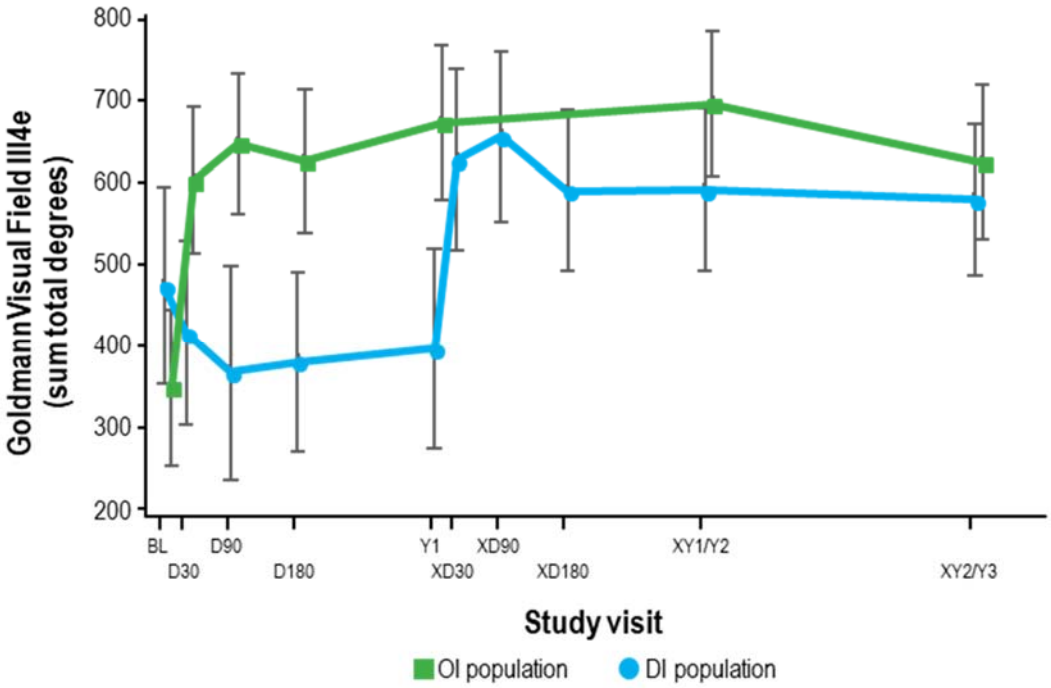
Goldmann visual field

The mean sum total degrees of Goldmann visual field (III4e) almost doubled in the intervention group (from 332.9 to 673.9) by Year 1, indicating improved peripheral vision following bilateral administration of VN. This enlarged area of retinal sensitivity is attributable to increased photoreceptor function, consistent with the increase in MLMT scores and light sensitivity observed in patients in the intervention arm.

No such improvement was observed in the control arm, in which mean sum total degrees fell from 427.1 to 397.8, with a mean difference between arms of 378.7 (95% CI: 145.5, 612.0; post-hoc p = 0.0059).

Results of Goldmann kinetic perimetry testing using the smaller III4e stimulus through to Year 3 are presented in Figure 15. The improvement in peripheral vision observed by Year 1 was sustained through to Year 3. A rapid and sustained improvement was also observed in the Control/Delayed Intervention group.

Figure 15: Mean Goldmann visual field – Year 3



Abbreviations: DI, delayed intervention; OI, original intervention.

Source: Maguire 2017 [143]
Error bars represent standard errors.

Humphrey visual field, macula threshold

Macula sensitivity threshold on Humphrey VF testing increased following administration to Year 1 from a mean of 16.1 dB to 24.0 dB, with no meaningful change observed in the control arm – a difference of 7.9 dB (95% CI: 3.5, 12.2; post-hoc p = 0.0005).

Figure 16: Humphrey Visual Field mean macula threshold over time (ITT)

Humphrey visual field, foveal sensitivity

No significant difference was observed between arms with Humphrey foveal sensitivity threshold at Year 1 – difference 0.04 (95% CI -7.1, 7.2; post-hoc p = 0.18).

Figure 17: Humphrey Visual Field foveal sensitivity over time (ITT)

9.6.1.1.7. Contrast sensitivity (exploratory endpoint)

Figure 18 presents results for contrast sensitivity testing from baseline through to year 1 for both the intervention and control groups.

Figure 18: Log contrast sensitivity over time (ITT)

9.6.1.1.8. Visual function questionnaire (exploratory endpoint)

For both patient and parent-completed surveys, VFQ scores of patients who received treatment increased significantly following administration, indicating a reduction in the perceived difficulty of daily living activities which was sustained through follow-up. The mean scores of controls did not change (Figure 19 and Figure 20).

Figure 19: Visual function questionnaire parent scores (ITT)

[redacted]

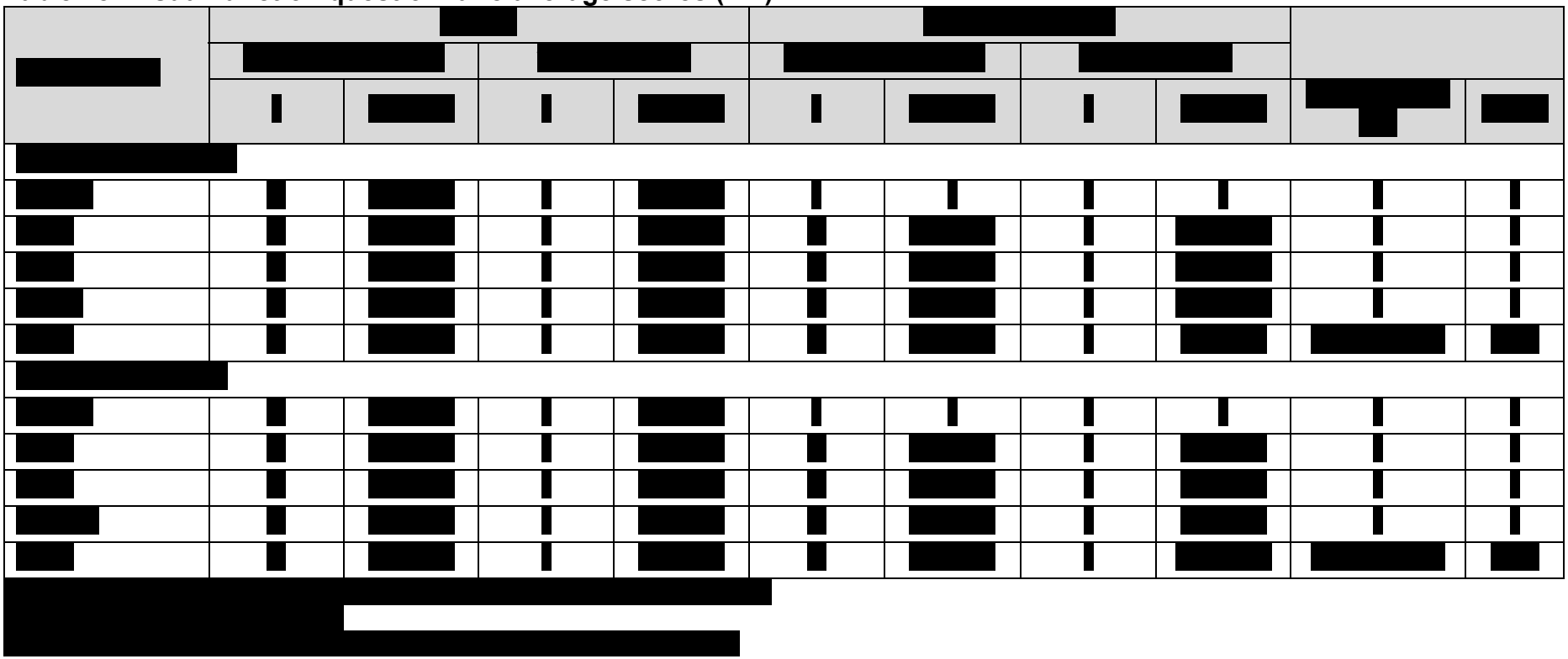
Figure 20: Visual Function Questionnaire subject scores (ITT)

[redacted]

Quantitative results are provided in Table 18. Group mean ± SD change from baseline ranged from 1.8 ± 1.9 at Day 30 to 2.6 ± 1.8 at Year 1 for patient-completed surveys and from 3.1 ± 2.2 to 3.9 ± 1.9 for parent/guardian-completed surveys.

[redacted] Differences in the baseline to Year 1 change between the two groups were statistically significant for both patients (post-hoc p = 0.001) and parents/guardians (post-hoc p = 0.002).

Table 18: Visual function questionnaire average scores (ITT)



9.6.1.2 Study 101

Study 101 was a dose-escalation study that principally assessed the safety of the technology. Efficacy outcomes that were tested for statistical significance are summarised in Table 19.

Light sensitivity results based on FST are available for 7.5 years of follow-up. These are presented below the table in Figure 21.

Table 19: Outcomes and analyses from Study 101

Study name	A Phase 1 Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE)
Size of study groups	12 patients received voretigene neparvovec: • 3 in low dose group • 6 in middle dose group • 3 in high dose group
Study duration	2 years, 15 year follow-up
Type of analysis	The analysed efficacy and safety populations included all subjects who received study drug
Primary objective: To evaluate the safety of voretigene neparvovec	
The primary objective of this study was to evaluate the safety of voretigene neparvovec. This outcome is relevant to the decision problem (Table 1). Information on adverse events in provided in Section 9.7.	
Exploratory outcome: Mean change in visual acuity from baseline to Year 1 – injected eyes A statistically significant improvement in visual acuity was observed from baseline to Year 1.	
Unit	LogMAR units
Effect size	-0.4233
p-value	0.0003 (post-hoc)
Statistical test	Post-hoc analysis using mixed effects linear regression models with random intercepts and accounting for correlations arising from repeated measures
Exploratory outcome: Mean change in visual acuity from baseline to Year 1 – injected eyes vs uninjected eyes The change in LogMAR value from baseline to Year 1 was greater for injected eyes than for uninjected eye, however the difference was not statistically significant.	
Unit	LogMAR units
Effect size	-0.4233 (injected) vs -0.1525 (uninjected)
p-value	0.1019 (post-hoc)

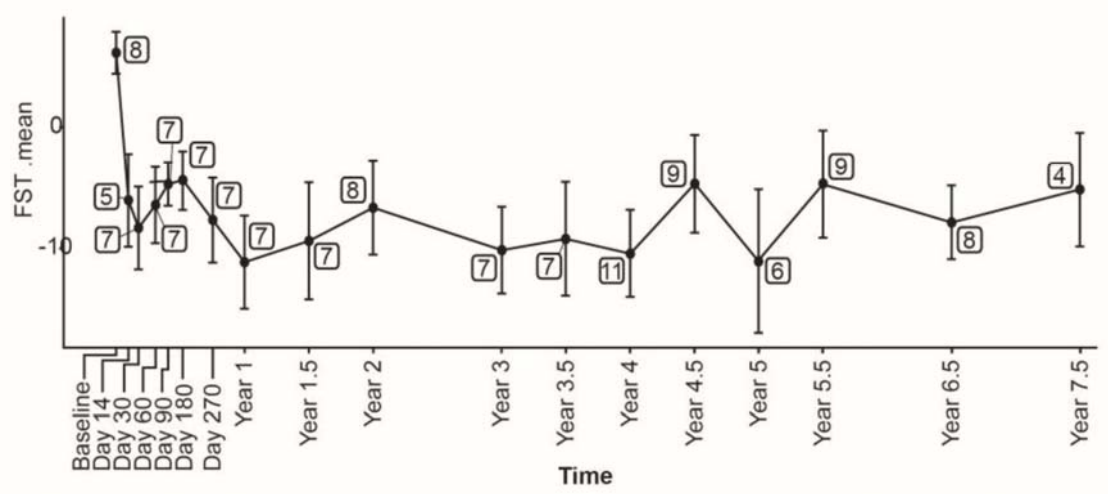
Statistical test	Post-hoc analysis using mixed effects linear regression models with random intercepts and accounting for correlations arising from repeated measures
Comments	
Visual acuity 9 patients (75%) demonstrated improved visual acuity. 7 of these demonstrated an improvement that was considered clinically significant (≥ 0.3 LogMAR unit decrease). Numerical improvement was also observed in the visual acuity of uninjected eyes (however this was not statistically significant [p = 0.1927]). This was hypothesised to be due to increased ability to fixate, for example due to reduced nystagmus following treatment of the other eye. This may explain the non-statistically significant result for mean change in VA for injected eyes vs uninjected eyes. **Visual field†** Substantial variation was observed in visual field tests as expected for patients with severe visual impairment. However improvements in the visual fields of all 12 patients were noted. **FST†** FST data were not available for all patients/time points as the equipment was not available at the start of the trial. In all patients tested light sensitivity in the injected eye increased from baseline. 57% of patients experienced a significant improvement (defined as a decrease of ≥ 10dB).	

Abbreviations: dB, decibels; FST, full-field light sensitivity threshold; LogMAR, logarithm of the minimum angle of resolution; VA, visual acuity.
Source: Maguire 2009 [16]; Study 101 CSR [14].
†Specified in decision problem (Table 1).

9.6.1.2.1. Study 101 7.5 year results

Improvements in light sensitivity in the first injected eye following treatment in Study 101 were maintained through to Year 7.5 (Figure 21). Note that only three out of twelve patients in Study 101 received the Phase 3 dose (and the licensed dose) of $1.5x10^{11}$ vg. The remaining nine patients received lower doses in this dose-escalation trial.

Figure 21: Mean (+/- SE) FST over time in the first injected eye†



Note: The numbers within the boxes represent the number of patients at each time point; time points with fewer than three observations and without baseline data were excluded from the analysis.
† Pooled data of the 3 different doses: 1.5x1010, 4.8x1010 and 1.5x1011 vg
Abbreviations: FST, full-field light sensitivity threshold; SE, standard error; vg, vector genomes.
Source: Chung 2019 [155]

9.6.1.3 Study 102

Study 102 was a follow-on to the dose-escalation safety study that principally assessed the safety of the technology. Efficacy outcomes that were tested for statistical significance are summarised in Table 20.

Four year follow-up data are available; results are presented and described below the table.

Table 20: Outcomes and analyses from Study 102

Study name	A Follow-On Study to Evaluate the Safety of Readministration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects with Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study
Size of study groups	11 – intervention (voretigene neparvovec)
Study duration	1 year, 15 year follow-up
Type of analysis	The analysed efficacy and safety populations included all subjects who received study drug
Primary objective: To evaluate the safety of voretigene neparvovec	
The primary objective of this study was to evaluate the safety of voretigene neparvovec. This outcome is relevant to the decision problem (Table 1). Information on adverse events in provided in Section 9.7.	

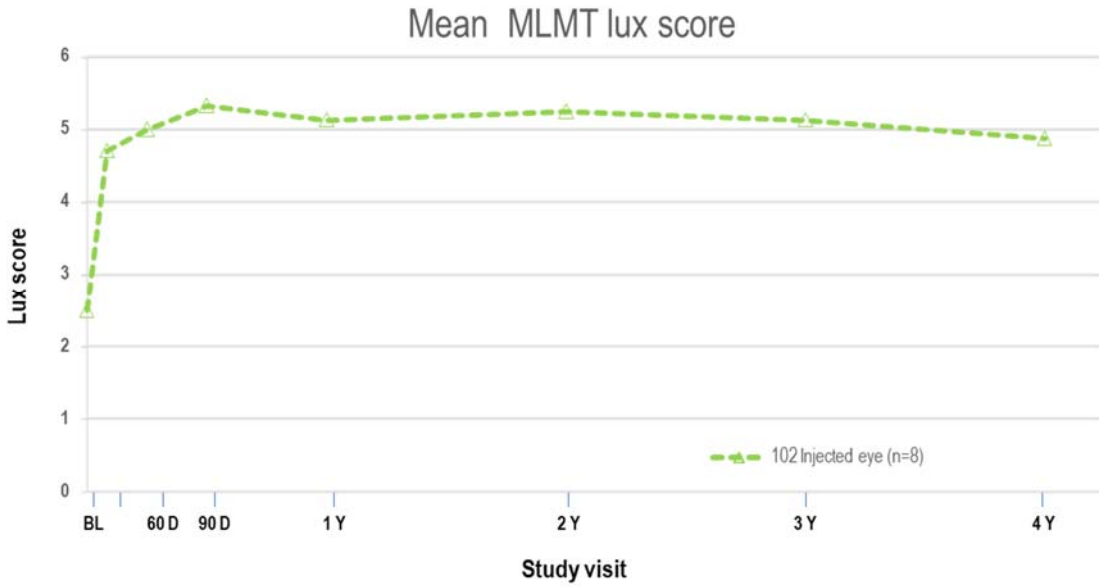
Exploratory outcome: Mean improvement in light sensitivity between baseline and Year 1 – contralateral eyes† There was a significant improvement in light sensitivity in contralateral eyes following administration with voretigene neparvovec.	
Unit	dB
Effect size	18.0364
p-value	< 0.0001 (post-hoc)
Statistical test	Post-hoc analysis using mixed effects linear regression models accounting for correlations arising from repeated measures.
Exploratory outcome: Difference in change in light sensitivity from baseline to Year 1 in 102-injected eyes vs 101-injected eyes The difference in the change in light sensitivity over the course of the study was significantly higher for contralateral eyes injected at the start of the study compared to the previously injected eyes.	
Unit	dB
Effect size	14.0636
p-value	0.0067 (post-hoc)
Statistical test	Post-hoc analysis using mixed effects linear regression models accounting for correlations arising from repeated measures.
Comments	
Mobility testing Eight of the 11 patients in the study were considered evaluable for mobility testing. All eight showed improvement of at least 1 light level using the 102-injected eye. Five of these (63%) passed the MLMT at the lowest light level.	

Source: Bennett 2016 [17]; Study 102 CSR [18]
†Specified in decision problem (Table 1)

9.6.1.3.1. Study 102 4-year results

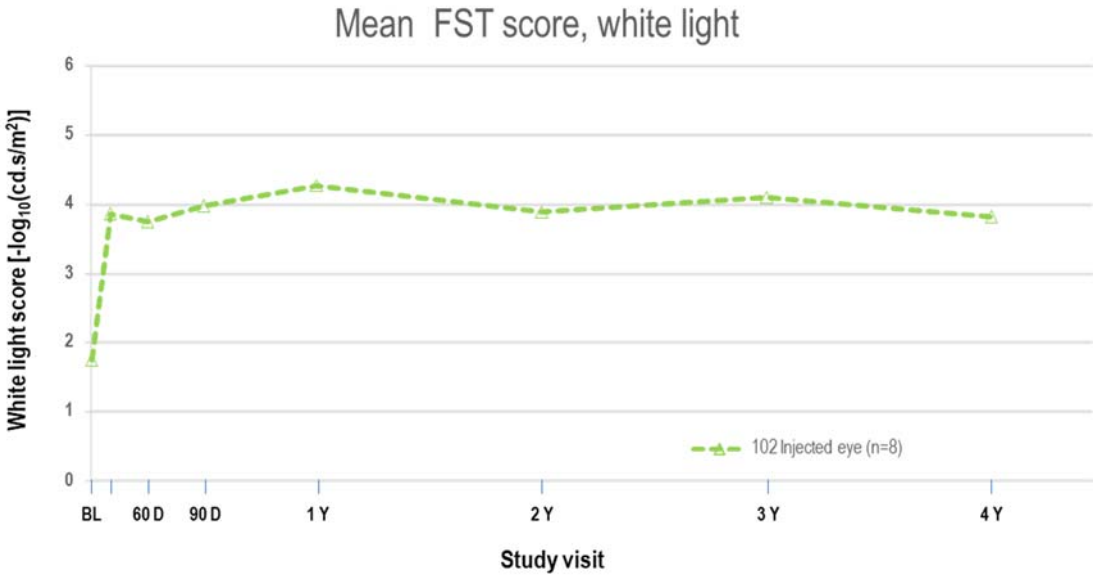
Rapidly achieved improvements in functional vision and light sensitivity were maintained for at least four years. The MLMT change score at one year relative to baseline was 2.6 ± 0.56. At four years the change relative to baseline was 2.4 ± 0.46 (Figure 22) [138]. Figure 22 and Figure 23 present the mean MLMT score and mean FST score for the contralateral eye injected in Study 102. These are the mean scores of eight patients who would have been eligible for the Phase 3 study.

Figure 22: MLMT Mean Score for 102-Injected Eye Through Year 4 (Study 102)



Abbreviations: MLMT, multi-luminance mobility test.
Source: Maguire 2017 [138]

Figure 23: FST Mean Score for 102-Injected Eye Through Year 4



Abbreviations: FST, full-field light sensitivity threshold.
Source: Maguire 2017 [138]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

All outcomes in the summary results tables (Table 15, Table 20 and Table 19) are based on analyses of the ITT population.

Where indicated, some results and figures in Section 9.6.1.1 (Study 301/302 results) reflect the mITT population, to account only for the patients who received treatment – one patient from each group withdrew from the study after randomisation but prior to receiving treatment (see Section 9.4.6 for more details).

9.7 Adverse events

- The safety database includes 41 patients (81 eyes in total).
- A single bilateral administration of VN via subretinal injection demonstrated a safety profile consistent with vitrectomy and subretinal injection. Adverse events related to the procedure were mostly transient, mild in nature, or treatable.
- There were three non-serious adverse events of retinal deposits in three (7%) of 41 patients that were considered related to VN. All three events were transient and resolved without sequalae.
- No deaths were reported, and no patients withdrew from any trials due to adverse events.
- Three patients experienced serious adverse events related to the administration procedure. These included intraocular pressure increased, retinal disorder and retinal detachment. No serious adverse events were considered related to the study drug.
- No deleterious immune responses were observed.
- Each trial has a 15 year safety follow-up plan – follow-up is ongoing.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

No specific systematic literature review was performed to identify literature on adverse events (AEs) over and above the review described in Section 9.1 and Appendix 1. Search criteria are provided in Table 6 and a PRISMA flow diagram in Figure 4.

9.7.2 Provide details of all important adverse events reported for each study.

Data presented in Section 9.7.2 are taken from the CSRs of the respective trials. Adverse events reported in the SmPC that are not reported in the CSRs are discussed in Section 9.7.3.

Data cut-off dates for the CSRs are provided at the start of each study's section.

9.7.2.1 Study 301/302

9.7.2.1.1. Period of data collection

Safety data presented in this section relate to the safety/mITT population (N = 29) – including Original Intervention and Control/Delayed Intervention patients – and the period between first injection and the data cut-off point (5th May 2017). By this point, all 20 (100%) Original Intervention subjects had completed the Year 3B study visit (i.e. three years after treatment of the second eye) and all nine (100%) Control/Delayed Intervention subjects had completed the Year 2B study visit. In addition, four (20%) Original Intervention subjects had completed the Year 4B study visit and two (22%) Control/Delayed Intervention subjects had completed the Year 3B study visit.

By the data cut-off no patients had discontinued the study due to TEAEs, and no deaths had occurred.

9.7.2.1.2. Treatment-emergent adverse events

From first injection date to the data-cut off point, the most frequently reported treatment emergent adverse events (TEAEs) for the overall study population by System Organ Class[6] (SOC) were gastrointestinal disorders and eye disorders (n = 17 [59%] for each), and nervous system disorders (n = 16 [55%]). The most frequently reported by Preferred Term[6] (PT) were headache (n = 13 [45%]), leukocytosis (n = 11 [38%]), and nausea and vomiting (n = 10 [34%] for each).

9.7.2.1.3. Drug-related adverse events and immune responses

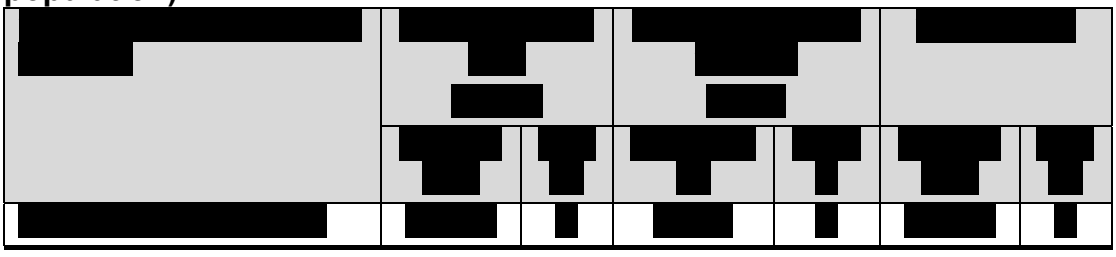
There were no TEAEs that were considered to be related to the study drug, and no deleterious immune responses.

9.7.2.1.4. Administration procedure-related adverse events

In total, 19 (66%) patients had 62 TEAEs that were considered to be related to the administration procedure – 13 (65%) Original Intervention patients, and six (67%) Control/Delayed Intervention patients. The most frequently occurring of these (by PT) were cataract (10 events in five [17%] subjects [rated mild in four patients, and moderate in one patient]), intraocular pressure increased (six events in four [14%] subjects), nausea (four events in three [10%] subjects), and retinal tear (three events in three [10%] subjects). Most of these were considered mild or moderate in intensity and were transient in nature. Perioperative IOP increases are common in patients undergoing vitrectomy [159], and can also be related to the perioperative steroid regimen [160].

A summary of TEAEs related to the administration procedure is provided in Table 21.

Table 21: Summary of administration procedure-related TEAEs in Study 301/302, from first injection to data cut-off (5th May 2017; mITT/safety population)



[6] According to the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy.

[redacted]

9.7.2.1.5. Serious adverse events

Overall, four patients (14%) experienced at least one serious adverse event (SAE) (summarised in Table 22), however in only one of these patients (3%) was the SAE considered to be related to the study drug administration procedure. No patients experienced SAEs that were considered to be related to the study drug.

One patient in the Control/Delayed Intervention group experienced an SAE of loss of foveal function in the second injected eye, 27 days after injection into that eye. The event was graded as moderate in severity and was considered to be related to the administration procedure and unlikely to be related to the study drug. The event was recovered/resolved with sequelae (the loss of foveal function appeared stable) 316 days later, although peripheral vision and improvements in full field light sensitivity remained intact in both eyes.

The SAEs considered unlikely to be related to the study drug or administration procedure were a possible seizure (in a patient with a pre-existing complex seizure disorder) and subsequent adverse drug reaction to anti-seizure medication; an adverse drug reaction to medications administered during oral surgery; and two SAEs of menorrhagia and one SAE of pneumonia.

Table 22: Summary of treatment-emergent SAEs in Study 301/302, from first injection to data cut-off (5th May 2017; mITT/safety population)

[redacted]

9.7.2.2 Study 102

9.7.2.2.1. Period of data collection

Safety data presented in this section relate to all study patients (N = 11) and the period up to the data cut-off point (10th October 2014 – four years after study initiation).

9.7.2.2.2. Treatment-emergent adverse events

By the data cut-off date the most frequently reported TEAEs by SOC were gastrointestinal disorders (n = 9 [82%]), eye disorders, infections and infestations, and renal and urinary disorders (n = 7 [64%] for each). The most frequently reported TEAEs by PT were pyrexia, influenza, blood creatinine increased, headache, hematuria and proteinuria (n = 4 [36%] for each) followed by cataract, dellen, abdominal discomfort, nausea, vomiting and oropharyngeal pain (n = 3 [27%] for each).

By the data cut-off no patients had discontinued the study due to TEAEs, and no deaths had occurred.

9.7.2.2.3. Drug-related adverse events and immune responses

There were no study drug-related TEAEs. Immune responses were minimal and without clinical correlates.

9.7.2.2.4. Administration procedure-related adverse events

Seven patients (64%) reported TEAEs considered to be related to the administration procedure (see Table 23). The most frequently reported TEAEs related to administration by PT were dellen (n = 3 [27%]), cataracts (n = 2 [18%]) and intraocular pressure increased (n = 2 [18%]).

Table 23: Summary of administration procedure-related TEAEs in Study 102 (Data cut-off 10th October 2014; safety population)

[redacted]

9.7.2.2.5. Serious adverse events

One SAE was reported, which was considered unlikely to be related to the study drug, but that resulted from treatment given for a previous TEAE (intraocular inflammation endophthalmitis), which was considered to be related to the administration procedure. Treatment with depo-steroids resulted in additional AEs, including an SAE of elevated IOP in the right eye. The patient was hospitalised and filtration surgery restored intraocular pressure to normal, however during the period of increased intraocular pressure optic nerve damage occurred that did not reverse.

9.7.2.3 Study 101

9.7.2.3.1. Period of data collection

Safety data presented in this section relate to all study patients (N = 12) and the period up to the data cut-off point (14th October 2014 – seven years after study initiation).

9.7.2.3.2. Treatment-emergent adverse events

By the data cut-off date 42 TEAEs were reported by the three patients in the low dose group, 80 were reported by the six patients in the medium dose group, and 35 were reported by the three patients in the high dose group. The most frequently reported TEAEs by SOC were infections and infestations (n = 11 [92%]), and eye disorders (n = 10 [83%]). By PT, the most frequently reported TEAEs were conjunctival hyperaemia (n = 8 [67%]), pyrexia (n = 7 [58%]), leukocytosis (n = 6 [50%]), and abdominal discomfort and headache (both n = 5 [42%]). There were no apparent effects of VN dose on TEAE incidence.

By the data cut-off no patients had discontinued due to TEAEs and no deaths had occurred.

9.7.2.3.3. Drug-related adverse events and immune responses

There were no study drug-related TEAEs. Immune responses were minimal and without clinical correlates.

9.7.2.3.4. Administration procedure-related adverse events

10 patients (83%) experienced TEAEs related to the study drug administration procedure (see Table 24). The most common was conjunctival hyperaemia (n = 8 [67%]). This included eye surface irritation, suture reaction, suture irritation and/or suture allergy. In some cases this was attributed to the use and persistence of slow-absorbing suture material at the incision site.

Table 24: Summary of administration procedure-related TEAEs in Study 101 (Data cut-off 14th October 2014; safety population)

[redacted]

9.7.2.3.5. Serious adverse events

One SAE was reported, which was considered unlikely to be related to the administration procedure or study drug. A patient in the low dose group experienced an anal fistula requiring hospitalisation, which was related to an underlying diagnosis of inflammatory bowel disease.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Across the clinical trial programme for VN, 81 eyes were treated in 41 patients (see Section 4.1 for a breakdown of patient numbers).

Voretigene neparvovec has a safety profile consistent with vitrectomy and subretinal injection, as most of the AEs in the trials were procedure-related. Most AEs tended to occur early and resolve over time, as would be expected from a single administration therapy.

The most common adverse reactions (incidence ≥5%) related to the administration procedure were conjunctival hyperaemia, cataract, increased intraocular pressure, retinal tear, dellen, macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain and maculopathy (wrinkling on the surface of the macula) [3].

The SmPC reports three non-serious adverse reactions of retinal deposits in three of 41 (7%) patients that were considered to be related to VN. All three of these events were a transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site, 1-6 days after injection and resolved without sequelae [3].

No patients discontinued due to TEAEs, and no deaths were recorded in any of the trials. No SAEs were considered related to the study drug, and three were considered related to the administration procedure. Two of these are discussed above in Section 9.7.2.1.5 (loss of foveal function) and Section 9.7.2.2.5 (elevated IOP). The SmPC reports one additional procedure-related SAE; one patient experienced retinal detachment [3].

Of particular interest were ocular AEs, which included macular disorders, elevated intraocular pressure, retinal tear, intraocular infections and/or inflammation, and cataracts. Most of these events were mild and transient in nature, requiring minimal or no intervention [4, 19]. During the peri-operative period leukocytosis was observed in many patients, related to the corticosteroid regimen [19].

In Study 101 conjunctival hyperaemia was reported in eight patients (67%) [14], although no patients experienced this AE in Study 102, and one patient experienced it in Study 301/302.

Although repeat experiments in large-animal models demonstrated a high degree of safety prior to the human trials, one area of uncertainty was the possibility of an immune response against the vector or the expressed protein, RPE65. This could be due to pre-existing immunity to the vector or as a result of re-administration to the contralateral eye.

Cell-mediated and humoral immune responses were minimal and were without clinical correlates [4, 16, 17]. In Study 301, with the exception of positive findings at 3 subject visits, all IFN-gamma ELISPOT assay (which detects T cell responses) results for the vector (AAV2 capsid) and gene product (RPE65) were negative in all patients at the time points evaluated [19]. In the majority of Study 301/302 patients, minimal or no change in antibody titer to AAV2 capsid was measured at any time point following vector administration [19].

To minimise inflammation associated with the surgery and to reduce the risk of an immune response, a peri-operative immunomodulatory regimen was required, lasting a minimum of 18 days up to a maximum of 30 days, depending on the timing of the administration to the second eye (see Table 5). To minimise the risk of infection during surgery, a topical broad spectrum microbicide was administered to the conjunctiva, cornea, and eyelids prior to surgery [3].

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

A meta-analysis was considered neither possible nor appropriate because:

- only Study 301 included a comparator arm;
- different doses were administered in Study 101; and
- voretigene neparvovec was administered to one eye in Study 101, the contralateral eye in Study 102, and bilaterally in Study 301/302.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The clinical evidence base for VN consists of a Phase 1 study [14, 16] with a continuation phase [17, 18] and a Phase 3 randomised controlled trial [4, 19] with a continuation phase [20]. In total, VN was administered to 81 eyes in 41 patients.

In Study 301 – the first randomised Phase 3 gene therapy trial for a genetic disease – VN was administered bilaterally to patients with *RPE65*-mediated IRD, the majority of whom were < 18 years old [4]. The disease is associated with an inexorable progression to complete blindness and no pharmacological treatments are currently available [1, 4].

Treatment with VN resulted in clinically meaningful and statistically significant improvements in navigational ability in low-to-moderate light conditions (measured by MLMT score), and in light sensitivity (measured by FST) [4]. Both are of critical importance in a disease in which nyctalopia (night blindness) is a defining characteristic.

Thirteen patients (62%) in the intervention arm experienced the maximum possible improvement in MLMT score one year after administration (i.e. they reached the best possible score for the MLMT), compared to no patients in the control arm. *RPE65*-mediated IRD is a progressive condition, with no evidence

of spontaneous sustained improvement in vision in any individual (41, 42), further highlighting the clinical significance of the trial results.

The lighting levels selected for the MLMT span a range that is routinely encountered in everyday situations (see Table 10). For example, an individual might safely navigate the interior of a train at night (125 lux) but be unable to navigate an outdoor train station at night (50 lux). Improvement of one level on the MLMT from passing at 125 lux to passing at 50 lux would allow the individual to safely navigate both environments. The ability to navigate in dimmer conditions than previously possible expands the range of environments individuals are able to navigate independently, having a positive impact on daily life.

Three patients in the control arm had a positive change score of +1, which was presumed to be due to test variability around the binary pass/fail cut-off, learning effect and/or increased ability to ambulate due to maturation – this latter reason was suspected for the only control patient who experienced a +2 change score, who was aged four at the time of randomisation [19].

Patients treated with VN experienced a mean improvement in FST > 2 log units, whereas mean FST did not change in the control arm (see Section 9.6.1.1) [4].

These improvements reflect restoration of RPE65 activity, which is crucial for light perception. Despite the absence of functional RPE65, photoreceptors degenerate slowly, so phenotypic recovery is possible through restoration of the enzyme [4]. However the requirement for viable cells into which copies of *RPE65* can be introduced means that patients with severe retinal degeneration will be ineligible for treatment with VN [3].

Changes in navigational ability and light sensitivity were rapid and were sustained through to the Year 1 visit of Study 301/302 [4]. Data from the continuation phase show that this was further maintained through to Year 4, and that similar improvements were also observed when the Control/Delayed Intervention group were treated after Year 1. Follow-up data from Study 102 show that MLMT and FST improvements are maintained through to Year 4

[138], and data from Study 102 show that FST improvements are maintained through to Year 7.5 [156].

Sustained visual improvements must be viewed in the context of the disease course under current care, which is one of inexorable decline towards complete blindness [4].

Improvements were also observed in Goldmann and Humphrey macula visual fields and visual acuity. Despite VA not being the primary target of the intervention for this rod-mediated disease, there was numerical (but not statistically significant) improvement using the Holladay scale, and statistically significant improvement when the Lange scale was used. These changes remained stable through the three years of follow-up (Section 9.6.1.1).

The observed increase in VF indicates an enlarged area of retinal sensitivity. This expanded peripheral vision probably contributed to the increased MLMT scores in patients treated with VN. The fact that the macula sensitivity threshold (which targets the central 4 degrees of field) improved but foveal sensitivity (which targets the most central, cone-enriched region of the macula) did not may be because the fovea contains almost exclusively cone cells. Cone cells are not the primary cells affected by *RPE65*-mediated IRD (a rod-mediated disease), minimising the potential for improvement from baseline, and they may not respond as favourably to administration of VN. Furthermore, the instructions for surgeons in the SmPC state that VN should not be administered in the immediate vicinity of the fovea to maintain foveal integrity [3].

Nonetheless, the Humphrey VF findings (both macular and foveal) demonstrate a lack of toxicity in terms of macular dysfunction, with a significant improvement observed in macula threshold.

No unacceptable barriers to VN administration were identified based on safety outcomes. In the 41 patients treated across the trials, only three adverse events of retinal deposits (non-serious) were considered related to VN. No patients discontinued from the studies due to TEAEs, and no deaths occurred. No SAEs were considered related to the study drug, and three were considered unrelated to the administration procedure (Section 9.7).

AEs related to the procedure were mostly transient, mild or treatable, and minimal immune responses to the vector or the expressed gene were observed.

NNT and NNH are not calculated as the endpoints in Study 301/302 (such as MLMT scores) did not include clear cut-offs defining success and failure.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

9.9.2.1 Strengths

In addition to traditional visual function endpoints – FST, VA and VF – Study 301 assessed the effect of bilateral administration of VN on functional vision. Use of a functional vision test (MLMT) as the primary endpoint means that greater insight can be gained into the effect that bilateral VN administration is likely to have on patients' daily lives.

Another strength of the clinical evidence base is the use of an untreated control arm in Study 301/302. The use of uninjected contralateral eyes as controls was considered in the design of the study [19]. However, this design is not appropriate for evaluating the effect of treatment on functional vision, and it does not allow assessment of systemic effects such as immune response to the vector or gene product.

The patient population in the studies reflects the characteristics of eligible patients in clinical practice; the majority of patients in Study 301/302 (65%) were < 18 years old.

9.9.2.2 Limitations

Study 301 was open label, as it was considered unethical to perform sham subretinal surgery in a paediatric population, and the procedure itself is not without risk. However, MLMT tests were filmed and assessed by off-site graders who were masked to treatment allocation and sequence (i.e. they were not told if a video showed a baseline test or a test performed one year post-administration).

Performance on the MLMT, and VA and VF, formed part of the eligibility criteria for the trial. Patients with better baseline functional vision and visual function were not eligible, so the study does not provide insights into the effect of treatment on the vision in this group of patients.

The nature of the MLMT means that there is a ceiling effect: patients who pass the test at the second lowest light level at baseline are only able to achieve a maximum 1 unit increase. Although nearly 2/3 of patients achieved the maximum possible increase following administration, compared to none in the control group, the mean increase in MLMT score of 1.8 is likely to be an underestimate because of this ceiling effect. There is also a floor effect – one patient, who was in the intervention group, did not pass the MLMT at the highest light level at baseline and also failed at Year 1. Two other patients also failed at baseline but as these were both withdrawn (see Section 9.4.6) they were not assessed at Year 1 and were assigned change scores of 0.

The novel endpoint and the clinical characteristics associated with the condition are unfamiliar to most clinicians. However, conventional measures of retinal and visual function such as FST and VF supported the MLMT findings.

In addition, good correlations existed between performance on these secondary outcomes measures and MLMT findings. The linear relationships between MLMT and FST were generally good to strong, indicating that subjects with better performances on the MLMT tended to have lower (i.e., better) FST changes. Similarly, the linear relationships between MT and Humphrey VF foveal sensitivity were generally good, indicating that subjects with better performances on the MLMT tended to have higher (i.e., better) foveal sensitivity changes. The linear relationships between MT and Humphrey VF macula threshold were generally fair to good, also indicating that subjects with better performances on the MLMT tended to have higher (i.e., better) macula threshold changes.

Designing a Phase 3 trial for an ultra-orphan disease poses unique challenges arising from the limited number of patients available to participate. As a consequence, the study had no patients under four years old, who could

potentially benefit greatly from treatment, although patients aged three upwards were eligible. It is especially challenging to measure navigational mobility and light sensitivity in very young children as they are required to follow instructions in the MLMT, and to fixate their vision in the FST test.

In Study 301/302, BCVA was calculated by averaging the BCVA of each eye. Bilateral BCVA (not assessed) is usually determined by the acuity of the best-seeing eye, so the averaging method used in this study may have underestimated BCVA. Another challenge associated with measuring VA in this patient population is that some patients had off-chart measurements (i.e. they were unable to read letters on any lines of the chart), so the Holladay and Lange scales were used to assign VA measurements to these patients. The EMA requested the latter be performed in a post-hoc analysis to minimise the risk of bias (Section 9.6.1.1.4).

Four-year data from Study 301, four-year data from Study 102 and 7.5-year data from Study 101_show sustained response to treatment, but longer-term efficacy remains unknown. Follow-up is ongoing.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical evidence base for VN is relevant to the decision problem specified in the NICE scope (Table 1) for the following reasons:

- Study 301, the pivotal Phase 3 trial, evaluated the efficacy and safety of VN versus BSC in patients with IRDs caused by *RPE65* mutations, as per the NICE scope

- The trial captured the range of outcomes defined in the NICE scope including clinical outcomes, adverse effects of treatment, and health-related quality of life (HRQL)

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Novartis is not aware of any factors that may influence the external validity of study results to patients in clinical practice. As in Study 301, eligibility for treatment will be dependent upon confirmation of biallelic *RPE65* mutations and sufficient viable retinal cells, and treatment will consist of bilateral administration of VN [3, 4].

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

Patient experience

10.1 Please outline the aspects of the condition that most affect patients' quality of life.

As described in Section 7.1, the disease usually manifests in children and young people, resulting in a lifelong impact on quality of life. Among the factors affecting quality of life are:

- Night blindness (nyctalopia)
- Depression, anxiety and emotional distress
- Lack of independence and ability to perform daily activities, including driving
- Reduced employment and productivity
- Disruption of education and development in children
- Reduced length of sleep

Further details are provided in Section 7.1.

10.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

RPE65-mediated IRD is a progressive condition, with no evidence of spontaneous sustained improvement in VA or VF in any individual (41, 42). Patients face an inexorable progression towards near-total blindness (1, 41, 46).

Reduced visual field and visual acuity are associated with lower HRQL [96, 161], so as patients' vision deteriorates they are likely to experience a decline in quality of life and mental health.

HRQL data derived from clinical trials

10.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on

whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

10.3.1 Trial HRQL methodology and consistency with reference case

In Study 301/302, a visual function questionnaire (VFQ) was completed by patients (or by the parents/guardians of paediatric patients) at baseline, days 30, 90 and 180, and year 1. The questionnaire was designed to assess activities of daily living relevant to individuals with *RPE65*-mediated IRD, and was developed to be similar in style to the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).

Existing instruments such as the NEI VFQ-25 [162], the Visual Activities Questionnaire [163], and the Low Luminance Questionnaire [164] were not considered suitable for use in this patient population, as no single instrument is adequately comprehensive of the experience of patients with *RPE65*-mediated IRD, and all include items that were either not relevant to individuals with *RPE65*-mediated IRD, or were difficult to interpret within the context of this condition (e.g. some activities would be straightforward in well-lit environments but impossible in dimly lit places) [165].

The VFQ used in Study 301/302 cannot be used to generate utility values as it is not sufficiently similar to existing instruments (e.g. the NEI VFQ-25) to permit application of existing mapping algorithms [166], and no valuation studies or mapping algorithms specific to the VFQ are available such that preference-based utility values could be generated; as such, the VFQ is not consistent with

the NICE reference case, and these data are not suitable for use in the cost-effectiveness analysis.

10.3.2 Trial HRQL results

Descriptions of methodology and results are provided in Section 9.4.1.1.8 and Section 9.6.1.1.8, respectively.

Mapping

10.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

Mapping was not possible; see Section 10.3.1.

HRQL studies

10.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic review was conducted to identify studies from the published literature reporting health state utility values (HSUVs) associated with patients with visual impairment, including blindness. The searches were run on 27th July 2018, and were updated on 14th January 2019.

Details of search strings, databases searched, hand-searching, and inclusion/exclusion criteria are provided in Appendix 5.

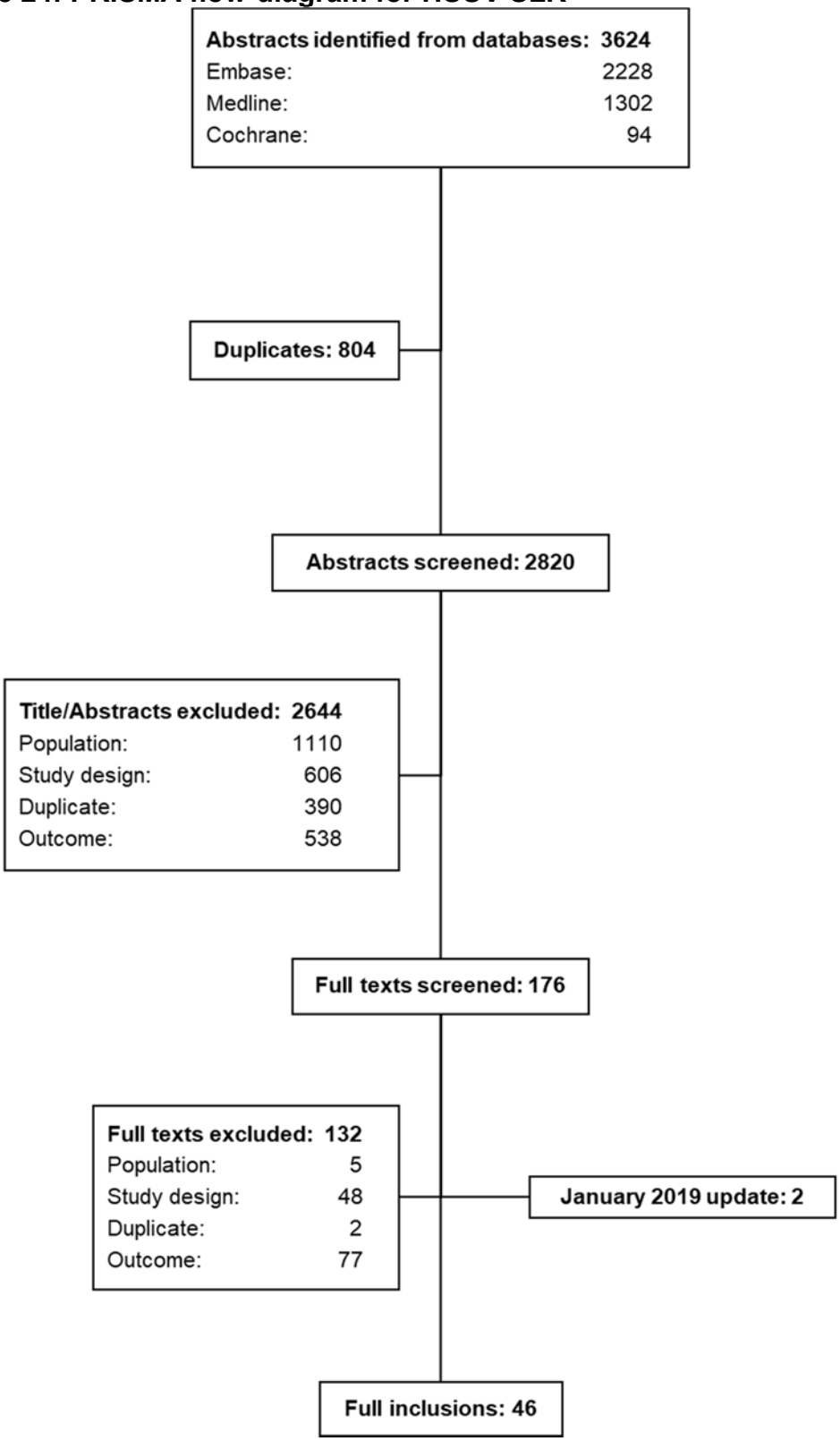
In the original search, 3,624 papers were identified through the electronic searches. Upon the removal of duplicate papers, 2,820 titles and abstracts were reviewed. A total of 176 papers were potentially relevant and were ordered for full paper review. At this stage, a further 132 papers were excluded. Hand searching yielded no additional relevant papers, resulting in a total of 44 papers for final inclusion in the original review.

In the January 2019 update, 145 papers were identified through the electronic searches. Upon the removal of duplicate papers, 127 titles and abstracts were reviewed. A total of five papers were potentially relevant and were ordered for full paper review. At this stage, a further three papers were excluded. Hand searching yielded no additional relevant papers, resulting in a total of two papers for final inclusion in the updated review.

Across the original review and the January 2019 update, a total of 46 studies were identified for final inclusion in the review.

The flow of studies through the review is reported in the PRISMA flow diagram in Figure 24. Separate PRISMA diagrams for the original and updated reviews are presented in Appendix 5.

Figure 24: PRISMA flow-diagram for HSUV SLR



10.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- **Population in which health effects were measured.**
- **Information on recruitment.**
- **Interventions and comparators.**
- **Sample size.**
- **Response rates.**
- **Description of health states.**
- **Adverse events.**
- **Appropriateness of health states given condition and treatment pathway.**
- **Method of elicitation.**
- **Method of valuation.**
- **Mapping.**
- **Uncertainty around values.**
- **Consistency with reference case.**
- **Results with confidence intervals.**

Overall, the review identified 46 studies that were eligible for inclusion in the utility review. Of these, four studies reported mapping algorithms to predict EQ-5D from condition-specific measures of quality of life [166-169].

Summaries of the included studies reporting utility values and their relevance to the NICE reference case, and the four studies reporting mapping algorithms is provided in Appendix 5.

None of the included studies provided utility data for the population under consideration in this analysis. In order to inform utility values for the model health states, a bespoke utility study was conducted (see Section 10.9.1 and Appendix 9).

10.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable, as it was not possible to generate health state utility values on the basis of data collected in the clinical trials.

Adverse events

10.8 Please describe how adverse events have an impact on HRQL.

Voretigene neparvovec has a safety profile consistent with vitrectomy and subretinal injection, as most of the AEs in the trials were procedure-related (see Section 9.7.3). Ocular AEs included macular disorders, elevated IOP, retinal tear, intraocular infections and/or inflammation, and cataracts, most of which required minimal or no intervention due to their mild and transient nature.

Treatment or procedure-related AEs in the Original Intervention arm of Study 301 considered to have an effect on quality of life, and which occurred in more than one patient, were:

- Cataract
- Eye inflammation
- Increased IOP

Retinal tear considered to be related to the administration procedure occurred in two patients in Study 301; however, retinal tears are assumed to be corrected during the administration surgery, and so are not expected to impact quality of life.

As utility values could not be derived from data collected in Study 301, direct estimates of the effects of these AEs on quality of life are not available. Therefore, utility decrements were sourced from the literature (See Section 10.9.2) for use in the cost-effectiveness model.

Additionally, a scenario analysis is considered in which an additional disutility of 0.1 is applied for one month in all patients to account for any discomfort or inconvenience associated with the administration procedure.

None of the above are expected to have a major impact on patients' overall quality of life.

Quality-of-life data used in cost-effectiveness analysis

10.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Utility values used in the base-case of the cost-effectiveness analysis are summarised in Table 25.

Table 25: Summary of quality-of-life values for the base-case cost-effectiveness analysis

State†	Mean utility value	Standard deviation	Reference in submission	Justification
Health state 1	0.519	0.16	Acaster Lloyd 2018 (Appendix 9)	See Section 10.9.1
Health state 2	0.363	0.11		
Health state 3	0.223	0.10		
Health state 4	0.141	0.09		
Health state 5	-0.039	0.07		
Cataract	0.14 decrement	-	Appendix J of NICE guideline 82 on AMD [170]	See Section 10.9.2
Eye inflammation	0.30 decrement	-		
Increased IOP	0.10 decrement	-	Assumption based on Pershing 2014 [171]	
Carer disutility for carers of children	0.08 decrement	-	Wittenberg 2013 [172]	See Section 10.9.3
Carer disutility for carers of adults	0.04 decrement	-	Assumption based on Wittenberg 2013 [172]	

Abbreviations: AMD, age-related macular degeneration; IOP, intraocular pressure.
Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
† Note that no adjustment was made to utility values on the basis of age. Given that utility values for all model health states (-0.04 to 0.52) sit well below population norms for all ages [173], it is considered that vision loss is the dominant driver of quality of life.

10.9.1 Health state utility values

A systematic literature review (SLR) was conducted to identify utility values in individuals with *RPE65*-mediated IRD (see Section 10.5); however no utility data were identified in this population (see Section 10.6). A bespoke utility study was therefore conducted to estimate utility values associated with each of the model health states. Full details of this study are provided in Appendix 9.

Given the ultra-rare nature of the condition, it was not considered feasible to recruit a representative sample of patients such that utility data could be collected prospectively. An alternative approach was therefore taken in which clinicians assessed a series of vignettes in terms of their impact on standard generic HRQL instruments (HUI3 and EQ-5D-5L); this approach has been taken previously in rare conditions [174-176].

The study consisted of two stages:

1. Health state development

    - Health state descriptions (vignettes) were developed, with input from an expert advisory board, patients and carers, and interviews with clinicians

    - The resulting five vignettes described different levels of visual function in *RPE65*-mediated IRD, corresponding to each of the health states in the model

2. Health state valuation

    - Six retina specialists (including UK and US experts), all with experience in IRD, were interviewed to provide a proxy valuation of each vignette using the HUI3 and EQ-5D-5L questionnaires

    - The HUI3 was scored in line with developer instructions; the EQ-5D-5L was scored using the van Hout el al algorithm [177]

The resulting utility values are presented in Table 26. Despite the small sample size of six clinicians, the standard deviations around the utility estimates are relatively low, indicating a high level of agreement between the clinical experts.

The HUI3 scores ranged between 0.52 (moderate VI) and -0.04 (HM, LP, NLP), with a range between the best and worst health states of 0.56. The EQ-5D-5L scores for each health state were found to be higher than the corresponding HUI3 score, with a range from 0.71 to 0.15; the overall range was 0.56, and therefore highly congruent with the HUI3 scores.

Table 26: Utility values from the Acaster Lloyd study

State	Utility value	
	HUI3, mean (SD)	EQ-5D-5L, mean (SD)
Health state 1	0.52 (0.16)	0.71 (0.09)
Health state 2	0.36 (0.11)	0.62 (0.04)
Health state 3	0.22 (0.10)	0.52 (0.07)
Health state 4	0.14 (0.09)	0.35 (0.06)
Health state 5	-0.04 (0.07)	0.15 (0.11)

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

An extensive review of the performance of generic health utility instruments has previously found that the EQ-5D (3-level version) had poor convergent validity when used in visual disorders; half of the identified studies did not demonstrate a statistically significant correlation with clinical measures [178]. While there was less evidence for the HUI3, all but one study demonstrated good validity [178]. This is likely because the HUI3 includes a vision component. HUI3 was therefore preferred for the base-case.

10.9.1.1 Scenarios

10.9.1.1.1. EQ-5D-5L values from the Acaster Lloyd study

A scenario is presented in which the EQ-5D-5L values from the Acaster Lloyd study are used.

10.9.1.1.2. Values from the published literature (Brown et al 1999)

Forty-four publications were identified in the HSUV SLR (see Section 10.6), three of which have been used in NICE appraisals previously[7]: Czoski-Murray et al (2009) [179], Brown et al (1999) [180] and Brown et al (2000) [181].

Given that the utility values presented by Czoski-Murray et al are associated with some limitations [182], and the Brown et al (2000) values do not include the NLP health state (see Section 12.1.6 for health state definitions), the Brown et al (1999) values were selected for use in scenario analyses.

Brown et al (1999) reported utility values for different levels of VA in the best-seeing eye, using the time trade-off (TTO) method [180]. These values are presented in Table 27 alongside the corresponding health states and values used in the model. Where more than one reported utility value corresponded to a single health state, health state utility values were assumed to reflect the crude average of these values.

Table 27: Brown et al utility values

VA in best-seeing eye, Snellen (LogMAR)	TTO utility value	Health state	Value used in each health state
20/40 (0.30)	0.80	Moderate VI	0.75
20/50 (0.40)	0.77		
20/70 (0.54)	0.74		
20/100 (0.70)	0.67		
20/200 (1.00)	0.66	Severe VI	0.65
20/300 (1.18)	0.63		
20/400 (1.30)	0.54	Profound VI	0.54
CF	0.52	CF	0.52
HM-NLP	0.35	HM, LP, NLP	0.35

Abbreviations: CF, counting fingers; HM, hand motion; LogMAR, logarithm of the minimum angle of resolution; LP, light perception; NLP, no light perception; VA, visual acuity; VI, visual impairment; TTO, time trade-off.
Source: Brown et al 2003 [180]

The utility values were determined from 325 patients (120 men and 215 women) with a mean age of 67.5 years (range 28–87 years). The most common causes

[7] NICE appraisals were identified using the following search terms: retinitis pigmentosa, leber congenital amaurosis, blindness, visual impairment, age-related macular degeneration, diabetic retinopathy, choroidal neovascularisation, retinal vein occlusion, diabetic macular oedema, postchiasmatic lesions, optic neuropathy, and macular telangiectasia.

of vision loss were AMD, diabetic retinopathy, retinal detachment, retinal vein obstruction and cataracts.

10.9.1.1.3. Utility increment to account for improved light sensitivity

Voretigene neparvovec is associated with improved light sensitivity, even when controlling for health state as defined by VA and VF (see Section 4.2.5). An exploratory scenario is therefore considered in which a hypothetical utility increment of 0.05 is applied to the mildest three health states in the VN arm only.

10.9.2 Adverse event disutilities

Adverse events included in the cost-effectiveness analysis are cataracts, eye inflammation, and increased IOP (see Section 10.8). Disutilities for AEs are applied as a one-off QALY loss at the time of VN treatment. The QALY loss associated with each included AE is calculated as the product of the utility decrement, the duration in months and the proportion of patients experiencing each event in Study 301/302 [4].

The utility decrements and durations of event for cataracts and eye inflammation were sourced from Appendix J of NICE guideline 82 on age-related macular degeneration (AMD) [170]. In the absence of other data, the utility decrement for increased IOP is conservatively assumed to be the same as that for uncontrolled/severe glaucoma [171]. The duration of increased IOP is assumed to be one month, given that all increased IOP events observed in Study 301/302 were fully resolved within one month [19].

Table 28: AE disutilities

Event in OI arm	Utility decrement	Duration (months)	Proportion of patients
Cataract	0.14	1.0	15%
Eye inflammation	0.30	3.6	10%
Increased IOP†	0.10	1.0	20%

Abbreviations: AE, adverse event; IOP, increased intraocular pressure; OI, Original Intervention.
†No disutility data associated with increased IOP were identified.

10.9.2.1 Scenarios

A hypothetical scenario is considered in which an additional disutility of 0.1 is applied for one month in all patients to account for any discomfort or inconvenience associated with the administration procedure.

10.9.3 Carer disutility

A systematic review by Wittenberg et al found that parents of children with activity limitations have a 0.08 lower EQ-5D score than parents of children without activity limitations [172]. This carer disutility is applied to individuals in the four most severe health states up to the age of 18. In the absence of other data, it is assumed that the disutility for carers of adults with *RPE65*-mediated IRD is half that of carers of children with *RPE65*-mediated IRD (i.e. a disutility of 0.04).

10.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical experts informed the development of health state vignettes and estimated utility values as part of the Acaster Lloyd study. See Section 10.9.1 and Appendix 9 for further details.

10.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Health-related quality of life is assumed to stay constant within individual health states.

10.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials were excluded from the analysis.

10.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

State-specific HRQL estimates were used in the economic model; no specific baseline quality of life was assumed beyond this.

10.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant within health states. As patients progress through the model towards poorer health states over time, worsening HRQL is implied over time also.

10.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

As described in Section 10.9.2, disutility scores are applied to capture the effect of treatment or procedure-related AEs associated with VN at the start of the model.

Treatment continuation rules

10.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**
- **Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

A treatment continuation rule has not been considered because VN is approved as a one-time treatment. No data exist on the safety and efficacy associated with repeat injections. Detachment of the retina associated with multiple

vitrectomies could lead to irreversible damage to the retina and consequently to patients' vision. This is of particular importance in paediatric populations, as the anatomy of the eye changes between childhood and adulthood [183, 184].

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

A systematic review was conducted to retrieve studies reporting cost-effectiveness data for VN compared with BSC in *RPE65*-mediated IRD. The searches were run on 8th March 2018, and were updated on 11th January 2019.

Details of search strings, databases searched, hand searching and inclusion/exclusion criteria are provided in Appendix 3.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in Table 29 below. Other headings should be used if necessary.

The following inclusion and exclusion criteria were applied to identify published and unpublished cost-effectiveness studies (Table 29).

Table 29: Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with IRD caused by *RPE65* gene mutations
Interventions	• Voretigene neparvovec • Best supportive care
Outcomes	• Direct costs • Utilities

	• ICER • LYs • QALYs
Study design	• Economic evaluation alongside clinical trials • Economic evaluation modelling studies
Language restrictions	English
Search dates	From inception of database to 8th March 2018 (original search) and 11th January 2019 (updated search)
Exclusion criteria	
Population	IRD due to gene mutations other than *RPE65*
Interventions	• Gene therapy using other vectors (e.g. rAAV2-CBSB-hRPE65, tgAAG76, rAAV2-CB-hRPE65, rAAV2/4.hRPE65, rAAV2-hRPE65) • Other oral preventive drugs (e.g. QLT091001, oral synthetic cis-retinoid)
Outcomes	None
Study design	Reviews/editorials/notes/opinions/case reports
Language restrictions	Languages other than English
Search dates	None

Abbreviations: ICER, incremental cost-effectiveness ratio; IRD, inherited retinal dystrophies; LY, life year; QALY, quality-adjusted life year; RPE65, retinal pigment epithelium 65kDa protein.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

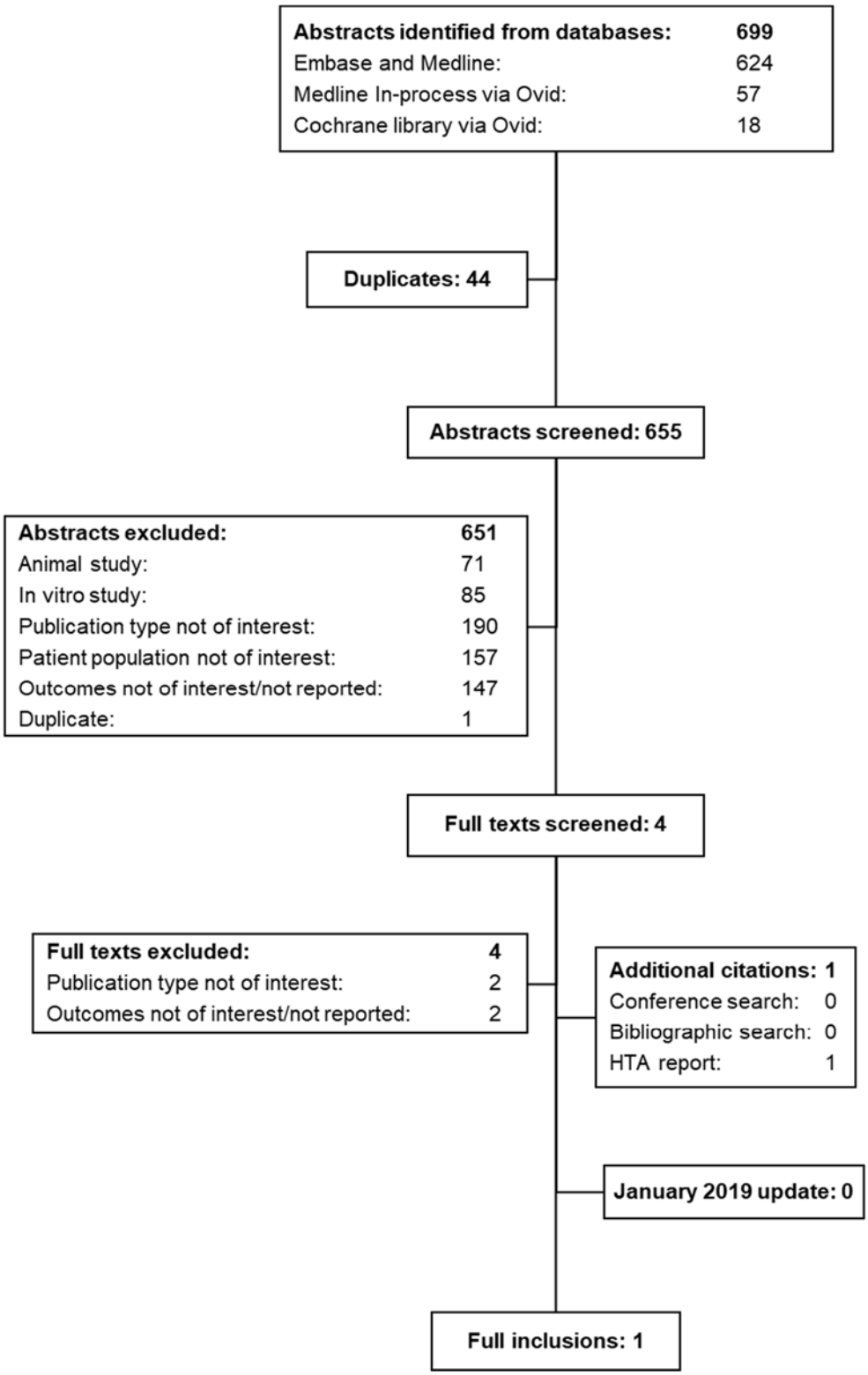
In the original search, 699 papers were identified through the electronic searches. Upon the removal of duplicate papers, 655 titles and abstracts were reviewed. A total of four papers were potentially relevant and were ordered for full paper review. At this stage, a further four papers were excluded. Hand searching yielded one additional relevant paper, resulting in a total of one paper for final inclusion in the original review.

In the January 2019 update, 124 papers were identified through the electronic searches. Upon the removal of duplicate papers, 80 titles and abstracts were reviewed. None of these papers were relevant so none were ordered for full paper review. Hand searching yielded no additional relevant papers.

Across the original review and the January 2019 update, one study was identified for final inclusion in the review.

The flow of studies through the review is reported in the PRISMA flow diagram in Figure 25. Separate PRISMA diagrams for the original and updated reviews are presented in Appendix 3.

Figure 25: PRISMA flow diagram for published and unpublished cost-effectiveness evidence



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in Table 30.

Hand searching of HTA websites identified one record from the Institute for Clinical and Economic Review (ICER). ICER developed an economic model to estimate the cost-effectiveness of VN for vision loss associated with biallelic *RPE65*-mediated IRD compared to standard of care (SoC) [185]. The study is described in Table 30.

Table 30: Summary of identified economic evaluations

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
ICER 2018	US	VN *vs.* standard of care (SoC)	Reflects the Study 301 trial population. Assumed mean age of 15 years and 43% male. An alternative population was modelled with a mean age of three years.	Direct medical costs as well as direct nonmedical costs and indirect costs for education, productivity loss, informal care, and nursing home care.	Utility values were based on visual ability in terms of VA or VF (i.e. health states). VN provided patients with an additional 1.3-2.1 QALYs if treated at age 15, and 2.7-4.4 additional QALYs if treated at age 3.	Incremental cost per QALY: • Age 15: $228,000 - $644,000 • Age 3: $16,000 - $288,000

Abbreviations: ICER, Institute for Clinical and Economic Review; QALY, quality-adjusted life year; SoC, standard of care; US, United States; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in Table 31.

Table 31: Quality assessment of ICER 2018 study [185]

Study question	Response (yes/no/not clear/N/A)
1. Was the research question stated?	Yes
2. Was the economic importance of the research question stated?	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes
5. Were the alternatives being compared clearly described?	Yes
6. Was the form of economic evaluation stated?	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes
8. Was/were the source(s) of effectiveness estimates used stated?	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes
12. Were the methods used to value health states and other benefits stated?	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Yes
14. Were productivity changes (if included) reported separately?	Yes
15. Was the relevance of productivity changes to the study question discussed?	Yes
16. Were quantities of resources reported separately from their unit cost?	Yes
17. Were the methods for the estimation of quantities and unit costs described?	Yes
18. Were currency and price data recorded?	Yes
19. Were details of price adjustments for inflation or currency conversion given?	Yes
20. Were details of any model used given?	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes
22. Was the time horizon of cost and benefits stated?	Yes
23. Was the discount rate stated?	Yes

24. Was the choice of rate justified?	Yes
25. Was an explanation given if cost or benefits were not discounted?	Yes
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes
27. Was the approach to sensitivity analysis described?	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes
29. Were the ranges over which the parameters were varied stated?	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes
31. Was an incremental analysis reported?	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes
33. Was the answer to the study question given?	Yes
34. Did conclusions follow from the data reported?	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes
36. Were generalisability issues addressed?	Yes

Abbreviations: N/A, not applicable.

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

- Voretigene neparvovec is associated with an ICER of [redacted] per QALY gained when compared against BSC, assuming the proposed PAS price.
- Voretigene neparvovec is associated with significant QALY gains (20 undiscounted QALYs gained versus BSC), and therefore qualifies for additional weighting. ICERs at list price and PAS price are significantly below the weighted threshold of £200,000 per QALY.
- The conclusion of cost-effectiveness at a threshold of £200,000 per QALY gained was found to be robust to extensive sensitivity and scenario analyses.
- Cost-effectiveness was assessed using a Markov state-transition model, with health states defined based on progressive visual impairment.
- Although MLMT was the primary endpoint in Study 301/302, no data are available linking this outcome to costs, utilities or mortality, and no data are available on the long-term change in this outcome – it was therefore not possible to define health states based on MLMT.
- MLMT is a functional endpoint that captures changes in light sensitivity (FST), visual acuity (VA) and visual field (VF), and so health states defined

by a combination of these three endpoints were considered; however, FST is associated with similar challenges to MLMT in terms of data availability.

- Model health states were therefore defined based on either VA or VF, whichever was worst at each time point.
- Short-term data on clinical effectiveness are taken from Study 301/302 (the pivotal clinical trial).
- Longer-term evidence on the baseline decline in visual function over time is taken from RPE65 NHx (a retrospective chart review in individuals with *RPE65*-mediated inherited retinal dystrophy).
- The treatment effect of VN is assumed to be maintained for 40 years, followed by a 10-year waning period; a residual treatment effect is applied for the remainder of the model time horizon.
- Utility values are taken from a bespoke utility study, conducted to estimate utility values associated with each of the pre-defined model health states.
- Considered costs include acquisition, administration and monitoring costs associated with VN; healthcare resource use costs; and costs associated with adverse events.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The population considered in this analysis is individuals with *RPE65*-mediated IRD who have sufficient viable retinal cells[9]. This is in line with the population

[9] Sufficient viable retinal cells was defined in Study 301 as 1) an area of retina within the posterior pole of > 100 micron thickness as shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy; or 3) remaining visual field within 30º of fixation.

considered in Study 301/302 [4] (see Section 4.1), the Marketing Authorisation for VN [3] (see Section 3.1), and the final scope issued by NICE [186] (see Section 1).

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

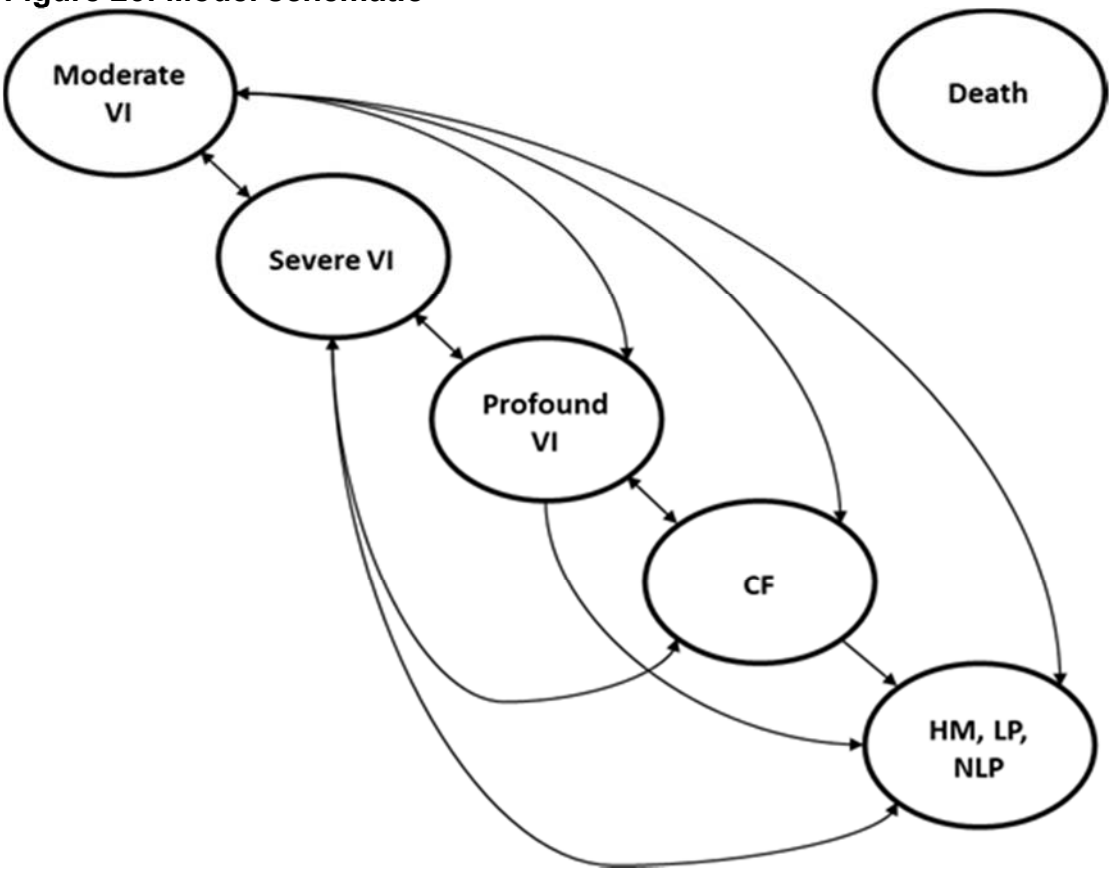
Not applicable.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

The model schematic is presented in Figure 26.

Figure 26: Model schematic



Abbreviations: CF, counting fingers; HM, hand motion; NLP, no light perception; VI, visual impairment.

The economic model adopted a Markov state transition structure. Cohort based models have been used previously in the modelling of VN [185], other products

in retinitis pigmentosa [187], and other retinal conditions [188]. Patient-level approaches have also been used in retinal conditions due to the ability to model vision in both eyes [188]. However, this was considered less important in this case due to the bilateral nature of the disease and relative symmetry of visual impairment (Section 6.1.3) [189]. Scenarios considering either the average of vision in the two eyes or in the best-seeing eye only are associated with a negligible difference in results (see Section 12.5.11). Furthermore, the advantages of a patient-level approach would be limited by a relative lack of available data with which to generate statistical relationships.

The model was structured around the following health states:

- HS1: Moderate visual impairment (VI)
- HS2: Severe VI
- HS3: Profound VI
- HS4: Counting fingers (CF)
- HS5: Hand motion (HM), light perception (LP) to no light perception (NLP)
- HS6: Death

Health state definitions are detailed in Section 12.1.6.

Patients were exposed to the risk of mortality in all health states (other than HS6). Mortality associated with visual impairment has been observed previously (see Section 12.1.8.4) [95], and such effects have been included in previous health technology appraisals in retinal conditions [190]. However, most sources of such effects are derived in older populations. Christ et al found that visual impairment affects mortality directly after adjustment is made for covariates, including chronic conditions and other health indicators [191]. Visual impairment was also found to affect mortality indirectly through self-rated health and disability. The base-case analysis therefore assumes that visual impairment is associated with an increased risk of mortality, and this is removed in a scenario analysis.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

Costs, quality of life and mortality in individuals with *RPE65*-mediated IRD are expected to vary depending on level of visual impairment. In this model, visual impairment was defined based on the worst of VA and VF. Health state definitions and justifications for the use of VA and VF are provided in Section 12.1.6.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Component of model	Assumption	Justification
Model structure	Implementing a maximum age of 100 years is approximately equivalent to modelling a lifetime time horizon	1.15% of males and 2.73% of females are expected to survive past 100 years of age [192]; a 100-year time horizon is therefore expected to capture the majority of lifetime costs and QALYs
	The benefit of VN is observed at 1 month	A statistically significant difference from baseline was observed in the Original Intervention arm of Study 301 at 1 month (see Figure 10)
	In the first year, individuals may move to either better or worse health states	Data from Study 301 are used to inform the transitions in the first year, and movement to both better and worse states was observed in both arms of the clinical trial
	Beyond the first year, individuals may only move to worse health states	Expert clinical opinion confirmed that without intervention both VA and VF worsen over time [9]
	The health state distribution based on the first year of trial data in the Original Intervention arm is maintained for 40 years	A long-term treatment effect is supported by UK clinical experts [9] on the basis of the VN clinical trial programme and preclinical studies (see Section 12.2.1 for further details)
	Following the 40-year maintenance of treatment effect, this treatment effect is assumed to wane over a 10-year period	This assumption is based on UK clinical expert advice [9]
	In the long-term phase, the probability of progressing to a worse health state is assumed to be reduced by 25% in the VN arm	It is considered implausible that VN patients would experience the same decline as BSC patients following a period of time in which this decline is greatly reduced; in the absence of data an estimate of 25% is assumed

Component of model	Assumption	Justification
Clinical data	Patients included in Study 301 are representative of the UK population of individuals with *RPE65*-mediated IRD, who have sufficient viable retinal cells†	The trial population is considered to be broadly representative of the real-world population of interest because: • Inclusion and exclusion criteria are not considered to be overly restrictive, given that of the 36 screen subjects, only five (14%) were screen failures • Recruiting centres are expected to be broadly representative of real-world treatment centres, given that VN will be administered at a small number of specialised treatment centres
	Patients included in the natural history study (RPE65 NHx) are representative of the UK population of individuals with *RPE65*-mediated IRD, who have sufficient viable retinal cells	*RPE65* NHx is a retrospective chart review study, and so may be expected to reflect the real-world patient population
	In the initial phase, patients with no transition data move the same number of health states as those in the previous health state	The transitions that were not observed are expected to be possible in clinical practice; in the absence of evidence to inform these transitions directly, data relating to the next least severe health state were considered the best estimates of these parameters
	The most appropriate distribution for the long-term multistate survival model is the Weibull distribution	The Weibull distribution performed well on both AIC and BIC measures, and visual fit based on inspection of the residuals (Section 12.1.8.3.3)
	Increased visual impairment is associated with excess mortality	Christ et al [95] demonstrated that worsening in VA is associated with a statistically significant increase in mortality

Component of model	Assumption	Justification
Utility data	The disutility for carers of adults with *RPE65*-mediated IRD is half that of carers of children with *RPE65*-mediated IRD	This is assumed in the absence of other data. A scenario is considered in which carer disutility is excluded.
Cost data	Individuals leave school at age 18, and retire at age 65	50.4% of 18 year olds are in full-time education [193]. The current age for receiving a state pension is 65 years [194].

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IRD, inherited retinal dystrophies; NHx, natural history study; QALY, quality-adjusted life year; RPE65, retinal pigment epithelium 65 kDa protein; VA, visual acuity; VI, visual impairment; VN, voretigene neparvovec.
† Sufficient viable retinal cells was defined in Study 301 as 1) an area of retina within the posterior pole of > 100 micron thickness as shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy; or 3) remaining visual field within 30º of fixation.

12.1.6 Define what the model's health states are intended to capture.

The modelled health states are intended to capture progressively severe levels of visual impairment[10] and death. MLMT was the primary endpoint in Study 301/302, however no data are available linking this outcome to costs, utilities or mortality, and no data are available on the long-term change in this outcome. MLMT is an objective measure of functional vision that captures changes in each of FST, VA and VF (see Section 9.4.1.1.1), and so health states defined by a combination of these three endpoints were considered; however, FST is associated with similar challenges to MLMT in terms of data availability. It was therefore determined that visual impairment would be modelled based on a combination of VA and VF[11]. A scenario analysis is considered in which health states are defined based on VF only, on the basis that VN was not associated with a statistically significant difference in VA using the Holladay scale; however it should be noted that VN was associated with a statistically significant difference in VA in a post-hoc analysis using the Lange scale (see Section 9.6.1.1.4).

Modelled health states are determined based on the worse of VA and VF[12], with cut-off points between health states derived using American Medical Association (AMA) guidelines [195] (see Table 32).

Table 32: AMA guidelines on impairment classes

Impairment class	VA (LogMAR)	VF (º)
Moderate low vision	Better than 1.0	> 240
Severe low vision	1.0 – 1.4	≤ 240 and > 144
Profound low vision	1.4 – 1.8	≤ 144 and > 48
Near-blindness	Worse than 1.8	≤ 48
Total blindness	NLP	No VF

Abbreviations: AMA, American Medical Association; LogMAR, Logarithm of the Minimum Angle of Resolution; NLP, no light perception; VA, visual acuity; VF, visual field.
Source: AMA 2007 [195]

[10] Progressively severe levels of visual impairment are expected to be associated with increased costs, lower utility values and an increased risk of death.
[11] The cost-effectiveness analysis conducted by ICER in the US setting (VN vs. standard of care) also considered health states based on a combination of VA and VF [185].
[12] Although overall visual impairment may be considered a function of both VA and VF, there is no consensus on the most appropriate form of this function. A simplified approach was therefore taken in which health states are defined based on the worst of the two quantities.

AMA guidelines are used rather than UK Royal National Institute of Blind People (RNIB) guidelines, because unlike the RNIB guidelines, the AMA guidelines provide clear numerical cut-off points for different health states, avoiding ambiguity in interpretation. The manufacturer is not aware of any other guidelines that use unambiguous cut-off points. In addition, the AMA guidelines divide level of visual impairment into five categories, as compared with the two categories considered in the RNIB guidelines; this allows for greater granularity when modelling changes in vision.

According to the RNIB guidelines [196], all patients in health state 2 (severe visual impairment) onwards would be classified as blind, and a proportion of patients in health state 1 (moderate visual impairment) would be classified as blind, depending on the extent of visual field loss; blindness is classified as any of the following:

- Visual acuity of 3/60 (~1.3 logMAR) to 6/60 (1.0 logMAR) with a full field of vision
- Visual acuity of up to 6/24 (~0.6 logMAR) with a moderate reduction of field of vision or with a central part of vision that is cloudy or blurry
- Visual acuity of 6/18 (~0.5 logMAR) or even better if a large part of their field or a lot of peripheral field is missing

Visual field health state occupation is defined in the model based on Goldmann perimetry testing using a III4e target (other VF tests were used in Study 301/302 but these do not inform model health states; see Section 9.4.1.1.6).

Modelled health states (see Table 33) align with the AMA guidelines, except in the two worst health states – 'near-blindness' and 'total blindness' are re-categorised as 'CF'[13] and 'HM, LP, NLP' on the basis that:

[13] Using the Holladay scale for VA, CF is assigned the VA score of 3. Note that although the Holladay and Lange scales are associated with differing scores in the clinical analysis, use of the Lange scale would not result in differing health state assignment.

- Brown et al [180] found the CF health state to be associated with substantially different utility values compared with the HM, LP and NLP states

- In the natural history data used to model long-term changes in VA and VF, few observations in the HM, LP and NLP states were recorded, and so it was considered reasonable to group these states

Table 33: Modelled health states (excluding death)

	Worst of:		
Health state	**VA (LogMAR)**		**VF (º)**
HS1: Moderate VI	Better than 1.0	or	> 240
HS2: Severe VI	1.0 – 1.4	or	≤ 240 and > 144
HS3: Profound VI	1.4 – 1.8	or	≤ 144 and > 48
HS4: CF	1.8 – 3.0	or	≤ 48
HS5: HM, LP, NLP	Worse than 3.0 or an indication of HM, LP, or NLP		-

Abbreviations: AMA, American Medical Association; CF, counting fingers; HM, hand motion; HS, health state; LogMAR, Logarithm of the Minimum Angle of Resolution; LP, light perception; NLP, no light perception; VA, visual acuity; VF, visual field; VI, visual impairment.

In the base-case, health state membership is assigned based on the worst of VA and VF in the 'average eye'[14], with the best-seeing eye[15] considered in a scenario analysis. Modelling the average eye as opposed to the best-seeing eye allows for changes in both eyes to be captured; however, the difference in results between the two approaches is negligible (see Section 12.5.11).

[14] The average eye is calculated by averaging the VA and VF observed in each eye at each time point.
[15] The best-seeing eye is defined as the eye that would be placed in the mildest health state at the time point being considered.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in Table 34.

Table 34: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Outcomes	Cost per QALY gained; additional outcomes reported	This approach is in line with the NICE reference case [197].	NICE 2013 [197]
Time horizon	Lifetime (maximum age of 100 years)	A lifetime time horizon captures differential outcomes over the lifetime of the individual. This approach is in line with NICE guidance, which states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared [197].	NICE 2013 [197]
Discount rate for costs and outcomes	3.5%	This is in line with current NICE guidance [197]. A scenario analysis is considered in which costs and outcomes are discounted at 1.5%. Discount rates of 1.5% are consistent with those which may be considered by the NICE Appraisal Committee if it is highly likely that, on the basis of the evidence presented, long-term health benefits (normally at least 30 years) are likely to be achieved and that the technology does not commit the NHS to significant irrecoverable costs [198]. A discount rate of 1.5% may be appropriate for VN as it is a one-time treatment, and in Study 301 14/20 (70%) of patients were in the best health state (i.e. moderate VI) at Year 1 following treatment; and this effect is expected to be long-term.	NICE 2013 [197]
Perspective	NHS and PSS in England and Wales	The perspective on cost is that of the NHS and PSS in England and Wales, in line with current NICE guidance [197]. Costs falling outside of the healthcare system are included in scenario analyses. The perspective on outcomes includes direct health effects for patients and carers, in line with current NICE guidance [197].	NICE 2013 [197]
Cycle length	1 year	This reflects the relatively slow rate of visual decline in this population (Section 6.1.3). Half-cycle correction is implemented using the life table method[16]. In the first cycle, the model is 1/12th cycle corrected to reflect the rapid improvement in	Study 301 CSR [19]

[16] The time in a given cycle is estimated by taking the average of the number of people at the start and end of the cycle.

Factor	Chosen values	Justification	Reference
		the Original Intervention arm which is observed at approximately 1 month (Figure 10) [19].	

Abbreviations: CSR; clinical study report NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life year; VI, visual impairment; VN, voretigene neparvovec.

12.1.8 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

The model consists of two phases:

- Initial phase
- Long-term phase; in the VN arm, the long-term phase is split into:
    - Maintenance of treatment effect
    - Waning of treatment effect
    - Residual treatment effect

In the initial phase, data from Study 301 are used to inform the transition probabilities between baseline and Year 1 in each of the BSC and VN arms. Significant changes in outcomes beyond Year 1 were not observed in the Original Intervention arm of Study 301/302 (Section 9.6.1.1). Therefore, data from Years 2 and 3, whilst available, were not used directly because the distribution of patients across health states would be essentially the same as the assumption of maintenance beyond Year 1: only one subject in the Original Intervention arm was observed to transition between health states during Years 2 and 3. In Year 1, individuals may move to either better or worse health states.

In the long-term phase, natural history data in individuals with *RPE65*-mediated IRD are used to model the long-term decline in visual function in this population. In this phase, individuals may only progress to a worse health state.

In the VN arm, a relative risk reduction (RRR) is applied to the health state transitions implied by the natural history data[17]. The way in which this RRR changes over time is presented in Table 35 and Figure 27 (see Section 12.2.1 for further details).

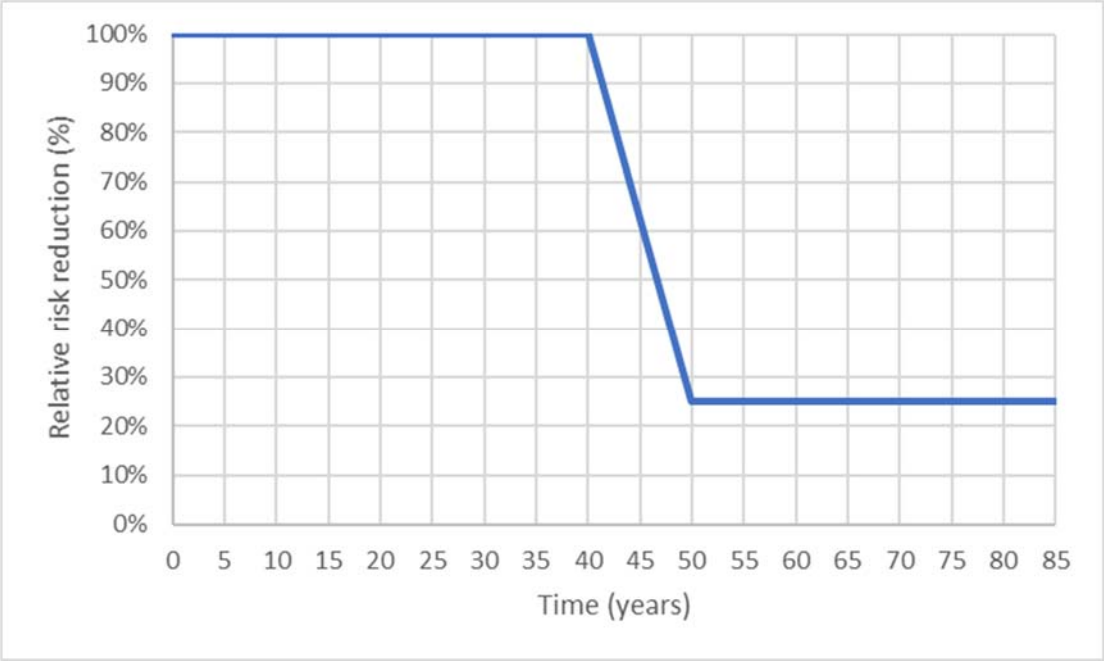
[17] Note that the RRR following the maintenance period is applied to the natural history transitions from the *start* of the multistate survival model, rather than those specific to the patient's current age.

Table 35: Time periods within the long-term phase for VN patients

Time period	Description	RRR compared with natural history transitions	Rationale
Maintenance of treatment effect	The Year 1 health state distribution is maintained for 40 years	100%	• A long-term treatment effect is supported by UK clinical experts (Section 12.2.4) [9] on the basis of the VN clinical trial programme and preclinical studies • See Section 12.2.1 for further details
Waning of treatment effect	The treatment effect wanes over a period of 10 years	Declining linearly from 100% to 25%	• This assumption is based on UK clinical expert advice [9]
Residual treatment effect	A residual treatment effect is applied for the remainder of the model time horizon	25%	• A residual treatment effect is assumed because it is considered implausible that VN patients would experience the same decline as BSC patients following a period in which a substantial reduction in decline is observed • In the absence of other data, an arbitrary residual effect of 25% is assumed • Scenario analyses considering values of 0% (i.e. no residual effect) and 50% are associated with negligible changes in the ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; RRR, relative risk reduction; VN, voretigene neparvovec.

Figure 27: Relative risk reduction compared with natural history transitions in the VN arm over time



Abbreviations: VN, voretigene neparvovec.

Clinical data used in the economic evaluation include:

- Baseline health state distributions (Section 12.1.8.1)
- In-trial transition probabilities (Section 12.1.8.2)
- Long-term multistate survival model (Section 12.1.8.3)
- Mortality (Section 12.1.8.4)
- AEs (Section 12.2.3)
- MLMT and FST (Section 12.1.8.5)

12.1.8.1 Baseline health state distributions

Baseline health state distributions were available from each of Study 301 [19] and RPE65 NHx (a retrospective chart review in individuals with *RPE65*-

mediated inherited retinal dystrophy) [28][18]. Data from Study 301 were used in the base-case to ensure consistency with clinical data used in the initial phase.

Baseline data were generated for the base-case and each of the following scenarios (including all relevant combinations):

- Data taken from RPE65 NHx (a retrospective chart review in individuals with *RPE65*-mediated inherited retinal dystrophy; see Section 12.1.8.3.1) [28]
- Health states based on VF only (see Section 12.1.6.)
- Health states based on best-seeing eye (see Section 12.1.6.)

For each combination of options, the average age and gender distribution were generated. The baseline health state distribution used in the base-case is presented in Table 36.

Table 36: Baseline health state distribution

	HS1	HS2	HS3	HS4	HS5
Baseline health state	23%	32%	23%	19%	3%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

12.1.8.2 In-trial transition probabilities

In order to inform the initial phase of the cost-effectiveness model, transition probability (TP) matrices were required for each of the VN and BSC arms. Crossover data[19] were included in the VN arm in a scenario in order to make best use of data from a small number of patients; however, this analysis does not reflect a randomised comparison, and so is not presented in the base-case.

TP data were generated for the base-case and each of the following scenarios (including all relevant combinations):

- Crossover data included

[18] A natural history study in individuals with RPE65-mediated IRD; see Section 12.1.8.3.1 for further details.
[19] In this analysis, Control/Delayed Intervention patients at one year (i.e. at the point at which these patients cross over to receive treatment) are combined with Original Intervention patients at baseline.

- Health states based on VF only (see Section 12.1.6.)
- Health states based on best-seeing eye (see Section 12.1.6.)

12.1.8.2.1. Count data

Transition count data were calculated based on observations at baseline and 1-year follow-up in Study 301. No data were available at 1-year follow-up for the two withdrawn patients, and so this analysis is based on the mITT population including patients who did not withdraw. Data were therefore available for 20 patients in the VN arm and nine patients in the BSC arm. The only exception to this is in scenarios in which health states were based on VF only: one observation is missing at baseline in the VN arm, and so transition probabilities could only be calculated in 19 patients

Count data for the base-case are presented in Table 37 and Table 38 for the BSC and VN arms, respectively.

Table 37: Health state transition count data (BSC arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	3	0	0	0	0
	HS2	1	2	0	1	0
	HS3	0	0	1	0	0
	HS4	0	0	1	0	0
	HS5	0	0	0	0	0

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care.

Table 38: Health state transition count data (VN arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**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

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: VN, voretigene neparvovec.

12.1.8.2.2. Exact TP approach

No data are available to inform TPs from health state 5 (hand motion to no light perception) in any of the considered scenarios. Whilst one patient (3%) of 31 trial participants was in health state 5 at baseline, this patient subsequently withdrew from the study.

Two options are therefore included in the model:

- Patients in health states with no transition data move the same number of health states as those patients in the next least severe health state (base-case)
    - For example, in the VN arm the probability of moving from HS4 to HS1 (a three-state improvement) was 50%. Under this assumption, the probability of moving from HS5 to HS2 (a three-state improvement) would be set to 50%.
- Patients in health states with no transition data remain in the same state at Year 1

In the base-case, patients in health states with no transition data are assumed to move the same number of health states as those patients in the next least severe health state. This assumption was chosen on the basis that the transitions which were not observed were expected to be possible in clinical practice; in the absence of evidence to inform these transitions directly, data relating to the next least severe health state were considered the best estimates of these parameters. TP matrices calculated on this basis are presented in Table 39 and Table 40. This approach is referred to as the 'exact TP' approach. The exact TP approach was preferred to the 'adjusted TP' approach (see below) because this approach best represented the trial data as observed; the adjusted TP approach was considered in sensitivity analysis.

Table 39: Exact TP matrix (BSC arm)

		Health state at 1-year follow-up				
Health state at baseline		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**
	HS1	100%	0%	0%	0%	0%

	HS2	25%	50%	0%	25%	0%
	HS3	0%	0%	100%	0%	0%
	HS4	0%	0%	100%	0%	0%
	HS5	0%	0%	0%	100%	0%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; TP, transition probability.

Table 40: Exact TP matrix (VN arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	100%	0%	0%	0%	0%
	HS2	83%	17%	0%	0%	0%
	HS3	50%	50%	0%	0%	0%
	HS4	50%	0%	25%	25%	0%
	HS5	0%	50%	0%	25%	25%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: TP, transition probability; VN, voretigene neparvovec.

12.1.8.2.3. Adjusted TP approach (scenario only)

It was observed that when using the exact TP approach, some transitions were associated with zero probabilities, despite being theoretically possible. For example, in Table 40, 50% of patients in health state 4 at baseline move to health state 1, while no patients move to health state 2. This is likely due to the low patient numbers in Study 301.

An alternative approach was therefore considered in which the count data were adjusted according to the following steps:

- The proportions of patients moving into health state 1 from each other health state were assumed to be the same as in the exact TP approach, given that these transitions are relatively well populated

- In health states 2 to 4, observed transitions were adjusted according to the proportion of patients observed to improve (move to a milder health state), deteriorate (move to a worse health state), or remain stable (remain in the same health state)

- This was either calculated for each state separately, or aggregated for all states – referred to as the 'adjusted TP (state-dependent)' and 'adjusted TP (state-independent)'[20] approaches, respectively

- The count data for those improving, deteriorating and remaining in the same health state for each of the state-dependent and state-independent approaches are presented in Table 41 and Table 42, respectively.

Table 41: Deterioration/improvement (BSC arm)

Health state at baseline	Deteriorated	Stable	Improved
HS2	1	2	0
HS3	0	1	0
HS4	0	0	1
HS5	0	0	0
Overall (state-independent)	1	3	1

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care.

Table 42: Deterioration/improvement (VN arm)

Health state at baseline	Deteriorated	Stable	Improved
HS2	0	1	0
HS3	0	0	3
HS4	0	1	1
HS5	0	0	0
Overall (state-independent)	0	2	4

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: VN, voretigene neparvovec.

Transition probabilities are reassigned as follows:

- The proportion who deteriorated is split evenly across all health states between health state 2 and 5 that are worse than the starting health state

- The proportion who improved is split evenly across all health states between health state 2 and 5 that are better than the starting health state

[20] The state-independent approach allows for the use of limited available data to be maximised, but relies on the assumption that improvement or deterioration is independent of starting health state; results from this scenario analysis are therefore interpreted with caution.

- The proportion remaining in the same state is assumed to be the same as in the exact TP approach

If the state-independent approach is taken, there may be a proportion assumed to improve from health state 2, or a proportion assumed to deteriorate from health state 5; in this case, this proportion is assumed to remain in the starting health state. The state-dependent and state-independent adjusted TPs are presented in Table 43 to Table 46.

Table 43: Adjusted TP matrix, state-dependent (BSC arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	100%	0%	0%	0%	0%
	HS2	25%	50%	8%	8%	8%
	HS3	0%	0%	100%	0%	0%
	HS4	0%	50%	50%	0%	0%
	HS5	0%	33%	33%	33%	0%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; TP, transition probability.

Table 44: Adjusted TP matrix, state-dependent (VN arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	100%	0%	0%	0%	0%
	HS2	83%	17%	0%	0%	0%
	HS3	50%	50%	0%	0%	0%
	HS4	50%	13%	13%	25%	0%
	HS5	0%	25%	25%	25%	25%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: TP, transition probability; VN, voretigene neparvovec.

Table 45: Adjusted TP matrix, state-independent (BSC arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	100%	0%	0%	0%	0%
	HS2	25%	60%	5%	5%	5%
	HS3	0%	20%	60%	10%	10%
	HS4	0%	10%	10%	60%	20%
	HS5	0%	7%	7%	7%	80%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; TP, transition probability.

Table 46: Adjusted TP matrix, state-independent (VN arm)

		Health state at 1-year follow-up				
		HS1	**HS2**	**HS3**	**HS4**	**HS5**
Health state at baseline	**HS1**	100%	0%	0%	0%	0%
	HS2	83%	17%	0%	0%	0%
	HS3	50%	33%	17%	0%	0%
	HS4	50%	17%	17%	17%	0%
	HS5	0%	22%	22%	22%	33%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: TP, transition probability; VN, voretigene neparvovec.

12.1.8.3 Long-term multistate survival model

In order to inform the long-term natural history of the disease under standard of care, patient-level data from the "Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the *RPE65* Gene (RPE65 NHx)" study were used [28].

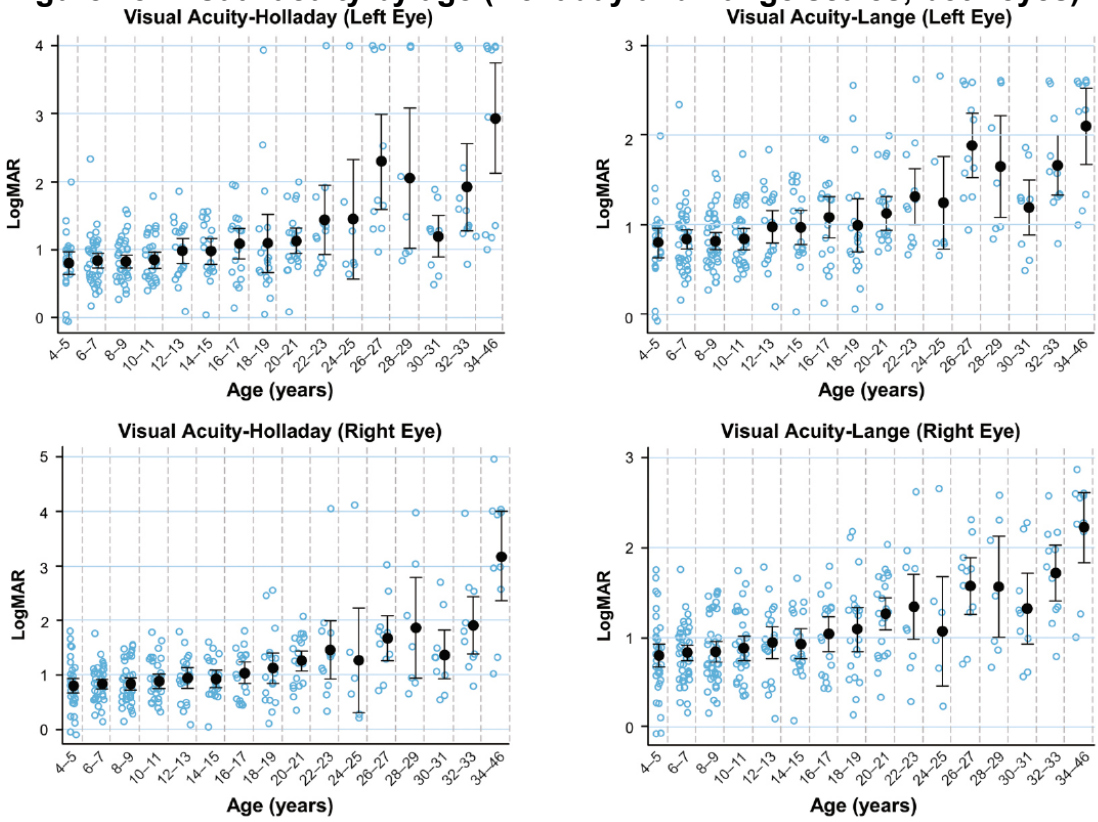
12.1.8.3.1. Data

RPE65 NHx is a retrospective chart review study designed to describe the natural history of retinal degenerative disease in individuals with confirmed biallelic mutations in the *RPE65* gene [28]. All patients with confirmed mutations, from seven international centres, were enrolled in this study and their charts were collected, after redaction of protected health information. Longitudinal ocular history and visual function testing data were abstracted from the collected charts and analysed.

A total of 70 subject charts are included in the dataset, with a mean age of 15 (the youngest participant was one year old, and the oldest 43 years old). The mean duration of follow-up was 7.28 years. Previous analysis of the dataset found that a statistically significant effect of age on VA ($p<0.001$) was observed for both the left and right eyes, regardless of whether scales adapted from Lange or Holladay were used for the conversion of "off-chart" assessments to LogMAR [28]. The relationship was non-linear, with different rates of change depending on age. There was a high degree of individual variability; however, in general, VA worsened with age (Figure 28). There was a negative

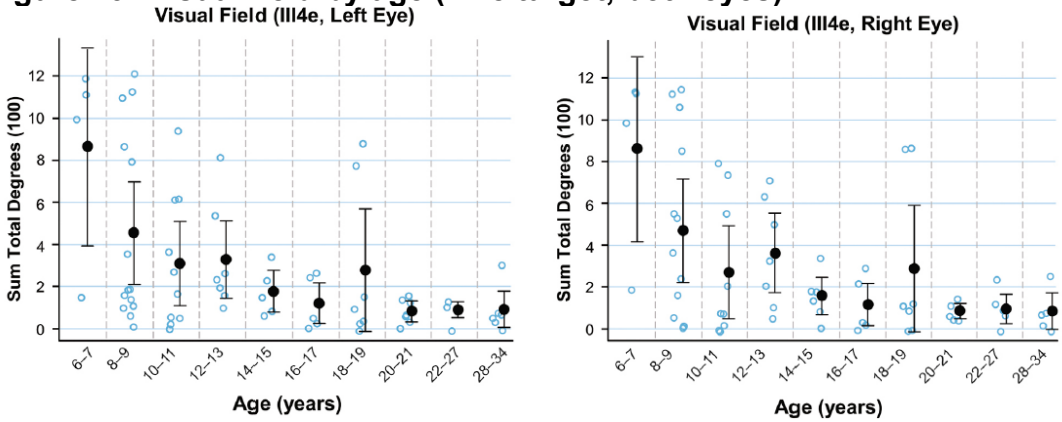
relationship between age and Goldmann kinetic VF for both eyes. When age increased, VF decreased (worsened) (Figure 29).

Figure 28: Visual acuity by age (Holladay and Lange scales, both eyes)



Abbreviations: LogMAR, Logarithm of the Minimum Angle of Resolution.
Source: Chung 2018 [199]

Figure 29: Visual field by age (III4e target, both eyes)



Source: Chung 2018 [199]

12.1.8.3.2. Methods

A multistate model of disease progression was developed using methods detailed by Crowther & Lambert [200]. Multistate models have recently been

the subject of NICE Decision Support Unit guidance [201] in the context of oncology modelling (specifically, in contrast to the use of partitioned survival models).

A multistate survival model allows for the risk of moving between health states to vary over time, as may be expected in clinical practice. Multiple alternative survival distributions can be tested to determine the most plausible extrapolation of observed data, including the assumption of constant risk (i.e. the exponential distribution). In addition, by parameterising the risks of moving between health states, this approach allows for parameters determining the long-term health state distribution to be tested in univariate and probabilistic sensitivity analysis.

The statistical model of disease progression and definitions of health states mirrored that used in the economic evaluation more generally (described in Section 12.1.6); however, no death events were observed in the natural history data, and so transitions to the 'Dead' health state were applied separately (see Section 12.1.8.4). Last observation carried forward was used for missing data (but '0' scores were not imputed).

The multistate model was pre-specified as progressive only, so progression was enforced (i.e. patients were not allowed to 'improve' health states between visits); this was both consistent with the understanding of the progressive nature of the disease and was also associated with a simplified implementation (vs models which permit backwards progression).

The model was estimated as a parametric multistate (five state) Markov model [200]. The Markov assumption implies that the probability of movement to another state does not depend on time in the current state (i.e. the model is memoryless).

The multistate package in Stata was used to estimate statistical models; a single statistical model is estimated, containing parameters representing each possible transition within the multistate model. This approach assumes proportionality between baseline hazard functions and the transition intensities within the same distributional model. Six parametric distributions were tested

(exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma). These models were compared using the Akaike and Bayesian information criterion (AIC and BIC, respectively) and analysis of the Cox Snell residuals [202]. Simulation was used to provide illustrative plots of the resulting distributions across health states for a cohort beginning in the mildest health state (moderate VI).

12.1.8.3.3. Results

67 patients were included in the analysis. Baseline characteristics and demographics are reported elsewhere [28]. Table 47 reports the starting distribution of patients across health states.

Table 47: Baseline health state distribution

Health state	Frequency	Percent
HS1	32	47%
HS2	16	24%
HS3	8	12%
HS4	10	15%
HS5	2	3%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

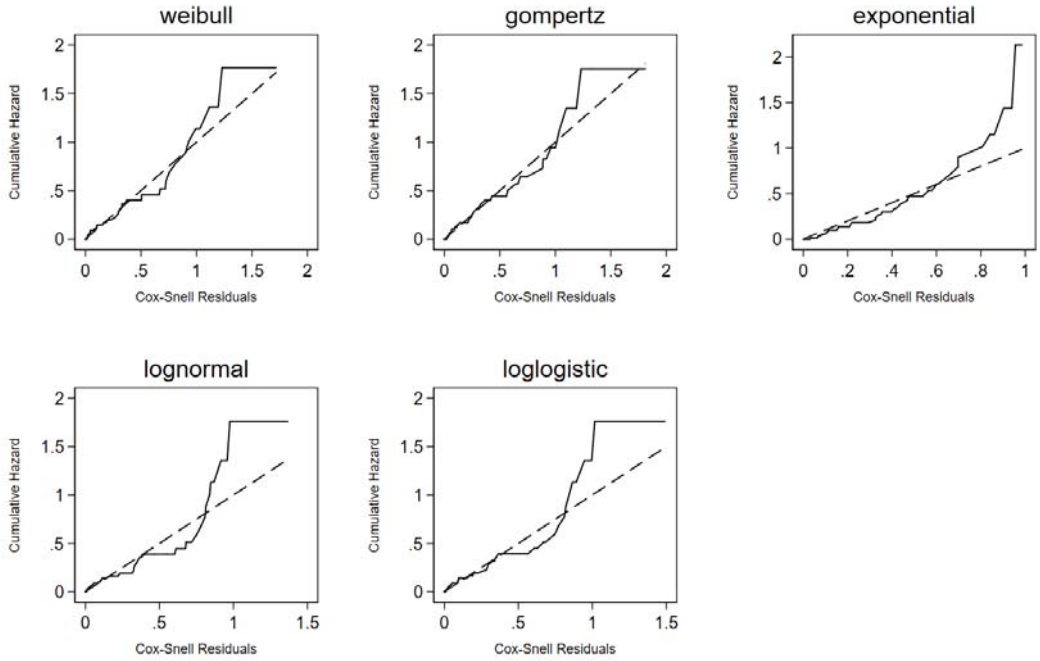
There were 28 transitions between health states observed. AIC and BIC are compared in Table 48: Weibull, log-normal, and log-logistic models performed similarly well. Only the exponential model performed notably poorly. Note that the generalised gamma model did not converge, and so results for this distribution are not available. Visual analysis of the residuals suggested the Weibull and Gompertz models provided the best fits (Figure 30). Given that the Weibull distribution performed well on both statistical fit and visual inspection, this distribution was selected for the model base-case.

Table 48: Model diagnostics

Model	ll(null)	ll(model)	df	AIC	BIC
Weibull	-82.9	-58.2	11	138.3	176.6
Gompertz	-83.7	-58.5	11	139.0	177.3
Exponential	-87.7	-63.1	10	146.3	181.1
Log-normal	-83.6	-59.6	11	141.2	179.4
Log-logistic	-83.1	-59.2	11	140.5	178.7

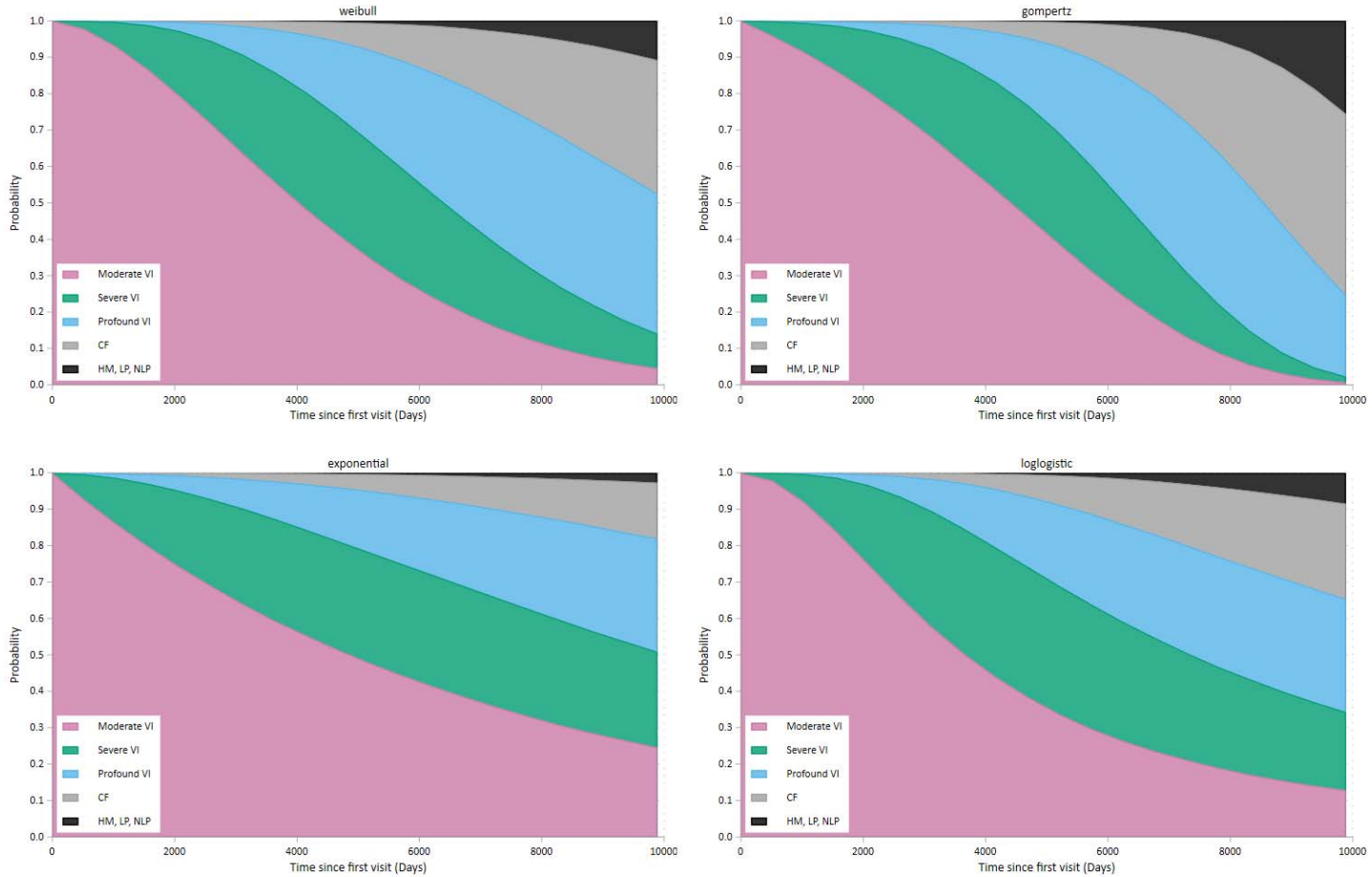
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degrees of freedom; ll, log-likelihood.

Figure 30: Cox-Snell residuals



Simulated health state membership for a cohort starting in the mildest health state (moderate VI) is provided in Figure 31. Note plots for the log-normal distribution are not supported by software at this time.

Figure 31: Simulated distribution across health states over time (cohort starting in health state 1)



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment.

Statistical models are presented in Table 49.

Table 49: Statistical models of disease progression†

	Weibull	Gompertz	Exponential	Log-logistic	Log-normal
HS1 to HS3	-17.60 (2502.4)	-18.19 (3363.2)	-17.55 (2450.5)	9.918 (2293.3)	5.585 (459.6)
HS1 to HS4	-17.60 (2502.4)	-18.19 (3363.2)	-17.55 (2450.5)	9.918 (2293.3)	5.585 (459.6)
HS1 to HS5	-17.60 (2502.4)	-18.19 (3363.2)	-17.55 (2450.5)	9.918 (2293.3)	5.585 (459.6)
HS2 to HS3	0.149 (0.484)	0.258 (0.484)	0.256 (0.484)	0.0559 (0.340)	0.0409 (0.355)
HS2 to HS4	-2.249* (1.069)	-2.139* (1.069)	-2.142* (1.069)	1.399* (0.610)	1.390** (0.533)
HS2 to HS5	-17.60 (2154.4)	-18.18 (3038.9)	-17.55 (2221.9)	9.884 (1905.5)	5.464 (413.8)
HS3 to HS4	-0.791 (0.565)	-0.777 (0.568)	-0.433 (0.556)	0.607 (0.379)	0.552 (0.389)
HS3 to HS5	-17.62 (1841.1)	-18.25 (2540.3)	-17.55 (2131.3)	10.12 (1927.2)	5.775 (432.1)
HS4 to HS5	-1.497* (0.706)	-1.674* (0.738)	-1.016 (0.690)	0.997* (0.444)	1.093* (0.464)
Constant	-14.30*** (2.053)	-9.539*** (0.469)	-8.861*** (0.378)	8.212*** (0.270)	8.220*** (0.277)
ln (p)	0.517*** (0.147)				
gamma		0.000314** (0.000)			
ln (gamma)				-0.665*** (0.150)	
ln (sigma)					-0.0495 (0.134)

† Standard errors in parentheses.
* p < 0.05, ** p < 0.01, *** p < 0.001
Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

12.1.8.3.4. Implementation

The survival models presented in Table 49 allow for the calculation of transition rates; however, transition probabilities are required for implementation in the cost-effectiveness model. The standard method for converting rates to probabilities ($p = 1 - e^{-rt}$) is not applicable in the context of competing risks, as in a multistate survival model [203]. Transition rates generated from a multistate survival model can be converted to probabilities by either:

- Generating probabilities within a statistical software package such as Stata; or

- Using the process presented in Jones et al [203] to implement the conversion in Excel directly

The latter option was chosen to allow for straightforward implementation of PSA and for increased model transparency. The transition probability formulae were derived using the computer algebra system wxMaxima. Output of analyses conducted in wxMaxima can be found in Appendix 8.

12.1.8.4 Mortality

Background mortality is modelled using general population life tables for England and Wales[21] [192], with a health state-specific mortality effect applied using data derived from Christ et al [95] (see Table 50).

Table 50: Relationship between baseline VA and mortality

Baseline VA level (LogMAR)	HR† (95% CI)
0	1.00 (1.00-1.00)
0.3	1.03 (1.01-1.06)
0.4	1.05 (1.01-1.09)
0.6	1.08 (1.02-1.15)
1.0	1.18 (1.05-1.32)

† Compared with 20/20 vision (LogMAR 0).
Abbreviations: CI, confidence interval; HR, hazard ratio; LogMAR, Logarithm of the Minimum Angle of Resolution; VA, visual acuity.
Source: Christ 2014 [95]

Key limitations of hazard ratios sourced from Christ et al are as follows:

- The study population includes individuals aged 65 to 84 years, which differs substantially from the mean baseline age of 15 years in Study 301/302

- The study was conducted in the years between 1993 and 2003; the resulting data therefore may not be applicable to current mortality rates

[21] A weighted average of life tables for men and women was generated using the distribution at baseline in Study 301/302.

- The hazard ratios in Christ et al are based on baseline VA level, rather than current VA level as is required in the cost-effectiveness model

- Available data is not able to distinguish between the four worst health states, given that the lower bound of the second mildest health state is equivalent to VA of 1.0

Despite limitations in data from Christ et al, no alternative data were identified linking visual impairment to a mortality effect; hazard ratios associated with baseline VA were therefore assumed to be applicable to current VA. Hazard ratios applied in each model health state are presented in Table 51.

Table 51: Mortality effect used in the model

	HS1	HS2	HS3	HS4	HS5
Mortality HR	1.08	1.18	1.18	1.18	1.18

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception. Abbreviations: HR, hazard ratio.

A scenario is presented in which mortality in all health states is assumed to reflect general population life tables, with no adjustment to reflect the impact of visual impairment[22].

12.1.8.5 MLMT and FST

Average MLMT and FST scores by health state were calculated for each of the VN and BSC arms (see Table 52) to allow for illustrative graphs of the change in these measures over time. The following assumptions were made in order to make best use of a limited number of observations in each health state:

- All observations for which the individual had previously received VN contributed to the calculations in the VN arm, including individuals in the Control/Delayed Intervention of Study 301/302 arm following crossover

[22] Note that the exclusion of a mortality effect associated with visual impairment is associated with a negligible change in the ICER.

- All observations for which the individual had not previously received VN contributed to the calculations in the BSC arm, including baseline data for individuals in both trial arms in Study 301

Table 52: MLMT and FST score by health state

Clinical outcome	Trial arm	HS1	HS2	HS3	HS4	HS5
MLMT	BSC	3.91	2.84	3.29	1.86	-1.00
	VN	5.92	5.08	4.62	-0.29	-1.00
FST	BSC	-1.61	-1.67	-1.42	-1.26	-1.19
	VN	-4.15	-3.20	-2.56	-1.34	-1.19

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; FST, full-field light sensitivity threshold; MLMT, multi-luminance mobility testing; VN, voretigene neparvovec.

12.2 Clinical parameters and variables

12.2.1 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Costs and outcomes are extrapolated to a lifetime time horizon based on the modelled health state distribution over time.

In the VN arm, improvements in vision are assumed to be maintained for 40 years. Data on the duration of treatment effect are available from the clinical trial program and preclinical studies.

Clinical trial program

There is no evidence of loss of treatment effect over time with the latest available trial follow-up data (Section 9.6). In Study 101/102, improvements in light sensitivity (measured by FST, which is correlated with MLMT [133]) were maintained over maximum follow-up periods of 7.5 and four years post-treatment, respectively [155]. In Study 301/302, improvements in MLMT and FST were sustained over maximum follow-up periods of 4 years for OI patients and 3 years for DI patients [156].

Preclinical studies

Comparisons between *RPE65* gene mutation-associated diseases in humans, dogs and mice are complex and conclusions should be drawn carefully. However, an approximation of efficacy maintenance for treatments similar to VN in dogs for 9.4 years [204] and in mice for 18 months [205] can be estimated as equivalent to >65 and >60 [206] human years, respectively. These animal models support the long-term efficacy of VN, which has not declined over time during clinical testing.

Lifetime of RPE cells

In a normal state, human retinal pigment epithelial (RPE) cells do not undergo mitosis on a regular basis like gastrointestinal or skin epithelial cells. RPE cells form early in development and subsequently remain dormant, undergoing minimal proliferation throughout life. It is anticipated that the *RPE65* gene will therefore remain active during the lifetime of RPE cells.

Clinical expert feedback

Clinical experts in the UK noted the absence of long-term data (Section 12.2.4), but were in agreement that based on currently available trial data and animal data described above, assuming a stabilisation effect with VN was reasonable. One clinical expert suggested that the possibility of a treatment effect lasting throughout patients' lifetimes should not be ruled out, because VN was developed with an improved understanding of vector design and manufacturing. Additionally, vector delivery, surgical techniques and dosing were optimised based on lessons learned from other gene therapy trials.

A 40-year treatment effect was assumed to represent a reasonable midpoint between the absolute minimum (7.5 years of follow-up data with no loss of efficacy) and potential maximum based on preclinical data and clinical expert opinion (lifetime treatment effect of around 70 years).

Scenario analyses are included in which alternative durations of treatment effect are considered. The waning of this treatment effect, and the residual

treatment effect assumed for the remaining lifetime of patients, are described in Section 12.1.8.

12.2.2 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Excess mortality in individuals with visual impairment is determined by current visual acuity. This relationship was estimated using data from Christ et al [95] but is associated with some limitations (see Section 12.1.8.4). A scenario is therefore considered in which mortality is not assumed to differ depending on level of visual impairment.

12.2.3 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Modelled AEs include all those:

- considered to be related to either the treatment or the administration procedure[23] in the Original Intervention arm of Study 301 [19]
- occurring in greater than one patient
- expected to be associated with an impact on quality of life and/or cost

Retinal tear considered to be related to the administration procedure occurred in two patients in Study 301; however, retinal tears are assumed to be corrected during the administration surgery, and so are not expected to impact on either cost or quality of life. Modelled AEs therefore include:

- Cataract

[23] No AEs in Study 301/302 were considered related to the study drug; modelled adverse events therefore represent administration-procedure related AEs occurring in greater than one patient.

- Eye inflammation
- Increased intraocular pressure (IOP)

The proportions of patients experiencing each of the modelled AEs are presented in Table 53.

Table 53: Adverse event probabilities

Adverse event	Proportion of patients
Cataract	15%
Eye inflammation	10%
Increased intraocular pressure	20%

Source: Study 301 CSR [19]

12.2.4 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical advice was sought from six leading experts in the fields of ophthalmology and inherited retinal dystrophies. These included clinical ophthalmologists, consultant ophthalmic/vitreoretinal surgeons, and a consultant genetic counsellor. Feedback was collected via one-on-one interviews. A formal script was not used, but key topics of discussion included:

- Suitability of model health states
- Resource use and costs associated with the procedure and monitoring
- Arrangements for genetic testing
- Estimation of patient numbers
- Treatment duration effect and waning
- Age at diagnosis

Feedback collected from these interviews were used to inform model development. Uncertainty due to differences of opinion was explored using sensitivity analysis.

Details of the participating experts are provided in Appendix 12.

12.2.5 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Table 54 below.

Table 54 includes all variables applied in the model base-case, with the exception annual healthcare resource use costs which can be found in Appendix 10. These parameters are varied using the gamma distribution, assuming an arbitrary range of +/- 15% in the absence of other uncertainty estimates.

Table 54: Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source
Maximum age	100	100.00 to 100.00 (Not varied)	N/A
Annual discount rate (costs)	0.035	0.04 to 0.04 (Not varied)	
Annual discount rate (outcomes)	0.035	0.04 to 0.04 (Not varied)	
Time to VN benefit (months)	1	1.00 to 1.00 (Not varied)	
Duration of treatment effect, years (VN)	40	30.00 to 30.00 (Not varied)	Sections 12.1.8 and 12.2.1
Waning period, years	10	10.00 to 10.00 (Not varied)	
RRR vs. natural history data (VN)	0.25	0.25 to 0.25 (Not varied)	
Multistate model, Weibull (VA+VF, average eye): HS1 to HS3	-17.596	-4922.25 to 4887.06 (Not varied)	Analysis of RPE65 NHx [28]
Multistate model, Weibull (VA+VF, average eye): HS1 to HS4	-17.596	-4922.25 to 4887.06 (Not varied)	
Multistate model, Weibull (VA+VF, average eye): HS1 to HS5	-17.596	-4922.25 to 4887.06 (Not varied)	
Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	0.149	-0.80 to 1.10 (Normal)	

Variable	Value	Range or 95% CI (distribution)	Source
Multistate model, Weibull (VA+VF, average eye): HS2 to HS4	-2.249	-4.34 to -0.15 (Normal)	
Multistate model, Weibull (VA+VF, average eye): HS2 to HS5	-17.600	-4240.07 to 4204.88 (Not varied)	
Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	-0.791	-1.90 to 0.32 (Normal)	
Multistate model, Weibull (VA+VF, average eye): HS3 to HS5	-17.620	-3626.09 to 3590.85 (Not varied)	
Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	-1.497	-2.88 to -0.11 (Normal)	
Multistate model, Weibull (VA+VF, average eye): Constant	-14.298	-18.32 to -10.27 (Normal)	
Multistate model, Weibull (VA+VF, average eye): Ancillary	0.517	0.23 to 0.80 (Normal)	
Acaster Lloyd (HUI-3), utility value, HS1	0.519	0.39 to 0.65 (Beta)	Acaster Lloyd utility study (Appendix 9)
Acaster Lloyd (HUI-3), utility value, HS2	0.363	0.27 to 0.45 (Beta)	
Acaster Lloyd (HUI-3), utility value, HS3	0.223	0.14 to 0.30 (Beta)	
Acaster Lloyd (HUI-3), utility value, HS4	0.141	0.07 to 0.21 (Beta)	
Acaster Lloyd (HUI-3), utility value, HS5	-0.039	-0.09 to 0.02 (Normal)	
AE utility decrement: cataract	0.142	0.12 to 0.16 (Gamma)	NICE guideline [NG82] Appendix J [170]
AE utility decrement: eye inflammation	0.3	0.26 to 0.35 (Gamma)	
AE duration: cataract	1	0.85 to 1.15 (Gamma)	
AE duration: eye inflammation	3.6	3.06 to 4.14 (Gamma)	
AE utility decrement: increased IOP	0.1	0.00 to 0.04 (Gamma)	Conservatively assumed to be associated with the same utility decrement as for

Variable	Value	Range or 95% CI (distribution)	Source
			uncontrolled/severe glaucoma. (Pershing 2014 [171])
AE duration: increased IOP	1	0.85 to 1.15 (Gamma)	All increased IOP events observed in Study 301 were resolved within one month (Study 301 CSR [19])
AE probability: cataract	0.15	0.13 to 0.17 (Beta)	Study 301 CSR [19]
AE probability: eye inflammation	0.1	0.09 to 0.12 (Beta)	
AE probability: increased IOP	0.2	0.17 to 0.23 (Beta)	
Carer disutility, school age, HS1	0	0.00 to 0.00 (Not varied)	Assumption
Carer disutility, school age, HS2	0.08	0.07 to 0.09 (Gamma)	Wittenberg 2013 [172]
Carer disutility, school age, HS3	0.08	0.07 to 0.09 (Gamma)	
Carer disutility, school age, HS4	0.08	0.07 to 0.09 (Gamma)	
Carer disutility, school age, HS5	0.08	0.07 to 0.09 (Gamma)	
Carer disutility, working age, HS1	0	0.00 to 0.00 (Not varied)	Assumption
Carer disutility, working age, HS2	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, working age, HS3	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, working age, HS4	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, working age, HS5	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, retirement age, HS1	0	0.00 to 0.00 (Not varied)	
Carer disutility, retirement age, HS2	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, retirement age, HS3	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, retirement age, HS4	0.04	0.03 to 0.05 (Gamma)	
Carer disutility, retirement age, HS5	0.04	0.03 to 0.05 (Gamma)	

Variable	Value	Range or 95% CI (distribution)	Source
VN acquisition cost	613410.00	613410.00 to 613410.00 (Not varied)	N/A
PAS discount	[redacted]	[redacted]	N/A
Cost per surgery	2265.09	1925.33 to 2604.85 (Gamma)	NHS reference Costs 2017-18: Weighted average of BZ81B (complex vitreous retinal procedures, 19 years and over, with CC score 0-1) and BZ82Z (very complex or complex vitreous retinal procedures, 18 years and under), assuming 65% <18 years as in Study 301. [207]
Number of surgeries	2	2.00 to 2.00 (Not varied)	N/A
Prednisone: units/pack	100	100.00 to 100.00 (Not varied)	BNF [208]
Prednisone: cost/pack	89.00	89.00 to 89.00 (Not varied)	
Prednisone: mg/unit	5.00	5.00 to 5.00 (Not varied)	
Average weight (kg)	51.50	51.50 to 51.50 (Not varied)	Study 301 CSR [19]
Prednisone 1mg/kg/day: number of days	14.00	14.00 to 14.00 (Not varied)	
Prednisone 0.5mg/kg/day: number of days	6.80	5.78 to 7.82 (Gamma)	
OCT unit cost	114.46	97.29 to 131.63 (Gamma)	NHS Reference Costs 2017-18: Weighted average of Retinal Tomography, 19 years and over and 18 years and under: BZ88A and BZ88B [207]
OCT resource use in Year 1 (VN arm)	4	3.40 to 4.60 (Gamma)	Expert clinical opinion.
Sufficient viable retinal cells: cost per test	114.46	97.29 to 131.63 (Gamma)	NHS Reference Costs 2017-18: Weighted average of Retinal Tomography, 19 years and over and 18 years and under: BZ88A and BZ88B [207]

Variable	Value	Range or 95% CI (distribution)	Source
Sufficient viable retinal cells: proportion of individuals	0.95	0.81 to 1.00 (Beta)	Clinical expert opinion [9]
Cost per event: cataract	913.42	776.41 to 1050.44 (Gamma)	NHS Reference Costs 2017-18: Weighted average of non-elective short stay and day case codes for Phacoemulsification Cataract Extraction and Lens Implant:BZ34A, B and C [207]
Cost per event: eye inflammation	37.00	31.45 to 42.55 (Gamma)	PSSRU 2018: Cost per GP visit lasting 9.22 minutes (including direct care staff costs, with qualification costs) [209]
Cost per event: increased IOP	37.00	31.45 to 42.55 (Gamma)	
School age (years)	18	18.00 to 18.00 (Not varied)	N/A
Retirement age (years)	65	65.00 to 65.00 (Not varied)	
Mortality HR, HS1	1.08	1.02 to 1.15 (Gamma)†	Christ 2014 [95]
Mortality HR, HS2	1.18	1.01 to 1.39 (Gamma)†	
Mortality HR, HS3	1.18	1.01 to 1.39 (Gamma)†	
Mortality HR, HS4	1.18	1.01 to 1.39 (Gamma)†	
Mortality HR, HS5	1.18	1.01 to 1.39 (Gamma)†	

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: AE, adverse event; HR, hazard ratio; HUI-3, Health Utilities Index Mark 3; IOP, intraocular pressure; OCT, optical coherence tomography; RRR, relative risk reduction; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.
†Note that a minimum hazard ratio of 1 was enforced as is was not considered plausible that visual impairment could result in reduced mortality.

12.3 Resource identification, measurement and valuation

All costs were valued in 2019 UK pounds. Where necessary[24], costs were inflated to 2017/18[25] prices using the hospital and community health services (HCHS) pay and prices index from the *Unit Costs of Health and Social Care,* as issued by the Personal Social Services Research Unit (PSSRU) [209].

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There is no specific Healthcare Resource Group (HRG) for *RPE65*-mediated IRD. The economic model is structured to align with the clinical pathway of care (Section 12.1.4), with costs based on health state and age (Section 12.3.7).

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review was performed to identify studies reporting cost/resource use outcomes for patients with *RPE65*-mediated IRD, RP/LCA, visual impairment and blindness.

Details of search strings, databases searched, hand-searching, and inclusion/exclusion criteria are provided in Appendix 4.

No studies were identified reporting costs/resource use for *RPE65*-mediated IRD, so a broader search was conducted to inform development of the economic model (see below). The searches were run on 27th July 2018, and were updated on 14th January 2019.

[24] Only costs from prior to 2018 were inflated; in particular, costs from the most recent releases of the Unit Costs of Health and Social Care and NHS reference costs were not inflated.
[25] The most recent edition of the Unit Costs of Health and Social Care includes inflation indices up to 2017/18.

In the original search, 3,062 papers were identified through the electronic searches. Upon the removal of duplicate papers, 2,507 titles and abstracts were reviewed. A total of 165 papers were potentially relevant and were ordered for full paper review. At this stage, a further 77 papers were excluded. Hand searching yielded three additional relevant papers, resulting in a total of 91 papers for final inclusion in the original review.

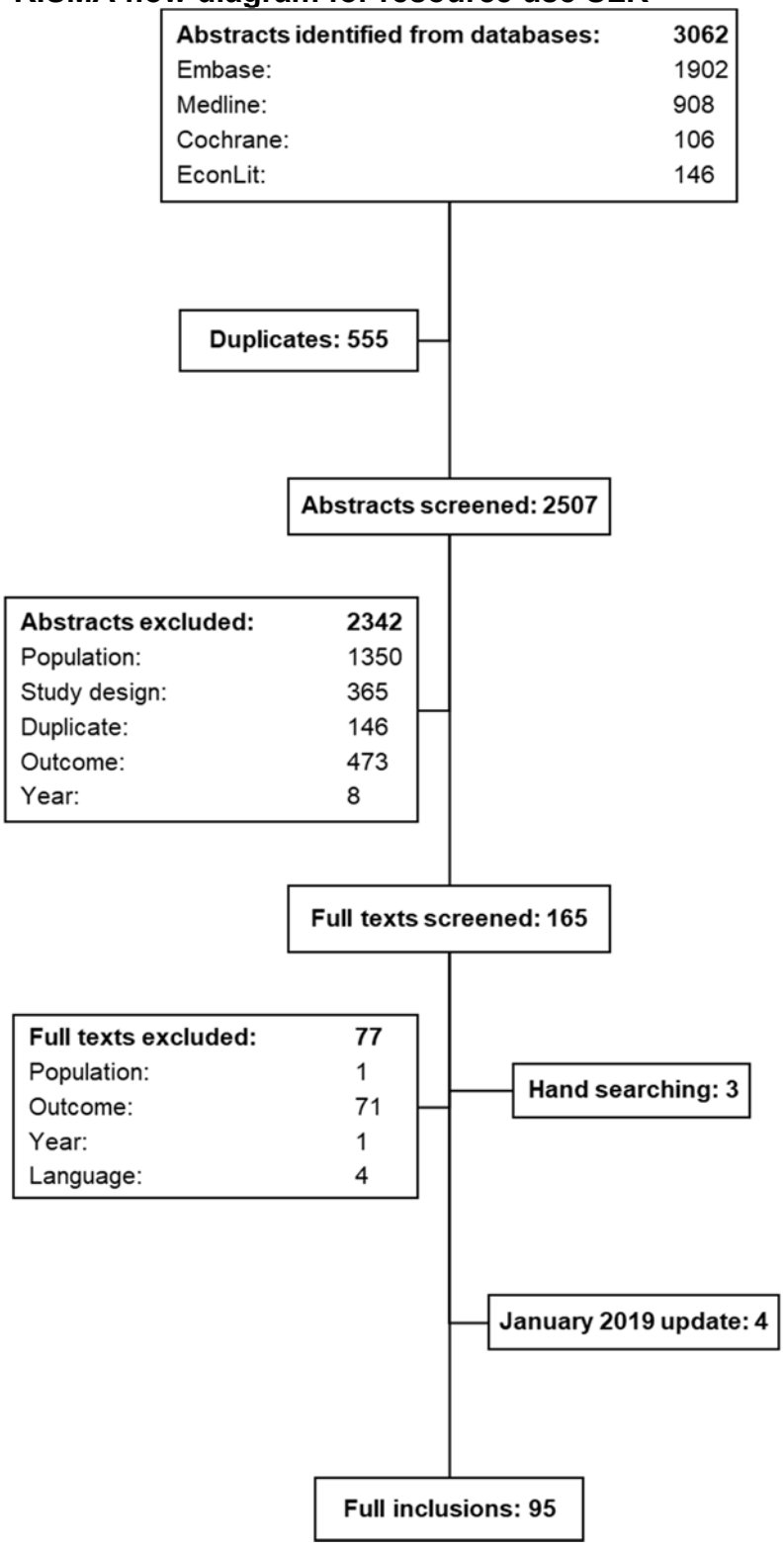
In the January 2019 update, 202 papers were identified through the electronic searches. Upon the removal of duplicate papers, 181 titles and abstracts were reviewed. A total of seven papers were potentially relevant and were ordered for full paper review. At this stage, a further three papers were excluded. Hand searching yielded no additional relevant papers, resulting in a total of four papers for final inclusion in the updated review.

Across the original review and the January 2019 update, a total of 95 studies were identified for final inclusion in the review.

The flow of studies through the review is reported in the PRISMA flow diagram in Figure 32. Separate PRISMA diagrams for the original and updated reviews are presented in Appendix 4.

A summary of the UK studies reporting cost/resource use data is provided in Appendix 4.

Figure 32: PRISMA flow diagram for resource use SLR



12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[26].

Details are provided in Section 12.2.4.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price of VN is £613,410 per patient.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A confidential simple discount patient access scheme (PAS) has been proposed, and the PAS price of [redacted] per patient has been used in the de novo cost-effectiveness model.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in Table 55. Please consider all significant costs associated with treatment that may be of interest to commissioners.

Costs associated with VN are presented in Table 55; no costs other than healthcare resource use associated with visual impairment are modelled in the BSC arm (see Section 12.3.7).

Costs associated with administration, monitoring, and testing for sufficient viable retinal cells are described in Sections 12.3.6.1, 12.3.6.2 and 12.3.6.3, respectively. A scenario is considered in which genetic testing costs are included (see Section 12.3.6.4); the exclusion of genetic testing costs from the model base-case is based on UK clinical expert feedback that standardised

[26] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

access to genetic testing for patients with IRD will come into effect from March 2019 [9].

Table 55: Costs per treatment/patient associated with the technology in the cost- effectiveness model

Items	Value	Source
Price of the technology per patient†	[redacted] £613,410.00 (list price)	Section 12.3.5
Administration costs‡	£2,438.46	Section 12.3.6.1
Monitoring costs	£457.83	Section 12.3.6.2
Sufficient viable retinal cells testing costs	£120.48	Section 12.3.6.3
Total cost per treatment/patient	[redacted] **£618,691.87 (assuming list price)**	-

†Cost of two subretinal injections (one in each eye) administered on separate occasions.
‡Cost of two surgeries plus oral prednisone regimen.
Abbreviations: PAS, patient access scheme.

12.3.6.1 Administration costs

Voretigene neparvovec is administered as two subretinal injections (one in each eye) on separate occasions at least six days apart. A regimen of oral prednisone beginning three days prior to the first injection (see Table 5) was specified in the trial protocol for Study 301/302 [19]. The cost per surgery for each subretinal injection was taken from the NHS National Schedule of Reference Costs [207], and calculated as the weighted average of codes for complex and very complex, vitreous retinal procedures for children and adults (see Table 56). The calculated cost per surgery is £2,265, based on the distribution of adults (≥ 18 years; 35%) and children (<18 years; 65%) in Study 301/302.

Table 56: Currency codes for complex and very complex vitreous retinal procedures

Currency code	Currency description	Unit cost
BZ81B	Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1	£1,771
BZ82Z	Very Complex or Complex, Vitreous Retinal Procedures, 18 years and under	£2,537

Abbreviations: CC, comorbidity and complication.

The costs of prednisone were sourced from the British National Formulary [208] (see Table 57).

Table 57: Prednisone costs

Drug	Units/pack	Cost/pack	mg/unit	Cost/unit
Prednisone	100	£89.00	5	£0.89

The average time between the two surgeries in Study 301/302 was 8.8 days [19]. With reference to the dosing regimen presented in Section 8.7, it is assumed that:

- A dose of 1 mg/kg/day is applied for seven days for each of the two surgeries (totalling 14 days)
- A dose of 0.5 mg/kg/day is applied for 1.8 days between the two surgeries, and five days following the second surgery (totalling 6.8 days)
- The average weight of the population is 51.5 kg, as observed at baseline in Study 301 [19]

The modelled number of units per day and total cost for each dose is presented in Table 58. The total cost of prednisone as implemented in the model is £173.37.

Table 58: Prednisone resource use and total costs

Dose	Units/day†	Number of days	Total cost
1 mg/kg/day	11	14	£137.06
0.5 mg/kg/day	6	6.8	£36.31

† Calculated as the mg/kg/day multiplied by the average weight of the population (51.5 kg), divided by the mg/unit, and rounded up to the nearest whole number.

12.3.6.2 Monitoring costs

In the first year following treatment with VN, four monitoring visits including OCT are assumed to be required; this estimate was informed based on expert clinician opinion [9]. The cost of OCT is assumed to be £114, calculated as the weighted average of retinal tomography currency codes in the NHS National Schedule of Reference Costs 2017-18 (BZ88A and BZ88B) [207].

12.3.6.3 Sufficient viable retinal cells testing costs

The costs of all tested individuals are assumed to be incurred by individuals in the VN arm of the model; sufficient viable retinal cells are expected to be found in 95% of tested individuals[27] [9].

Testing for sufficient viable retinal cells is conducted using OCT; the cost of OCT is assumed to be £114 (see Section 12.3.6.2). The cost per VN patient is calculated to be £120 (i.e. £114/0.95).

12.3.6.4 Genetic testing costs (scenario only)

Genetic testing costs were considered in a scenario analysis. It was assumed that the costs of genetic testing include the costs of the test itself, in addition to the cost of a consultation prior to testing.

As in Section 12.3.6.3, the costs of all tested individuals are assumed to be incurred by individuals in the VN arm of the model. *RPE65* mutations are expected to be found in approximately 7.5% of tested individuals [85], and sufficient viable retinal cells are expected to be found in 95% (see Section 12.3.6.3) of tested individuals.

Since *RPE65* testing occurs prior to testing for sufficient viable retinal cells, the cost of *RPE65* testing is divided by 0.075 x 0.95 = 0.07125 to generate the cost applied to each VN patient.

The modelled cost per test for the *RPE65* gene is £773.50 - the average of the cost of sequencing the entire coding region of genes in Manchester and Oxford [210]. The cost of a consultation prior to genetic testing is £97.94 (i.e. the average cost of an ophthalmologic outpatient visit [207]). The cost per VN patient is therefore calculated to be £12,231 (i.e. (£773.50 + £97.94)/(0.075 x 0.95)).

[27] Clinical expert opinion gave estimates between 55% and 95% for the proportion of tested individuals with sufficient viable retinal cells. The upper end of this range was select to ensure that total budget impact is not underestimated.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost-effectiveness model.

Health state costs are assumed to vary by age group:

- School age
- Working age
- Retirement age

Individuals are assumed to leave school at age 18, and retirement is assumed to occur at age 65.

In the base-case, only costs incurred by the NHS and PSS (healthcare resource use) are considered; scenarios are considered in which:

- Costs incurred by other government departments are included
- All societal costs are included, including productivity loss

12.3.7.1 Healthcare resource use

Healthcare resource use categories considered in the model for each age group are presented in Table 59.

Costs associated with ophthalmic services and home modifications are excluded from the analysis due to a lack of available data. Costs associated with more severe visual impairment are therefore expected to be underestimated.

Table 59: Healthcare resource use categories by age

School-age	Working-age	Retirement-age
Hospitalisation	Hospitalisation	Hospitalisation
Low vision rehabilitation	Low vision rehabilitation	Low vision rehabilitation
Low vision aids	Low vision aids	Low vision aids
Depression	Depression	Depression
-	-	Residential care
-	-	Community care

12.3.7.2 Non-healthcare resource use (scenario only)

Non-healthcare resource use categories considered in the model for each age group are presented in Table 60.

The following costs are excluded from the analysis due to a lack of available data:

- The Daily Living component of the Personal Independence Payment
- The Access to Work scheme
- Support with higher education
- Early years educational support
- Transport to appointments

Costs associated with more severe visual impairment are therefore expected to be underestimated.

Table 60: Non-healthcare resource use categories by age

School-age	Working-age	Retirement-age
Education	-	-
Carer's Allowance	Carer's Allowance	Carer's Allowance
Personal Independence Payment	Personal Independence Payment	Personal Independence Payment
-	Employment and Support Allowance	-
-	Universal Credit/Working Tax Credit	-
-	Blind Person's Tax Allowance	-
-	-	Attendance Allowance
-	-	Pension Credit
Caregiver productivity loss	Caregiver productivity loss	Caregiver productivity loss
-	Productivity loss	-

12.3.7.3 Total resource use by health state

Total annual healthcare and non-healthcare resource use costs by health state in each age group are presented in Table 61 and Table 62, respectively. Derivations of health state costs are available in Appendix 10.

No published costs or resource use are available that are specific to individuals with *RPE65*-mediated IRD; sources considering visual impairment and blindness more generally have therefore been used. In the absence of costs specific to each health state, it has been assumed that costs of blindness apply to health state 2 onwards, on the basis that all patients in these states would be classified as blind according to RNIB guidelines (see Section 12.1.6). Costs in health state 1 are assumed to be half that in other states, on the basis that an unknown proportion of these patients would be classified as blind according to RNIB guidelines.

Table 61: Annual healthcare resource use costs by age group and health state

Health state	Annual cost		
	School age	Working age	Retirement age
HS1	£298	£298	£7,696
HS2	£596	£596	£15,392
HS3	£596	£596	£15,392
HS4	£596	£596	£15,392
HS5	£596	£596	£15,392

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

Table 62: Annual non-healthcare resource use costs by age group and health state (scenario only)

Health state	Annual cost		
	School age	Working age	Retirement age
HS1	£7,626	£11,130	£4,852
HS2	£15,252	£22,260	£9,705
HS3	£15,252	£22,260	£9,705
HS4	£15,252	£22,260	£9,705
HS5	£15,252	£22,260	£9,705

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

Adverse-event costs

12.3.8 Complete Table 63 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Costs associated with each modelled AE (Section 12.2.3) are sourced from the NHS National Schedule of Reference Costs [207] and the Unit Costs of Health and Social Care [209], and are detailed in Table 63.

Table 63: List of adverse events and summary of costs included in the cost- effectiveness model

Adverse events	Items	Value	Reference
Cataract	Hospital costs	£896.65	NHS Reference Costs 2017-18: Weighted average of non-elective short stay and day case codes for Phacoemulsification Cataract Extraction and Lens Implant: BZ34A, BZ34B and BZ34C [207]
Eye inflammation	GP visit†	£37.00	Unit Costs of Health and Social Care 2018: Cost per GP visit lasting 9.22 minutes (including direct care staff costs, with qualification costs) [209]
Increased IOP	GP visit†	£37.00	Unit Costs of Health and Social Care 2018: Cost per GP visit lasting 9.22 minutes (including direct care staff costs, with qualification costs) [209]

Abbreviations: GP, general practitioner; IOP, intraocular pressure.
† Given that adverse events associated with eye inflammation and increased IOP are expected to be relatively minor, the cost of one GP visit is assumed.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

No additional costs were considered.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It was not possible to include costs for some components of healthcare and non-healthcare resource use due to a lack of available data; see Sections 12.3.7.1 and 12.3.7.2 for further details.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been

confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Scenario analyses were performed in which key structural assumptions were varied, and ICERs were reported. Considered scenarios are presented in Table 64.

Table 64: Scenario analyses performed

Area of uncertainty	Base-case	Scenario(s)	Relevant section of submission
Perspective	Healthcare system	• Government departments • Societal	Section 1
Discount rate	3.5% for costs and outcomes	• 1.5% for costs and outcomes • No discounting for costs and outcomes	Section 12.1.7
Eye approach	Average eye	Best-seeing eye	Section 12.1.6
Health state definition	VA and VF	VF only	Section 12.1.6
Source of baseline characteristics	Phase 3 trial	Natural history data	Section 12.1.8.1
TP approach	Exact TP	• Adjusted TP (state-dependent) • Adjusted TP (state-independent)	Section 12.1.8.2
Health states with no data	Same movement as in next least severe state	Remain in the same state	Section 12.1.8.2
Cross-over data	Cross-over data excluded	Cross-over data included	Section 12.1.8.2
Duration of treatment effect	40 years	• 20 years • 30 years • 50 years • Lifetime (100 years)	Sections 12.1.8 and 12.2.1
Waning period	10 years	• 5 years • 20 years	Section 12.1.8
Long-term RRR for natural history transitions in VN arm	25%	• 0%	Section 12.1.8

Area of uncertainty	Base-case	Scenario(s)	Relevant section of submission
		• 50%	
Multistate model distribution	Weibull	• Gompertz • Log-logistic • Log-normal • Exponential	Section 12.1.8.3.3
Mortality effect	Mortality effect included	No mortality effect	Section 12.1.8.4
Source of utility values	Acaster Lloyd (HUI3)†	• Acaster Lloyd (EQ-5D-5L) (Appendix 9) • Brown et al, 2003 [211]	Section 10.9.1
Carer disutility	Included	Excluded	Section 10.9.3
Light sensitivity utility increment	Not included	Hypothetical utility increment of 0.05 in HS1 to HS3	Section 10.9.1.1.3
Disutility associated with the administration procedure	Not included	Hypothetical disutility of 0.1 applied for one month in all patients	Section 10.9.2
Costs of genetic testing	Excluded	Included	Section 12.3.6.4
Healthcare resource use in first health state	Half that in other health states	Excluded	Section 12.3.7.1

Abbreviations: HS, health state; HUI-3, Health Utilities Index Mark 3; RRR, relative risk reduction; TP, transition probability; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Upper and lower bounds used in univariate and probabilistic sensitivity analysis (PSA), and distributions used in PSA are reported in Table 54. In addition to the parameters listed in Table 54, count data used to determine the TP matrices in the initial phase of the model were also varied in PSA. For use in PSA only, an arbitrary prior of 0.1 was added to each transition, and the Dirichlet distribution was used.

12.4.2.1 Univariate sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or +/- 15% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

12.4.2.2 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

12.4.3 Complete Table 65 as appropriate to summarise the variables used in the sensitivity analysis.

Table 65: Combinations of variables used in multi-way scenario-based sensitivity analysis (base-case analysis highlighted)

Treatment duration (years)	Waning period (years)	RRR in the long-term phase
20	5	0%
20	5	25%
20	5	50%

Treatment duration (years)	Waning period (years)	RRR in the long-term phase
20	10	0%
20	10	25%
20	10	50%
20	20	0%
20	20	25%
20	20	50%
30	5	0%
30	5	25%
30	5	50%
30	10	0%
30	10	25%
30	10	50%
30	20	0%
30	20	25%
30	20	50%
40	5	0%
40	5	25%
40	5	50%
40	10	0%
40	**10**	**25%**
40	10	50%
40	20	0%
40	20	25%
40	20	50%
50	5	0%
50	5	25%
50	5	50%
50	10	0%
50	10	25%
50	10	50%
50	20	0%
50	20	25%
50	20	50%
100 (lifetime)	5	0%
100 (lifetime)	5	25%
100 (lifetime)	5	50%
100 (lifetime)	10	0%
100 (lifetime)	10	25%
100 (lifetime)	10	50%
100 (lifetime)	20	0%
100 (lifetime)	20	25%

Treatment duration (years)	Waning period (years)	RRR in the long-term phase
100 (lifetime)	20	50%

Abbreviations: RRR, relative risk reduction.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Variables marked as 'not varied' in Table 54 were omitted from univariate and probabilistic sensitivity analysis:

- Drug costs (including acquisition of VN and prednisone) were omitted because these are considered to be known quantities.
- Model choices (including time horizon, discount rates etc.) were omitted because they are considered to be structural assumptions, as opposed to uncertain parameters; these assumptions were considered in scenario analyses.
- Parameters defining the multistate survival model were omitted where the specific transition was not observed in RPE65 NHx, and so the transition was effectively considered to be impossible.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in Table 66.

The confidential simple discount PAS used in the cost-effectiveness model is currently under review by the Department of Health. Results are therefore presented both with and without the proposed PAS (Table 66 and Table 67, respectively).

Table 66: Base-case results (proposed PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£46,300	25.46	3.9	-	-	-	-
VN	[redacted]	25.51	10.8	[redacted]	0.05	6.8	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; VN, voretigene neparvovec.

Table 67: Base-case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£46,300	25.46	3.9	-	-	-	-
VN	£656,754	25.51	10.8	£610,454	0.05	6.8	£89,173

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VN, voretigene neparvovec.

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The proportion of individuals in each health state at the end of the first year (in each model arm) is presented in Table 68. The clinical trial results and model results are relatively congruent; some differences are observed because baseline health state distributions were pooled across the two trial arms before applying treatment-specific transition probabilities. As may be expected, larger differences are observed in the BSC arm than in the VN arm, due to the baseline distribution in the smaller sample of BSC patients (N=10) differing more substantially from the overall baseline distribution (which is influenced more by the baseline distribution of VN patients, who made up approximately two-thirds of the trial population; see Table 69).

Table 68: Summary of model results compared with clinical data

		% in each health state at Year 1	
		Clinical trial result	**Model result**
BSC arm	HS1	44%	31%
	HS2	22%	16%
	HS3	22%	42%
	HS4	11%	11%
	HS5	0%	0%
VN arm	HS1	70%	70%
	HS2	20%	18%
	HS3	5%	5%
	HS4	5%	6%
	HS5	0%	1%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

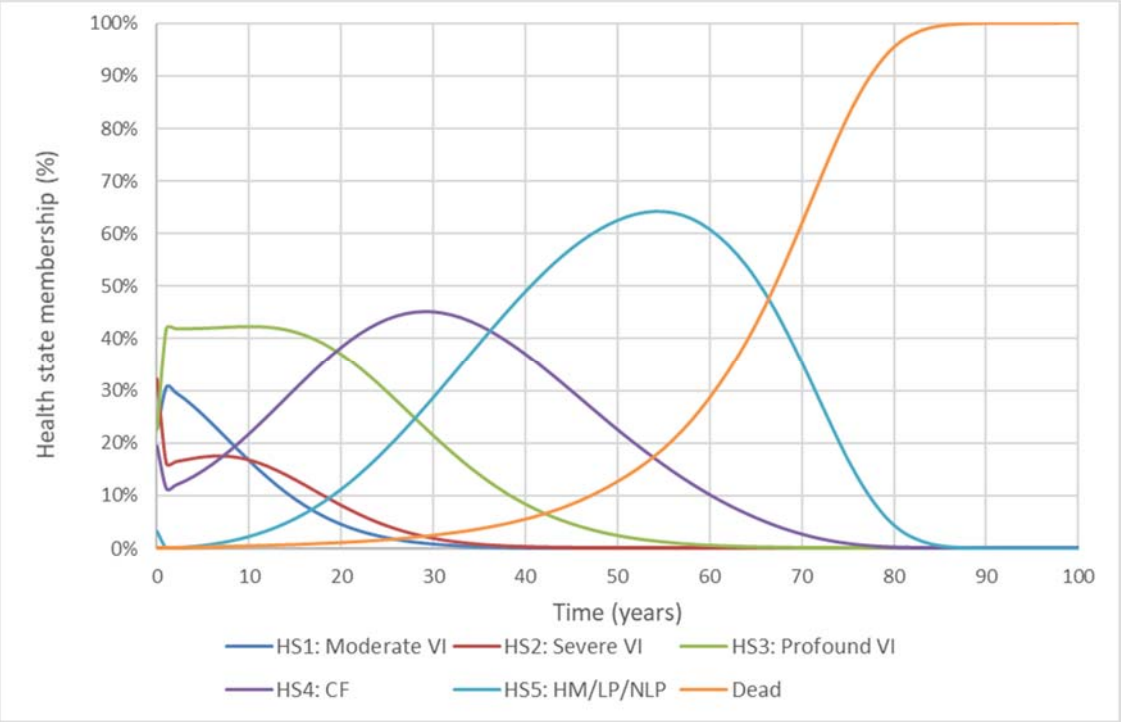
Table 69: Baseline health state distributions

Health state	Baseline health state distribution		
	BSC (Control/Delayed Intervention, N=10)	VN (Original Intervention, N=21)	Overall (N=31)
HS1	30%	19%	23%
HS2	40%	29%	32%
HS3	10%	29%	23%
HS4	10%	24%	19%
HS5	10%	0%	3%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

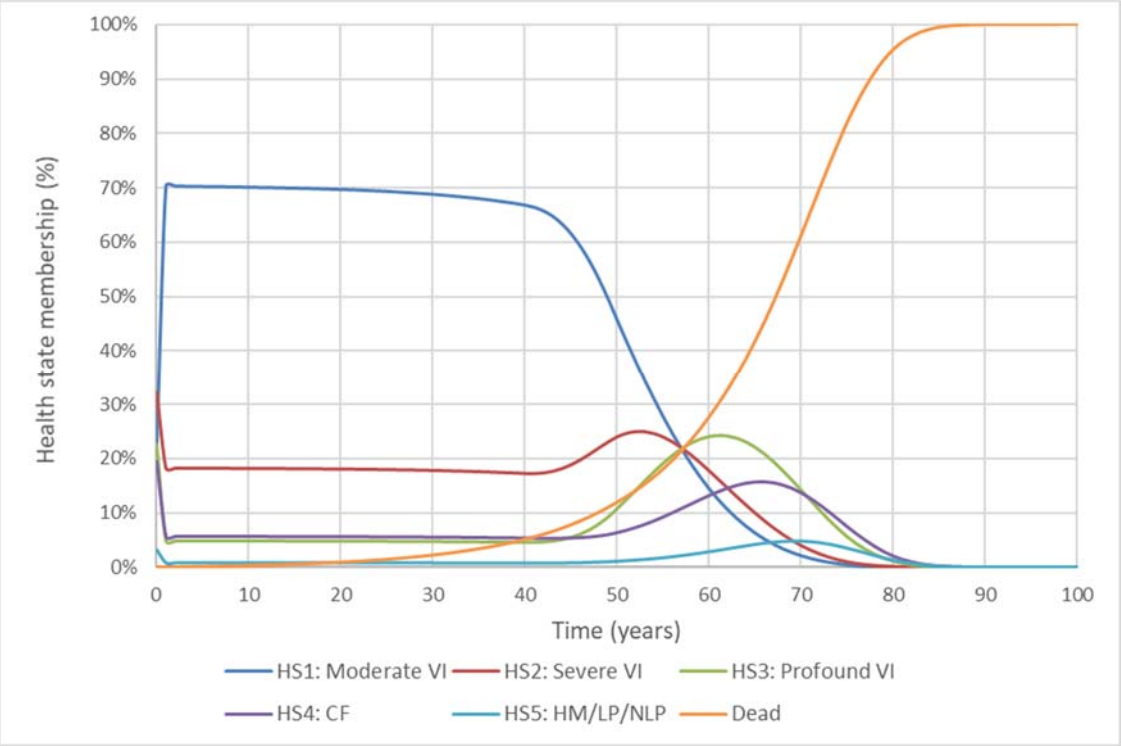
12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 33: Markov trace (BSC arm)



Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment.

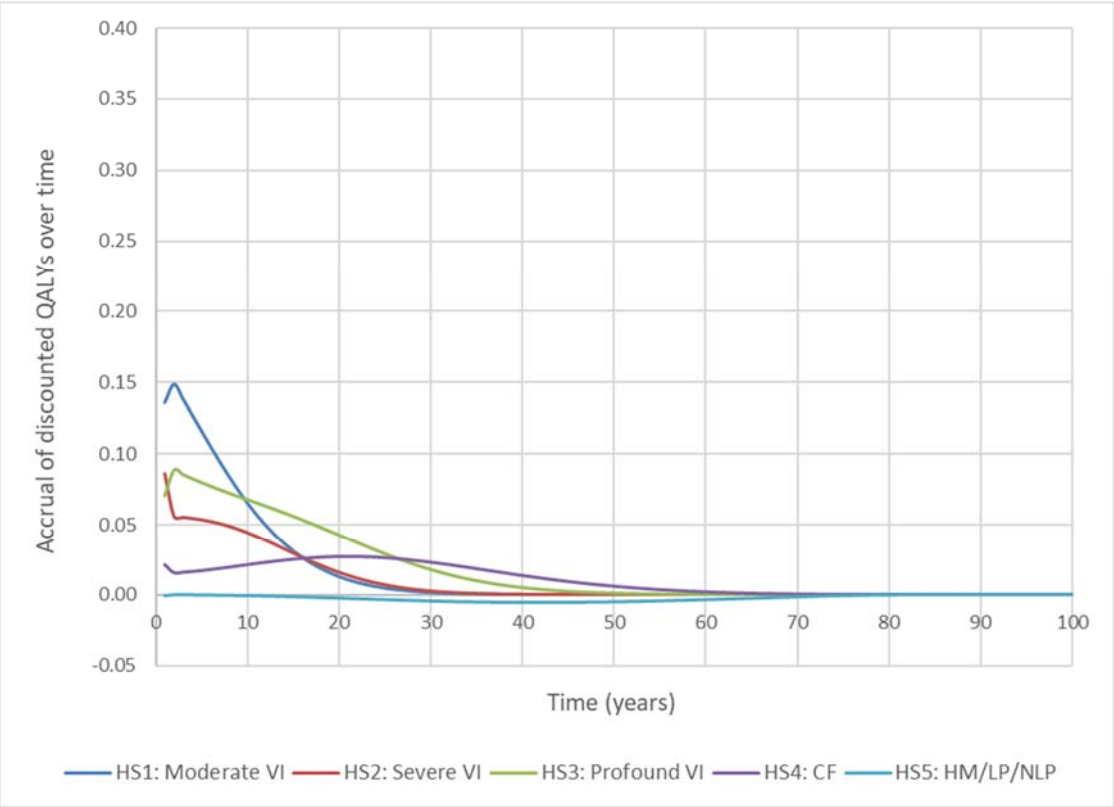
Figure 34: Markov trace (VN arm)



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.

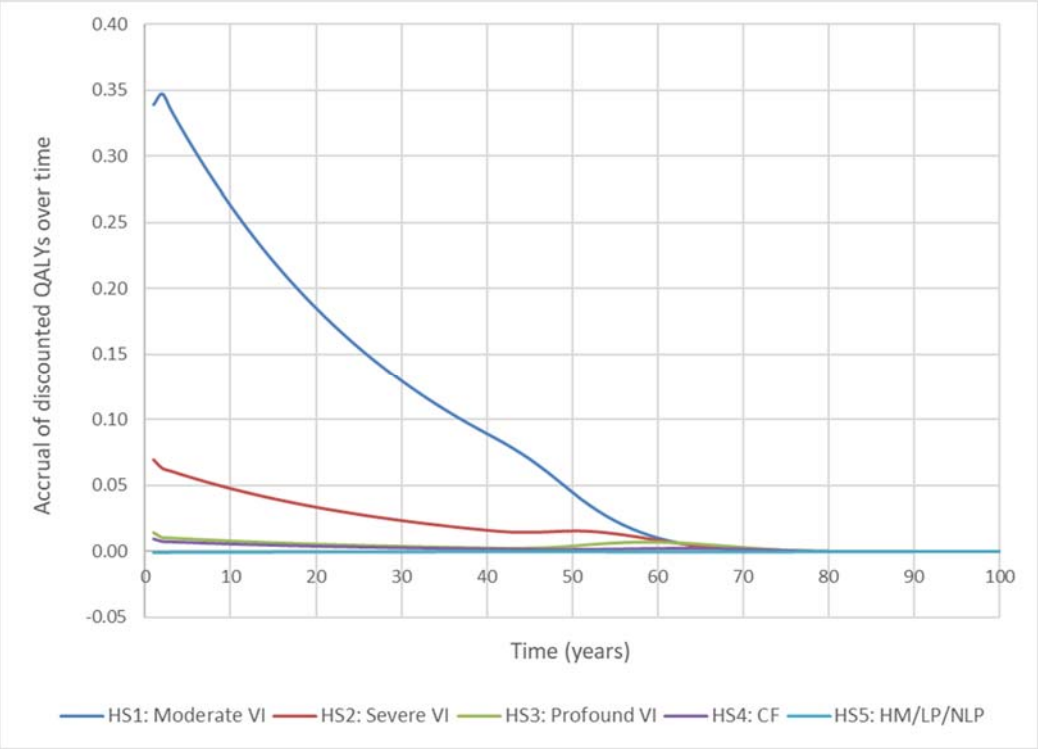
12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 35: Discounted QALY accrual at each time point (BSC arm)



Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment.

Figure 36: Discounted QALY accrual at each time point (VN arm)



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment; VN, voretigene neparvovec.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

A summary of life year gain by health state is presented in Table 70; a summary of QALY gain by health state is presented in Section 12.5.6 (Table 71), below.

Table 70: Summary of LY gain by health state

Health state	LYs (BSC)	LYs (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	2.8	16.9	14.1	14.1	43%
HS2: Severe VI	2.5	4.8	2.3	2.3	7%
HS3: Profound VI	7.8	1.7	-6.0	6.0	18%
HS4: CF	7.1	1.7	-5.4	5.4	17%
HS5: HM, LP, NLP	5.2	0.3	-5.0	5.0	15%
Total	25.5	25.5	0.0	32.9	100%

Abbreviations: AE, adverse event; BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; LY, life year; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 71: Summary of QALY gain by health state

Health state	QALYs (BSC)	QALYs (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	1.5	8.8	7.3	7.3	66%
HS2: Severe VI	0.9	1.8	0.8	0.8	8%
HS3: Profound VI	1.7	0.4	-1.3	1.3	12%
HS4: CF	1.0	0.2	-0.8	0.8	7%
HS5: HM, LP, NLP	-0.2	0.0	0.2	0.2	2%
AE disutility	0.00	-0.01	-0.01	0.01	0%
Carer disutility	-0.96	-0.37	0.59	0.59	5%
Total	3.9	10.8	6.8	11.1	100%

Abbreviations: AE, adverse event; BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

The undiscounted QALY gains associated with VN are 20.0 in the base case. The difference between the undiscounted and discounted QALY gains is driven by the modelling of long-term benefits in the VN arm and the low utility values associated with more severe health states.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table 72.

As in Section 12.5.1, results are presented assuming both the proposed PAS price and the list price for VN (Table 72 and Table 73, respectively).

Table 72: Summary of costs by category of cost per patient (proposed PAS price)

Item	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
VN acquisition, administration and monitoring	£0	[redacted]	[redacted]	[redacted]	[redacted]
AEs	£0	£146	£146	£146	[redacted]
Healthcare resource use	£46,300	£37,917	-£8,383	£8,383	[redacted]
Total	£46,300	[redacted]	[redacted]	[redacted]	100%

Abbreviations: AE, adverse event; BSC, best supportive care; PAS, patient access scheme; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 73: Summary of costs by category of cost per patient (list price)

Item	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
VN acquisition, administration and monitoring	£0	£618,571	£618,571	£618,571	99%
AEs	£0	£146	£146	£146	0%
Healthcare resource use	£46,300	£37,917	-£8,383	£8,383	1%
Total	£46,300	£656,754	£610,454	£627,100	100%

Abbreviations: AE, adverse event; BSC, best supportive care; VN, voretigene neparvovec.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table 74.

With the exception of costs associated with healthcare resource use, all costs are applied in the first model cycle. Table 74 therefore presents costs by health state for healthcare resource use only.

Table 74: Summary of healthcare resource use costs by health state per patient

Health state	Cost ([redacted]	Cost (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	£836	£9,624	£8,787	£8,787	17%
HS2: Severe VI	£1,503	£10,567	£9,064	£9,064	17%
HS3: Profound VI	£5,004	£9,542	£4,538	£4,538	9%
HS4: CF	£9,620	£6,528	-£3,092	£3,092	6%
HS5: HM, LP, NLP	£29,337	£1,656	-£27,681	£27,681	52%
Total	£46,300	£37,917	-£8,383	£53,162	100%

Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table 75.

Table 75: Summary of adverse event costs per patient

Adverse event	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
Cataract	£0.00	£137.01	£137.01	£137.01	93%
Eye inflammation	£0.00	£3.70	£3.70	£3.70	2%
Increased IOP	£0.00	£7.40	£7.40	£7.40	5%
Total	£0.00	£148.11	£148.11	£148.11	100%

Abbreviations: BSC, best supportive care; IOP, intraocular pressure; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis.

As in Section 12.5.1, results are presented assuming each of the proposed PAS price (Table 76 and Figure 37) and the list price (Table 77 and Figure 38) for VN.

Table 76: Results of one-way sensitivity analysis (proposed PAS price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Multistate model, Weibull (VA+VF, average eye): Constant	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): Ancillary	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS1	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS3	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS4	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS5	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS2	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	[redacted]	[redacted]

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

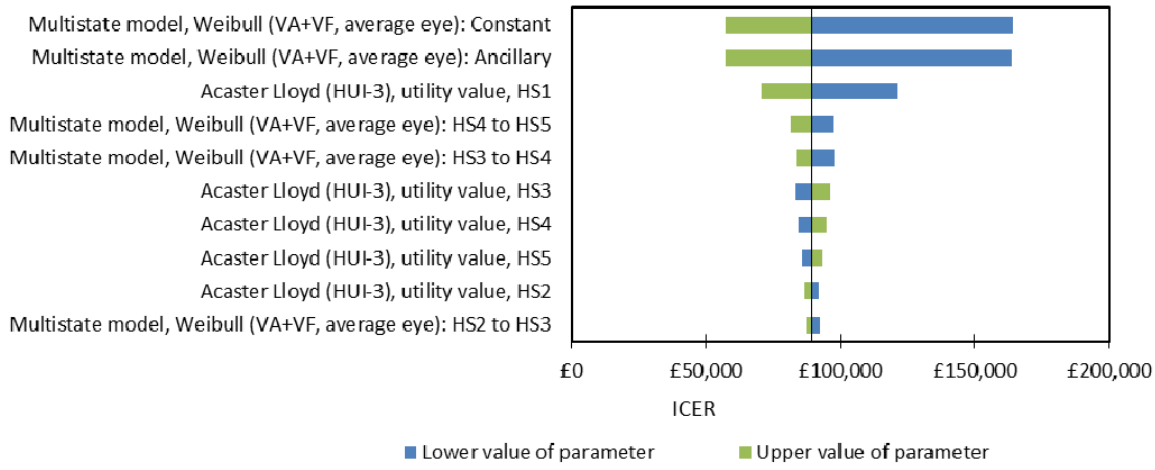
Figure 37: Tornado diagram (proposed PAS price)

Table 77: Results of one-way sensitivity analysis (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Multistate model, Weibull (VA+VF, average eye): Constant	£163,942	£57,269
Multistate model, Weibull (VA+VF, average eye): Ancillary	£163,809	£57,189
Acaster Lloyd (HUI-3), utility value, HS1	£121,221	£70,527
Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	£97,358	£81,673
Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	£97,850	£83,356
Acaster Lloyd (HUI-3), utility value, HS3	£83,210	£96,056
Acaster Lloyd (HUI-3), utility value, HS4	£84,248	£94,710
Acaster Lloyd (HUI-3), utility value, HS5	£85,744	£92,887
Acaster Lloyd (HUI-3), utility value, HS2	£91,959	£86,551
Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	£92,198	£87,280

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

Figure 38: Tornado diagram (list price)



Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis.

Results of scenario analyses are presented in Table 78 and Table 79, assuming each of the proposed PAS price and the list price for VN, respectively. Results of multi-way scenario analyses are presented in Table 80 and Table 81, assuming each of the proposed PAS price and the list price for VN, respectively.

Table 78: Results of scenario analyses (proposed PAS price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	6.85	[redacted]	0%
UK government perspective	[redacted]	6.85	[redacted]	-3%
Societal perspective	[redacted]	6.85	[redacted]	-27%
1.5% discount rate for costs and outcomes	[redacted]	12.03	[redacted]	-44%
0% discount rate for costs and outcomes	[redacted]	19.99	[redacted]	-68%
Health states based on best-seeing eye	[redacted]	6.88	[redacted]	0%
Health states based on VF only	[redacted]	5.97	[redacted]	15%
Baseline characteristics from natural history data	[redacted]	6.69	[redacted]	2%
Adjusted TP (state dependent)	[redacted]	6.75	[redacted]	1%
Adjusted TP (state independent)	[redacted]	7.22	[redacted]	-5%
Health states with no data: remain in same state	[redacted]	6.74	[redacted]	2%
Use cross-over data in VN arm	[redacted]	6.34	[redacted]	8%
Duration of treatment effect: 20 years	[redacted]	5.65	[redacted]	22%
Duration of treatment effect: 30 years	[redacted]	6.39	[redacted]	8%
Duration of treatment effect: 50 years	[redacted]	7.09	[redacted]	-4%
Duration of treatment effect: lifetime (100 years)	[redacted]	7.22	[redacted]	-6%
Waning period: 5 years	[redacted]	6.80	[redacted]	1%
Waning period: 20 years	[redacted]	6.93	[redacted]	-1%
Residual RRR (following waning period): 0%	[redacted]	6.76	[redacted]	1%
Residual RRR (following waning period): 50%	[redacted]	6.94	[redacted]	-2%
Gompertz multistate model distribution	[redacted]	7.36	[redacted]	-7%
Log-logistic multistate model distribution	[redacted]	6.44	[redacted]	6%
Log-normal multistate model distribution	[redacted]	6.36	[redacted]	7%
Exponential multistate model distribution	[redacted]	5.89	[redacted]	15%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
No mortality effect	[redacted]	6.89	[redacted]	-1%
Utility values: Acaster Lloyd (EQ-5D-5L)	[redacted]	6.25	[redacted]	9%
Utility values: Brown et al	[redacted]	4.88	[redacted]	40%
Carer disutility excluded	[redacted]	6.25	[redacted]	9%
Hypothetical light sensitivity increment (0.05 in HS1-HS3)	[redacted]	8.02	[redacted]	-15%
Hypothetical administration procedure disutility (0.1 for 1 month)	[redacted]	6.84	[redacted]	-1%
Include eligibility testing costs	[redacted]	6.85	[redacted]	2%
No healthcare resource use in HS1	[redacted]	6.85	[redacted]	-2%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment.
Abbreviations: ICER, incremental cost-effectiveness ratio; UK, United Kingdom; VF, visual field; VN, voretigene neparvovec; QALY, quality-adjusted life year; RRR, relative risk reduction; TP, transition probability.

Table 79: Results of scenario analyses (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	£610,454	6.85	£89,173	0%
UK government perspective	£593,564	6.85	£86,706	-3%
Societal perspective	£460,402	6.85	£67,254	-25%
1.5% discount rate for costs and outcomes	£600,163	12.03	£49,905	-44%
0% discount rate for costs and outcomes	£581,734	19.99	£29,108	-67%
Health state based on best-seeing eye	£611,328	6.88	£88,857	0%
Health states based on VF only	£610,028	5.97	£102,252	15%
Baseline characteristics from natural history data	£609,228	6.69	£91,040	2%
Adjusted TP (state dependent)	£610,454	6.75	£90,461	1%
Adjusted TP (state independent)	£610,454	7.22	£84,580	-5%
Health states with no data: remain in same state	£610,454	6.74	£90,538	2%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Use cross-over data in VN arm	£611,818	6.34	£96,432	8%
Duration of treatment effect: 20 years	£615,220	5.65	£108,951	22%
Duration of treatment effect: 30 years	£613,694	6.39	£96,023	8%
Duration of treatment effect: 50 years	£606,216	7.09	£85,506	-4%
Duration of treatment effect: lifetime (100 years)	£603,506	7.22	£83,628	-6%
Waning period: 5 years	£610,953	6.80	£89,797	1%
Waning period: 20 years	£609,072	6.93	£87,859	-1%
Residual RRR (following waning period): 0%	£611,451	6.76	£90,387	1%
Residual RRR (following waning period): 50%	£609,033	6.94	£87,714	-2%
Gompertz multistate model distribution	£610,583	7.36	£82,944	-7%
Log-logistic multistate model distribution	£609,988	6.44	£94,757	6%
Log-normal multistate model distribution	£609,623	6.36	£95,804	7%
Exponential multistate model distribution	£608,548	5.89	£103,289	15%
No mortality effect	£609,968	6.89	£88,591	-1%
Utility values: Acaster Lloyd (EQ-5D-5L)	£610,454	6.25	£97,598	9%
Utility values: Brown et al	£610,454	4.88	£125,069	40%
Carer disutility excluded	£610,454	6.25	£97,655	9%
Hypothetical light sensitivity increment (0.05 in HS1-HS3)	£610,454	8.02	£76,103	-15%
Hypothetical administration procedure disutility (0.1 for 1 month)	£610,454	6.84	£89,280	-1%
Include eligibility testing costs	£622,685	6.85	£90,960	1%
No healthcare resource use in HS1	£601,667	6.85	£87,889	-2%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment.
Abbreviations: ICER, incremental cost-effectiveness ratio; UK, United Kingdom; VF, visual field; VN, voretigene neparvovec; QALY, quality-adjusted life year; RRR, relative risk reduction; TP, transition probability.

Table 80: Results of multi-way scenario sensitivity analysis (proposed PAS price)

Duration of treatment effect (years)	Waning period (years)	ICER		
		Residual RRR (following waning period) = 0%	Residual RRR (following waning period) = 25%	Residual RRR (following waning period) = 50%
20	5	[redacted]	[redacted]	[redacted]
20	10	[redacted]	[redacted]	[redacted]
20	20	[redacted]	[redacted]	[redacted]
30	5	[redacted]	[redacted]	[redacted]
30	10	[redacted]	[redacted]	[redacted]
30	20	[redacted]	[redacted]	[redacted]
40	5	[redacted]	[redacted]	[redacted]
40	10	[redacted]	[redacted]	[redacted]
40	20	[redacted]	[redacted]	[redacted]
50	5	[redacted]	[redacted]	[redacted]
50	10	[redacted]	[redacted]	[redacted]
50	20	[redacted]	[redacted]	[redacted]
Lifetime (100)	5	[redacted]	[redacted]	[redacted]
Lifetime (100)	10	[redacted]	[redacted]	[redacted]
Lifetime (100)	20	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; RRR, relative risk reduction.

Table 81: Results of multi-way scenario sensitivity analysis (list price)

Duration of treatment effect (years)	Waning period (years)	ICER		
		Residual RRR (following waning period) = 0%	Residual RRR (following waning period) = 25%	Residual RRR (following waning period) = 50%
20	5	£117,352	£111,031	£103,789
20	10	£114,620	£108,951	£102,375
20	20	£109,047	£104,543	£99,241
30	5	£99,952	£97,101	£93,676
30	10	£98,606	£96,023	£92,899
30	20	£95,806	£93,706	£91,163
40	5	£91,150	£89,797	£88,173
40	10	£90,387	£89,173	£87,714
40	20	£88,817	£87,859	£86,724
50	5	£86,373	£85,836	£85,215
50	10	£85,965	£85,506	£84,976
50	20	£85,252	£84,920	£84,545
Lifetime (100)	5	£83,628	£83,628	£83,628
Lifetime (100)	10	£83,628	£83,628	£83,628
Lifetime (100)	20	£83,628	£83,628	£83,628

Abbreviations: ICER, incremental cost-effectiveness ratio; RRR, relative risk reduction.

12.5.13 Present results of the probabilistic sensitivity analysis.

Assuming each of the proposed PAS price and the list price for VN, the results of 10,000 PSA simulations were plotted on the CEP (Figure 39 and Figure 41, respectively) and a CEAC was generated (Figure 40 and Figure 42, respectively).

Assuming the proposed PAS price for VN, the average incremental costs over the simulated results were [redacted], and the average incremental QALYs were 6.7, giving a probabilistic ICER of [redacted]; this is highly congruent with deterministic changes in costs and QALYs of [redacted] and 6.8, respectively. The proportion of simulations considered cost-effective assuming the weighted cost-effectiveness threshold - calculated for each simulation individually dependent on the number of undiscounted QALYs gained - is 75%.

Assuming the list price for VN, the average incremental costs over the simulated results were £611,613, and the average incremental QALYs were 6.7, giving a

probabilistic ICER of £91,572; this is highly congruent with deterministic changes in costs and QALYs of £610,454 and 6.8, respectively. The proportion of simulations considered cost-effective assuming the weighted cost-effectiveness threshold - calculated for each simulation individually dependent on the number of undiscounted QALYs gained - is 72%.

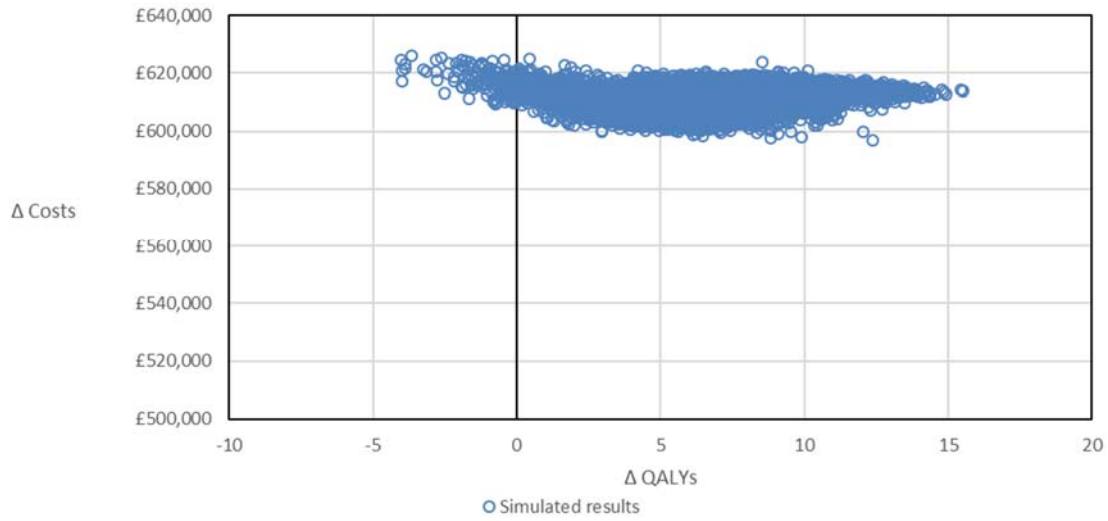
Figure 39: CEP (proposed PAS price)

[redacted]

Figure 40: CEAC (proposed PAS price)

[redacted]

Figure 41: CEP (list price)



Abbreviations: CEP, cost-effectiveness plan; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 42: CEAC (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme.

12.5.14 What were the main findings of each of the sensitivity analyses?

For all considered parameters, univariate sensitivity analysis resulted in ICERs that fell below the weighted threshold of £200,000 per QALY gained (assuming either the proposed PAS price or the list price for VN); varying all but three parameters resulted in ICERs that fell below the standard HST threshold of £100,000 per QALY gained.

Five of the ten most influential parameters in univariate sensitivity analysis are those describing the long-term multi-state survival model; however, this result should be treated with caution given that highly correlated parameters (i.e. the regression coefficients) are being varied as if they are independent from one another. This conservative approach was taken as it was not considered appropriate to exclude these parameters from univariate sensitivity analysis. Other influential parameters are the health state utility values.

Only four of the considered scenarios are associated with increases in the ICER of more than 10%:

- Health states defined based on VF only

- 20-year treatment effect for VN
- Exponential distribution used for the multi-state survival model
- Utility values taken from Brown et al

Note that this remained the case when assuming either the proposed PAS price or the list price for VN. See Sections 12.1.6, 12.2.1, 12.1.8.3.3 and 10.9.1 for further details on why these approaches were not taken in the model base-case.

Several analyses were associated with substantial decreases in the ICER, including applying a societal perspective, discount rates of 1.5%, and the inclusion of a hypothetical light sensitivity increment.

Multi-way scenario analyses considering the interaction of the duration of the VN treatment effect, the duration of the waning period and the magnitude of the residual treatment effect resulted in best and worst case scenarios ranging between [redacted] and [redacted] when assuming the proposed PAS price for VN, or between £83,628 and £117,352 when assuming list price.

Assuming each of the proposed PAS price and the list price for VN, probabilistic sensitivity analysis showed that the probability of VN being cost-effective is 75% and 72%, respectively.

12.5.15 What are the key drivers of the cost results?

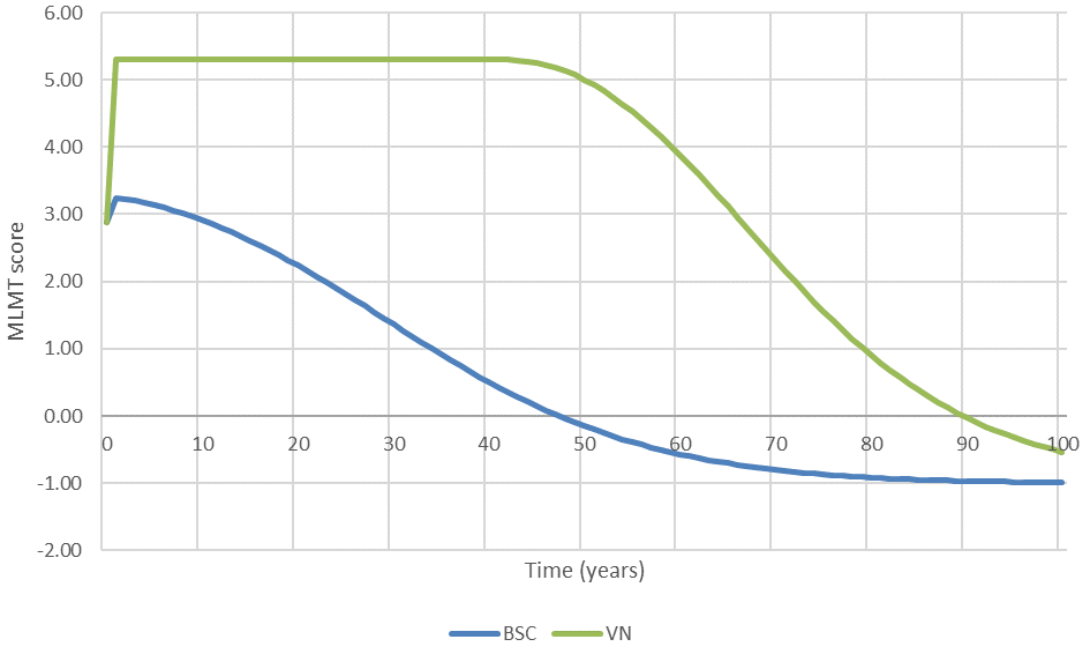
The key drivers of the cost-effectiveness results are the assumed discount rates, the perspective taken, the duration of treatment effect and the choice of utility values.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

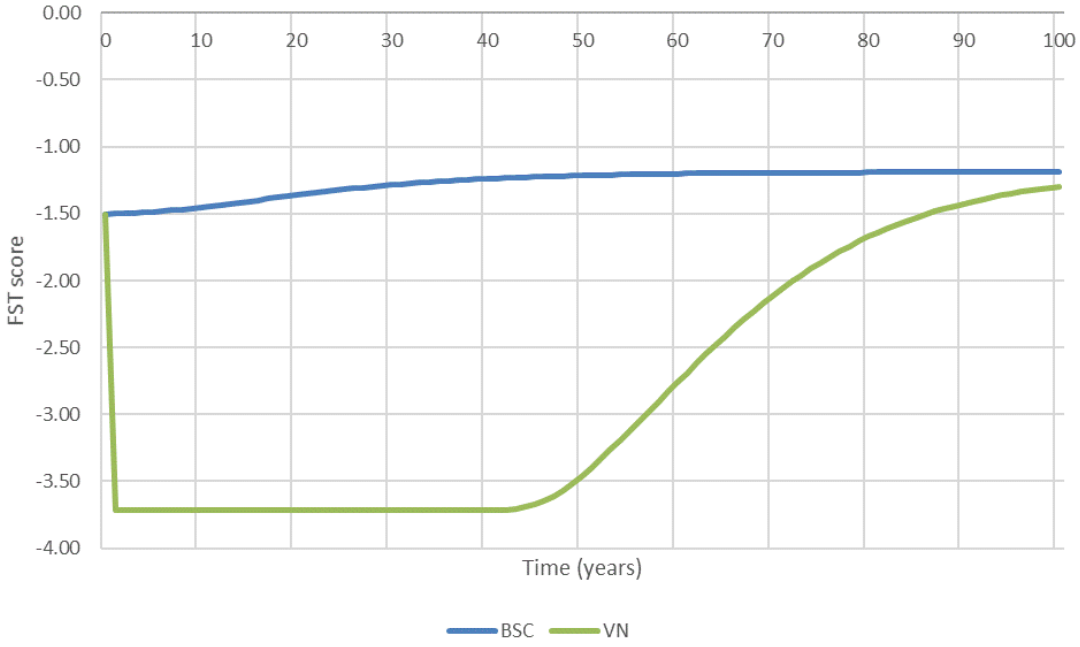
Illustrative MLMT and FST changes over time (see Section 12.1.8.5) are presented in Figure 43 and Figure 44, respectively.

Figure 43: Illustrative MLMT over time



Note: Higher MLMT scores indicate improved functional vision.
Abbreviations: BSC, best supportive care; MLMT, multi-luminance mobility test; VN, voretigene neparvovec.

Figure 44: Illustrative FST over time



Note: Lower FST scores indicate improved light sensitivity.
Abbreviations: BSC, best supportive care; FST, full-field light sensitivity threshold; VN, voretigene neparvovec.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in Table 1.

Subgroup analyses were not performed – see Section 9.4.4.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also

present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The cost-effectiveness model has been verified by the model developers and by health economists not involved in the construction of the model. The model was verified using standard procedures:

- Cell-by-cell checks of logic and consistency
- Logical tests of model outputs

In the absence of other sources of long-term data in this disease area, it has not been possible to cross-validate model outcomes against external sources.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Only one economic analysis was identified from the published literature (see Section 11). ICER developed an economic model to estimate the cost-

effectiveness of VN for vision loss associated with biallelic *RPE65*-mediated IRD compared to standard of care (SoC) in the US setting [185]. A comparison of the total costs and QALYs between the analysis presented in this submission and the ICER analysis is presented in Table 82.

Table 82: Comparison of outcomes in current analysis and ICER analysis

	BSC arm		VN arm	
	Total costs	**Total QALYs**	**Total costs†**	**Total QALYs**
Analysis presented in this submission	£46,300	3.9	[redacted]	10.8
ICER analysis	$213,399	16.0	$1,039,019	17.3

Abbreviations: BSC, best supportive care; ICER, Institute for Clinical and Economic Review; PAS, patient access scheme; QALY, quality-adjusted life year; VN, voretigene neparvovec.
† Proposed PAS price assumed.

Given that the analyses use different currencies, different acquisition costs are assumed, and the costs of healthcare resource use can differ substantially between the two countries, it may be expected that total costs would differ between the two analyses.

However, the ICER analysis is associated with a significantly smaller QALY gain compared with the current analysis (1.3 vs. 6.8). Given that the effect of VN on mortality is negligible, this effect is driven by differing assumptions around utility values. Average utility values over time (alive patients only) in the current analysis and the ICER analysis are presented in Figure 45 and Figure 46, respectively; it can be seen that the current analysis is associated with a larger gap between the VN and BSC arms, and lower utility values overall.

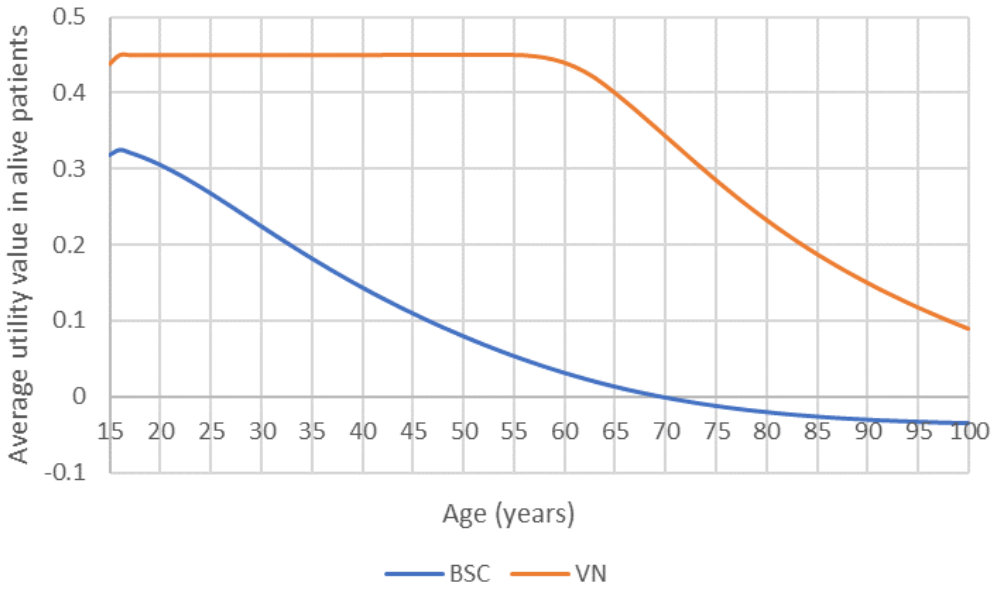
The approach taken in the current analysis is considered to be more appropriate than that of the ICER analysis on the basis that:

- The ICER analysis uses utility values taken from individuals with diabetic retinopathy, which may be expected to differ substantially from those in individuals with *RPE65*-mediated IRD

- The ICER analysis uses only three health states (not visually impaired, visually impaired and blind); however, both the Acaster Lloyd study (Appendix 9) and the study by Brown et al [180] demonstrate differing utility values within the 'blind' health state

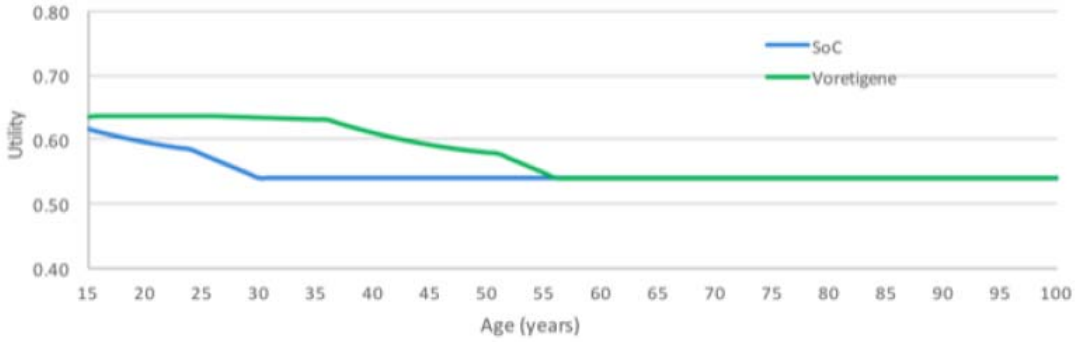
- In the absence of patient-level data, it was necessary for the ICER analysis to make simplified assumptions about how VA and VF change over time.

Figure 45: Average utility value over time in alive patients (current analysis



Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

Figure 46: Average utility value over time in alive patients (ICER analysis)



Abbreviations: ICER, Institute for Clinical and Economic Review; SoC, standard of care.
Source: ICER 2018 [185]

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis was designed to be relevant to all patients eligible for VN as defined in the scope.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A key strength of this analysis is that a range of scenarios were considered, and the results were found to be relatively robust to alternative assumptions. An additional strength is that the modelled utility values were taken from a bespoke utility study, and did not rely on HRQL data from older populations with different vision conditions, as in previous analyses [185]. Wherever possible, all relevant costs were considered, with key insights on the types of costs to include provided by a patient focus group conducted to support this analysis [97].

A key limitation of the analysis is that it was not possible to capture improvements in either MLMT (the primary endpoint in the pivotal clinical trial) or light sensitivity; however, a scenario considering an arbitrary utility increment for improved light sensitivity was associated with an improved ICER, and so the results of the base-case analysis are expected to be conservative.

Health state transitions in both the initial phase and the long-term phase were based on low patient numbers and short follow-up, somewhat increasing the level of uncertainty in model outcomes. In the absence of long-term data, there was also uncertainty around the long-term treatment effect associated with VN.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Following the collection of long-term follow-up data, further information may be available on the duration of the VN treatment effect, reducing the uncertainty around the estimate of cost-effectiveness.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

- The budget impact associated with the introduction of VN is manageable and predictable, with 78 patients in England estimated to be suitable for treatment. It is anticipated that voretigene neparvovec gene therapy will fit a specialised centre model, with diagnosis, counselling, treatment and follow-up performed at no more than a few centres nationally.
- Assuming the PAS price for VN, the net budget impact is estimated to be [redacted] in Year 1, [redacted] in each of Years 2 to 4, and [redacted] in Year 5. This does not exceed the budget impact threshold of £20 m in any of the first three years.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

As described in Section 6.2, the number of existing eligible patients in England in 2019 is estimated to be 78. The number of incident eligible patients in each of the first five years is presented in Table 83.

Table 83: Number of incident eligible patients per year

Year	Number of incident eligible patients
Year 1	2.91
Year 2	2.93
Year 3	2.95
Year 4	2.98
Year 5	3.00

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

In the scenario in which VN is not available, BSC is the only available option and so is associated with 100% market share.

In the scenario in which VN is available, it is assumed that:

- All existing patients are treated within the first five years of VN becoming available (see assumed timing in Table 84), to account for product availability and healthcare system resourcing.
- All incident patients are treated in the year they become eligible for treatment.

Table 84: Timing of treatment of existing patients

Year	% of existing patients treated per year
Year 1	3%
Year 2	29%
Year 3	29%
Year 4	29%
Year 5	10%

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

In addition to technology costs, other costs associated with the introduction of VN, and considered in the budget impact analysis, are:

- Administration costs
- Monitoring costs
- Sufficient viable retinal cells testing costs
- Adverse event costs

See Sections 12.3.6 and 12.3.8 for further details.

13.4 Describe any estimates of resource savings associated with the use of the technology.

VN is associated with reduced healthcare resource use, including reduced costs for:

- Hospitalisation
- Low vision rehabilitation
- Low vision aids
- Depression

Annual healthcare resource use costs for BSC and VN patients are taken from Years 1 to 5 of the cost-effectiveness model, and reflect the modelled health state distribution at each time point.

See Section 12.3.7 for further details.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The following cost categories were not included due to a lack of available data:

- Ophthalmic services
- Home modifications

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

VN is associated with substantial cost savings that fall outside of the NHS and PSS, including reduced costs for:

- Education

- Social security

See Section 12.3.7 for further details.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Base-case estimates of the budget impact associated with the introduction of VN are presented in Table 85 and Table 86, assuming each of the proposed PAS price and the list price, respectively. Scenario analyses considering the key uncertainties in the budget impact estimates are presented in Table 87 and Table 88, assuming each of the proposed PAS price and the list price, respectively.

Table 85: Expected budget impact (proposed PAS price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs in scenario without VN	£41,938	£42,587	£44,343	£46,173	£48,067
Total costs in scenario with VN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: VN, voretigene neparvovec.

Table 86: Expected budget impact (list price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs in scenario without VN	£41,938	£42,587	£44,343	£46,173	£48,067
Total costs in scenario with VN	£3,291,787	£15,889,011	£15,902,027	£15,915,026	£6,733,015
Net budget impact	£3,249,850	£15,846,423	£15,857,684	£15,868,853	£6,684,947

Abbreviations: VN, voretigene neparvovec.

Table 87: Budget impact scenario analyses (proposed PAS price)

Scenario	Rationale	Net budget impact				
		Year 1	Year 2	Year 3	Year 4	Year 5
55% of patients have sufficient viable retinal cells	• Clinical experts estimated the proportion of patients with sufficient viable retinal cells to be between 55% and 95% • The upper end of this range was conservatively assumed in the base-case; however, the lower end represents a plausible estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30% of patients are diagnosed	• Clinical experts estimated the proportion of patients who are diagnosed to be between 30% and 50% • The upper end of this range was conservatively assumed in the base-case; however, the lower end represents a plausible estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80% of patients are diagnosed	• Following the introduction of VN, it may be expected that the diagnosis rate would increase • A hypothetical scenario is therefore considered in which a higher proportion of patients are diagnosed. This scenario is considered unlikely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 88: Budget impact scenario analyses (list price)

Scenario	Rationale	Net budget impact				
		Year 1	Year 2	Year 3	Year 4	Year 5
55% of patients have sufficient viable retinal cells	• Clinical experts estimated the proportion of patients with sufficient viable retinal cells to be between 55% and 95% • The upper end of this range was conservatively assumed in the base-case; however, the lower end represents a plausible estimate	£2,579,935	£9,370,596	£9,383,185	£9,395,770	£4,456,176
30% of patients are diagnosed	• Clinical experts estimated the proportion of patients who are diagnosed to be between 30% and 50% • The upper end of this range was conservatively assumed in the base-case; however, the lower end represents a plausible estimate	£1,894,225	£8,969,568	£8,976,435	£8,983,254	£3,825,708
80% of patients are diagnosed	• Following the introduction of VN, it may be expected that the diagnosis rate would increase • A hypothetical scenario is therefore considered in which a higher proportion of patients are diagnosed. This scenario is considered unlikely	£5,283,287	£26,161,706	£26,179,558	£26,197,251	£10,973,807

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The key limitation of the budget impact analysis is uncertainty around the estimates of patient numbers. Depending on the sources of data used to inform the prevalence of RP and LCA, and the proportions of cases that are due to *RPE65* mutations, the estimated number of patients with *RPE65*-mediated IRD ranges from 57 to 564 (see Section 6.1.1). However, the patient numbers assumed in this analysis (178) are based on sources expected to best reflect the prevalence in England (see Section 6.2).

The proportion of patients with sufficient viable retinal cells and the proportion of patients who are diagnosed were estimated by clinical experts, and so are subject to some uncertainty. However, scenario analyses are considered in which alternative assumptions are made.

The budget impact analysis uses annual healthcare resource use costs generated by the cost-effectiveness model and so is associated with the same limitations for:

- The modelling of the health state distribution over time; and
- The calculation of cost inputs.

However, the key driver of cost per patient is the acquisition cost of VN (see Section 12.5.8), which is a known parameter.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

VN is associated with improved vision, and therefore a reduction in the substantial costs and detrimental effects associated with visual impairment and blindness.

A patient focus group was conducted to identify the 'hidden' costs of blindness, including many costs falling outside of the NHS and personal social services [97].

Costs associated with visual impairment and blindness incurred by government departments other than the NHS include those for education and social

security, as well as minor costs associated with discounted rail travel and television licenses (see Section 14.2).

Out-of-pocket costs borne by patients with visual impairment include those for transport to eye appointments, home modifications, and specialist toys for affected children (see Section 14.3). Patients are also often required to pay upfront to access discounts available to those who are registered as visually impaired, and incur higher household expenses due to vision-related limitations. In addition, many patients experience a loss of earnings due to vision-related unemployment.

Friends and family members of individuals with visual impairment spend an estimated 11.9 hours per week as caregivers (see Section 14.4), and so may be expected to experience a loss of earnings. Caregivers incur out-of-pocket expenses associated with accompanying patients to eye appointments.

Details on the non-financial impact of visual impairment on patients and caregivers can be found in Section 7.2.1 and 7.2.2.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Table 89: Costs incurred by government departments other than the NHS

Government department	Types of cost in those with visual impairment and blindness
Department for Education	• Early years educational support • Support for children educated in mainstream schools • Education in specialist schools • Support for individuals in higher education
Department for Work and Pensions	• Carer's Allowance • Personal Independence Payment • Employment and Support Allowance • Universal Credit/Working Tax Credit • Attendance Allowance • Pension Credit • Access to Work scheme
HM Revenue and Customs	• Loss of taxes due to vision-related unemployment • Blind Person's Tax Allowance
Department for Transport	• Provision of discounted rail travel • Provision of discounted bus travel
Department of Culture, Media and Sport	• Provision of discounted television license

Abbreviations: NHS, National Health Service.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Costs borne by patients that are not reimbursed by the NHS are as follows:

- Loss of earnings due to vision-related unemployment
- Public transport or taxis to eye appointments
- Accommodation where specialist healthcare or testing is not available locally
- Home modifications (beyond those covered by the NHS)
- Specialist toys for affected children

- Upfront costs of applying for benefits such as Blue Badge parking permits and cinema cards

- Higher household costs due to vision-related limitations

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

In a Portuguese study on the use of informal care by people with vision impairment, 39.6% of respondents reported using informal care [212]. In blind patients who receive informal care in a US study, mean time spent by caregivers was shown to be 4.3 hours per day [121].

Assuming a weighted average, family members providing care are therefore estimated to spend 11.9 hours per week on caregiving activities.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

There are three ongoing/planned studies assessing the clinical effectiveness of voretigene neparvovec:

- A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2) Administered via Subretinal Injection (Ongoing; NCT03602820)

    - This study is collecting efficacy and AE data 15 years after subretinal injection in each patient enrolled in the clinical trials.

- A Patient Registry Study for Patients Treated With Voretigene Neparvovec (Ongoing; NCT03597399)

- The objective of this study is to collect long-term safety information (i.e., for 5 years after treatment) associated with VN (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products, for patients treated in the US.

- A Post-Authorisation, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec (Planned; Q3 2019)

    - This planned registry-based study is a post-approval commitment requested by the EMA (Category 1 PASS). It will collect long-term safety information as described above.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Voretigene neparvovec is among the first treatments of its kind. It is the first pharmacologic treatment for an IRD, and Study 301/302 was the first randomised Phase 3 gene therapy trial for a genetic disease.

The methodology and results of the Phase 3 trial (Study 301) provide support for gene-based approaches to treating rare genetic diseases. The manufacturing techniques used might potentially be applied to the treatment of IRD with different genetic causes, and to genetic diseases involving other organ systems.

Voretigene neparvovec therefore not only has potential to improve the lives of patients with *RPE65*-mediated IRD, but also to advance the broader field of gene therapy.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical

effectiveness data to evaluate the benefits of the technology over the next 5 years.

As part of a European regulatory requirement [2] the company will have to follow up all patients who received VN in the main studies for 15 years, in order to characterise the long-term effectiveness, safety and durability of the medicine, and establish a registry to collect long-term safety data in patients treated with VN in clinical practice (further details on registry studies are provided in Section 14.5).

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

As described above, all patients enrolled in the main studies will be followed up for 15 years to characterise long-term effectiveness of VN.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The SmPC stipulates that treatment must be initiated and administered by retinal surgeons experienced in performing macular surgery [3]. Additionally, before being permitted to administer VN, surgeons and pharmacists are required to participate in a mandatory educational program (Section 8.7.1). Treatment centres will need to meet the EMA risk management plan criteria described in Section 8.6.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

It is not anticipated that any additional infrastructure would be required following the introduction of VN. Although genetic testing would need to become more routine to allow for equal access across England and Wales, a single national testing network composed of seven Genomic Laboratory Hubs – of which three of will perform ophthalmologic genetic testing – has already been established

(see Section 5.2). Treatment will only take place at a small number of specialist IRD centres (Section 8.6).

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

Not applicable. A fundamental requirement of a Managed Access Arrangement proposal is that it addresses a significant uncertainty in the evidence base. Although the ICER is sensitive to the assumed treatment effect duration beyond 7.5 years (i.e. maximum available follow-up), data collection beyond 7.5 years would place a significant administrative burden on the NHS. Furthermore as part of a European regulatory requirement [2] the company will have to follow up all patients who received VN in the main studies for 15 years, in order to characterise the long-term effectiveness and safety of the medicine, and establish a registry to collect long-term safety data in patients treated with VN in clinical practice. Consequently any data collection arrangements as part of a Managed Access Arrangement over a shorter time period would add limited value.

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Not applicable.

15.2 Describe the specifics of the MAA proposal, including:

- **The duration of the arrangement, with a rationale**
- **What evidence will be collected to reduce uncertainty**
- **How this evidence will be collected and analysed**
- **The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA**
- **Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)**
- **Funding arrangement, including any commercial proposals or financial risk management plans**
- **The roles and responsibilities of clinical and patient groups during the MAA**
- **What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed**

Not applicable.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Not applicable.

16 References

1. European Medicines Agency. *New gene therapy for rare inherited disorder causing vision loss recommended for approval*. 2018; Available from: https://www.ema.europa.eu/news/new-gene-therapy-rare-inherited-disorder-causing-vision-loss-recommended-approval.
2. European Medicines Agency, *Luxturna: EPAR - Medicine overview*. 2019.
3. European Medicines Agency, *Luxturna: EPAR - Product Information*. 2019.
4. Russell, S., et al., *Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial.* The Lancet, 2017. **390**: p. 849-860.
5. Novartis. *Novartis receives European licence for Luxturna®▼ (voretigene neparvovec), the first one-time gene therapy to improve visual acuity in people with rare inherited retinal disease*. 2018; Available from: https://www.novartis.co.uk/news/media-releases/novartis-receives-european-licence-luxturnav-voretigene-neparvovec-first-one.
6. National Institute for Health and Care Excellence, *TA155: Ranibizumab and pegaptanib for the treatment of age-related macular degeneration*. 2008.
7. National Institute for Health and Care Excellence, *TA294: Aflibercept solution for injection for treating wet age-related macular degeneration*. 2013.
8. National Institute for Health and Care Excellence, *Holoclar for treating limbal stem cell deficiency after eye burns*. 2017.
9. Novartis, *Data on file: Clinical expert interview transcripts*. 2019.
10. Berger, W., B. Kloeckener-Gruissem, and J. Neidhardt, *The molecular basis of human retinal and vitreoretinal diseases.* Progress in Retinal and Eye Research, 2010. **29**(5): p. 335-375.
11. European Medicines Agency, *Luxturna: Orphan Maintenance Assessment Report*. 2019.
12. European Medicines Agency, *Public summary of opinion on orphan designation: Adenovirus-associated viral vector serotype 2 containing the human RPE65 gene for the treatment of Leber's congenital amaurosis*. 2012.
13. European Medicines Agency, *Public summary of opinion on orphan designation: Adenovirus-associated viral vector serotype 2 containing the human RPE65 gene for the treatment of retinitis pigmentosa*. 2015.
14. Spark Therapeutics, *Clinical Study Report (Study 101): A Phase 1 Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE)*. 2015.
15. Massof, R.W., et al., *Bilateral symmetry of vision disorders in typical retinitis pigmentosa.* The British Journal of Ophthalmology, 1979. **63**(2): p. 90-96.

16. Maguire, A.M., et al., *Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial.* The Lancet, 2009. **374**: p. 1597-1605.
17. Bennett, J., et al., *Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial.* The Lancet, 2016. **388**: p. 661-672.
18. Spark Therapeutics, *Clinical Study Report (Study 102): A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects with Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study*. 2015.
19. Spark Therapeutics, *Clinical Study Report (Study 301): A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)*. 2016.
20. Spark Therapeutics, *Clinical Study Report Addendum 2017 (Study 301): A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)*. 2018.
21. Chung, D.C., et al., *Novel mobility test to assess functional vision in patients with inherited retinal dystrophies.* Clinical & Experimental Ophthalmology, 2018. **46**: p. 247-259.
22. GOV.UK. *Equality Act 2010*. [Text] 2010.
23. Verma, A., et al., *Mutational Screening of LCA Genes Emphasizing RPE65 in South Indian Cohort of Patients.* PLOS ONE, 2013. **8**: p. e73172.
24. NHS England. *Genomic Laboratory Hubs*. 2018; Available from: https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/.
25. Health Service Journal. *Exclusive: Genomic trusts named but 18 months from full operation*. 2018; Available from: https://www.hsj.co.uk/service-design/exclusive-genomic-trusts-named-but-18-months-from-full-operation/7023670.article.
26. *RetNet: Summaries of Genes and Loci Causing Retinal Diseases*. 2018 2018.
27. Chiang, J.P.-w. and K. Trzupek, *The current status of molecular diagnosis of inherited retinal dystrophies.* Current Opinion in Ophthalmology, 2015. **26**(5): p. 346-351.
28. Spark Therapeutics, *Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the RPE65 Gene*. 2017.
29. Bertelsen, M., et al., *Prevalence of generalized retinal dystrophy in Denmark.* Ophthalmic Epidemiology, 2014. **21**(4): p. 217-223.
30. Ammann, F., D. Klein, and A. Franceschetti, *Genetic and epidemiological investigations on pigmentary degeneration of the retina and allied disorders in Switzerland.* Journal of the Neurological Sciences, 1965. **2**(2): p. 183-196.

31. Chizzolini, M., et al., *Good epidemiologic practice in retinitis pigmentosa: from phenotyping to biobanking.* Current Genomics, 2011. **12**(4): p. 260-266.
32. Haim, M., *Epidemiology of retinitis pigmentosa in Denmark.* Acta Ophthalmologica Scandinavica. Supplement, 2002: p. 1-34.
33. Hu, D.N., *Prevalence and mode of inheritance of major genetic eye diseases in China.* Journal of Medical Genetics, 1987. **24**(10): p. 584-588.
34. Nájera, C., et al., *Epidemiology of retinitis pigmentosa in the Valencian community (Spain).* Genetic Epidemiology, 1995. **12**(1): p. 37-46.
35. Na, K.-H., et al., *Prevalence, Age at Diagnosis, Mortality, and Cause of Death in Retinitis Pigmentosa in Korea-A Nationwide Population-based Study.* American Journal of Ophthalmology, 2017. **176**: p. 157-165.
36. Bundey, S. and S.J. Crews, *A study of retinitis pigmentosa in the City of Birmingham. I Prevalence.* Journal of Medical Genetics, 1984. **21**: p. 417-420.
37. Bunker, C.H., et al., *Prevalence of retinitis pigmentosa in Maine.* American Journal of Ophthalmology, 1984. **97**(3): p. 357-365.
38. Hartong, D.T., E.L. Berson, and T.P. Dryja, *Retinitis pigmentosa.* Lancet (London, England), 2006. **368**(9549): p. 1795-1809.
39. Peterlin, B., et al., *Prevalence of retinitis pigmentosa in Slovenia.* Clinical Genetics, 1992. **42**(3): p. 122-123.
40. Stone, E.M., *Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture.* American Journal of Ophthalmology, 2007. **144**(6): p. 791-811.
41. Grøndahl, J., *Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway.* Clinical Genetics, 1987. **31**(4): p. 255-264.
42. Morimura, H., et al., *Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or Leber congenital amaurosis.* Proceedings of the National Academy of Sciences, 1998. **95**: p. 3088-3093.
43. Wang, F., et al., *Next generation sequencing-based molecular diagnosis of retinitis pigmentosa: identification of a novel genotype-phenotype correlation and clinical refinements.* Human genetics, 2014. **133**(3): p. 331-345.
44. Bocquet, B., et al., *Homozygosity mapping in autosomal recessive retinitis pigmentosa families detects novel mutations.* Molecular Vision, 2013. **19**: p. 2487-2500.
45. Coppieters, F., et al., *Genetic screening of LCA in Belgium: predominance of CEP290 and identification of potential modifier alleles in AHI1 of CEP290-related phenotypes.* Human Mutation, 2010. **31**(10): p. E1709-1766.
46. Xu, F., et al., *Novel RPE65 mutations associated with Leber congenital amaurosis in Chinese patients.* Molecular Vision, 2012. **18**: p. 744-750.
47. Dharmaraj, S.R., et al., *Mutational analysis and clinical correlation in Leber congenital amaurosis.* Ophthalmic Genetics, 2000. **21**(3): p. 135-150.
48. Hanein, S., et al., *Leber congenital amaurosis: comprehensive survey of the genetic heterogeneity, refinement of the clinical definition, and*

genotype-phenotype correlations as a strategy for molecular diagnosis. Human Mutation, 2004. **23**(4): p. 306-317.
49. Lotery, A.J., et al., *Mutation analysis of 3 genes in patients with Leber congenital amaurosis.* Archives of Ophthalmology (Chicago, Ill.: 1960), 2000. **118**(4): p. 538-543.
50. Simonelli, F., et al., *Clinical and molecular genetics of Leber's congenital amaurosis: a multicenter study of Italian patients.* Investigative Ophthalmology & Visual Science, 2007. **48**(9): p. 4284-4290.
51. Simovich, M.J., et al., *Four novel mutations in the RPE65 gene in patients with Leber congenital amaurosis.* Human Mutation, 2001. **18**(2): p. 164.
52. Astuti, G.D.N., et al., *Comprehensive genotyping reveals RPE65 as the most frequently mutated gene in Leber congenital amaurosis in Denmark.* European journal of human genetics: EJHG, 2016. **24**(7): p. 1071-1079.
53. Bocquet, B., et al., *Relative frequencies of inherited retinal dystrophies and optic neuropathies in Southern France: assessment of 21-year data management.* Ophthalmic Epidemiology, 2013. **20**(1): p. 13-25.
54. Eisenberger, T., et al., *Increasing the yield in targeted next-generation sequencing by implicating CNV analysis, non-coding exons and the overall variant load: the example of retinal dystrophies.* PloS One, 2013. **8**(11): p. e78496.
55. Haer-Wigman, L., et al., *Diagnostic exome sequencing in 266 Dutch patients with visual impairment.* European journal of human genetics: EJHG, 2017. **25**(5): p. 591-599.
56. Mamatha, G., et al., *Screening of the RPE65 gene in the Asian Indian patients with leber congenital amaurosis.* Ophthalmic Genetics, 2008. **29**(2): p. 73-78.
57. Sitorus, R.S., B. Lorenz, and M.N. Preising, *Analysis of three genes in Leber congenital amaurosis in Indonesian patients.* Vision Research, 2003. **43**(28): p. 3087-3093.
58. Vallespin, E., et al., *Mutation screening of 299 Spanish families with retinal dystrophies by Leber congenital amaurosis genotyping microarray.* Investigative Ophthalmology & Visual Science, 2007. **48**(12): p. 5653-5661.
59. Xu, Y., et al., *Molecular genetics of Leber congenital amaurosis in Chinese: New data from 66 probands and mutation overview of 159 probands.* Experimental Eye Research, 2016. **149**: p. 93-99.
60. Henderson, R.H., et al., *An assessment of the apex microarray technology in genotyping patients with Leber congenital amaurosis and early-onset severe retinal dystrophy.* Investigative Ophthalmology & Visual Science, 2007. **48**(12): p. 5684-5689.
61. Zernant, J., et al., *Genotyping microarray (disease chip) for Leber congenital amaurosis: detection of modifier alleles.* Investigative Ophthalmology & Visual Science, 2005. **46**(9): p. 3052-3059.
62. Galvin, J.A., et al., *Clinical phenotypes in carriers of Leber congenital amaurosis mutations.* Ophthalmology, 2005. **112**(2): p. 349-356.

63. Booij, J.C., et al., *Identification of mutations in the AIPL1, CRB1, GUCY2D, RPE65, and RPGRIP1 genes in patients with juvenile retinitis pigmentosa.* Journal of Medical Genetics, 2005. **42**(11): p. e67.
64. Li, L., et al., *Detection of variants in 15 genes in 87 unrelated Chinese patients with Leber congenital amaurosis.* PloS One, 2011. **6**(5): p. e19458.
65. Li, Y., et al., *Comprehensive Molecular Screening in a cohort of Chinese patients with Leber Congenital Amaurosis or Severe early childhood onset retinal dystrophy.* Investigative Ophthalmology & Visual Science, 2016. **57**(12): p. 666-666.
66. Sundaresan, P., et al., *Mutations that are a common cause of Leber congenital amaurosis in northern America are rare in southern India.* Molecular Vision, 2009. **15**: p. 1781-1787.
67. Chen, Y., et al., *Comprehensive mutation analysis by whole-exome sequencing in 41 Chinese families with Leber congenital amaurosis.* Investigative Ophthalmology & Visual Science, 2013. **54**(6): p. 4351-4357.
68. Rim, T.H., et al., *Four-year nationwide incidence of retinitis pigmentosa in South Korea: a population-based retrospective study from 2011 to 2014.* BMJ open, 2017. **7**(5): p. e015531.
69. Wright, C.B., T.M. Redmond, and J.M. Nickerson, *A History of the Classical Visual Cycle*, in *Progress in Molecular Biology and Translational Science*. 2015, Elsevier. p. 433-448.
70. Palczewski, K., *Chemistry and Biology of the Initial Steps in Vision: The Friedenwald Lecture.* Investigative Ophthalmology & Visual Science, 2014. **55**: p. 6651-6672.
71. Cai, X., S.M. Conley, and M.I. Naash, *RPE65: Role in the Visual Cycle, Human Retinal Disease, and Gene Therapy.* Ophthalmic Genetics, 2009. **30**: p. 57-62.
72. Pennesi, M., R. Weleber, and P. Yang, *BMJ Best Practice - Retinitis pigmentosa*, in *BMJ Best Practice*. 2018.
73. RNIB. *Retinitis pigmentosa*. RNIB - Supporting people with sight loss 2014 2014-02-19T15:48:28+00:00.
74. Koenekoop, R.K., *Natural History of Inherited Retinal Disease (IRD) in Patients with Mutations in the Retinal Pigment Epithelial 65 Protein (RPE65) or Lecithin:Retinol Acyltransferase (LRAT) Genes.* Investigative Ophthalmology & Visual Science, 2017. **58**: p. 2010-2010.
75. Paunescu, K., et al., *Longitudinal and cross-sectional study of patients with early-onset severe retinal dystrophy associated with RPE65 mutations.* Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie, 2005. **243**: p. 417-426.
76. Chung, D.C., et al., *The Natural History of Disease Progression in Patients With RPE65-Mediated Inherited Retinal Dystrophies.* Investigative Ophthalmology & Visual Science, 2016. **57**: p. 6588-6588.
77. Kumaran, N., et al., *A Cross-Sectional and Longitudinal Study of Retinal Sensitivity in RPE65-Associated Leber Congenital Amaurosis.* Investigative Ophthalmology & Visual Science, 2018. **59**(8): p. 3330-3339.

78. RNIB, *Understanding – Retinitis pigmentosa and other inherited retinal dystrophies*. 2017. p. 48.
79. Grover, S., et al., *Rate of visual field loss in retinitis pigmentosa.* Ophthalmology, 1997. **104**: p. 460-465.
80. National Library of Medicine (US). *Genetics Home Reference - Retinitis pigmentosa*. Genetics Home Reference 2010; Available from: https://ghr.nlm.nih.gov/condition/retinitis-pigmentosa.
81. Francis, P.J., *Genetics of inherited retinal disease.* Journal of the Royal Society of Medicine, 2006. **99**: p. 189-191.
82. Weleber, R.G., et al., *Leber Congenital Amaurosis*, in *GeneReviews®*, M.P. Adam, et al., Editors. 1993, University of Washington, Seattle: Seattle (WA).
83. National Library of Medicine (US). *Genetics Home Reference - Leber congenital amaurosis*. Genetics Home Reference 2010; Available from: https://ghr.nlm.nih.gov/condition/leber-congenital-amaurosis.
84. den Hollander, A.I., et al., *Leber congenital amaurosis: genes, proteins and disease mechanisms.* Progress in Retinal and Eye Research, 2008. **27**(4): p. 391-419.
85. Kumaran, N., et al., *Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions.* British Journal of Ophthalmology, 2017. **101**: p. 1147-1154.
86. Jan, J.E., et al., *Eye-Poking.* Developmental Medicine & Child Neurology, 1994. **36**: p. 321-325.
87. Department of Health, *Certificate of Visual Impairment: Explanatory Notes for Consultant Ophthalmologists and Hospital Eye Clinic Staff in England*. 2017.
88. Retina UK. *Cataracts*. 2018; Available from: https://retinauk.org.uk/about-inherited-sight-loss/cataracts-and-macular-oedema/cataracts/.
89. Strong, S., G. Liew, and M. Michaelides, *Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention.* British Journal of Ophthalmology, 2017. **101**(1): p. 31-37.
90. RNIB, *Factsheet: the Role of a Qualified Teacher of learners with Vision Impairment (QTVI)*. 2016.
91. RNIB. *Choosing a school*. RNIB - Supporting people with sight loss 2014 2014-02-24T17:26:10+00:00.
92. National Health Service. *Genetic testing and counselling*. nhs.uk 2016.
93. MeiraGTx Holdings. *Corporate overview (Slide 14 - "RPE65 deficiency: Phase I/II Study Design"*. 2019; Available from: https://jpmorgan.metameetings.net/events/healthcare19/sessions/25871-meiragtx-holdings/presentation_slides.
94. Office for National Statistics. *England population mid-year estimate*. 2018; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop.
95. Christ, S.L., et al., *Longitudinal Relationships Among Visual Acuity, Daily Functional Status, and Mortality: The Salisbury Eye Evaluation Study.* JAMA Ophthalmology, 2014. **132**: p. 1400-1406.

96. Knauer, C. and N. Pfeiffer, *The value of vision.* Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie, 2008. **246**: p. 477-482.
97. pH Associates, *Exploration of the burden of blindness for patients with inherited retinal dystrophies in the UK*. 2019.
98. Sonksen, P.M. and N. Dale, *Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes.* Developmental Medicine & Child Neurology, 2002. **44**: p. 782-791.
99. Khorrami-Nejad, M., et al., *The Impact of Visual Impairment on Quality of Life.* Medical Hypothesis, Discovery and Innovation in Ophthalmology, 2016. **5**: p. 96-103.
100. RNIB, *Children and young people in England: RNIB Evidence-based review*. 2016.
101. Green, D., et al., *The Cost of Blindness in the Republic of Ireland 2010-2020.* Journal of Ophthalmology, 2016. **2016**: p. 4691276.
102. RNIB, *People of working age: RNIB evidence-based review*. 2016.
103. Rahi, J.S., P.M. Cumberland, and C.S. Peckham, *Visual Impairment and Vision-Related Quality of Life in Working-Age Adults: Findings in the 1958 British Birth Cohort.* Ophthalmology, 2009. **116**: p. 270-274.
104. Black, A., et al., *Mobility performance with retinitis pigmentosa.* Clinical and Experimental Optometry, 1997. **80**(1): p. 1-12.
105. Geruschat, D.R., K.A. Turano, and J.W. Stahl, *Traditional measures of mobility performance and retinitis pigmentosa.* Optometry and Vision Science: Official Publication of the American Academy of Optometry, 1998. **75**(7): p. 525-537.
106. Kuyk, T., J.L. Elliott, and P.S. Fuhr, *Visual correlates of mobility in real world settings in older adults with low vision.* Optometry and Vision Science: Official Publication of the American Academy of Optometry, 1998. **75**(7): p. 538-547.
107. Bhuvaneswari, M., et al., *Assessment of Psychological and Psycho-physiological Problems Among Visually Impaired Adolescents.* Iranian Journal of Psychiatry and Behavioral Sciences, 2016. **10**: p. e3895.
108. Bolat, N., et al., *Depression and anxiety levels and self-concept characteristics of adolescents with congenital complete visual impairment.* Turk Psikiyatri Dergisi = Turkish Journal of Psychiatry, 2011. **22**: p. 77-82.
109. Ishtiaq, R., et al., *Psychosocial implications of blindness and low vision in students of a school for children with blindness.* Pakistan Journal of Medical Sciences, 2016. **32**: p. 431-434.
110. Mojon-Azzi, S.M., A. Sousa-Poza, and D.S. Mojon, *Impact of low vision on well-being in 10 European countries.* Ophthalmologica. Journal International D'ophtalmologie. International Journal of Ophthalmology. Zeitschrift Fur Augenheilkunde, 2008. **222**: p. 205-212.
111. Chaumet-Riffaud, A.E., et al., *Impact of Retinitis Pigmentosa on Quality of Life, Mental Health, and Employment Among Young Adults.* American Journal of Ophthalmology, 2017. **177**: p. 169-174.
112. Mindell, J.A. and C.M. De Marco, *Sleep Problems of Young Blind Children.* Journal of Visual Impairment & Blindness, 1997. **1**.

113. Adeoti, C. and E.E. Akang, *Disorders of the sleep-wake cycle in blindness.* West African Journal of Medicine, 2010. **29**: p. 163-168.
114. Leger, D., et al., *Sleep disorders in children with blindness.* Annals of Neurology, 1999. **46**: p. 648-651.
115. Leger, D., et al., *Prevalence of sleep/wake disorders in persons with blindness.* Clinical Science (London, England: 1979), 1999. **97**: p. 193-199.
116. Brézin, A.P., et al., *Prevalence and burden of self-reported blindness, low vision, and visual impairment in the French community: a nationwide survey.* Archives of Ophthalmology (Chicago, Ill.: 1960), 2005. **123**: p. 1117-1124.
117. Brézin, A.P., et al., *Prevalence and burden of self-reported blindness and low vision for individuals living in institutions: a nationwide survey.* Health and Quality of Life Outcomes, 2005. **3**: p. 27.
118. Lafuma, A., et al., *Nonmedical economic consequences attributable to visual impairment: a nation-wide approach in France.* The European journal of health economics: HEPAC: health economics in prevention and care, 2006. **7**: p. 158-164.
119. Schmier, J.K., et al., *Impact of visual impairment on use of caregiving by individuals with age-related macular degeneration.* Retina (Philadelphia, Pa.), 2006. **26**: p. 1056-1062.
120. FamilyConnect (American Foundation for the Blind). *Five Tips to Encourage Healthy Relationships Between Blind Children and Their Siblings*. 2019; Available from: http://www.familyconnect.org/info/after-the-diagnosis/emotional-impact/5-tips-to-encourage-healthy-relationships-with-siblings/135.
121. Braich, P.S., et al., *Burden and Depression in Caregivers of Blind Patients in New York State.* Ophthalmic Epidemiology, 2016. **23**: p. 162-170.
122. Braich, P.S., et al., *Burden and depression in the caregivers of blind patients in India.* Ophthalmology, 2012. **119**: p. 221-226.
123. Strawbridge, W.J., M.I. Wallhagen, and S.J. Shema, *Impact of spouse vision impairment on partner health and well-being: a longitudinal analysis of couples.* The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 2007. **62**: p. S315-322.
124. Köberlein, J., et al., *The economic burden of visual impairment and blindness: a systematic review.* BMJ Open, 2013. **3**: p. e003471.
125. GOV.UK. *Check if a health condition affects your driving*. GOV.UK 2018.
126. GOV.UK. *Visual disorders: assessing fitness to drive*. GOV.UK 2018.
127. Pezzullo, L., et al., *The economic impact of sight loss and blindness in the UK adult population.* BMC health services research, 2018. **18**: p. 63.
128. National Institute for Health and Care Excellence. *Insertion of a subretinal prosthesis system for retinitis pigmentosa | Guidance and guidelines | NICE*. 2015.
129. National Institute for Health and Care Excellence. *Insertion of an epiretinal prosthesis for retinitis pigmentosa | Guidance and guidelines | NICE*. 2015.

130. Simon-Kucher & Partners, *UK KOLs interview summary: Luxturna in RPE65m IRD*. 2018.
131. NHS England, *Highly Specialised Services 2017*. 2017. p. 64.
132. Hui, D.J., et al., *Safety Study by Validated Immunoassays in a Phase III Study of Subjects with Inherited Retinal Dystrophy Due to Mutations in the Gene Encoding Human Retinal Pigment Epithelium-Specific Protein 65 (RPE65) Injected with Adeno-Associated Viral Vectors.* Molecular Therapy, 2016. **24**: p. S72-S73.
133. Chung, D.C.R., Stephen; Bennett, Jean; Maguire, Albert; Wellman, Jennifer; Yu, Zi-Fan; Tillman, Amy; High, Katherine, *Correlation of Multi-luminance Mobility Testing With Visual Function Tests in a Phase 3 Trial of Voretigene Neparvovec for Biallelic RPE65-mediated Inherited Retinal Disease*. 2017.
134. Leroy, B.P., et al., *Phase 3 Efficacy and Safety Study of Voretigene Neparvovec (AAV2-hRPE65v2) in Subjects with RPE65-Mediated Inherited Retinal Dystrophy.* Ophthalmologica, 2016. **236**(Suppl 1): p. 2.
135. Leroy, B.P., et al. *Year 1 time to mobility test completion in a voretigene neparvovec trial in subjects with RPE65 mutation–associated inherited retinal disease*. in *18th EURETINA Congress*. 2018.
136. Ashtari, M., et al., *The Role of the Human Visual Cortex in Assessment of the Long-Term Durability of Retinal Gene Therapy in Follow-on RPE65 Clinical Trial Patients.* Ophthalmology, 2017. **124**(6): p. 873-883.
137. Bennett, J., et al., *AAV2 gene therapy readministration in three adults with congenital blindness.* Science Translational Medicine, 2012. **4**(120): p. 120ra15.
138. Maguire, A.M., et al., *Year 4 Results for a Phase 1 Trial of Voretigene Neparvovec in Biallelic RPE65-Mediated Inherited Retinal Disease [oral presentation]*, in *The American Society of Retina Specialists 35th Annual Meeting 2017*. 2017: Boston, MA, USA.
139. Maguire, A.M., et al., *Safety and efficacy of gene transfer for Leber's congenital amaurosis.* The New England Journal of Medicine, 2008. **358**: p. 2240-2248.
140. Simonelli, F., et al., *Gene Therapy for Leber's Congenital Amaurosis is Safe and Effective Through 1.5 Years After Vector Administration.* Molecular Therapy, 2010. **18**(3): p. 643-650.
141. Testa, F., et al., *Three Year Follow-Up after Unilateral Subretinal Delivery of Adeno-Associated Virus in Patients with Leber Congenital Amaurosis Type 2.* Ophthalmology, 2013. **120**(6): p. 1283-1291.
142. Ashtari, M., et al., *The human visual cortex responds to gene therapy-mediated recovery of retinal function.* The Journal of Clinical Investigation, 2011. **121**(6): p. 2160-2168.
143. Maguire, A.M., et al., *Phase 3 trial update of voretigene neparvovec in biallelic RPE65 mutation-associated inherited retinal disease [oral presentation]*, in *The American Academy of Ophthalmology (AAO) Annual Meeting 2017*. 2017: New Orleans, LA, USA.
144. Russell, S., et al., *Two-Year Results for a Phase 3 Trial of Voretigene Neparvovec in Biallelic RPE65-mediated Inherited Retinal Disease*

[poster], in *The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting 2017*. 2017: Baltimore, MD, USA.
145. Russell, S. *Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65mutation–associated inherited retinal disease*. in *Association of Research in Vision and Ophthalmology (ARVO) annual meeting*. 2018.
146. Leroy, B.P., et al., *Year 3 Results and Age-Stratified Analyses for a Phase 3 Trial of Voretigene Neparvovec in RPE65 Mutation–Associated Inherited Retinal Disease*, in *18th EURETINA Congress, 20–23 September 2018, Vienna, Austria*. 2018.
147. Maguire, A.M. *PA074 Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial*. in *American Academy of Ophthalmology annual meeting*. 2018.
148. Geruschat, D., A.K. Bittner, and G. Dagnelie, *Orientation and Mobility Assessment in Retinal Prosthetic Clinical Trials.* Optometry and vision science : official publication of the American Academy of Optometry, 2012. **89**(9): p. 1308-1315.
149. Nau, A.C., et al., *A Standardized Obstacle Course for Assessment of Visual Function in Ultra Low Vision and Artificial Vision.* Journal of Visualized Experiments : JoVE, 2014(84).
150. Anstice, N.S. and B. Thompson, *The measurement of visual acuity in children: an evidence-based update.* Clinical and Experimental Optometry, 2014. **97**(1): p. 3-11.
151. Holladay, J.T., *Visual acuity measurements.* Journal of Cataract & Refractive Surgery, 2004. **30**: p. 287-290.
152. Lange, C., et al., *Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT).* Graefe's Archive for Clinical and Experimental Ophthalmology, 2009. **247**: p. 137-142.
153. Pelli, D.G. and P. Bex, *Measuring contrast sensitivity.* Vision research, 2013. **90**: p. 10-14.
154. Novartis, *(Draft) Psychometric evaluation of the modified Visual Function Questionnaire (VFQ-25) using data from AAV2-hRPE65v2-301 (voretigene neparvovec) phase III trial*. 2019.
155. Chung, D.C., et al., *Long-term effect of voretigene neparvovec on the full-field light sensitivity threshold test of patients with RPE65 mutation-associated inherited retinal dystrophy: post-hoc analysis of Phase I trial data*, in *Abstract submitted to ARVO 2019 Annual Meeting*. 2019.
156. Drack, A.V., et al. *How long does gene therapy last? 4 Year follow-up of Phase 3 Voretigene Neparvovec Trial in RPE65–Associated LCA/Inherited Retinal Disease*. in *Abstract submitted to AAPOS 45th Annual Meeting*. 2019.
157. Novartis, *(Draft) Summary of Product Characteristics - Luxturna*. 2018.
158. Elliott, D.B., K. Sanderson, and A. Conkey, *The reliability of the Pelli-Robson contrast sensitivity chart.* Ophthalmic & Physiological Optics: The Journal of the British College of Ophthalmic Opticians (Optometrists), 1990. **10**(1): p. 21-24.
159. Han, D.P., et al., *Mechanisms of intraocular pressure elevation after pars plana vitrectomy.* Ophthalmology, 1989. **96**(9): p. 1357-1362.

160. Phulke, S., et al., *Steroid-induced Glaucoma: An Avoidable Irreversible Blindness.* Journal of Current Glaucoma Practice, 2017. **11**(2): p. 67-72.
161. McKean-Cowdin, R., et al., *Severity of Visual Field Loss and Health Related Quality of Life.* American journal of ophthalmology, 2007. **143**(6): p. 1013-1023.
162. Mangione, C.M., et al., *Development of the 25-item National Eye Institute Visual Function Questionnaire.* Archives of Ophthalmology (Chicago, Ill.: 1960), 2001. **119**(7): p. 1050-1058.
163. Sloane, M.E., et al. *The Visual Activities Questionnaire: Developing an instrument for assessing problems in everyday visual tasks.* . in *Technical Digest, Noninvase Assessment of the Visual System, Topical Meeting of the Optical Society of America*. 1992.
164. Owsley, C., et al., *Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy.* Investigative Ophthalmology & Visual Science, 2006. **47**(2): p. 528-535.
165. Tolley, C., et al. *Qualitative interviews to inform development of a patient reported outcome (PRO) strategy in RLBP1 retinitis pigmentosa (RLBP1 RP)*. in *ISPOR 20th Annual European Congress*. 2017.
166. Kay, S. and A. Ferreira, *Mapping the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) to EQ-5D utility scores.* Ophthalmic Epidemiology, 2014. **21**(2): p. 66-78.
167. Browne, C., et al., *Estimating quality-adjusted life years from patient-reported visual functioning.* Eye (Basingstoke), 2012. **26**(10): p. 1295-1301.
168. Dixon, P., H. Dakin, and S. Wordsworth, *Generic and disease-specific estimates of quality of life in macular degeneration: mapping the MacDQoL onto the EQ-5D-3L.* Quality of Life Research, 2016. **25**(4): p. 935-45.
169. Payakachat, N., et al., *Predicting EQ-5D utility scores from the 25-item National Eye Institute Vision Function Questionnaire (NEI-VFQ 25) in patients with age-related macular degeneration.* Quality of Life Research, 2009. **18**(7): p. 801-813.
170. National Institute for Health and Care Excellence, *NICE guideline [NG82]: Age-related macular degeneration (Appendix J)*. 2018.
171. Pershing, S., et al., *Cost-effectiveness of treatment of diabetic macular edema.* Annals of Internal Medicine, 2014. **160**(1): p. 18-29.
172. Wittenberg, E. and L.A. Prosser, *Disutility of illness for caregivers and families: a systematic review of the literature.* PharmacoEconomics, 2013. **31**(6): p. 489-500.
173. Janssen, B. and A. Szende, *Population Norms for the EQ-5D*, in *Self-Reported Population Health: An International Perspective based on EQ-5D*, A. Szende, B. Janssen, and J. Cabases, Editors. 2014, Springer Netherlands: Dordrecht. p. 19-30.
174. Lloyd, A.T., I; Gallop, K; Moseley, S; Donato, BMK; L'Italien, G, *Effect of Asfotase Alfa Treatment on Health States and Ambulatory Function in Patients with Hypophosphatasia* in *Annual Meeting of the American Society for Bone and Mineral Research, 2017*. 2017.
175. Pastores, G.B., J; Hughes, J; Rogers, Y; Stenson, C; Clark, A; Lloyd, A; Alvarez, I; Jain, M; Kha, A; Monavari, A *Estimation of resource use*

and quality of life in phenylketonuria (PKU) patients in Ireland in *13th International Congress of Inborn Errors of Metabolism 2017*. 2017.
176. National Institute for Health and Care Excellence, *HST6: Asfotase alfa for treating paediatric-onset hypophosphatasia*. 2017.
177. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 2012. **15**(5): p. 708-715.
178. Longworth, L., et al., *A systematic review of the psychometric properties of generic preference-based measures of health in four conditions*. 2014: NIHR Journals Library.
179. Czoski-Murray, C., et al., *Valuing condition-specific health states using simulation contact lenses.* Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 2009. **12**(5): p. 793-799.
180. Brown, G.C., *Vision and quality-of-life.* Transactions of the American Ophthalmological Society, 1999. **97**: p. 473-511.
181. Brown, G.C., et al., *Utility values and age-related macular degeneration.* Archives of Ophthalmology (Chicago, Ill.: 1960), 2000. **118**(1): p. 47-51.
182. Butt, T., et al., *Simulation contact lenses for AMD health state utility values in NICE appraisals: a different reality.* British Journal of Ophthalmology, 2015. **99**(4): p. 540-544.
183. Gan, N.Y. and W.-C. Lam, *Special considerations for pediatric vitreoretinal surgery.* Taiwan Journal of Ophthalmology, 2018. **8**(4): p. 237-242.
184. Shields, R.A., et al., *Postoperative Adverse Events, Interventions, and the Utility of Routine Follow-Up After 23-, 25-, and 27-Gauge Pars Plana Vitrectomy.* Asia-Pacific Journal of Ophthalmology (Philadelphia, Pa.), 2019.
185. Institute for Clinical and Economic Review (ICER), *Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value.* 2018: p. 128.
186. National Institute for Health and Care Excellence, *Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations - Final scope*. 2018.
187. Vaidya, A., et al., *The cost-effectiveness of the Argus II retinal prosthesis in Retinitis Pigmentosa patients.* BMC ophthalmology, 2014. **14**: p. 49.
188. Taylor, M., et al., *A United Kingdom-based economic evaluation of ranibizumab for patients with retinal vein occlusion (RVO).* Journal of Medical Economics, 2014. **17**(6): p. 423-434.
189. Kumaran, N., et al., *Gene therapy for Leber congenital amaurosis.* Expert Review of Ophthalmology, 2018. **13**(1): p. 11-15.
190. National Institute for Health and Care Excellence. *Aflibercept solution for injection for treating wet age-related macular degeneration | Guidance and guidelines | NICE*. 2013.
191. Christ, S.L., et al., *Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation*

modeling. Investigative Ophthalmology & Visual Science, 2008. **49**(8): p. 3318-3323.
192. Office for National Statistics. *National life tables: England and Wales*. 2018; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables.
193. GOV.UK. *Participation in education, training and employment: 2016*. GOV.UK 2017.
194. GOV.UK. *Proposed new timetable for State Pension age increases*. GOV.UK 2017.
195. American Medical Association, *AMA Guides to the Evaluation of Permanent Impairment*. 2007.
196. RNIB. *The criteria for certification*. Available from: https://www.rnib.org.uk/eye-health/registering-your-sight-loss/criteria-certification.
197. National Institute for Health and Care Excellence, *Guide to the methods of technology appraisal*. 2013.
198. National Institute for Health and Care Excellence, *Interim Process and Methods of the Highly Specialised Technologies Programme - Updated to reflect 2017 changes*. 2017.
199. Chung, D.C., et al., *The Natural History of Inherited Retinal Dystrophy due to Biallelic Mutations in the RPE65 Gene.* American Journal of Ophthalmology, 2018.
200. Crowther, M.J. and P.C. Lambert, *Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences.* Statistics in Medicine, 2017. **36**(29): p. 4719-4742.
201. NICE Decision Support Unit, *Partitioned survival analysis TSD – NICE Decision Support Unit*. 2017.
202. Akaike, H., *A New Look at the Statistical Model Identification.* IEEE Transactions on Automatic Control, 1974. **AC-19**(6): p. 716-723.
203. Jones, E., D. Epstein, and L. García-Mochón, *A Procedure for Deriving Formulas to Convert Transition Rates to Probabilities for Multistate Markov Models.* Medical Decision Making: An International Journal of the Society for Medical Decision Making, 2017. **37**(7): p. 779-789.
204. Cideciyan, A.V., et al., *Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement.* Proceedings of the National Academy of Sciences of the United States of America, 2013. **110**(6): p. E517-525.
205. Lai, C.-M., et al., *Recombinant adeno-associated virus type 2-mediated gene delivery into the Rpe65-/- knockout mouse eye results in limited rescue.* Genetic Vaccines and Therapy, 2004. **2**: p. 3.
206. Dutta, S. and P. Sengupta, *Men and mice: Relating their ages.* Life Sciences, 2016. **152**: p. 244-248.
207. National Health Service. *Reference costs | NHS Improvement*. 2018; Available from: https://improvement.nhs.uk/resources/reference-costs/.
208. National Institute for Health and Care Excellence. *BNF: British National Formulary*. [CorporatePage] 2018.

209. Personal Social Services Research Unit. *Unit Costs of Health and Social Care | PSSRU*. 2018; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/.
210. NHS UK Genetic Testing Network. *Retinal Degeneration Disorders 55 Gene Panel (Oxford RGC), Retinal Degeneration Disorders 105 Gene panel (Manchester RGC)* UK Genetic Testing Network 2018; Available from: https://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/?token=a247f183f3be268f472d1144ce25bf80c6c6c85e4d63665ff2939e2d3f4d9e23&query=Retinal+degeneration+disorders.
211. Brown, M.M., et al., *Health care economic analyses and value-based medicine.* Survey of Ophthalmology, 2003. **48**(2): p. 204-223.
212. Marques, A.P., et al., *The use of informal care by people with vision impairment.* PLOS ONE, 2018. **13**(6): p. e0198631.

17 Appendices

Appendix 1 – Search strategy for clinical evidence

Appendix 2 – Search strategy for adverse events

Appendix 3 – Search strategy for economic evidence

Appendix 4 – Resource identification, measurement and valuation

Appendix 5 – Search strategy for health state utility values

Appendix 6 – Patient demography and baseline characteristics

Appendix 7 – Visual function questionnaire

Appendix 8 – Outputs of analyses conducted in wxMaxima

Appendix 9 – Acaster Lloyd utility study

Appendix 10 – Costing table

Appendix 11 – Phase 3 Year 1 graphs

Appendix 12 – Details of clinical experts interviewed

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

This addendum supersedes the results section in the company's original submission as an error was identified in the codebase. The error is explained in appendix A, and the revised results are presented in this addendum, mirroring the sections in the original submission. The impact of the correction on the results is small.

1.1 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

1.1.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness

analysis with the patient access scheme. A suggested format is available in Table 1.

The confidential simple discount PAS used in the cost-effectiveness model is currently under review by the Department of Health. Results are therefore presented both with and without the proposed PAS (Table 1 and Table 2, respectively).

Table 1: Base-case results (proposed PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£46,473	25.46	3.6	-	-	-	-
VN	[redacted]	25.50	10.7	[redacted]	0.04	7.1	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; VN, voretigene neparvovec.

Table 2: Base-case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	£46,473	25.46	3.6	-	-	-	-
VN	£658,486	25.50	10.7	£612,013	0.04	7.1	£86,635

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VN, voretigene neparvovec.

1.1.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The proportion of individuals in each health state at the end of the first year (in each model arm) is presented in Table 3. The clinical trial results and model results are relatively congruent; some differences are observed because baseline health state distributions were pooled across the two trial arms before applying treatment-specific transition probabilities. As may be expected, larger differences are observed in the BSC arm than in the VN arm, due to the baseline distribution in the smaller sample of BSC patients (N=10) differing more substantially from the overall baseline distribution (which is influenced more by the baseline distribution of VN patients, who made up approximately two-thirds of the trial population; see Table 4).

Table 3: Summary of model results compared with clinical data

		% in each health state at Year 1	
		Clinical trial result	**Model result**
BSC arm	HS1	44%	31%
	HS2	22%	16%
	HS3	22%	42%
	HS4	11%	11%
	HS5	0%	0%
VN arm	HS1	70%	70%
	HS2	20%	18%
	HS3	5%	5%
	HS4	5%	6%
	HS5	0%	1%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

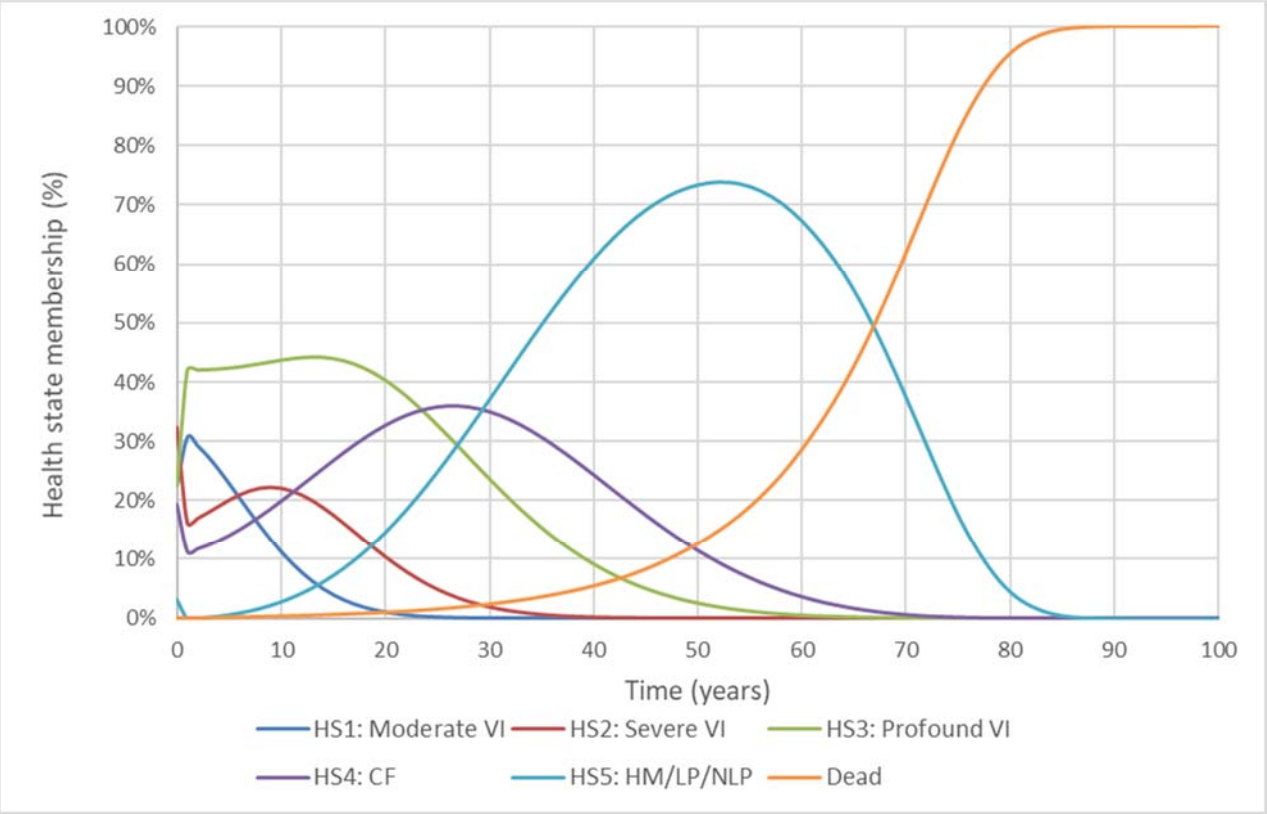
Table 4: Baseline health state distributions

Health state	Baseline health state distribution		
	BSC (Control/Delayed Intervention, N=10)	VN (Original Intervention, N=21)	Overall (N=31)
HS1	30%	19%	23%
HS2	40%	29%	32%
HS3	10%	29%	23%
HS4	10%	24%	19%
HS5	10%	0%	3%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

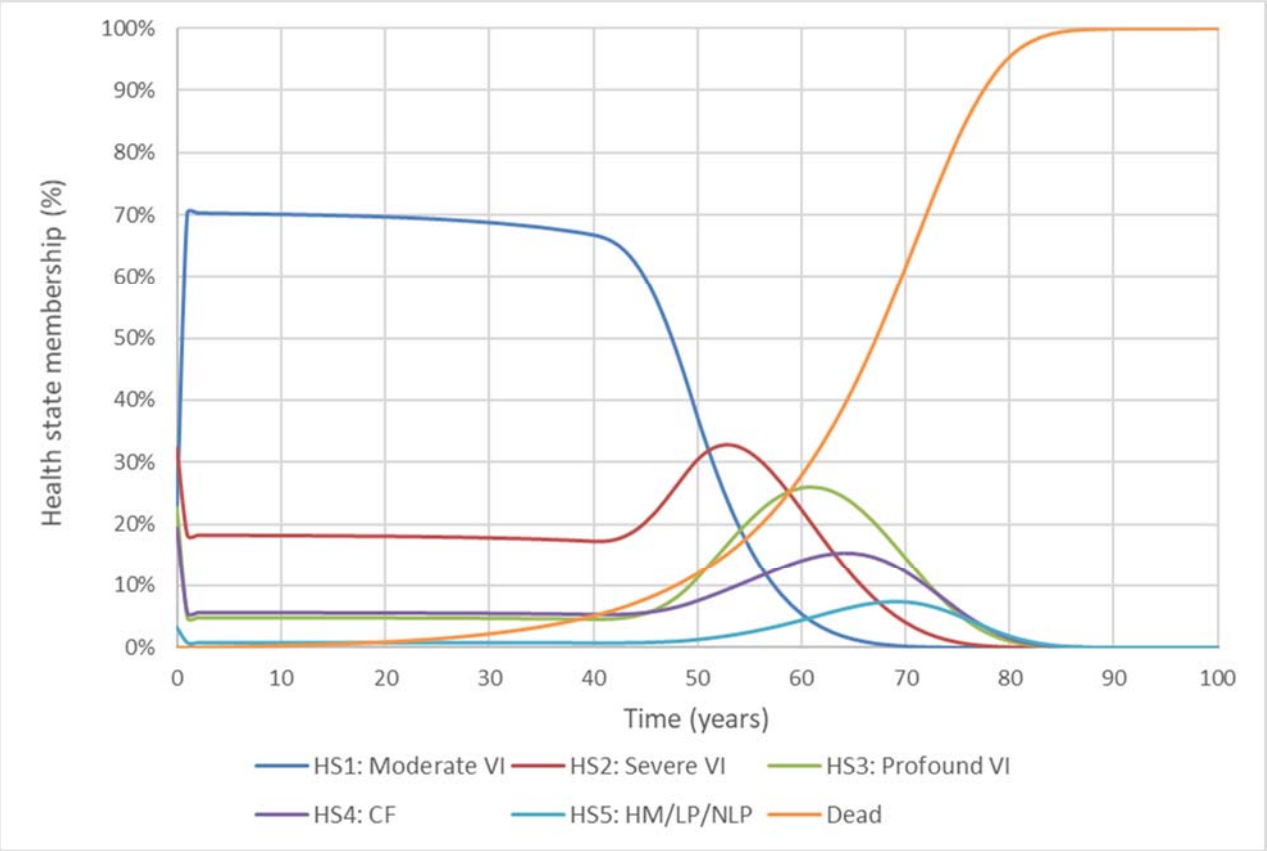
1.1.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 1: Markov trace (BSC arm)



Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment.

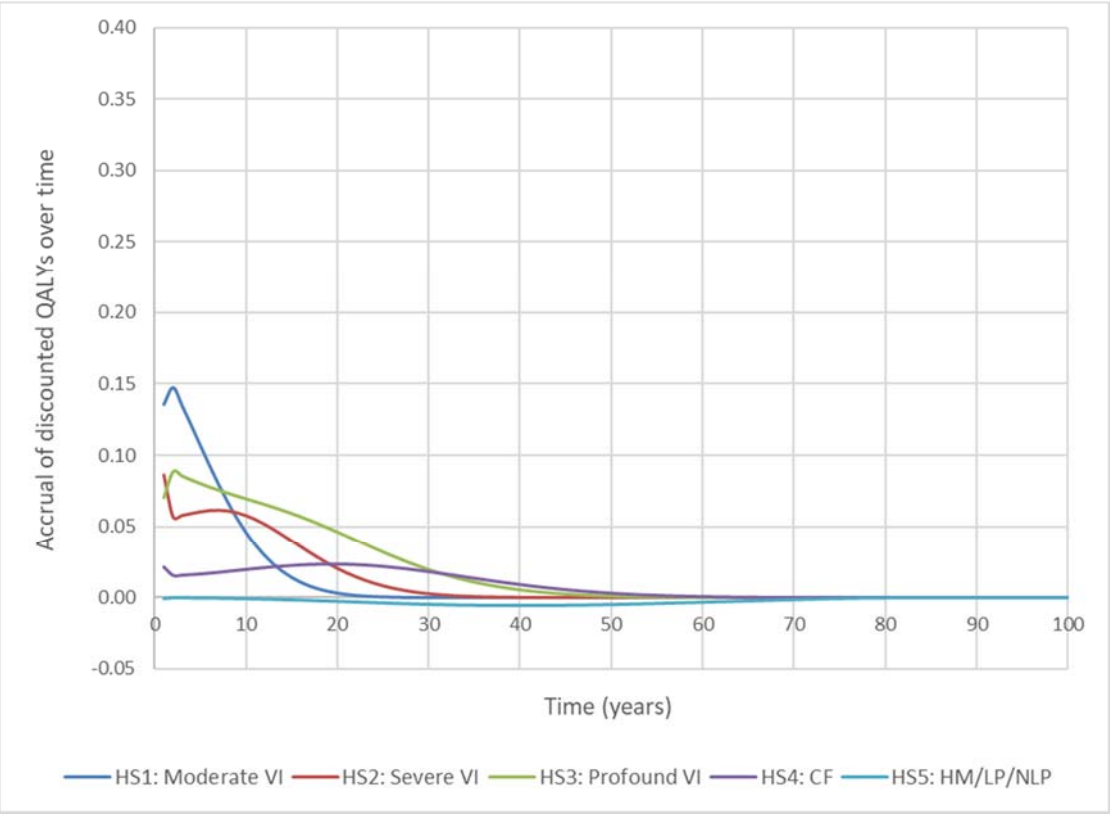
Figure 2: Markov trace (VN arm)



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.

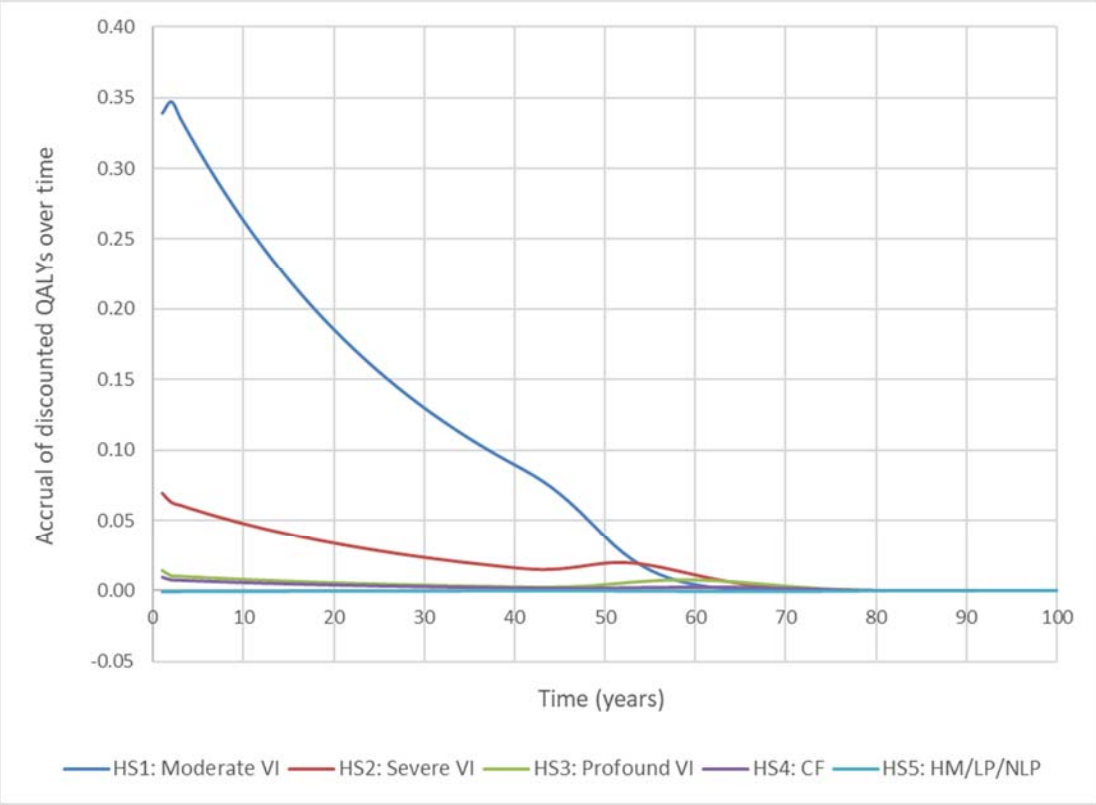
1.1.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Figure 3: Discounted QALY accrual at each time point (BSC arm)



Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment.

Figure 4: Discounted QALY accrual at each time point (VN arm)



Abbreviations: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment; VN, voretigene neparvovec.

1.1.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

A summary of life year gain by health state is presented in Table 5; a summary of QALY gain by health state is presented in Section 1.1.6 (Table 6), below.

Table 5: Summary of LY gain by health state

Health state	LYs (BSC)	LYs (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	2.2	16.7	14.5	14.5	44%
HS2: Severe VI	3.0	5.0	2.0	2.0	6%
HS3: Profound VI	8.1	1.8	-6.3	6.3	19%
HS4: CF	5.8	1.7	-4.0	4.0	12%
HS5: HM, LP, NLP	6.4	0.3	-6.0	6.0	18%
Total	25.5	25.5	0.0	32.8	100%

Abbreviations: AE, adverse event; BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; LY, life year; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.

1.1.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table 6: Summary of QALY gain by health state

Health state	QALYs (BSC)	QALYs (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	1.2	8.7	7.5	7.5	68%
HS2: Severe VI	1.1	1.8	0.7	0.7	6%
HS3: Profound VI	1.8	0.4	-1.4	1.4	13%
HS4: CF	0.8	0.2	-0.6	0.6	5%
HS5: HM, LP, NLP	-0.2	0.0	0.2	0.2	2%
AE disutility	0.00	-0.01	-0.01	0.01	0%
Carer disutility	-0.99	-0.38	0.61	0.61	5%
Total	3.6	10.7	7.1	11.1	100%

Abbreviations: AE, adverse event; BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; QALY, quality-adjusted life year; VI, visual impairment; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

1.1.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

The undiscounted QALY gains associated with VN are 20.3 in the base case. The difference between the undiscounted and discounted QALY gains is driven by the modelling of long-term benefits in the VN arm and the low utility values associated with more severe health states.

1.1.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table 7.

As in Section 1.1.1, results are presented assuming both the proposed PAS price and the list price for VN (Table 7 and Table 8, respectively).

Table 7: Summary of costs by category of cost per patient (proposed PAS price)

Item	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
VN acquisition, administration and monitoring	£0	[redacted]	[redacted]	[redacted]	[redacted]
AEs	£0	£146	£146	£146	[redacted]
Healthcare resource use	£46,473	£39,648	-£6,824	£6,824	[redacted]
Total	£46,473	[redacted]	[redacted]	[redacted]	100%

Abbreviations: AE, adverse event; BSC, best supportive care; PAS, patient access scheme; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 8: Summary of costs by category of cost per patient (list price)

Item	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
VN acquisition, administration and monitoring	£0	£618,571	£618,571	£618,571	99%
AEs	£0	£146	£146	£146	0%
Healthcare resource use	£46,473	£39,648	-£6,824	£6,824	1%
Total	£46,473	£658,486	£612,013	£625,541	100%

Abbreviations: AE, adverse event; BSC, best supportive care; VN, voretigene neparvovec.

1.1.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table 9.

With the exception of costs associated with healthcare resource use, all costs are applied in the first model cycle. Table 9 therefore presents costs by health state for healthcare resource use only.

Table 9: Summary of healthcare resource use costs by health state per patient

Health state	Cost ([redacted]	Cost (VN)	Increment	Absolute increment	% absolute increment
HS1: Moderate VI	£661	£7,810	£7,149	£7,149	13%
HS2: Severe VI	£1,804	£12,686	£10,882	£10,882	20%
HS3: Profound VI	£5,248	£10,032	£4,785	£4,785	9%
HS4: CF	£5,715	£6,712	£997	£997	2%
HS5: HM, LP, NLP	£33,046	£2,408	-£30,638	£30,638	56%
Total	£46,473	£39,648	-£6,824	£54,451	100%

Abbreviations: BSC, best supportive care; CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

1.1.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table 10.

Table 10: Summary of adverse event costs per patient

Adverse event	Cost (BSC)	Cost (VN)	Increment	Absolute increment	% absolute increment
Cataract	£0.00	£137.01	£137.01	£137.01	93%
Eye inflammation	£0.00	£3.70	£3.70	£3.70	2%
Increased IOP	£0.00	£7.40	£7.40	£7.40	5%
Total	£0.00	£148.11	£148.11	£148.11	100%

Abbreviations: BSC, best supportive care; IOP, intraocular pressure; VN, voretigene neparvovec.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Sensitivity analysis results

1.1.11 Present results of deterministic one-way sensitivity analysis.

As in Section 1.1.1, results are presented assuming each of the proposed PAS price (Table 11 and Figure 5) and the list price (Table 12 and Figure 6) for VN.

Table 11: Results of one-way sensitivity analysis (proposed PAS price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Multistate model, Weibull (VA+VF, average eye): Ancillary	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): Constant	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS1	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS3	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS5	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS4	[redacted]	[redacted]
Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	[redacted]	[redacted]
Acaster Lloyd (HUI-3), utility value, HS2	[redacted]	[redacted]

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

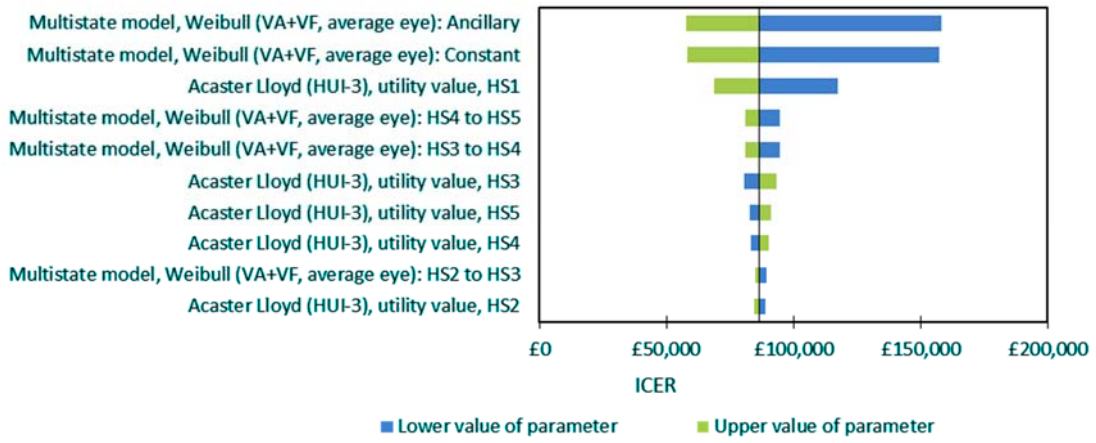
Figure 5: Tornado diagram (proposed PAS price)

Table 12: Results of one-way sensitivity analysis (list price)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Multistate model, Weibull (VA+VF, average eye): Ancillary	£158,320	£57,969
Multistate model, Weibull (VA+VF, average eye): Constant	£157,427	£58,092
Acaster Lloyd (HUI-3), utility value, HS1	£117,376	£68,654
Multistate model, Weibull (VA+VF, average eye): HS4 to HS5	£94,458	£80,961
Multistate model, Weibull (VA+VF, average eye): HS3 to HS4	£94,525	£81,074
Acaster Lloyd (HUI-3), utility value, HS3	£80,723	£93,480
Acaster Lloyd (HUI-3), utility value, HS5	£82,748	£90,904
Acaster Lloyd (HUI-3), utility value, HS4	£83,135	£90,442
Multistate model, Weibull (VA+VF, average eye): HS2 to HS3	£89,299	£84,775
Acaster Lloyd (HUI-3), utility value, HS2	£88,863	£84,516

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

Figure 6: Tornado diagram (list price)



Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.
Abbreviations: BSC, best supportive care; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

1.1.12 Present results of deterministic multi-way scenario sensitivity analysis.

Results of scenario analyses are presented in Table 13 and Table 14, assuming each of the proposed PAS price and the list price for VN, respectively. Results of multi-way scenario analyses are presented in Table 15 and Table 16, assuming each of the proposed PAS price and the list price for VN, respectively.

Table 13: Results of scenario analyses (proposed PAS price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	7.06	[redacted]	0%
UK government perspective	[redacted]	7.06	[redacted]	-3%
Societal perspective	[redacted]	7.06	[redacted]	-28%
1.5% discount rate for costs and outcomes	[redacted]	12.32	[redacted]	-43%
0% discount rate for costs and outcomes	[redacted]	20.31	[redacted]	-66%
Health states based on best-seeing eye	[redacted]	7.17	[redacted]	-2%
Health states based on VF only	[redacted]	6.14	[redacted]	15%
Baseline characteristics from natural history data	[redacted]	6.99	[redacted]	1%
Adjusted TP (state dependent)	[redacted]	6.91	[redacted]	2%
Adjusted TP (state independent)	[redacted]	7.41	[redacted]	-5%
Health states with no data: remain in same state	[redacted]	6.95	[redacted]	2%
Use cross-over data in VN arm	[redacted]	6.58	[redacted]	8%
Duration of treatment effect: 20 years	[redacted]	5.70	[redacted]	25%
Duration of treatment effect: 30 years	[redacted]	6.54	[redacted]	9%
Duration of treatment effect: 50 years	[redacted]	7.35	[redacted]	-5%
Duration of treatment effect: lifetime (100 years)	[redacted]	7.52	[redacted]	-8%
Waning period: 5 years	[redacted]	7.02	[redacted]	1%
Waning period: 20 years	[redacted]	7.16	[redacted]	-2%
Residual RRR (following waning period): 0%	[redacted]	6.98	[redacted]	1%
Residual RRR (following waning period): 50%	[redacted]	7.17	[redacted]	-2%
Gompertz multistate model distribution	[redacted]	7.46	[redacted]	-5%
Log-logistic multistate model distribution	[redacted]	6.72	[redacted]	4%
Log-normal multistate model distribution	[redacted]	6.61	[redacted]	6%
Exponential multistate model distribution	[redacted]	6.09	[redacted]	15%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
No mortality effect	[redacted]	7.10	[redacted]	-1%
Utility values: Acaster Lloyd (EQ-5D-5L)	[redacted]	6.45	[redacted]	9%
Utility values: Brown et al	[redacted]	5.09	[redacted]	38%
Carer disutility excluded	[redacted]	6.46	[redacted]	9%
Hypothetical light sensitivity increment (0.05 in HS1-HS3)	[redacted]	8.24	[redacted]	-15%
Hypothetical administration procedure disutility (0.1 for 1 month)	[redacted]	7.06	[redacted]	-1%
Include eligibility testing costs	[redacted]	7.06	[redacted]	1%
No healthcare resource use in HS1	[redacted]	7.06	[redacted]	-2%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment.
Abbreviations: ICER, incremental cost-effectiveness ratio; UK, United Kingdom; VF, visual field; VN, voretigene neparvovec; QALY, quality-adjusted life year; RRR, relative risk reduction; TP, transition probability.

Table 14: Results of scenario analyses (list price)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	£612,013	7.06	£86,635	0%
UK government perspective	£594,780	7.06	£84,195	-3%
Societal perspective	£456,954	7.06	£64,685	-25%
1.5% discount rate for costs and outcomes	£605,187	12.32	£49,111	-43%
0% discount rate for costs and outcomes	£593,779	20.31	£29,233	-66%
Health state based on best-seeing eye	£611,769	7.17	£85,320	-2%
Health states based on VF only	£611,019	6.14	£99,533	15%
Baseline characteristics from natural history data	£610,981	6.99	£87,410	1%
Adjusted TP (state dependent)	£612,013	6.91	£88,514	2%
Adjusted TP (state independent)	£612,013	7.41	£82,636	-5%
Health states with no data: remain in same state	£612,013	6.95	£88,061	2%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Use cross-over data in VN arm	£613,120	6.58	£93,165	8%
Duration of treatment effect: 20 years	£615,526	5.70	£108,054	25%
Duration of treatment effect: 30 years	£614,667	6.54	£93,975	8%
Duration of treatment effect: 50 years	£606,973	7.35	£82,527	-5%
Duration of treatment effect: lifetime (100 years)	£603,333	7.52	£80,247	-7%
Waning period: 5 years	£612,501	7.02	£87,278	1%
Waning period: 20 years	£610,539	7.16	£85,270	-2%
Residual RRR (following waning period): 0%	£612,840	6.98	£87,749	1%
Residual RRR (following waning period): 50%	£610,682	7.17	£85,228	-2%
Gompertz multistate model distribution	£611,757	7.46	£82,049	-5%
Log-logistic multistate model distribution	£611,650	6.72	£91,046	4%
Log-normal multistate model distribution	£611,576	6.61	£92,501	6%
Exponential multistate model distribution	£609,602	6.09	£100,154	15%
No mortality effect	£611,645	7.10	£86,087	-1%
Utility values: Acaster Lloyd (EQ-5D-5L)	£612,013	6.45	£94,898	9%
Utility values: Brown et al	£612,013	5.09	£120,191	38%
Carer disutility excluded	£612,013	6.46	£94,785	9%
Hypothetical light sensitivity increment (0.05 in HS1-HS3)	£612,013	8.24	£74,306	-15%
Hypothetical administration procedure disutility (0.1 for 1 month)	£612,013	7.06	£86,735	-1%
Include eligibility testing costs	£624,244	7.06	£88,366	1%
No healthcare resource use in HS1	£604,864	7.06	£85,623	-2%

Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment.
Abbreviations: ICER, incremental cost-effectiveness ratio; UK, United Kingdom; VF, visual field; VN, voretigene neparvovec; QALY, quality-adjusted life year; RRR, relative risk reduction; TP, transition probability.

Table 15: Results of multi-way scenario sensitivity analysis (proposed PAS price)

Duration of treatment effect (years)	Waning period (years)	ICER		
		Residual RRR (following waning period) = 0%	Residual RRR (following waning period) = 25%	Residual RRR (following waning period) = 50%
20	5	[redacted]	[redacted]	[redacted]
20	10	[redacted]	[redacted]	[redacted]
20	20	[redacted]	[redacted]	[redacted]
30	5	[redacted]	[redacted]	[redacted]
30	10	[redacted]	[redacted]	[redacted]
30	20	[redacted]	[redacted]	[redacted]
40	5	[redacted]	[redacted]	[redacted]
40	10	[redacted]	[redacted]	[redacted]
40	20	[redacted]	[redacted]	[redacted]
50	5	[redacted]	[redacted]	[redacted]
50	10	[redacted]	[redacted]	[redacted]
50	20	[redacted]	[redacted]	[redacted]
Lifetime (100)	5	[redacted]	[redacted]	[redacted]
Lifetime (100)	10	[redacted]	[redacted]	[redacted]
Lifetime (100)	20	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; RRR, relative risk reduction.

Table 16: Results of multi-way scenario sensitivity analysis (list price)

Duration of treatment effect (years)	Waning period (years)	ICER		
		Residual RRR (following waning period) = 0%	Residual RRR (following waning period) = 25%	Residual RRR (following waning period) = 50%
20	5	£116,202	£110,229	£103,278
20	10	£113,419	£108,054	£101,742
20	20	£107,816	£103,489	£98,351
30	5	£97,663	£95,074	£91,894
30	10	£96,326	£93,975	£91,068
30	20	£93,594	£91,642	£89,222
40	5	£88,507	£87,278	£85,730
40	10	£87,749	£86,635	£85,228
40	20	£86,190	£85,270	£84,127
50	5	£83,407	£82,890	£82,252
50	10	£82,976	£82,527	£81,973
50	20	£82,227	£81,880	£81,463
Lifetime (100)	5	£80,247	£80,247	£80,247
Lifetime (100)	10	£80,247	£80,247	£80,247
Lifetime (100)	20	£80,247	£80,247	£80,247

Abbreviations: ICER, incremental cost-effectiveness ratio; RRR, relative risk reduction.

1.1.13 Present results of the probabilistic sensitivity analysis.

Assuming each of the proposed PAS price and the list price for VN, the results of 10,000 PSA simulations were plotted on the CEP (Figure 7 and Figure 9, respectively) and a CEAC was generated (Figure 8 and Figure 10, respectively).

Assuming the proposed PAS price for VN, the average incremental costs over the simulated results were [redacted], and the average incremental QALYs were 6.8, giving a probabilistic ICER of [redacted]; this is relatively congruent with deterministic changes in costs and QALYs of [redacted] and 7.1, respectively. The proportion of simulations considered cost-effective assuming the weighted cost-effectiveness threshold - calculated for each simulation individually dependent on the number of undiscounted QALYs gained - is 78%.

Assuming the list price for VN, the average incremental costs over the simulated results were £612,018, and the average incremental QALYs were 6.8, giving a

probabilistic ICER of £89,878; this is relatively congruent with deterministic changes in costs and QALYs of £612,013 and 7.1, respectively. The proportion of simulations considered cost-effective assuming the weighted cost-effectiveness threshold - calculated for each simulation individually dependent on the number of undiscounted QALYs gained - is 75%.

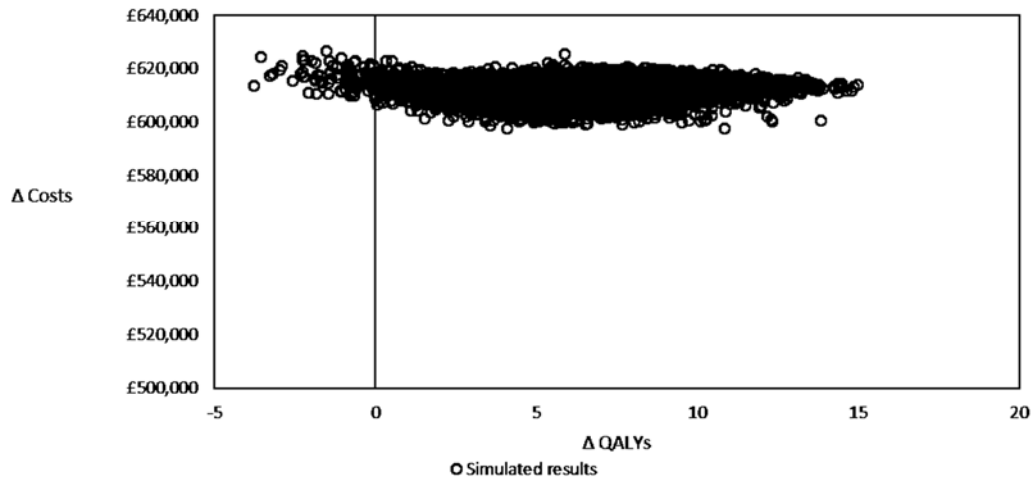
Figure 7: CEP (proposed PAS price)

[redacted]

Figure 8: CEAC (proposed PAS price)

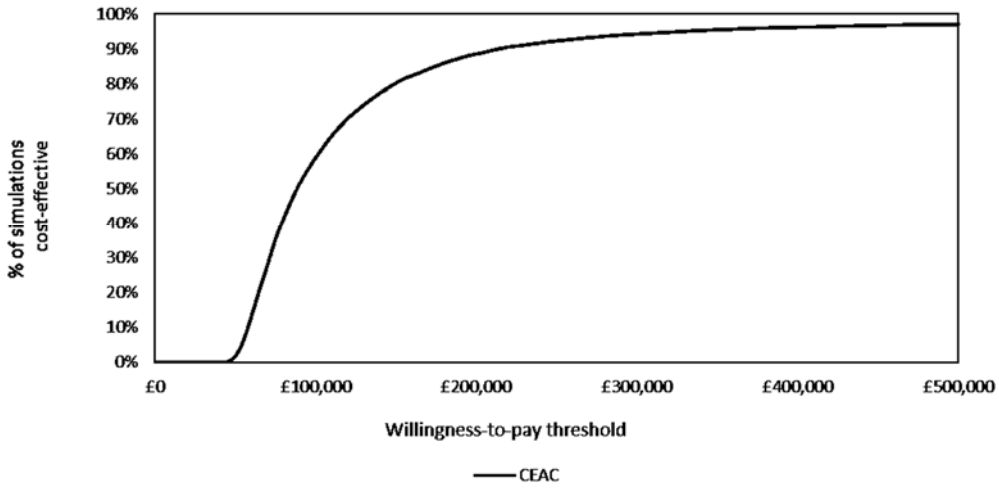
[redacted]

Figure 9: CEP (list price)



Abbreviations: CEP, cost-effectiveness plan; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 10: CEAC (list price)



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme.

1.1.14 What were the main findings of each of the sensitivity analyses?

For all considered parameters, univariate sensitivity analysis resulted in ICERs that fell below the weighted threshold of £203,000 per QALY gained (assuming either the proposed PAS price or the list price for VN); varying all but three parameters resulted in ICERs that fell below the standard HST threshold of £100,000 per QALY gained.

Five of the ten most influential parameters in univariate sensitivity analysis are those describing the long-term multi-state survival model; however, this result should be treated with caution given that highly correlated parameters (i.e. the regression coefficients) are being varied as if they are independent from one another. This conservative approach was taken as it was not considered appropriate to exclude these parameters from univariate sensitivity analysis. Other influential parameters are the health state utility values.

Only four of the considered scenarios are associated with increases in the ICER of more than 10%:

- Health states defined based on VF only
- 20-year treatment effect for VN

- Exponential distribution used for the multi-state survival model
- Utility values taken from Brown et al

Note that this remained the case when assuming either the proposed PAS price or the list price for VN. See Sections 12.1.6, 12.2.1, 12.1.8.3.3 and 10.9.1 for further details on why these approaches were not taken in the model base-case.

Several analyses were associated with substantial decreases in the ICER, including applying a societal perspective, discount rates of 1.5%, and the inclusion of a hypothetical light sensitivity increment.

Multi-way scenario analyses considering the interaction of the duration of the VN treatment effect, the duration of the waning period and the magnitude of the residual treatment effect resulted in best and worst case scenarios ranging between [redacted] and [redacted] when assuming the proposed PAS price for VN, or between £80,247 and £116,202 when assuming list price.

Assuming each of the proposed PAS price and the list price for VN, probabilistic sensitivity analysis showed that the probability of VN being cost-effective is 78% and 75%, respectively.

1.1.15 What are the key drivers of the cost results?

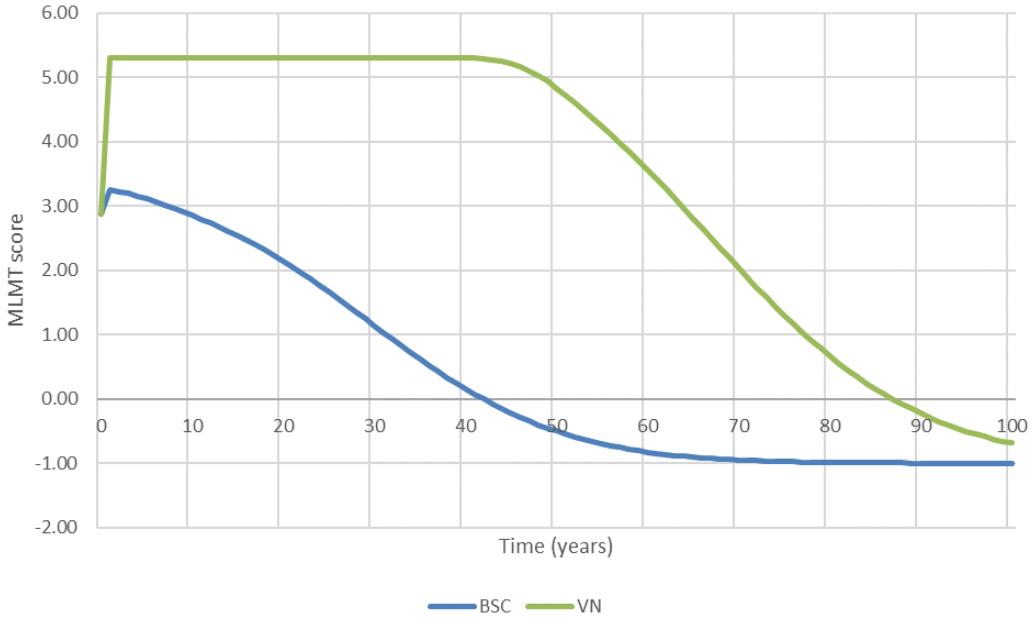
The key drivers of the cost-effectiveness results are the assumed discount rates, the perspective taken, the duration of treatment effect and the choice of utility values.

Miscellaneous results

1.1.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

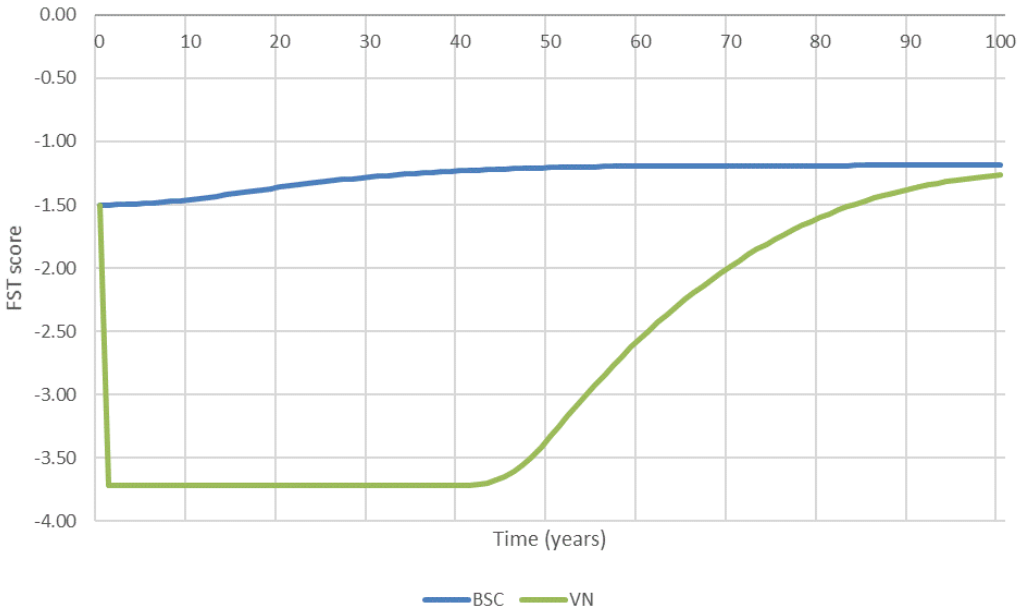
Illustrative MLMT and FST changes over time (see Section 12.1.8.5) are presented in Figure 11 and Figure 12, respectively.

Figure 11: Illustrative MLMT over time



Note: Higher MLMT scores indicate improved functional vision.
Abbreviations: BSC, best supportive care; MLMT, multi-luminance mobility test; VN, voretigene neparvovec.

Figure 12: Illustrative FST over time



Note: Lower FST scores indicate improved light sensitivity.
Abbreviations: BSC, best supportive care; FST, full-field light sensitivity threshold; VN, voretigene neparvovec.

1.2 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

1.2.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in Table 1.

Subgroup analyses were not performed – see Section 9.4.4.

1.2.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

1.2.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

1.2.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also

present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

1.2.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

1.3 Validation

1.3.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The cost-effectiveness model has been verified by the model developers and by health economists not involved in the construction of the model. The model was verified using standard procedures:

- Cell-by-cell checks of logic and consistency
- Logical tests of model outputs

In the absence of other sources of long-term data in this disease area, it has not been possible to cross-validate model outcomes against external sources.

1.4 Interpretation of economic evidence

1.4.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Only one economic analysis was identified from the published literature (see Section 11). ICER developed an economic model to estimate the cost-

effectiveness of VN for vision loss associated with biallelic *RPE65*-mediated IRD compared to standard of care (SoC) in the US setting [185]. A comparison of the total costs and QALYs between the analysis presented in this submission and the ICER analysis is presented in Table 17.

Table 17: Comparison of outcomes in current analysis and ICER analysis

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]†	[redacted]
Analysis presented in this submission	£46,473	3.6	[redacted]	10.7
ICER analysis	$213,399	16.0	$1,039,019	17.3

Abbreviations: BSC, best supportive care; ICER, Institute for Clinical and Economic Review; PAS, patient access scheme; QALY, quality-adjusted life year; VN, voretigene neparvovec.
† Proposed PAS price assumed.

Given that the analyses use different currencies, different acquisition costs are assumed, and the costs of healthcare resource use can differ substantially between the two countries, it may be expected that total costs would differ between the two analyses.

However, the ICER analysis is associated with a significantly smaller QALY gain compared with the current analysis (1.3 vs. 7.1). Given that the effect of VN on mortality is negligible, this effect is driven by differing assumptions around utility values. Average utility values over time (alive patients only) in the current analysis and the ICER analysis are presented in Figure 13 and Figure 14, respectively; it can be seen that the current analysis is associated with a larger gap between the VN and BSC arms, and lower utility values overall.

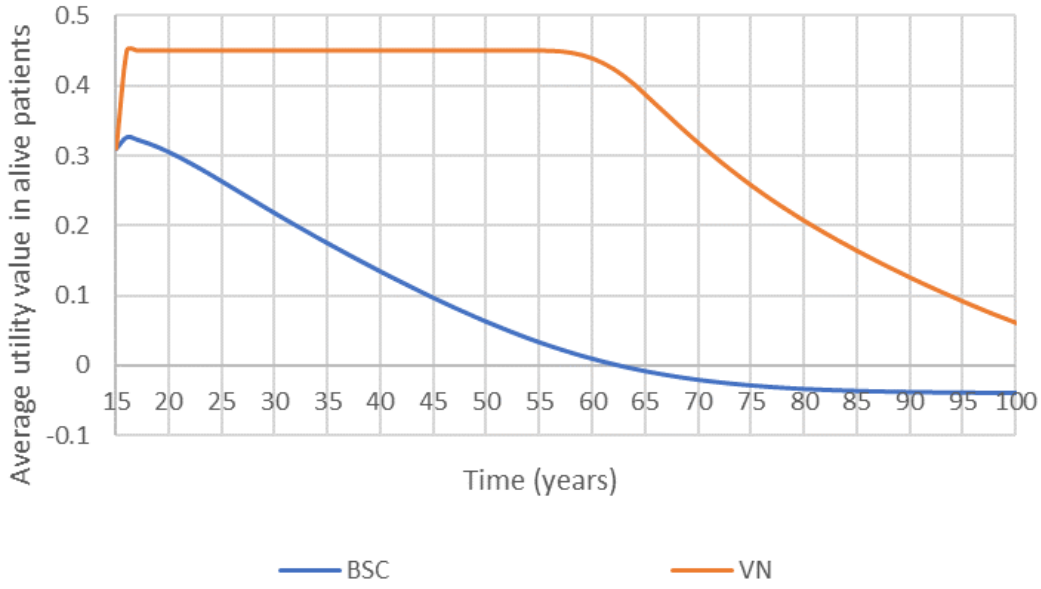
The approach taken in the current analysis is considered to be more appropriate than that of the ICER analysis on the basis that:

- The ICER analysis uses utility values taken from individuals with diabetic retinopathy, which may be expected to differ substantially from those in individuals with *RPE65*-mediated IRD

- The ICER analysis uses only three health states (not visually impaired, visually impaired and blind); however, both the Acaster Lloyd study (Appendix 9) and the study by Brown et al [180] demonstrate differing utility values within the 'blind' health state

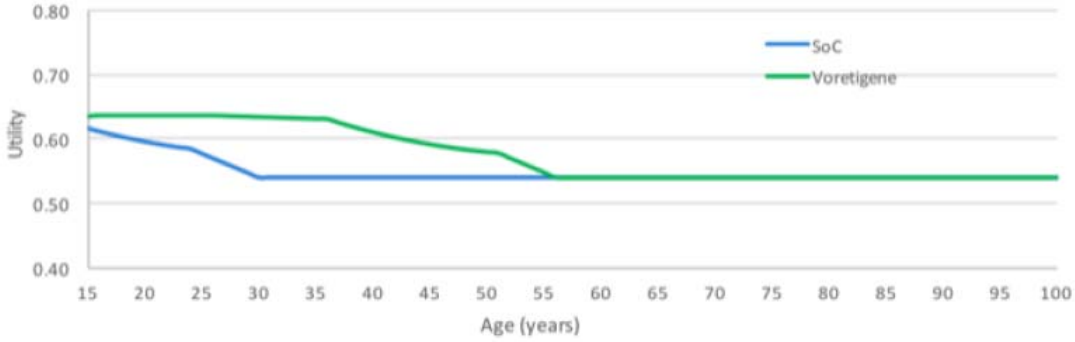
- In the absence of patient-level data, it was necessary for the ICER analysis to make simplified assumptions about how VA and VF change over time.

Figure 13: Average utility value over time in alive patients (current analysis



Abbreviations: BSC, best supportive care; VN, voretigene neparvovec.

Figure 14: Average utility value over time in alive patients (ICER analysis)



Abbreviations: ICER, Institute for Clinical and Economic Review; SoC, standard of care.
Source: ICER 2018 [185]

1.4.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis was designed to be relevant to all patients eligible for VN as defined in the scope.

1.4.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A key strength of this analysis is that a range of scenarios were considered, and the results were found to be relatively robust to alternative assumptions. An additional strength is that the modelled utility values were taken from a bespoke utility study, and did not rely on HRQL data from older populations with different vision conditions, as in previous analyses [185]. Wherever possible, all relevant costs were considered, with key insights on the types of costs to include provided by a patient focus group conducted to support this analysis [97].

A key limitation of the analysis is that it was not possible to capture improvements in either MLMT (the primary endpoint in the pivotal clinical trial) or light sensitivity; however, a scenario considering an arbitrary utility increment for improved light sensitivity was associated with an improved ICER, and so the results of the base-case analysis are expected to be conservative.

Health state transitions in both the initial phase and the long-term phase were based on low patient numbers and short follow-up, somewhat increasing the

level of uncertainty in model outcomes. In the absence of long-term data, there was also uncertainty around the long-term treatment effect associated with VN.

1.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Following the collection of long-term follow-up data, further information may be available on the duration of the VN treatment effect, reducing the uncertainty around the estimate of cost-effectiveness.

Appendix A: RPE65 NHx statistical analysis

During the process of responding to clarification questions from the ERG for NICE, it was identified that the company were unable to recreate the results of the statistical analysis of the RPE65 NHx data.

Further investigations were performed, and it was discovered that the variation was caused by differences in a constructed dataset between execution of the code. This dataset was constructed of demographic, visual acuity, and visual field datasets, which must be combined to identify which health state an individual is in (because health states represent combinations of visual field and visual acuity). The issue was determined to be caused by erroneous merging of these data. Essentially this merge procedure (Stata's merge m:m command) introduced variability because it relied on the order in which the data are sorted; this should never be the case when merging datasets. The use of this merge procedure 1) discarded some valid observations and 2) led to an element of random variability because random sorting appeared to be occurring during the merge procedure.

In addition to this, during further code review other modifications were identified which may improve the statistical analysis. This included re-implementing imputation based on last observation carried forward (LOCF) of '0' scores for VA and VF; manual review of the data suggested that these 0's were erroneous rather true 0's.

The consequence of correcting this merge command is that additional observations are included in the analysis. Overall, the revised analysis suggests a slightly shorter time to progression towards poorer health states. In the base-case the number of observed transitions increased to 35. Revised statistical models are presented in Table 19 and diagnostic information presented in Table 18 and Figure 15.

Table 18: Revised model diagnostic data

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	283	-99.84588	-72.1818	11	166.3636	206.4635
Gompertz	283	-101.4888	-73.83043	11	169.6609	209.7608
Exponential	283	-106.9358	-80.46559	10	180.9312	217.3856
Log-normal	283	-100.4937	-73.96959	11	169.9392	210.0391
Log-logistic	283	-99.94929	-72.31193	11	166.6239	206.7238

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information criterion; df, degrees of freedom; ll, log-likelihood; Obs, observations.

Table 19: Revised statistical models (average eye)†

	Weibull	Gompertz	Exponential	Log-logistic	Log-normal
HS1 to HS3	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.407** (0.531)	1.418** (0.487)

HS1 to HS4	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.392** (0.532)	1.086** (0.420)
HS1 to HS5	-18.30 (2711.3)	-17.25 (1609.5)	-17.31 (1655.3)	8.476 (1003.5)	5.385 (476.2)
HS2 to HS3	-0.601 (0.420)	-0.513 (0.419)	-0.342 (0.417)	0.514* (0.261)	0.528 (0.285)
HS2 to HS4	-2.999** (1.042)	-2.910** (1.042)	-2.740** (1.041)	1.689** (0.524)	1.636*** (0.451)
HS2 to HS5	-18.32 (2122.2)	-17.28 (1319.0)	-17.31 (1457.1)	8.559 (821.1)	5.438 (419.7)
HS3 to HS4	-1.372** (0.517)	-1.404** (0.535)	-0.805 (0.500)	0.936** (0.304)	0.959** (0.336)
HS3 to HS5	-18.36 (1990.8)	-17.37 (1194.3)	-17.31 (1565.6)	8.769 (888.2)	5.749 (496.0)
HS4 to HS5	-1.553* (0.658)	-1.555* (0.666)	-1.008 (0.646)	1.003** (0.377)	1.075* (0.419)
Constant	-14.95*** (1.859)	-9.211*** (0.355)	-8.588*** (0.289)	7.986*** (0.190)	8.018*** (0.203)
ln (p)	0.586*** (0.125)				
gamma		0.000316*** (0.0000825)			
ln (gamma)				-0.785*** (0.132)	
ln (sigma)					-0.143 (0.120)
N	283	283	283	283	283

† Standard errors in parentheses.
* p < 0.05, ** p < 0.01, *** p < 0.001
Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

Figure 15: Revised Cox-Snell residuals (average eye)

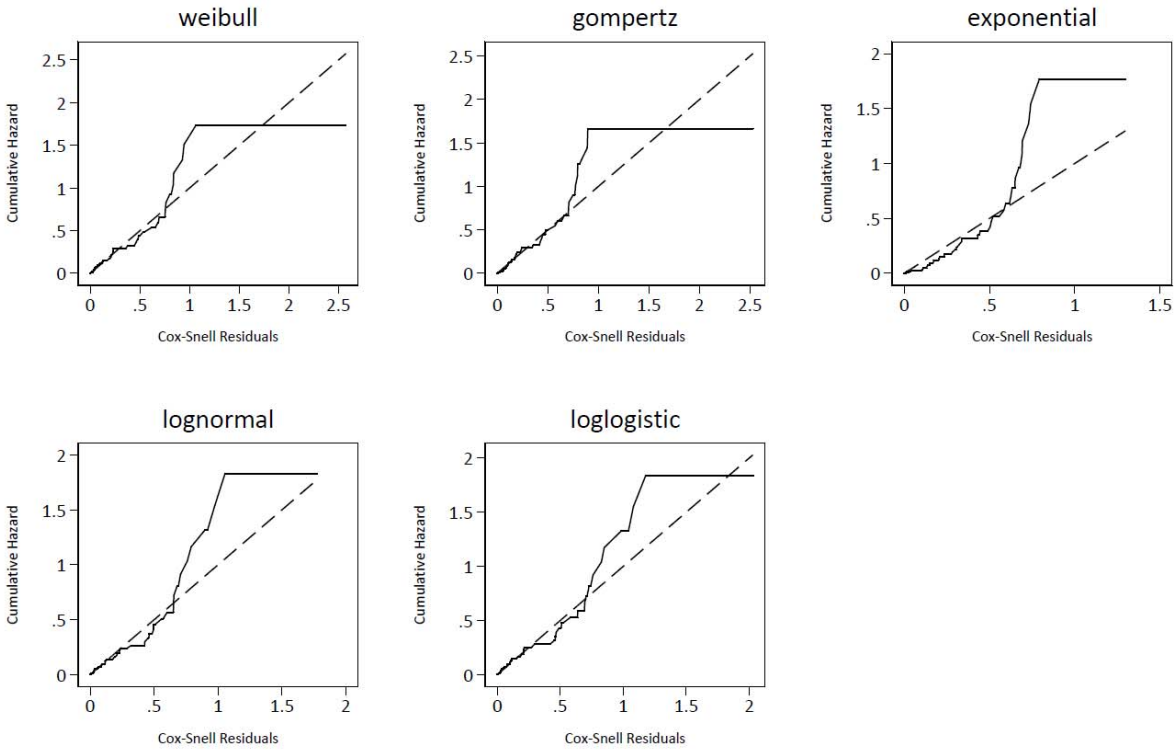
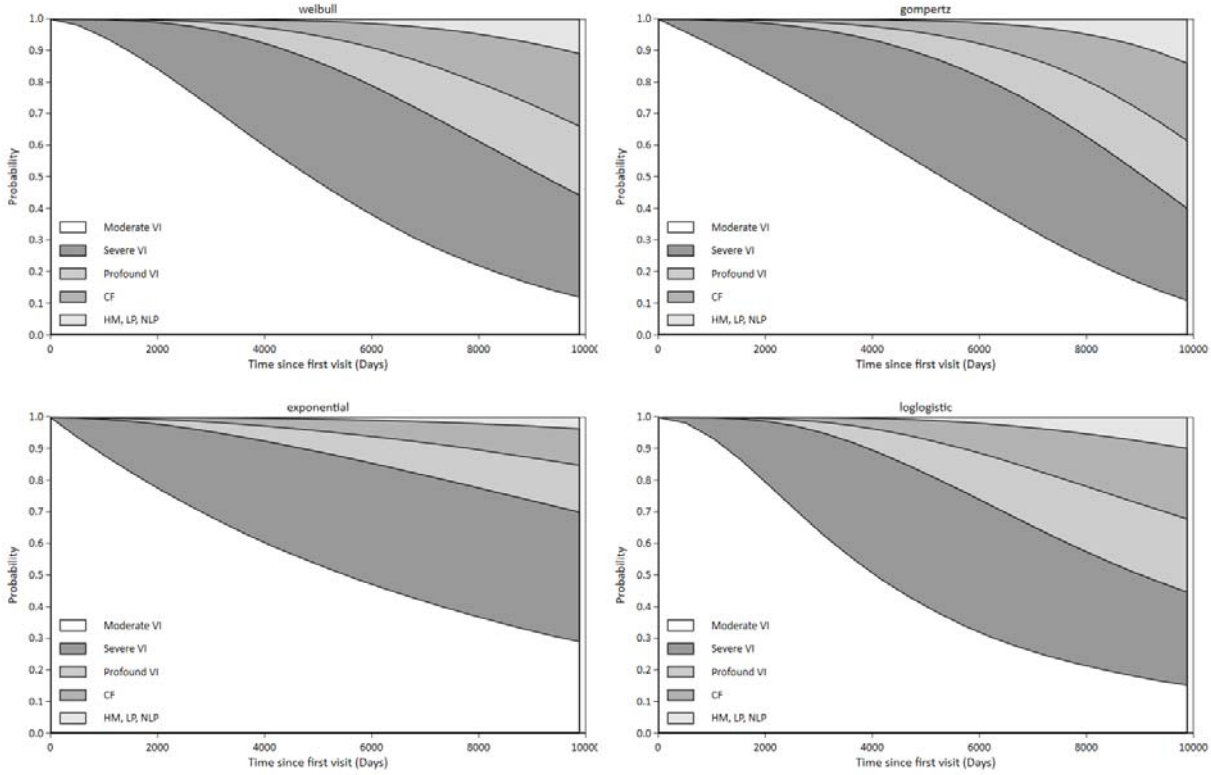


Figure 16: Revised distribution across health states over time (patients starting in HS 1)



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Highly Specialised Technologies Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Dear Company,

The Evidence Review Group, PenTAG, and the technical team at NICE have looked at the submission received on 12 February 2019 by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **5pm** on **20 March 2019**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Literature searching

A1. **Priority Question:** Appendix 2 states that no additional literature review for adverse events was conducted. Please clarify how evidence on adverse events was identified from the existing systematic review.

A2. **Priority Question:** Please indicate which sources were used for the search for ongoing and recently completed clinical trials as mentioned on page 4 of Appendix 1.

A3. **Priority Question:** Please confirm that the company did not carry out any searches for the intervention in question (voretigene neparvovec/Luxturna) in either the clinical or the cost effectiveness searches (Appendix 1 and Appendix 3) and explain the rationale for this.

A4. **Priority Question:** Please clarify which database search results are presented in Appendix 1, Table 2 (page 9). It is not possible to get results for a Subject Heading search in Medline-in-process.

A5. Please whether any citation chasing of reference lists of the included studies was carried out for the clinical effectiveness review.

A6. Please clarify whether there is an error in reporting of the updated search tables from January 2019 (Appendix 1 Tables 4, 5 & 6)? The results of the individual lines of the search are all identical to those in the original search from March 2018.

A7. The numbers in the PRISMA flow diagram (Appendix 1 Figure 2, page 9) do not tally. Please provide correct numbers.

A8. Please provide a table of excluded studies, with reasons for exclusion.

A9. Please clarify how literature on prevalence of clinical diagnoses was identified?

Pivotal trial information

A10. **Priority Question:** What is the length of follow-up of visual function (VF) and visual acuity (VA) for the original intervention arm in Study 301/302? If this is greater than 3 years, please send updated versions of Figures 13 and 15 that reflect this.

A11. Please confirm that no deaths were observed in any studies of voretigene neparvovec or the RPE65 NHx study.

A12. In Study 301/302, please explain why sufficient viable retinal cells was determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole) rather than measuring rod length?

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A13. Please clarify the rationale for using a single injection per eye of VN. Is there a potential for increased effectiveness with multiple injections, and is there evidence beyond the licence (e.g. multiple administrations in humans) relating to safety?

A14. Was the subretinal injection in the same region of the retina (e.g. macular or peripheral) for all patients in Study 301, Study 302, Study 101 and Study 102?

A15. Do you consider age-related response to be a possibility? In Study 301/302, you performed an exploratory age-stratified analysis on <10 years or ≥10 years at time of injection. Have you performed any post-hoc analysis for other age groups? In the model, the resource use/costs used in the model were split by <18 years and ≥18 years so it would be useful to have subgroup data for adults only (i.e. <18 and ≥18 years) at time of injection.

A16. What evidence was used to assess the impact of the disease and the effect of treatment on families and carers? Please provide transcripts of the focus group with carers.

A17. Please provide the original AAV2-LRPE65v2-3Cl CSR dated 13 Dec 2016.

A18. Please provide CSR appendices for study 301/302 (appendix 16.1.1 protocol and protocol amendment; appendix 16.2.2 protocol violations / deviations; appendix 16.2.6 individual efficacy responses).

A19. Please provide a CONSORT diagram for Study 101/Study 102 similar to Figure 9 (page 93 company submission).

Safety study information

A20. **Priority Question:** What is the length of follow-up of VF and VA in Study 101/102? Please provide plots depicting mean VF and VA with respect to time (similar to Figure 15; page 108 company submission).

A21. Please provide CSR Appendices for Study 101 and Study 102 (appendix 16.2.1 discontinued subjects; appendix 16.2.7 adverse events).

Retrospective chart analysis

A22. Please provide a plot depicting VA for the average eye by age from RPE65 NHx (similar to Figure 28; page 184 company submission), indicating LogMAR 1.4 and 1.8 on the y-axis.

A23. Please provide a plot of VF for the average eye by age from RPE65 NHx (similar to Figure 29; page 184 company submission).

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Section B: Clarification on cost model and value for money

Literature searching

B1. **Priority question:** Please clarify which specific grey literature sources were searched for the cost effectiveness review as described on page 2 of Appendix 3?

B2. The numbers in the PRISMA flow diagram (Appendix 3 Figure 2, page 5) do not tally. Please provide correct numbers.

B3. The numbers in the PRISMA flow diagram (Appendix 4 Figure 2, page 35) do not tally. Please provide correct numbers.

B4. Please confirm whether the data extraction forms used were identical for the clinical effectiveness and the cost effectiveness systematic reviews, or whether different data was extracted for each review (Appendix 3 page 3)?

Clinical trials

B5. Considering the important role of the four clinical studies, please clarify how data from each study was used in the model. Please use the following table as a suggested format to present this information.

Study	Parameter used in model (resource ,outcome…)	Follow up
101, (n=11)		
102, (n=…)		
301, (n=…)		
302, (n=…)		

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Extrapolation of clinical outcomes

B6. **Priority Question:**

a. During years 2 and 3, 1 patient in the original intervention arm of Study 301/302 was observed transitioning between health states (section 12.1.8 company submission). Between which health states did this patient transition?

b. Please confirm that this transition occurred in Year 3. If so please provide a scenario analysis in which transition probabilities based on the data from this year (rather than Year 1) are used for the VN strategy in the long-term phase of the model (with adjustable duration of treatment effect, length of the waning period and long-term RRR).

B7. **Priority Question:** Following the methods outlined by Crowther & Lambert (2017; reference 200), please provide scenario analyses in which transition-specific distributions are fitted.

B8. **Priority Question:** Please demonstrate the Markov assumption for the multi-state model and send the results of this test.

B9. **Priority Question:** Please provide additional information regarding the data used to inform the long-term multi-state model, as follows:

- details regarding the baseline characteristics of patients, including geographical region
- study report and any related publications (e.g. conference abstracts and/or presentations) where available
- the nature and approximate timing of the 28 transitions observed within the RPE65 NHx study (e.g. between which health states)
- details of the Cox-Snell residual plots produced, including the number of transitions incorporated within the plot per patient
- if there are a sufficiently large number of transitions for an individual transition(s), provision of per-transition Cox-Snell (or equivalent) residual plots.[1]

B10. **Priority Question:** Please provide further details regarding the elicitation of clinical expert opinion concerning the anticipated duration of treatment effect and the treatment effect waning period? This should include:

- the specific question(s) asked, in particular questions concerning the existence of the treatment effect waning period and the assumption of linearity

[1] The Cox-Snell residual plot provides information regarding the fit of the MSM. There are a total of 28 transitions noted within the RPE65 NHx study, however the exact nature of these transitions (i.e. from and to specific health states) is currently unclear. Should there be enough transitions of a specific type (e.g. the majority of transitions were from HS1 to HS2), the ERG would like to see a plot showing how well the multi-state model fits the observed transitions of a specific type over time (given that only forward transitions are permitted by the MSM approach adopted). Alternative plots may be preferred by the company to look at specific transitions – Crowther and Lambert used the Nelson-Aalen estimate within their example (Crowther and Lambert, 2016, DOI: 10.1002/sim.7448) for each of the three transitions used in their model (please see Figure 2 in this paper for a presentation of the per-transition plots).

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- the verbatim responses given by the clinical experts, ideally in the form of an interview transcript or meeting minutes.

B11. Please confirm that 1 patient enrolled within the delayed intervention arm of Study 301/302 resided in health state (HS) 1 at baseline and HS2 at 1 year?

B12. Please provide a summary of BCVA and health state occupancy from the trial data (Study 301/302) for individual patients at baseline, 30 days, and 1 year (as per the model structure). Please use the following tables as a suggested format to present this information.

Table 1: BCVA

	Baseline	30 days	1 year
Patient 1	65	70	70
…			

Table 2: Health State Occupancy

	Baseline	30 days	1 year
Patient 1	Health state 2	Health state 1	Health state 1
…			

B13.

a. Please confirm which scale is used to define VA within the cost-effectiveness model (Holladay or Lange)?

b. Please confirm whether or not the transition for the 1 patient where baseline VF was missing was based only on VA.

c. Please provide a scenario where transitions within the model are informed only by VA (as opposed to VA + VF or VF only).

Health-related quality of life

B14. Please confirm the regions represented by the 6 clinicians interviewed as part of the vignette study. In addition, please provide further clarity regarding the order in which the questions were asked?

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Cost and Resource inputs

B15. Please provide evidence for the cost of oral prednisone from the British National Formulary (e.g. a timestamped screen shot of the BNF website, or excerpt from the hard copy from which the cost was taken)?

B16. Please provide an explanation for the methods used to inflate costs using the inflation indices reported by the Personal Social Services Research Unit (PSSRU)? More specifically, please provide a description of the use of hospital and community health service (HCHS) inflation indices which were recently discontinued.

Budget impact

B17. Please provide further information regarding the anticipated market uptake for voretigene neparvovec over its first 5 years of availability.

Section C: Textual clarifications and additional points

C1. Please can the company confirm that the diagram of the model schematic (Figure 26, page 163 company submission) contains two minor errors, and that it is actually possible for patients to transition from HS5 to HS4 and from HS5 to HS3 (within Year 1)?

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Highly Specialised Technologies Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Dear [Insert name],

The Evidence Review Group, PenTAG, and the technical team at NICE have looked at the submission received on 12 February 2019 by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **5pm** on **20 March 2019**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Literature searching

A1. Priority Question: Appendix 2 states that no additional literature review for adverse events was conducted. Please clarify how evidence on adverse events was identified from the existing systematic review.

Safety outcomes were included in the PICOS criteria for the systematic review described in Appendix 1 (see Table 7 in Section 17.1.6 of Appendix 1). The review identified publications associated with Studies 101, 102 and 301/302 (see Tables 7 and 8 in the company submission). Safety data from the clinical study reports (CSRs) of each of these studies are presented in Section 9.7 of the company submission.

A2. Priority Question: Please indicate which sources were used for the search for ongoing and recently completed clinical trials as mentioned on page 4 of Appendix 1.

Clinicaltrials.gov was searched for information on ongoing and recently completed trials. In addition, abstracts from the past three years of the conferences listed on page 5 of Appendix 1 were searched, as data on recently completed trials are usually presented at these conferences.

A3. Priority Question: Please confirm that the company did not carry out any searches for the intervention in question (voretigene neparvovec/Luxturna) in either the clinical or the cost effectiveness searches (Appendix 1 and Appendix 3) and explain the rationale for this.

Voretigene neparvovec/Luxturna does not appear in the search strings, however it is included in the PICOS criteria (see Table 7 in Section 17.1.6 of Appendix 1) and all relevant studies are expected to have been identified.

As the disease under consideration is rare, the number of hits was already low (699 hits from all databases as of 8th March 2018). Limiting the number of hits further by including terms for the intervention could have led to studies being missed from the review.

A4. Priority Question: Please clarify which database search results are presented in Appendix 1, Table 2 (page 9). It is not possible to get results for a Subject Heading search in Medline-in-process.

Medline-in-process searches were run on the OvidSP platform, where the in-process is grouped within the Medline database. Searches had already been performed in the Medline database via Embase.com. Limits for "in data review" or “in process” or “as supplied by publisher” or "pubmed not medline" were applied while running the searches on the Ovid platform to get only the in-process part. We agree that it is not possible to get results for a Subject Heading search in Medline-in-process, however, the same terms are captured in string #2.

A5. Please whether any citation chasing of reference lists of the included studies was carried out for the clinical effectiveness review.

Bibliographies of included papers were searched to identify relevant papers.

A6. Please clarify whether there is an error in reporting of the updated search tables from January 2019 (Appendix 1 Tables 4, 5 & 6)? The results of the

individual lines of the search are all identical to those in the original search from March 2018.

We agree that it would be preferable to provide fully updated tables for the January 2019 search, showing differences in the number of hits for each search string. Unfortunately, these tables are no longer retrievable. We attempted to retroactively generate the tables by re-running the searches on 14/03/19 and limiting by date (file name "Question A6 – search tables"). The number of new records in Table 5 fell from 39 to 34, possibly due to conversion of some records to indexed citations.

A7. The numbers in the PRISMA flow diagram (Appendix 1 Figure 2, page 9) do not tally. Please provide correct numbers.

Please find a corrected PRISMA diagram attached (file name "Question A7 – corrected PRISMA").

A8. Please provide a table of excluded studies, with reasons for exclusion.

Please find a table of excluded studies for each SLR attached (file name "Question A8 – excluded studies").

A9. Please clarify how literature on prevalence of clinical diagnoses was identified?

It is now considered more appropriate to assign a molecular diagnosis rather than a clinical one, as there is considerable overlap in clinical symptoms for the diagnoses of retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA), and there is no standardised method for assigning one diagnosis or the other.

As the assignment of molecular diagnoses to patients is a recent development, the majority of the published literature describes the disease in terms of clinical diagnoses. An SLR was performed to identify sources reporting epidemiology data for LCA and RP. For details of the search please see the attached document ("Question A9 – search strategy").

In Section 6.1.1 of the company submission all of the identified sources are used to produce a summary of the incidence and prevalence of RP and LCA, and the proportion of cases associated with RPE65 mutations.

In Section 6.2 of the company submission, the following selection criteria were applied to the identified studies to provide an estimate of patient numbers in England:

- Where one or more sources of UK data were available, the mean of these data points was taken.
- Otherwise, the average of all available data points from Western Europe and North America was taken.

Pivotal trial information

A10. **Priority Question:** What is the length of follow-up of visual function (VF) and visual acuity (VA) for the original intervention arm in Study 301/302? If this is greater than 3 years, please send updated versions of Figures 13 and 15 that reflect this.

The most recent data for visual field and visual acuity endpoints include four years of follow-up for original intervention patients, and three years of follow-up for delayed intervention patients. Figure 1 and Figure 2 present results for visual acuity and visual field, respectively.

Figure 1: VA using Holladay Scale, Observed Means Over Time, Both Eyes (mITT / Safety)

BL, baseline; LogMAR, logarithm of the minimum angle of resolution; SE, standard error; VA, visual acuity; X, cross over. Data presented as mean ± SE. For subjects with off-chart VA results, the Holladay scale was used.
Source: Figure 11.4, Study 301 CSR (Addendum 2018)

Figure 2: Goldmann Visual Field III4e Results over Time (mITT / Safety)

BL, baseline; SE, standard error; X, cross over. Values presented as mean ± SE in sum total degrees. For Control / Intervention subjects, the change is relative to the injection baseline after Year 1.
Source: Figure 11.8, Study 301 CSR (Addendum 2018)

A11. Please confirm that no deaths were observed in any studies of voretigene neparvovec or the RPE65 NHx study.

No deaths have been reported in the clinical development program for voretigene neparvovec.

The RPE65 NHx study is non-interventional, so deaths are not reported in the CSR.

Please note that RPE65 NHx is a natural history study, so patients did not receive voretigene neparvovec or any other intervention.

A12. In Study 301/302, please explain why sufficient viable retinal cells was determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole) rather than measuring rod length?

Retinal cell viability was determined based on a number of factors, rather than by optical coherence tomography (OCT) alone. Other tests used to determine the presence of sufficient viable retinal cells included inspection of the retina, and visual field testing. The inclusion criteria state that patients must have:

"sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy. Must have either:

1) an area of retina within the posterior pole of > 100 µm thickness shown on OCT;

2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or

3) remaining visual field within 30º of fixation as measured by III4e isopter or equivalent."

In the opinion of the principal investigators (retinal surgeons), 100 µm is the minimum retinal thickness required in order to safely perform the administration procedure. There is no available test that directly measures viability, however, so retinal thickness serves as the best available surrogate for viable retinal cells. A minimal area of viable cells is required to allow for the subretinal administration procedure to be performed and for the cells to enable transduction of the vector and production of the functional enzyme. Retinal thickness is an appropriate measure to estimate the presence of sufficient viable retinal cells and identify candidates for subretinal administration of voretigene neparvovec in this patient population.

OCT only provides structural information, which should be combined with functional information from other tests such as FST, VF testing and fundus autofluorescence.

In clinical practice, OCT examinations are likely to be more qualitative, and qualitative evidence of structure is more important than defining a threshold. Additional assessments of FST (white, red and blue), VF and VA may also add further information when assessing retinal viability.

A13. Please clarify the rationale for using a single injection per eye of VN. Is there a potential for increased effectiveness with multiple injections, and is there evidence beyond the licence (e.g. multiple administrations in humans) relating to safety?

Voretigene neparvovec is a one-time treatment, with a single injection in each eye and no repeat administration. No evidence exists on the safety or efficacy of multiple injections to the same eye.

Voretigene neparvovec is the first approved gene therapy for a retinal disease, and the trial program was designed to cautiously weigh benefits and risk. There is no evidence to date of a loss of efficacy following a single injection in each eye [1], so repeat administration was not explored.

Furthermore, the administration procedure is complex and not risk-free, and patients who have undergone multiple vitrectomies are more likely to experience adverse events including retinal detachment [1]. This is of particular importance in paediatric populations, as the anatomy of the eye changes between childhood and adulthood [2].

A14. Was the subretinal injection in the same region of the retina (e.g. macular or peripheral) for all patients in Study 301, Study 302, Study 101 and Study 102?

The same administration protocol applied in all studies. However, it was not always possible to target the same region of the retina; further details are provided below.

In the first three patients to be treated in Study 101, in Patient 1, the injection exposed the superonasal macula and the retina peripheral to the superonasal vascular arcade; the macula was exposed in Patients 2 and 3, with some extension beyond the temporal arcade in Patient 3 [3].

Out of all 12 patients in study 101, the vector was injected into the macula in nine patients, but not in three patients with substantial atrophy in this region. About half the macula was exposed in one patient. An epiretinal membrane that was noted during baseline studies in the injected eye of a patient was removed before injection. A foveal dehiscence was noted at the time of injection in this individual as some of the vector escaped from the foveal defect, reducing the total volume in the subretinal space by about 70% and resulting in the exposure of a third of the macula [4].

The surgical notes (from site source documents) for all 29 Phase 3 subjects treated at both the Children's Hospital of Philadelphia (CHOP) and the University of Iowa were reviewed. Using a definition of the macular area as that area of the retina located between the superior and inferior vascular arcades, the optic nerve, and about 15 degrees temporal to the fovea, a total of 57 of 58 injected eyes had obvious macular involvement.

A15. Do you consider age-related response to be a possibility? In Study 301/302, you performed an exploratory age-stratified analysis on <10 years or ≥10 years at time of injection. Have you performed any post-hoc analysis for other age groups? In the model, the resource use/costs used in the model were split by

<18 years and ≥18 years so it would be useful to have subgroup data for adults only (i.e. <18 and ≥18 years) at time of injection.

[redacted]

There is no evidence that the treatment effect of VN differs between age groups. Symptoms can first present at a range of ages, from infancy to adolescence [5], so the presence of sufficient viable retinal cells is considered more important than age in determining whether to treat patients (in accordance with the licensed indication).

In the cost-effectiveness model, some costs were determined by age; however, this approach was not taken on the expectation of differing efficacy across age groups, but on the basis that not all cost types are relevant to all ages; in particular, costs associated with education only apply to school-age individuals, and government-provided social security will apply differently to school-age, working-age and retirement-age individuals.

A16. What evidence was used to assess the impact of the disease and the effect of treatment on families and carers? Please provide transcripts of the focus group with carers.

Section 7.1.6 of the company submission describes the economic and health impact of the disease, and of visual impairment and blindness more generally, on caregivers. A UK clinical expert provided the statement that "patients with the condition often require full time support". The remainder of the information provided in Section 7.1.6 on the economic and health burden of caregiving for visually impaired individuals was supported by desk research.

The focus group was attended by patients but not carers, however issues experienced by carers were discussed. A transcript is not available, but a report on the focus group study is attached ("Question A16 – focus group report").

A17. Please provide the original AAV2-LRPE65v2-3Cl CSR dated 13 Dec 2016.

The CSR for study 301/302 was included in the reference pack accompanying the original company submission (file name: 'Spark Therapeutics (2016)'). Also provided is an addendum dated February 2018 (file name: 'Spark Therapeutics (2018)').

A18. Please provide CSR appendices for study 301/302 (appendix 16.1.1 protocol and protocol amendment; appendix 16.2.2 protocol violations / deviations; appendix 16.2.6 individual efficacy responses).

Information on protocol deviations in Study 301/302 can be found in section 10.3 of the original CSR for Study 301/302, including information on individual patients. Individual efficacy responses can be found in our response to question B12.

A19. Please provide a CONSORT diagram for Study 101/Study 102 similar to Figure 9 (page 93 company submission).

Please find a CONSORT-style diagram attached (file name "Question A19 – CONSORT").

Safety study information

A20. Priority Question: What is the length of follow-up of VF and VA in Study 101/102? Please provide plots depicting mean VF and VA with respect to time (similar to Figure 15; page 108 company submission).

As per the separate email to the NICE project manager, we require more time to address this question.

A21. Please provide CSR Appendices for Study 101 and Study 102 (appendix 16.2.1 discontinued subjects; appendix 16.2.7 adverse events).

No patients discontinued in Study 101 or Study 102. Summaries of adverse events are provided in Section 12 of the respective CSRs provided in the reference pack with the company submissions ("Spark Therapeutics (2015) Study 101 CSR", and "Spark Therapeutics (2015) Study 102 CSR").

Retrospective chart analysis

A22. Please provide a plot depicting VA for the average eye by age from RPE65 NHx (similar to Figure 28; page 184 company submission), indicating LogMAR 1.4 and 1.8 on the y-axis.

Please see Figure 3 below.

Figure 3: Visual acuity (Holladay) for the average eye, by age

A23. Please provide a plot of VF for the average eye by age from RPE65 NHx (similar to Figure 29; page 184 company submission).

Please see Figure 4 below. Please note that values of 0 have been treated as missing.

Figure 4: Visual field (III4e) for the average eye, by age

<u>Section B: Clarification on cost model and value for money</u>

As discussed in Appendix A, an error was identified in the Stata code for the multistate survival model such that it was not possible to reproduce the same statistical models between different runs of identical Stata code.

This error has now been corrected and the cost-effectiveness model updated; base-case results for the submitted model and the corrected model are presented in Table 1. A corrected cost-effectiveness model and results section are attached (file names

"VN_CEM_NICE_Corrected" and "SubmisionDossier_Results_Corrected", respectively). All scenario analyses presented in this document are run from the corrected base-case.

Table 1: Submitted and corrected base-case results (PAS price assumed)

	Costs		QALYs		ICER
	BSC	VN	BSC	VN	
Submitted base-case	£46,300	[redacted]	3.9	10.8	[redacted]
Corrected base-case	£46,473	[redacted]	3.6	10.7	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VN, voretigene neparvovec.

Literature searching

B1. Priority question: Please clarify which specific grey literature sources were searched for the cost effectiveness review as described on page 2 of Appendix 3?

Abstracts from the past three years of the conferences listed on page 5 of Appendix 1 were searched. In addition, the following databases were searched:

- Cost Effectiveness Analysis Registry (http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx)
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA) (http://www.inahta.org/)
- Institute for Clinical and Economic Review (https://icer-review.org/)
- Canadian Agency for Drugs and Technologies in Health (https://www.cadth.ca/)

B2. The numbers in the PRISMA flow diagram (Appendix 3 Figure 2, page 5) do not tally. Please provide correct numbers.

Please find a corrected PRISMA diagram attached (file name "Question B2 – corrected PRISMA").

B3. The numbers in the PRISMA flow diagram (Appendix 4 Figure 2, page 35) do not tally. Please provide correct numbers.

Please find a corrected PRISMA diagram attached (file name "Question B3 – corrected PRISMA").

B4. Please confirm whether the data extraction forms used were identical for the clinical effectiveness and the cost effectiveness systematic reviews, or whether different data was extracted for each review (Appendix 3 page 3)?

Different data extraction forms were used for each review.

Clinical trials

B5. Considering the important role of the four clinical studies, please clarify how data from each study was used in the model. Please use the following table as a suggested format to present this information.

The approach to incorporating data from each of the four clinical studies is presented in Table 2.

Table 2: Use of clinical trial data

Study	Parameter used in model (resource ,outcome…)	Follow up
Study 101 (n=12)	• No data from Study 101 were used in the model directly • [redacted]	[redacted]
Study 102 (n=11)	• No data from Study 102 were used in the model directly • [redacted]	[redacted]
Study 301 (n=29)	• VA and VF at baseline used to inform the baseline health state distribution	-
	• Average age and proportion of males at baseline used to inform the general population mortality rate	-
	• VA and VF at baseline and 1 year used to inform transition probabilities for the first year of the model	1 year
	• Adverse event probabilities	>3 years
	• Average patient weight at baseline used to calculate average costs of prednisone	-
	• Average number of days of prednisone treatment used to calculated average costs of prednisone	-
Study 302 (n=9)	• VA and VF at 1 year and 2 years in the Control/Delayed Intervention arm used to inform transition probabilities for the first year of the model, in the scenario in which crossover data are included	1 year

Abbreviations: VA, visual acuity; VF, visual field.

Extrapolation of clinical outcomes

B6. Priority Question:

a. During years 2 and 3, 1 patient in the original intervention arm of Study 301/302 was observed transitioning between health states (section 12.1.8 company submission). Between which health states did this patient transition?

In preparation of the response to this question, it was identified that the number of patients moving between health states after Year 1 was incorrectly reported for the base-case in the submission dossier.

- The submission dossier states that one patient moves from HS1 to HS2 between years 2 and 3 of Study 301 – this is only the case when health states are defined based on VF only.
- Health state transitions in the VN arm after year 1 - using the base-case definition of health states (i.e. defined based on the worse of VA and VF) – are presented in Table 3
    - It is noted that the circumstances of all three transitions suggest that these health state movements are temporary.

Table 3: Health state transitions in the VN arm after Year 1

Transition	Notes
One patient moved from HS2 to HS3 between year 1 and year 2, and moved back to HS2 between year 2 and year 3	This health state movement is based on small variations in VA, and so is not considered to represent a true health state change: • VA at year 1: 1.37 • VA at year 2: 1.41 • VA at year 3: 1.36
One patient moved from HS3 to HS4 between year 2 and year 3	This health state movement was due to a change in VA from 1.50 at year 2 to 2.05 at year 3. A cataract was reported in this patient at 1088 days (i.e. just prior to 3 years); it is therefore expected that this health state change may be temporary
One patient moved from HS1 to HS2 between year 2 and year 3	This patient returned to HS1 at Year 4 (note that health state occupancy at Year 4 is not available for all patients); this health state change has therefore been shown to be temporary

Abbreviations: VA, visual acuity; VF, visual field.

b. Please confirm that this transition occurred in Year 3. If so please provide a scenario analysis in which transition probabilities based on the data from this year (rather than Year 1) are used for the VN strategy in the long-term phase of the model (with adjustable duration of treatment effect, length of the waning period and long-term RRR).

As discussed in question B6a, health state transitions in the VN arm after Year 1 are expected to be temporary. However, a scenario analysis has been implemented in which transition probabilities (TPs) between baseline and Year 3 are implemented in the VN arm in place of TPs between baseline and Year 1:

- One patient starting in HS2 stays in HS2 rather than transitioning to HS1
- One patient starting in HS4 stays in HS4 rather than transitioning to HS3

The results are presented in Table 3 and are found to be similar to the results for the corrected base-case.

Table 4: Scenario analysis results (Year 3 TPs applied for VN)

	Costs		QALYs		ICER
	BSC	VN	BSC	VN	
Corrected base-case	£46,473	[redacted]	3.6	10.7	[redacted]
Scenario: Year 3 TPs applied for VN	£46,473	[redacted]	3.6	10.3	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TP, transition probability; VN, voretigene neparvovec.

B7. Priority Question: Following the methods outlined by Crowther & Lambert (2017; reference 200), please provide scenario analyses in which transition-specific distributions are fitted.

A scenario analysis has been implemented in which transition-specific distributions are fitted. Some transitions were not observed in the natural history study (see Table 5); the rates of these transitions were therefore set to be zero in the cost-effectiveness model.

For the remaining transitions, the best-fitting distribution was selected on the basis of Akaike information criterion (AIC)/Bayesian information criterion (BIC); an alternative scenario is also presented in which the rates of transitions based on only one event (HS1 to HS3, HS1 to HS4 and HS2 to HS4) are set to be zero.

The results of this scenario analysis are presented in Table 6, and are found to be similar to the corrected base-case. However, it is considered that in context of low patient numbers, a single statistical model – as implemented in the base-case – can be more reliably estimated.

Table 5: Statistical output

Transition	Number of events	Best-fitting distribution	Statistical output	
			Constant	ln(p)
HS1 to HS2	12	Weibull	-12.60121	0.4101494
HS1 to HS3	1	Exponential	-11.07259	N/A
HS1 to HS4	1	Exponential	-11.07259	N/A
HS1 to HS5	0	N/A	N/A	N/A
HS2 to HS3	11	Weibull	-18.66045	0.7846386
HS2 to HS4	1	Exponential	-10.97700	N/A
HS2 to HS5	0	N/A	N/A	N/A
HS3 to HS4	6	Weibull	-12.63060	0.3738487
HS3 to HS5	0	N/A	N/A	N/A
HS4 to HS5	3	Weibull	-17.01315	0.6889046

Table 6: Scenario analysis results (transition-specific distributions)

	Costs		QALYs		ICER
	BSC	VN	BSC	VN	
Corrected base-case	£46,473	[redacted]	3.6	10.7	[redacted]
Scenario: transition-specific distributions; transitions with one event included	£46,435	[redacted]	2.7	10.7	[redacted]
Scenario: transition-specific distributions; transitions with one event excluded	£46,392	[redacted]	2.8	10.7	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VN, voretigene neparvovec.

B8. Priority Question: Please demonstrate the Markov assumption for the multi-state model and send the results of this test.

We were unable to identify formal tests of the Markov assumption in this context, however an informal test is performed as described by Crowther.[1]

[1] https://www.mjcrowther.co.uk/pdf/ViCBiostat_Crowther2018.pdf

In order to test the assumption, interactions were introduced between coefficients (representing transitions) and time spent in the previous health state. For example, coefficients representing transitions from health state 2 (transitions 5, 6, and 7 for movements from health state 2 to health states 3, 4, and 5, respectively) were interacted with time spent in health state 1. Similarly, coefficients representing transitions from health state 3 were interacted with time spent in health state 2, etc.

Wald tests of the interaction terms were then performed to test the hypothesis that the coefficients of the interaction terms were simultaneously equal to zero. The test has a P value of 0.016 for the interactions relating to transitions from health state 2, which rejects the hypothesis that the 3 coefficients are simultaneously equal to zero. The null hypothesis could not be rejected for transitions from health state 3 and 4, though it should be noted that these transitions are informed by fewer events and therefore have less statistical power. Full details and statistical outputs are provided in the accompanying data on file.

As the probability of moving between health states is significantly affected by time in the previous health state, this suggests that the Markov assumption is not supported in the company model.

The decision to implement the natural history data as a multistate Markov model in this manner is driven by two primary factors:

1. **Study design:** The RPE65 NHx study was a retrospective chart review study designed to describe the natural history of retinal degenerative disease in individuals with confirmed biallelic mutations in the RPE65 gene. All patients with confirmed mutations, from seven international centres, were enrolled in this study and their charts were collected, after redaction of protected health information. Longitudinal ocular history and visual function testing data were abstracted from the collected charts and analysed.

   As a consequence of this study design, both the length of follow-up and period between observations differs between subjects. The presence of this kind of censoring creates a challenge for estimating the probability of moving between health states using simple empirical direct methods because some subjects will be observed partially during a given time interval. Furthermore, there is evidence that the rates of change in VA might change over time, and therefore the probability of moving between health states may also vary (1).

   Survival analysis provides a framework for dealing with both issues. The multistate model implemented is essentially a survival analysis with ‘time’ defined as time in the current health state and an ‘event’ being a movement to any alternative health state. Each possible transition (e.g. from health state 1 to 3, 1 to 4, etc.) is represented by a different hazard ratio (all of which are presented as being relative to the reference transition from health state 1 to 2).

2. **Data availability:** The use of a single statistical model was considered to represent an efficient use of the limited available data. Estimating transition-specific models such as those requested in B7 requires the estimation of increasingly large numbers of parameters from a relatively small dataset; the approach adopted, although relying on the Markov assumption, provides a more efficient use of this data.

B9. Priority Question: Please provide additional information regarding the data used to inform the long-term multi-state model, as follows:

- **details regarding the baseline characteristics of patients, including geographical region**
- **study report and any related publications (e.g. conference abstracts and/or presentations) where available**
- **the nature and approximate timing of the 28 transitions observed within the RPE65 NHx study (e.g. between which health states)**
- **details of the Cox-Snell residual plots produced, including the number of transitions incorporated within the plot per patient**
- **if there are a sufficiently large number of transitions for an individual transition(s), provision of per-transition Cox-Snell (or equivalent) residual plots.[2]**

Please see section 11.1 of the RPE65 NHx study report – provided in the submitted reference pack; see file "Spark Therapeutics (2017)" – for details of baseline characteristics including geographical region. Table 10.2 of the same study report provides details of enrolment by site.

The Cox-Snell residuals for viable transitions (i.e. >1 event; transitions 1, 5, 8, and 10) are provided in Figure 5, Figure 6, Figure 7, and Figure 8, respectively. The timing of transitions are provided in Table 7.

Table 7: Timing of transitions

Time (days)	1 HS1 - > HS2	2 HS1 - > HS3	3 HS1 - > HS4	4 HS1 - > HS5	5 HS2 - > HS3	6 HS2 - > HS4	8 HS3 - > HS4	10 HS4 - > HS5
450	0	0	1	0	0	0	0	0
575	1	0	0	0	0	0	0	0
756	1	0	0	0	0	0	0	0
798	1	0	0	0	0	0	0	0
847	0	0	0	0	1	0	0	0
923	1	0	0	0	0	0	0	0
925	1	0	0	0	0	0	0	0
1098	1	0	0	0	0	0	0	0
1582	0	0	0	0	0	0	1	0
1778	0	0	0	0	1	0	0	0
1807	1	0	0	0	0	0	0	0
1904	0	0	0	0	0	1	0	0
2250	0	0	0	0	1	0	0	0

[2] The Cox-Snell residual plot provides information regarding the fit of the MSM. There are a total of 28 transitions noted within the RPE65 NHx study, however the exact nature of these transitions (i.e. from and to specific health states) is currently unclear. Should there be enough transitions of a specific type (e.g. the majority of transitions were from HS1 to HS2), the ERG would like to see a plot showing how well the multi-state model fits the observed transitions of a specific type over time (given that only forward transitions are permitted by the MSM approach adopted). Alternative plots may be preferred by the company to look at specific transitions – Crowther and Lambert used the Nelson-Aalen estimate within their example (Crowther and Lambert, 2016, DOI: 10.1002/sim.7448) for each of the three transitions used in their model (please see Figure 2 in this paper for a presentation of the per-transition plots).

Time (days)	1 HS1 - > HS2	2 HS1 - > HS3	3 HS1 - > HS4	4 HS1 - > HS5	5 HS2 - > HS3	6 HS2 - > HS4	8 HS3 - > HS4	10 HS4 - > HS5
2388	1	0	0	0	0	0	0	0
2428	0	1	0	0	0	0	0	0
2554	0	0	0	0	1	0	0	0
3080	0	0	0	0	0	0	0	1
3356	1	0	0	0	0	0	0	0
3694	0	0	0	0	0	0	1	0
3721	1	0	0	0	0	0	0	0
3805	0	0	0	0	1	0	0	0
3850	0	0	0	0	1	0	0	0
3871	0	0	0	0	0	0	1	0
3982	1	0	0	0	0	0	0	0
4137	0	0	0	0	0	0	0	1
4254	1	0	0	0	0	0	0	0
4410	0	0	0	0	1	0	0	0
4915	0	0	0	0	1	0	0	0
5071	0	0	0	0	1	0	0	0
5216	0	0	0	0	1	0	0	0
5510	0	0	0	0	1	0	0	0
6234	0	0	0	0	0	0	1	0
6332	0	0	0	0	0	0	0	1
7132	0	0	0	0	0	0	1	0
7585	0	0	0	0	0	0	1	0

Figure 5: Cox-Snell residuals – Transition 1 (HS1 -> HS2). 12 events observed.

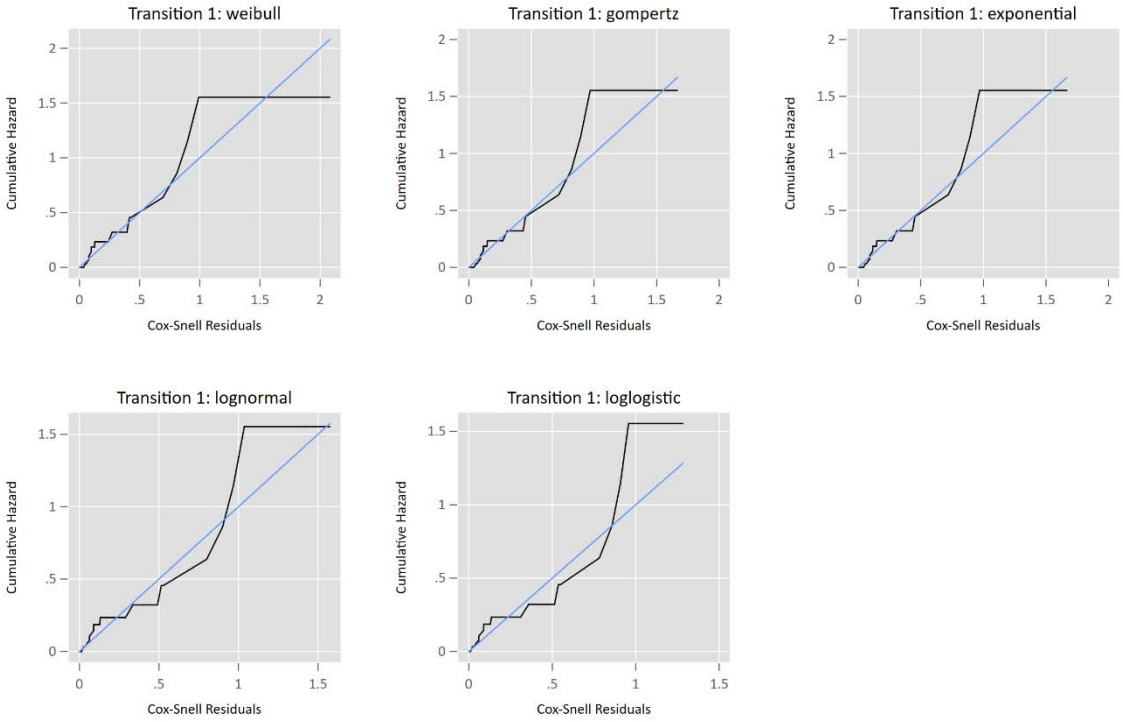


Figure 6: Cox-Snell residuals – Transition 5 (HS2 -> HS3). 11 events observed.

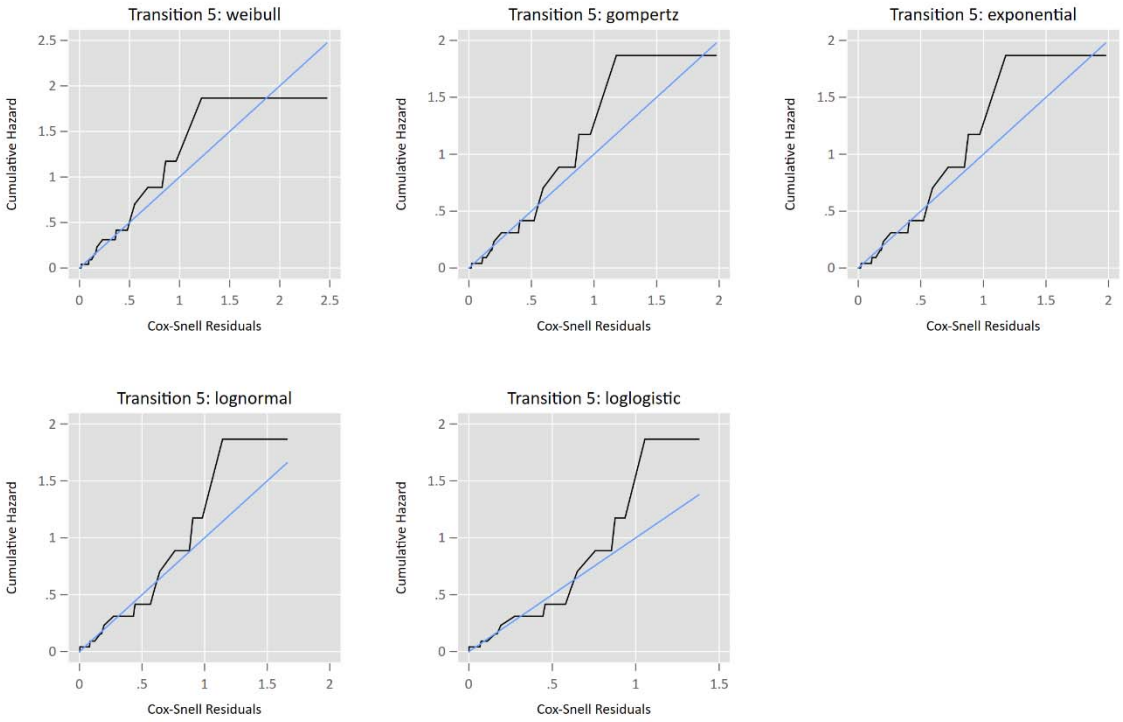


Figure 7: Cox-Snell residuals – Transition 8 (H3 -> HS4). 6 events observed.

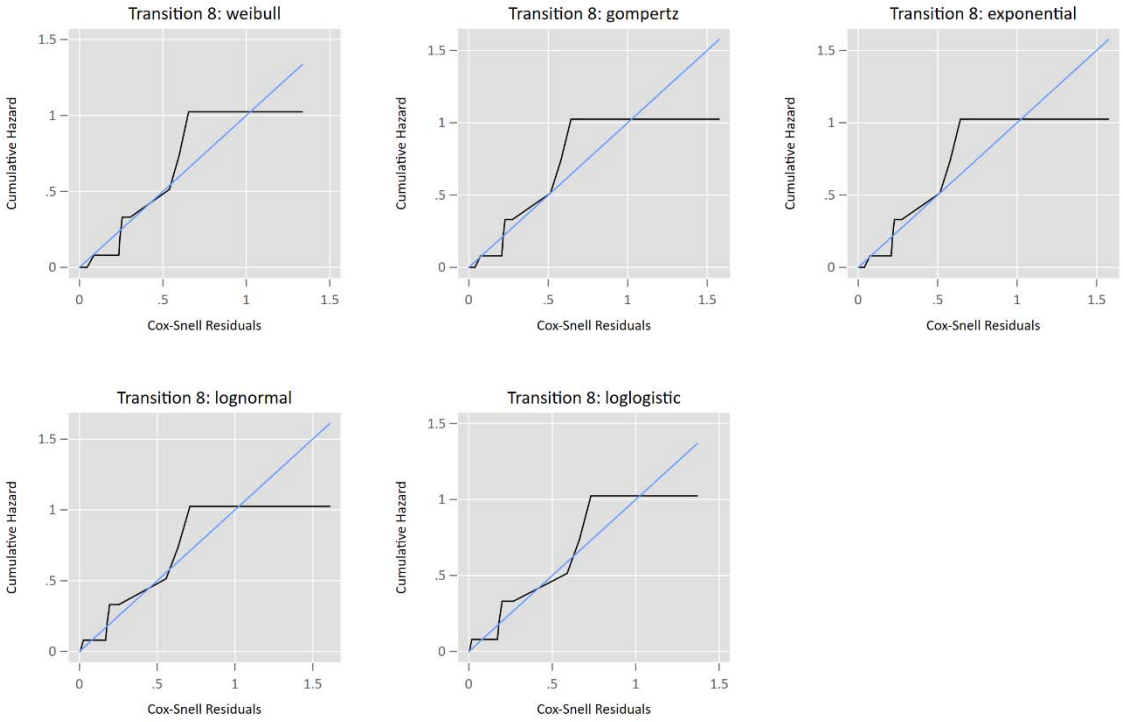
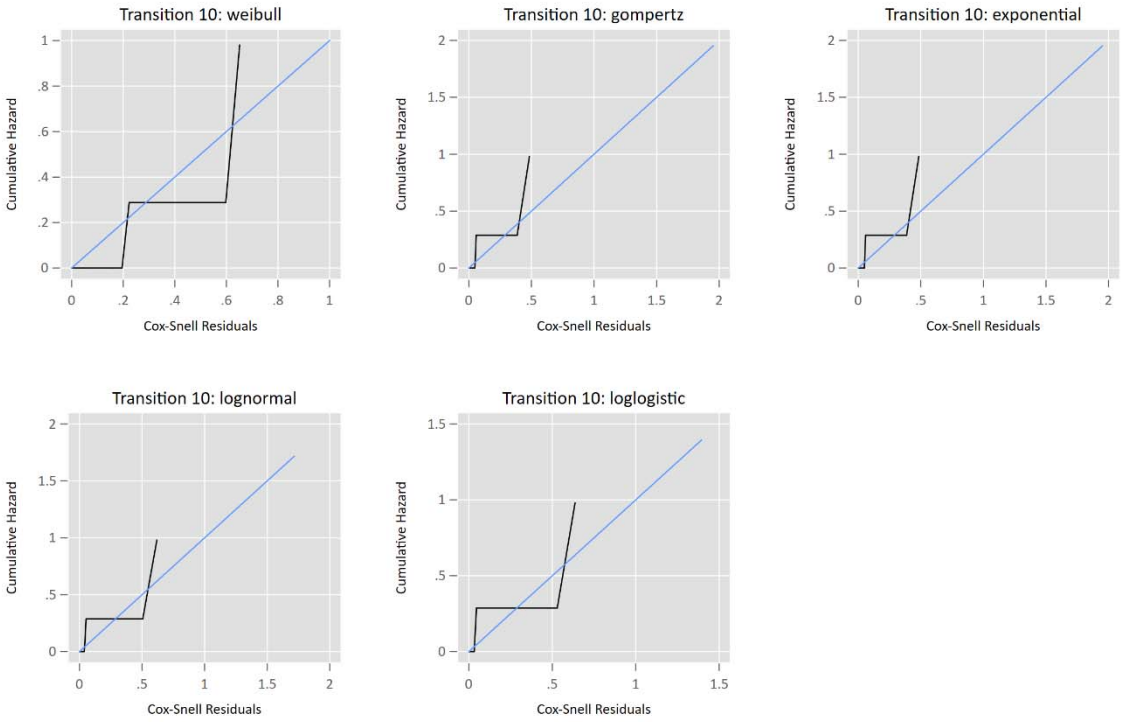


Figure 8: Cox-Snell residuals – Transition 10 (H4 -> HS5). 3 events observed.



B10. Priority Question: Please provide further details regarding the elicitation of clinical expert opinion concerning the anticipated duration of treatment effect and the treatment effect waning period? This should include:

- **the specific question(s) asked, in particular questions concerning the existence of the treatment effect waning period and the assumption of linearity**
- **the verbatim responses given by the clinical experts, ideally in the form of an interview transcript or meeting minutes.**

Novartis spoke to six clinical experts and explored their views on the expected duration of treatment with Luxturna and tested the plausibility of a potential base case of 30 years treatment effect followed by waning. Notes taken at this meeting are attached (file name "Question B10 – clinical expert feedback") to summarise the feedback received. Experts were mindful about the lack of long-term trial data, but generally agreed on the plausibility of a long-term effect, with one view that a lifetime effect may also be expected. The company base-case was developed based on the totality of evidence and feedback received.

B11. Please confirm that 1 patient enrolled within the delayed intervention arm of Study 301/302 resided in health state (HS) 1 at baseline and HS2 at 1 year?

This is correct – one patient in the delayed intervention arm moved from HS1 to HS2 in the first year following administration of VN.

B12. Please provide a summary of BCVA and health state occupancy from the trial data (Study 301/302) for individual patients at baseline, 30 days, and 1 year (as per the model structure). Please use the following tables as a suggested format to present this information.

Unlike in other vision conditions, visual acuity is not considered to be the most relevant outcome in individuals with RPE65-mediated IRD. It is inappropriate to consider VA in isolation on the basis that:

- Defining characteristics of the condition including nyctalopia, reduced light sensitivity and nystagmus cannot be fully captured by measuring VA alone
- Cone cells are not the primary cells affected by RPE65-mediated IRD (a rod-mediated disease), minimising the potential for improvement from baseline
- In individuals with RPE65-mediated IRD, loss of visual field and light sensitivity are the first symptoms, with loss of visual acuity occurring later; exclusion of VF would therefore fail to capture the full course of the disease

The following outcomes have therefore been provided in each of the BSC and VN arms in Table 8 and Table 9, respectively:

- MLMT score
- VA
- VF
- Health state

Table 8: Outcomes in BSC patients

	MLMT			VA			VF			Health state		
	Baseline	**30 days**	**1 year**	**Baseline**	**30 days**	**1 year**	**Baseline**	**30 days**	**1 year**	**Baseline**	**30 days**	**1 year**
Patient 1	3	3	4	0.88	0.83	0.85	1,042	1,015	793	1	1	1
Patient 2	2	2	1	1.27	1.13	1.11	535	421	349	2	2	2
Patient 3	4	4	5	0.91	0.88	0.81	518	399	474	1	1	1
Patient 4	3	2	2	1.50	1.53	1.63	30	84	61	4	3	3

	MLMT			VA			VF			Health state		
	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year
Patient 5	4	3	3	1.01	0.92	0.84	686	145	45	2	2	4
Patient 6	5	5	5	0.51	0.56	0.52	109	116	105	3	3	3
Patient 7	3	3	5	0.69	0.50	0.70	227	438	401	2	1	1
Patient 8	3	3	4	0.88	0.90	0.86	926	915	1,144	1	1	1
Patient 9	3	3	3	1.23	1.15	1.27	201	223	212	2	2	2

Abbreviations: BSC, best supportive care; MLMT, multi-luminance mobility testing; VA, visual acuity; VF, visual field.

Table 9: Outcomes in VN patients

	MLMT			VA			VF			Health state		
	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year
Patient 1	3	6	6	0.99	0.94	0.88	40	326	306	4	1	1
Patient 2	-1	-1	-1	1.87	1.95	2.94	0	NA	0	4	4	4
Patient 3	5	6	6	0.76	0.68	0.65	95	204	860	3	2	1
Patient 4	3	6	6	0.94	0.72	0.43	174	984	994	2	1	1
Patient 5	4	6	6	0.72	0.70	0.57	242	937	1,028	1	1	1
Patient 6	3	6	6	1.17	1.15	0.80	403	448	510	2	2	1
Patient 7	4	6	5	1.08	0.94	0.89	56	417	575	3	1	1
Patient 8	4	6	5	1.00	0.85	0.81	200	134	176	2	3	2
Patient 9	3	6	6	0.94	0.71	0.63	47	606	439	4	1	1
Patient 10	5	6	6	0.80	0.82	0.69	805	889	1,062	1	1	1

	MLMT			VA			VF			Health state		
	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year	Baseline	30 days	1 year
Patient 11	4	6	6	1.06	0.99	0.92	536	759	792	2	1	1
Patient 12	2	4	6	1.23	0.65	0.63	NA	928	1,081	2	1	1
Patient 13	3	6	6	0.85	0.88	0.78	133	440	609	3	1	1
Patient 14	4	6	6	1.19	1.14	0.91	806	926	1,334	2	2	1
Patient 15	5	6	6	0.99	0.82	0.87	1,418	1,463	1,405	1	1	1
Patient 16	3	3	4	2.06	1.54	1.54	88	90	107	4	3	3
Patient 17	3	5	5	1.09	1.20	1.15	114	210	543	3	2	2
Patient 18	2	4	3	1.60	1.38	1.33	245	332	268	3	2	2
Patient 19	2	4	4	1.59	1.34	1.37	50	233	245	3	2	2
Patient 20	5	6	6	0.81	0.84	0.71	1,209	1,155	1,150	1	1	1

Abbreviations: MLMT, multi-luminance mobility testing; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

B13.

a. Please confirm which scale is used to define VA within the cost-effectiveness model (Holladay or Lange)?

The Holladay scale is used to define VA within the cost-effectiveness model. However, it is noted that use of the Lange scale would have resulted in an identical health state distribution, given that:

- These scales only become relevant where VA is recorded as an individual being only able to recognise hand motion
- The Lange and Holladay scales would assign differing numerical scores to this health state, but would not result in an individual being assigned to a different model health state
    - In particular, the 'Hand motion' health state would be assigned a VA score of 3.0 LogMAR using the Holladay scale and 2.3 LogMAR using the Lange scale
    - If the Lange scale had been used, the cutoff for HS5 (hand motion, light perception, no light perception) would have been 2.3 LogMAR, resulting in the same patients belonging to this health state

b. Please confirm whether or not the transition for the 1 patient where baseline VF was missing was based only on VA.

This is correct – in the patient for whom baseline VF was missing, the baseline health state was determined based on VA only.

c. Please provide a scenario where transitions within the model are informed only by VA (as opposed to VA + VF or VF only).

Health states based on VA only are not considered to be appropriate on the basis that VA is not able to capture key characteristics of the condition (see question B12). However, a scenario analysis has been presented for completeness, with this context in mind.

For this scenario analysis, the following model inputs have been updated such that health states are determined only by VA:

- Baseline health state distribution
- In-trial transition probabilities
- Long-term multistate survival model

The results of this scenario analysis are presented in Table 10; the results of the corrected base-case analysis are also presented for reference.

This scenario is associated with a 33% increase in the ICER compared with the corrected base-case;
however, [redacted]

This increase in the ICER is driven by two factors:

- Health state definition based on VA only means that improvements in VF are not captured
    - Not accounting for VF is a serious limitation in the evaluation of both the course of the disease and the benefits associated with VN; we therefore

consider this scenario analysis to be inappropriate for decision making purposes.

- In this scenario, 48% of patients are in HS1 at baseline, compared with 23% in the base-case, creating a 'ceiling effect' in the VN arm

Table 10: Scenario analysis results (health states based only on VA)

	Costs		QALYs		ICER
	BSC	VN	BSC	VN	
Corrected base-case	£46,473	[redacted]	3.6	10.7	[redacted]
Scenario: health states based only on VA	£45,289	[redacted]	5.6	10.9	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VA, visual acuity; VN, voretigene neparvovec.

Health-related quality of life

B14. Please confirm the regions represented by the 6 clinicians interviewed as part of the vignette study. In addition, please provide further clarity regarding the order in which the questions were asked?

Seven clinicians were interviewed during the development of health state vignettes; regions represented by these clinicians are provided in Table 11.

A qualitative interview guide is provided in Appendix A of the attached study report (file name "Question B14 – utility study report") – this guide provides the order in which questions were asked to clinicians.

Table 11: Regions represented at each stage of the utility study

Study stage	Regions represented
HCP concept elicitation interviews	o [redacted]
Cognitive debrief interviews	o [redacted]

Cost and Resource inputs

B15. Please provide evidence for the cost of oral prednisone from the British National Formulary (e.g. a timestamped screen shot of the BNF website, or excerpt from the hard copy from which the cost was taken)?

The cost of oral prednisone was taken from the BNF website; a screenshot of the cost at this time was unfortunately not saved. The BNF has been contacted to confirm whether the removal of this cost from the website represents a website issue or a withdrawal/amendment to this cost.

B16. Please provide an explanation for the methods used to inflate costs using the inflation indices reported by the Personal Social Services Research Unit (PSSRU)? More specifically, please provide a description of the use of hospital and community health service (HCHS) inflation indices which were recently discontinued.

The submission dossier states that costs were inflated using the HCHS pay and prices index as reported by the PSSRU; this represents an error in the reporting of our methods.

The HCHS pay and prices index was originally used to inflate costs to 2016/2017 prices; following the availability of the Unit Costs of Health and Social Care 2018 – and the discontinuation of HCHS inflation indices – the reported percentage increase of 1.4% (New Health Services Index using CPI [Health]) between 2016/17 and 2017/18 was then applied to the previously inflated costs.

Budget impact

B17. Please provide further information regarding the anticipated market uptake for voretigene neparvovec over its first 5 years of availability.

The anticipated market uptake for voretigene neparvovec over its first 5 years of availability is based on assumptions around healthcare system resourcing, including treatment centre capacity, time to set up the treatment centres, time for patients to access genetic testing and counselling services. Given the small prevalent patient pool expected to be eligible for voretigene neparvovec, it is assumed that all prevalent patients will be treated within 5 years.

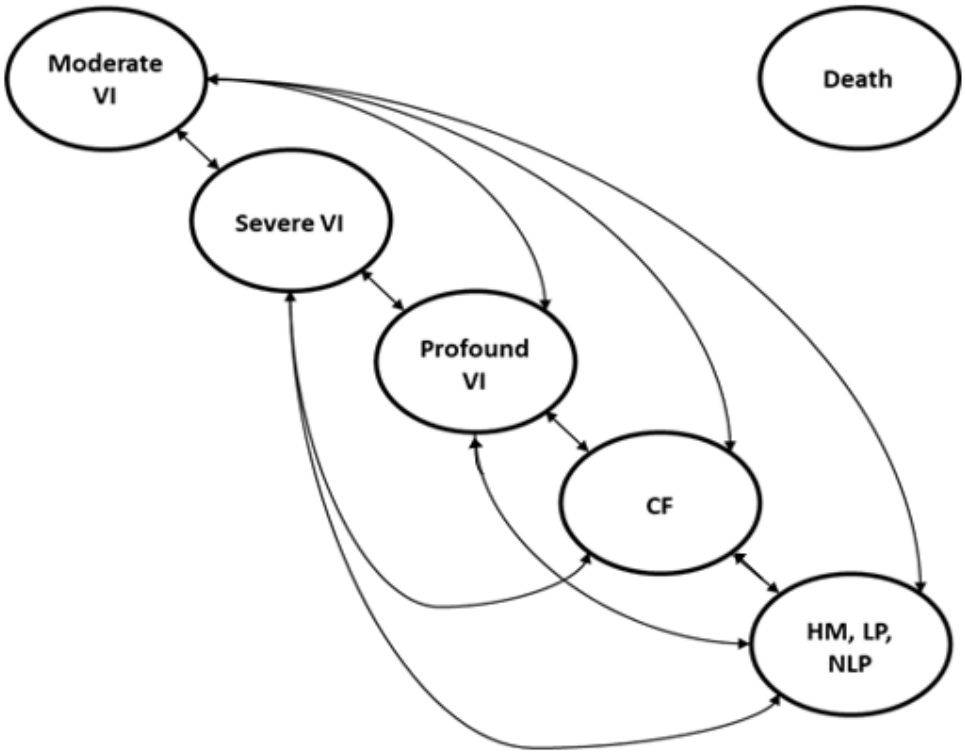
[redacted]

Section C: Textual clarifications and additional points

C1. Please can the company confirm that the diagram of the model schematic (Figure 26, page 163 company submission) contains two minor errors, and that it is actually possible for patients to transition from HS5 to HS4 and from HS5 to HS3 (within Year 1)?

This is correct - it is possible for patients to transition from HS5 to either HS3 or HS4 in Year 1. An updated model schematic is presented in Figure 9.

Figure 9: Updated model schematic



References

1. Shields, R.A., et al., *Postoperative Adverse Events, Interventions, and the Utility of Routine Follow-Up After 23-, 25-, and 27-Gauge Pars Plana Vitrectomy.* Asia-Pacific Journal of Ophthalmology (Philadelphia, Pa.), 2019.
2. Gan, N.Y. and W.-C. Lam, *Special considerations for pediatric vitreoretinal surgery.* Taiwan Journal of Ophthalmology, 2018. **8**(4): p. 237-242.
3. Maguire, A.M., et al., *Safety and efficacy of gene transfer for Leber's congenital amaurosis.* The New England Journal of Medicine, 2008. **358**: p. 2240-2248.
4. Maguire, A.M., et al., *Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial.* The Lancet, 2009. **374**: p. 1597-1605.
5. Russell, S., et al., *Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial.* The Lancet, 2017. **390**: p. 849-860.
6. Chung, D.C.R., Stephen; Bennett, Jean; Maguire, Albert; Wellman, Jennifer; Yu, Zi-Fan; Tillman, Amy; High, Katherine, *Correlation of Multi-luminance Mobility Testing With Visual Function Tests in a Phase 3 Trial of Voretigene Neparvovec for Biallelic RPE65-mediated Inherited Retinal Disease*. 2017.

Appendix A: RPE65 NHx statistical analysis

During the process of responding to clarification questions from the ERG for NICE, it was identified that the company was unable to recreate the results of the statistical analysis of the RPE65 NHx data.

Further investigations were performed, and it was discovered that the variation was caused by differences in a constructed dataset between execution of the code. This dataset was constructed of demographic, visual acuity, and visual field datasets, which must be combined to identify which health state an individual is in (because health states represent combinations of visual field and visual acuity). The issue was determined to be caused by erroneous merging of these data. Essentially this merge procedure (Stata's merge m:m command) introduced variability because it relied on the order in which the data are sorted; this should never be the case when merging datasets. The use of this merge procedure 1) discarded some valid observations and 2) led to an element of random variability because random sorting appeared to be occurring during the merge procedure.

In addition to this, during further code review other modifications were identified which may improve the statistical analysis. This included re-implementing imputation based on last observation carried forward (LOCF) of '0' scores for VA and VF; manual review of the data suggested that these 0's were erroneous rather true 0's.

The consequence of correcting this merge command is that additional observations are included in the analysis. Overall, the revised analysis suggests a slightly shorter time to progression towards poorer health states.

In the base-case the number of observed transitions increased to 35. Revised statistical models are presented in Table 13 and diagnostic information presented in Table 12 and Figure 10.

Table 12: Revised model diagnostic data

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	283	-99.84588	-72.1818	11	166.3636	206.4635
Gompertz	283	-101.4888	-73.83043	11	169.6609	209.7608
Exponential	283	-106.9358	-80.46559	10	180.9312	217.3856
Log-normal	283	-100.4937	-73.96959	11	169.9392	210.0391
Log-logistic	283	-99.94929	-72.31193	11	166.6239	206.7238

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information criterion; df, degrees of freedom; ll, log-likelihood; Obs, observations.

Table 13: Revised statistical models (average eye)†

	Weibull	Gompertz	Exponential	Log-logistic	Log-normal
HS1 to HS3	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.407** (0.531)	1.418** (0.487)
HS1 to HS4	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.392** (0.532)	1.086** (0.420)

HS1 to HS5	-18.30 (2711.3)	-17.25 (1609.5)	-17.31 (1655.3)	8.476 (1003.5)	5.385 (476.2)
HS2 to HS3	-0.601 (0.420)	-0.513 (0.419)	-0.342 (0.417)	0.514* (0.261)	0.528 (0.285)
HS2 to HS4	-2.999** (1.042)	-2.910** (1.042)	-2.740** (1.041)	1.689** (0.524)	1.636*** (0.451)
HS2 to HS5	-18.32 (2122.2)	-17.28 (1319.0)	-17.31 (1457.1)	8.559 (821.1)	5.438 (419.7)
HS3 to HS4	-1.372** (0.517)	-1.404** (0.535)	-0.805 (0.500)	0.936** (0.304)	0.959** (0.336)
HS3 to HS5	-18.36 (1990.8)	-17.37 (1194.3)	-17.31 (1565.6)	8.769 (888.2)	5.749 (496.0)
HS4 to HS5	-1.553* (0.658)	-1.555* (0.666)	-1.008 (0.646)	1.003** (0.377)	1.075* (0.419)
Constant	-14.95*** (1.859)	-9.211*** (0.355)	-8.588*** (0.289)	7.986*** (0.190)	8.018*** (0.203)
ln (p)	0.586*** (0.125)				
gamma		0.000316*** (0.0000825)			
ln (gamma)				-0.785*** (0.132)	
ln (sigma)					-0.143 (0.120)
N	283	283	283	283	283

† Standard errors in parentheses.
* p < 0.05, ** p < 0.01, *** p < 0.001
Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

Figure 10: Revised Cox-Snell residuals (average eye)

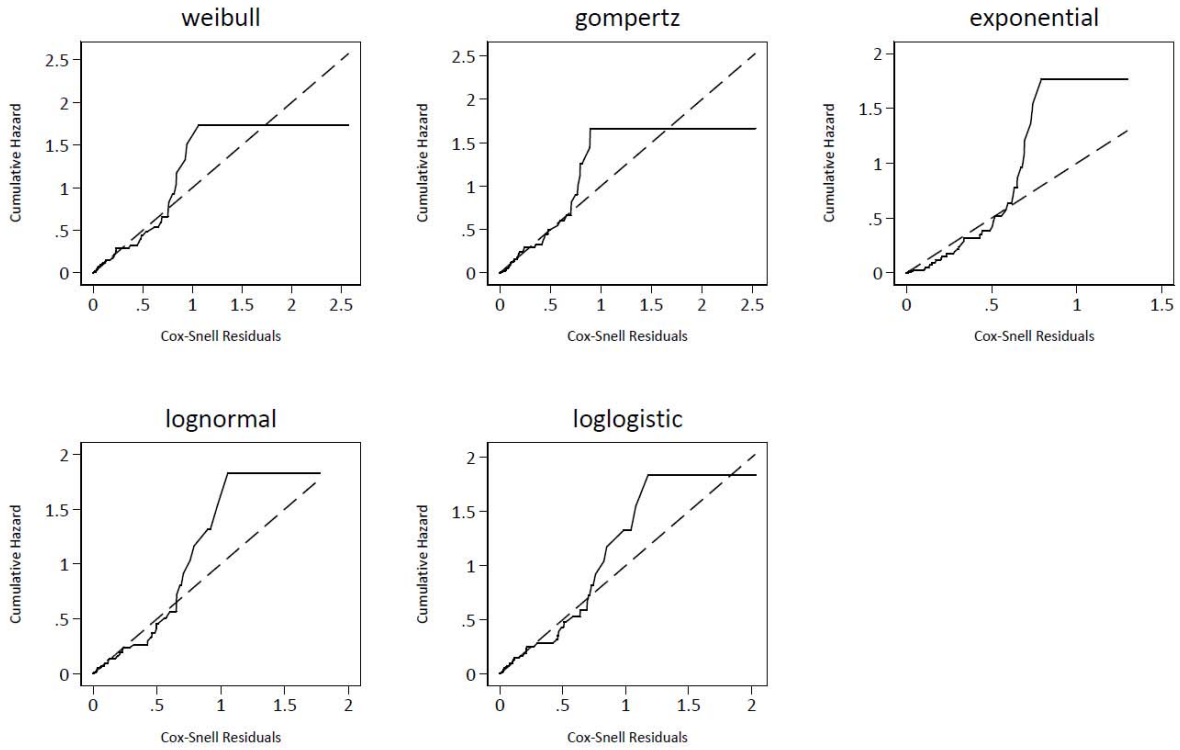
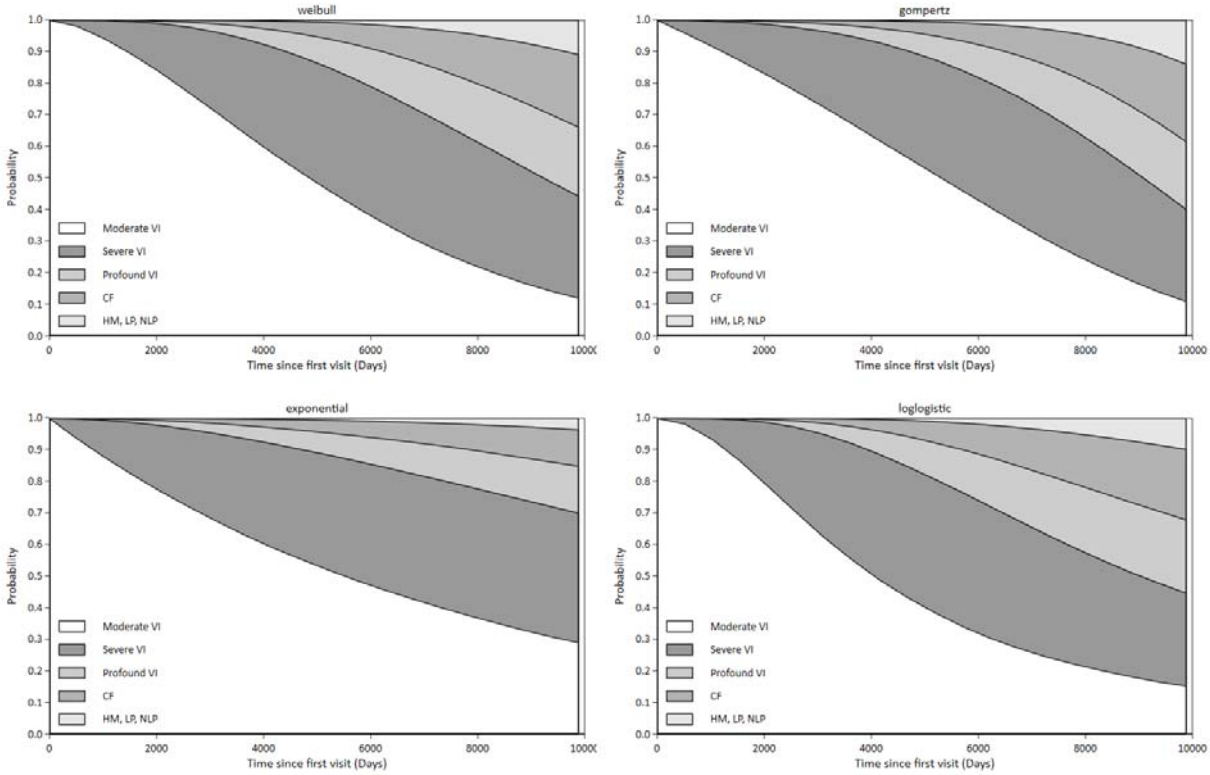


Figure 11: Revised distribution across health states over time (patients starting in HS 1)



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Highly Specialised Technologies Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Dear [Insert name],

The Evidence Review Group, PenTAG, and the technical team at NICE have looked at the submission received on 12 February 2019 by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **5pm** on **20 March 2019**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Safety study information

A20. Priority Question: What is the length of follow-up of VF and VA in Study 101/102? Please provide plots depicting mean VF and VA with respect to time (similar to Figure 15; page 108 company submission).

[redacted]

Plots of VA and VF over time in these studies are provided in Figures 1- 8 below. Given the low patient numbers, missing observations were imputed using last observation carried forward.

[redacted]

Results from the Phase 3 trial are presented in Question A10; these plots are expected to better represent the change in VA and VF (and response over time) given:

1. **A larger sample size**

   - Studies 101 and 102 were not powered to assess efficacy, as only 12 patients received treatment in Study 101 (of these only three received the licensed dose), and 11 of these received treatment in Study 102
   - This is reflected in the wide error bars around point estimates in the plots above.

2. **Administration of the licensed dose only**

   - Only three out of twelve participants received the licensed dose (used in the Phase 3 trial) in the eye injected in Study 101. Three participants received a ten-fold lower dose, and six participants received an approximately three-fold lower dose (see Table 1).

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Table 1: Dose groups in Study 101

Group	n	Dose administered (vg)	Dose relative to licensed dose (%)
Low dose	3	1.5×10^{10}	10
Medium dose	6	4.8×10^{10}	32
High dose	3	1.5×10^{11} vg	100

3. **Administration in the licensed population only (i.e. those with sufficient viable retinal cells)**

- The Phase 1 eligibility criteria permitted enrolment of patients with poorer baseline vision and retinal function than the Phase 3 trial.
  - [redacted]
    In Study 101, patients were ineligible if they had less than one disc area of retina that was not completely degenerated. Eligibility criteria in Study 301 were stricter, with patients needing to meet one or more of the following criteria:
    - an area of retina within the posterior pole of > 100 µm thickness shown on OCT; or
    - ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or
    - remaining visual field within 30º of fixation as measured III4e isopter or equivalent.

As described in the response to Question B12, visual acuity is not the most relevant outcome for patients with RPE65-mediated IRD. The disease primarily affects rod photoreceptors while cones are only affected on a later stage, preserving the central vision. Traditional visual function endpoints like VA and VF do not fully capture characteristic features of the condition such as night blindness (nyctalopia), reduced light sensitivity and nystagmus, and should not be interpreted in isolation. Doing so may result in underestimation of the effect of treatment.

In the context of these condition-specific features and the need for a clinically meaningful endpoint, the MLMT instrument was designed, with input from the FDA, and formed the primary endpoint of the Phase 3 trial. The MLMT integrates aspects of light sensitivity, VF and VA, and measures functional vision in a quantitative and standardised manner at specified light levels.

Although MLMT data are not available for the Phase 1 trial, an analysis of correlation between trial endpoints found that the linear relationships between MLMT and FST were generally good to strong, indicating that subjects with better performances on the MLMT tended to have lower (i.e., better) FST changes [1]. The duration of treatment effect used in the model is informed by the Phase 3 results and the Phase 1 FST results (see section 12.2.1 in the company submission).

References

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1. Chung DC, Russell SR, Bennett J, et al. 2017; https://iovs.arvojournals.org/article.aspx?articleid=2638049&resultClick=1. Accessed 20 March 2019.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Fight for Sight
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight for Sight is the UK's largest eye research funding charity dedicated to helping patients with eye disease. Fight for Sight receives no government funding and relies on donations from the public as well as corporate support to fund its work.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke to patients living with the condition about their experiences. We also consulted with clinical experts supporting patients with this condition as well.
Living with the condition	
6. What is it like to live with the condition? What do carers	The retinal pigment epithelium-specific 65 kDa protein is an isomerase encoded by the *RPE65* gene and is crucial for an enzymatic step to allow the functioning of the visual cycle. Mutations in the *RPE65* gene

experience when caring for someone with the condition?	have been shown to cause a subtype of leber congenital amaurosis (LCA), an early onset progressively degenerative retinal dystrophy that often leads to severe vision loss. One patient that we spoke to with the condition was registered as partially sighted at age 10 and was registered blind at age 17.Patients we spoke to report a feeling of extreme anxiety and worry when they started to notice changes within their vision, which can lead to depression and other mental health issues. People living with the condition have stated the condition robs them of opportunities in education, the labour market, and in day to day life that others with normal vision take for granted such as; socialising at night or driving. The condition often has a profound effect on parents, carers and loved ones. One patient spoke of the effect her diagnosis had on her parents, who had no idea that there was a history of this condition within their family. Even with the assistance of a guide dog, patients reported relying hugely on partners and other family members for assistance. One patient who has lost all functioning sight over the course of her life stated that she relied heavily on her husband with tasks such as cooking, or even knowing when lights are on or off in their home.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	n/a - there are no treatments available for this condition on the NHS.
8. Is there an unmet need for patients with this condition?	There is a huge unmet need for people living with RPE65. There are currently no treatments for people with this condition available on the NHS.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients that we spoke to did not feel that they knew enough about the genevtherapy technology to be able to comment on its advantages and disadvantages. However, they believe that this therapy and others in the future offer hope for people living with inherited retinal dystrophies tempered by the pragmatism that these are not “silver bullets” and will not “cure” their condition but could allow patients with this condition to have “functional” sight that could improve their quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	n/a
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with advanced disease where there has been loss of all photoreceptors, will not benefit from this gene therapy approach, as there needs to be viable photoreceptors for the therapy to be effective. However, with improvements in diagnosis patients could be diagnosed at an early age, allowing them to be good candidates for this therapy.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	n/a
Other issues	
13. Are there any other issues that you would like the committee to consider?	n/a
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is huge unmet need for therapies for this condition
- Inherited retinal dystrophies can have a profound effect on the lives of those living with the condition, as well as on parents, carers and loved ones
- Improving ability to navigate in the dark will be of huge benefit to patients living with RPE65
-

•

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Retina UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Retina UK was founded in 1976. We are the only UK charity dedicated solely to working for people affected by inherited sight loss. These conditions are the most common cause of visual impairment in the working age population and also cause around 30% of childhood sight loss. In 2018 we were in touch with 6,069 people affected by inherited sight loss, including those living with the conditions and their families. Our vision is a world where everyone with inherited sight loss is able to live a fulfilling life. By stimulating and funding medical research, we increase the understanding of these conditions and accelerate the search for treatments for the future. The information and support we provide helps people lead better lives, today. We ensure no-one with inherited sight loss need feel alone. We receive no statutory donations and rely entirely on the generosity of our fundraisers and partners to fund our vital work. Pharmaceutical / biotechnology company partnerships are as follows: **Income from pharmaceutical companies and biotech companies in last 12 months (01/05/2018 to 30/04/2019)** Meira GTX - £25,000 – contribution to economics & impact study Nightstar Therapeutics - £1,500 – event sponsorship Novartis - £25,000 – contribution to economics & impact study Piramal Group - £200 – unsolicited donation Second Sight - £498 – event sponsorship

	Income pledged Roche - £25,000 – contribution to economics and impact study PROQR Therapeutics - £25,000 – contribution to economics & impact study (subject to agreement being signed) PROQR Therapeutics - £2,000 – event sponsorship (subject to agreement being signed) Novartis - £5,000 – event sponsorship (subject to agreement being signed) Roche - £5,000 – event sponsorship (subject to agreement being signed) Novartis – £2,300 – honorarium payment for focus group recruitment
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Throughout April 2019 we conducted a large organisational survey, sent out to approximately 6,000 of our own contacts (people affected by inherited sight loss) and publicised more widely via social media and sector partners. We have used 916 completed surveys to inform our input to this submission about the experiences of patients and carers. Staff members and volunteers, particularly our Services team and Helpline volunteers, also engage in regular face to face, telephone and email conversations with the inherited sight loss community. This submission also draws on their feedback. Our input here reflects the experiences of those living with many types of inherited sight loss and we have been unable to restrict our information-gathering to those with the specific RPE65 genotype targeted by voretigene neparvovec, particularly as a large proportion of our community do not know their genetic diagnosis. However, 73.51% of survey respondents had a diagnosis of retinitis pigmentosa; 1.05% had a diagnosis of Leber's congenital amaurosis (LCA). Both of these conditions can be associated with faults in

	RPE65. We believe that the experiences described in this submission will reflect those of people affected by RPE65 mutations.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Retinitis pigmentosa and LCA cause progressive visual impairment, leading eventually to total sight loss. People with biallelic RPE65 mutations usually experience early onset, aggressive disease. Over half of survey respondents said that their sight loss condition had a severe or very severe impact on their overall quality of life. A further 36% said that there was a moderate impact on their quality of life. Respondents told us that their condition had a significant impact on their mental health. Almost three quarters said that they had experienced anxiety as a result of their sight loss; 62% had experienced stress; 41% had experienced depression; 33% had experienced loneliness. Overall, 92% described some sort of impact of their condition on their mental health. From our conversations with families affected by retinitis pigmentosa and LCA, we know that the progressive nature of the conditions leads to a continual series of losses, with associated grief, and that the need to continually adapt to increasing disability is highly stressful. Parents caring for affected children often fear for their child's future and many experience guilt due to the inherited nature of the condition. They face stress from managing the financial impact of reducing or giving up work to care for their child alongside additional expenses such as adaptive aids and travel to specialist appointments. Ninety seven per cent of survey respondents said that their sight loss affected their mobility, with 64% saying that this effect was significant or extreme. Ninety five percent told us that their condition impacted on their leisure time and hobbies, an effect that was significant or extreme in over half of respondents. Over three quarters felt that their career / job was affected, with this being significant or extreme in 46%, while over half of respondents told us that their condition had impacted on their education. A majority of respondents also said that their sight loss condition affected their social life, day-to-day routines, relationships and family life, and the likelihood of falls or accidents. Quotes from survey respondents: **"There's no cure for what I have. I'm just trying to adjust. I'm 21. Can't drive. Can't see in low light**

	or night, faces turn to shadows. Applied for supplemental benefits – still working on that, got denied the first time. This sucks, I don't want to go blind. It's very scary." **"I would like support and feel very lost, like I'm falling through the cracks."** **"Access to work: unfortunately the service does not work very well. This service has caused me too much stress and anxiety therefore I am no longer using it, even though I do need it."** **"I want to know what research is being done to find a cure. When I was diagnosed I was told to go away and enjoy what was left of my sight… basically just go and live with it. I live in hope that I will be cured."**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is currently no treatment available that can impact on either the progression or outcome of the condition. Many patients stop going to routine ophthalmology appointments because they see them as pointless. Thirty seven per cent of respondents to our survey did not have an ophthalmologist involved in their care. However, of those that did, over three quarters said that they were very or quite satisfied with the care they received from their ophthalmologist. NHS care currently consists of check-ups to assess the rate and degree of vision loss, signposting to support services such as mobility training and counselling, and genetics services. However, access to genetic counselling and testing is currently something of a postcode lottery. Over half of our survey respondents had not accessed genetic testing, with 34% not being aware of the service and a further 12% being under the impression that it was not available to them. **"I have had very little support from the NHS in my area, therefore I have had to turn to private healthcare."** **"I have seen a different doctor every single time I've had an appointment with ophthalmology. Feels like there is no continuity of care."** **"I tend to think now at my age there is nothing that can be done so I just try and get on with life. At**

	my request, my GP was able to refer me to Moorfields as I was so dissatisfied with (current ophthalmologist). I am glad I was able to go, as they were interested in me and didn't make me feel I was wasting their time."
8. Is there an unmet need for patients with this condition?	Yes. There is currently no treatment that slows or stops the progression of sight loss. A 2013 James Lind Priority Setting Partnership on inherited retinal dystrophies identified the highest priority research question as: **Can a treatment to slow down progression or reverse sight loss in inherited retinal diseases be developed?** Voretigene neparvovec is the first and only treatment for inherited sight loss to address the underlying cause and impact on disease progression. The need for treatments is urgent, particularly for those such as voretigene neparvovec that confer greater benefits with earlier administration. In aggressive, early-onset cases such as those associated with bi-allelic RPE65 mutations, successful treatment has the potential to have a huge influence at a critical stage of childhood development and learning.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have not had access to the patient population who received voretigene neparvovec during clinical trials. Our input here is therefore conjecture based on our understanding of the RP and LCA community. The key advantage of voretigene neparvovec over anything else currently available is that it can positively impact on the course and outcome of the condition; there is potential to arrest progression and retain the current level of vision, or even improve vision. Based on the evidence in section 6 above, this would have significant benefits in terms of quality of life, and responds to the top priority research question established by the Priority Setting Partnership. Voretigene neparvovec is designed for administration early in the course of the condition and is applicable to those experiencing childhood onset sight loss, where effective treatment could provide lifetime benefit in terms of education, employment and quality of life. One-time application would also be seen as an advantage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Potential disadvantages include surgical application and associated risks, and possible side effects including retinal damage and vision loss – some patients may prefer not to risk their remaining vision early in the disease course. Efficacy is variable. The treatment is only applicable to those with a specific genotype, and therefore not appropriate for the majority of the inherited sight loss community. Access to genetic testing to confirm genotype is not consistent across the country.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment will only benefit those with biallelic RPE65 mutations who still have sufficient viable retinal cells. This is a small proportion of the inherited sight loss community. Those with any other genotype or those with RPE65 whose retinal degeneration has progressed too far will not benefit. However, there are a number of other gene-specific therapies at various stages of the development pipeline, with the potential to treat a more significant proportion of the community and reduce the burden of lifetime disability. It is vital that the research community and biotech / pharma industry maintain momentum, and in this sense voretigene neparvovec is a trailblazer.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The treatment is only suitable to those with a specific genotype. Access to genetic testing is not consistent across the country, so those in areas where testing is not readily available will be unable to benefit from the treatment. Our survey results also suggest that a significant proportion of the inherited sight loss community are not aware of the availability of genetic testing or do not have an understanding of what it is and so will not be in a position to find out if they are eligible for treatment.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Severe early-onset sight loss and subsequent lifelong disability has far-reaching consequences in terms of economic and social burden. Treatments that arrest the progression of disability have the potential to alleviate this. It is vital that we make progress towards the availability of these treatments for a significant proportion of the inherited sight loss community. Voretigene neparvovec is a step change treatment – the first to use gene therapy and the first to address the underlying genetic pathology in RP and LCA in order to stop disease progression and even improve vision, thus preventing further disability.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Retinitis pigmentosa and Leber's congenital amaurosis have a huge impact on patients, their unpaid carers and entire families in every aspect of life, exacerbated by their progressive nature. • A treatment that slows, stops or reverses sight loss is the number one priority for the inherited sight loss community. • There is currently no available treatment that can impact on the progression of inherited sight loss conditions; voretigene	

neparvovec represents a significant step change that addresses an unmet need and could alleviate the burden of progressive disability.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

(I have not had time to canvas opinion from other colleagues for this, sorry, and so these views are my own).

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Royal College of Ophthalmologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? AW, Yes, honorary consultant in genetics and medical retina at Moorfields Eye Hospital. I see many patients and families with this class of disorder. I have filled this form
- RL, Yes, honorary consultant retinal surgeon at Oxford University Hospitals NHSFT
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix D - professional organisation statement template

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Highly Specialised Technology Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

I have looked at the number of families on the Moorfields database and there are 39. This does not include a handful recently diagnosed through the genomics England study.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is no present treatment. Patients and families are usually seen in a few specialist centres. The number above from Moorfields, might nearly include the whole cohort from England as the site has been the centre of trials leading to the referral of many.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Yes. There is a dominant allele giving rise to a very different phenotype. Secondly there are hypomorphic alleles giving a later less severe recessive phenotype. See https://www.ncbi.nlm.nih.gov/pubmed/?term=RPE65+hull for information on both of these. Otherwise I do not see an age-limit here, as even older patients have some retained retinal structure that suggests feasible benefit. However, all patients with the condition might benefit to some extent.

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

No. There are a handful of surgeons already adept at this type of surgery, that is delvivery of AAV to the subretinal space at Moorfields and Oxford. The surgery is not significantly different to present clinical vitrectomies. The impact will be limited as the number of patients affected is small and the treatment is relatively quick and only given once.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Yes see above. However, the technology is not widely available.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Not sure what this is asking. The surgery is standard and within the capabilities of specialist units. The treatment is already endorsed by FDA and the equivalent European agency. There are no clinical guidelines at present in the UK, but the treatment works and is approved by the FDA and the EMA. Patients have received approved treatments reimbursed by the relevant agencies in both the US and the EU.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

There is no alternative treatment for this disorder. The diagnosis and monitoring uses technology that is standard in specialist clinics (imaging, psychophysics, and electrophysiology).

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

This is meant to be a one-off treatment, being gene-replacement in a stationary cellular epithelium (retinal pigment epithelium) and so far efficacy continues for as long as follow-up has been possible, it seems from the literature. It is a single treatment given to each eye in an operation that takes about one hour. We do not yet have long term efficacy data, but a treatment effect has been seen so far as long as patients in the early trials have been monitored, which is up to 7 years so far. There are significant risks beyond what might be predicted from a standard eye operation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The treatment given in https://www.ncbi.nlm.nih.gov/pubmed/28712537 is feasible in specialist units, as is follow-up..The most important outcome is gain of navigation in which will likely have a significant effect on the independence of affected patients. We hope to that the inevitable slow deterioration will be prevented by the treatment. Yes, the treatment works. The treatment is approved by the FDA and EMA and these agencies do not approve new medicines without good evidence. There are many publications showing the benefits of RPE65 gene therapy using the vector developed by Spark Therapeutics.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side-effects reported in the various trials seemed very limited, to my reading and would not be a barrier to adoption of the treatment. A short course of steroids is needed which may cause transient side effects in the post-operative weeks. There are adverse reactions (red eye, transient blurred vision, etc.) but no more than would be expected or a similar eye operation.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Yes, over 200 publications with supportive evidence can be found here: https://www.ncbi.nlm.nih.gov/pubmed/?term=rpe65+gene+therapy

The results of the pivotal Phase III trial which involved 31 patients can be found here: https://www.ncbi.nlm.nih.gov/pubmed/28712537

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment was licensed; November 2018
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no specific guidelines, but patents undergoing this treatment would need to be managed in combination by ophthalmic medical geneticists and vitreoretinal surgeons within a medical genetics service. Genetic networks are in place across England. Patients with known molecular diagnoses who could benefit from treatment can be identified.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Currently there are no specific genetic treatments available in England. Management for affected patients is supportive and involves ensuring good liaison between clinical and educational care together with low vision aids as appropriate for children. For affected adults treatment is also supportive between clinical care, employers and social services. Low visual aids are provided for adults. Genetic counselling is provided via medical genetic services to affected families. In the United States Voretigene Neparvovec gained FDA approval in December 2017.
8. What impact would the technology have on the current pathway of care?	This treatment would provide the first treatment option for patients with the aim of stabilising vision and preventing further visual loss. The impact would be to improve mobility and independence for those patients very poor vision. In addition is treatment is given earlier in the course of the disease there is the potential to preserve central vision.
The use of the technology	
9. To what extent and in which population(s) is the technology	Not currently being used

being used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently being used
• How does healthcare resource use differ between the technology and current care?	NA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	NHS England currently directly commissions specialised ophthalmology services including the treatment of ocular genetic disorders. These are best managed by specialist networks which provide multidisciplinary services including diagnosis, testing, counselling and imaging as well as treatment. It is anticipated that the treatment would be used in this clinical setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This treatment can be implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services.
• If there are any rules (informal or formal) for	Not available for the UK as this is a new treatment

starting and stopping treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	n/a
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patient selection based on a molecular diagnosis for this treatment will need to be considered by clinicians with expertise in this area to enable patients who benefit from treatment to be identified and informed consent for treatment to be gained from patients.
12b. Consider whether these issues are different from issues with current care and why.	NA

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Robert MacLaren
2. Name of organisation	University of Oxford

3. Job title or position	Professor of Ophthalmology
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve vision and prevent blindness. The evidence shows improved mobility in low light levels.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	See above – improved vision, both in terms of visual acuity and low light sensitivity. The drug is a gene therapy treatment and we know that these also preserve vision by slowing down retinal degeneration over the longer term. The early preclinical studies showed preserved vision in RPE65 deficient dogs in up to 10 years after treatment, which represents their lifespan. The post-mortem examination confirmed retinal preservation anatomically at death.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, this an untreatable cause of blindness in children and gene therapy with Luxturna is approved in the USA (FDA) and throughout the EU (EMA).
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is currently no treatment and hence no guidelines exist.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No – all clinicians and allied health professionals managing patients with RPE65 mutations would agree that this is the only treatment.
• What impact would the technology have on the current pathway of care?	There are not that many patients affected – probably about 30-50 in the UK in total.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently in use.

• How does healthcare resource use differ between the technology and current care?	There is no use of the technology (gene therapy) in any eye department in the UK.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist tertiary care only.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training is required, but the equipment is already routinely used for other procedures.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, I expect it to help patients who would otherwise go blind.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	RPE65 is a recessive disease and patient groups in whom marriage between cousins is part of their culture will be disproportionately affected. Hence the disease is likely to impact on certain minority religious groups more than others.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The surgery is slightly more complicated but training can overcome this.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology is a one-off treatment, with both eyes being treated together within a short period of time.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I do not know.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, it may also lead the way for gene therapy treatments for other more complicated causes of genetic blindness.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, it is a conceptually whole new change.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, blindness caused by genetic disease, which is now the commonest cause of untreatable blindness in young people.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no significant side effects.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved vision – YES, in Phase III Increased duration of vision improvement – YES, in Phase I and II
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, mobility testing in dim light confirms that the genetic correction has been successful.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known
20. Are you aware of any relevant evidence that might	No, but this is a rare disease and there is not much data in terms of prospective randomised clinical trials. The pivotal Phase III (Russell et al., 2017) was published in the Lancet; 390(10097): 849-60

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	The data show comparable results in different centres using the same vector.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	See above comment 13 in relation to minority groups in whom marriage between cousins is accepted as normal.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Are there any people within the marketing authorisation for whom you would not consider	Yes, those who are completely blind with no light perception and no sign of residual photoreceptors seen on retinal scans.

offering voretigene neparvovec?	
24. How long do you expect the treatment effect of voretigene neparvovec to be maintained?	Many years – at least 10 years and probably decades thereafter.
25. How does the progressive nature of the condition affect: a) management of the condition? b) patients' quality of life?	Patients go blind, but they keep their other faculties.
26. The company consider nyctalopia (night blindness) a defining characteristic of the condition. How does nyctalopia affect patients, families and carers?	Difficulty seeing in the dark. It is a hallmark of RPE65 disease in the early stages and a careful history can help identify patients before there are any obvious signs of degeneration.

27. Multi-luminance mobility testing (MLMT) is used by the company as an assessment of functional vision in the clinical trials. What are the benefits and limitations of using this end point compared to traditional outcomes such as visual acuity or visual field?	It is a reliable endpoint that was approved by the FDA. Visual acuity showed an improved trend as a secondary outcome. Visual fields are too variable in this population group.

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- The treatment improves vision, but the real reason to give it is to preserve vision
- Treatment centres will need to have a good genetics department to confirm the RPE65 mutation
- Administering the treatment does not require any specialised equipment and the operation takes about 1-2 hours
- There are probably only about 30-50 patients in the UK who would be suitable
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Robert Johnson**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Fight for Sight
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: Participation in clinical trial for similar technology. ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I was born in October 1983 with an inherited retinal dystrophy which we now know to be Leber's Congenital Amaurosis (LCA). In my infancy my visual impairment presented as a tendency to gravitate towards well lit objects and away from those in the shade, and, as I became more mobile, to walk into doorframes and walls rather than through or past them. My mother, who has thankfully always been on-the-ball, apparently took to hanging toys from lampshades in order to attract my attention. She was also quick to highlight to our GP, and subsequently to the local hospital's Paediatric Consultant my strange behaviour in dimly lit surroundings, however the latter maintained that "many children are just clumsy" and eventually passed the case down to his Registrar, before my mother demanded a referral to Moorfields Eye Hospital. My diagnosis, initially Cone Rod Dystrophy, came in August 1986 at the age of three and a half. Despite their suspicions my parents recall feeling devastated at the news, no doubt fearing that I would not

	achieve in life the ambitions that non-disabled children take for granted. My mother has admitted that, had she not already been pregnant with my sister she would not have sought to have another child, incase they too were disabled. Whilst registered as Partially Sighted ("Sight Impaired" under the present system) support and advice for my parents, neither of whom had any prior experience of visually impaired people, was not forthcoming. They fought for me to attend the local village Primary School with appropriate learning support assistance, feeling that an intergrated environment would provide me with a more balanced education, and I was generally encouraged to learn and play as other children did. It was only when, in around 1993, that participation in a consultation for a new local organisation for visually impaired children, resulted in my parents accessing information on the support available, which at least enabled them to begin planning for my transition to Secondary School.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life.	Whilst originally diagnosed with Cone Rod Dystrophy my diagnosis has been confirmed more latterly as Leber's Congenital Amaurosis (LCA). In practical terms I cannot see at all in dark or dimly lit spaces, have poor acuity, contrast and colour vision, and also significant visual field loss. I rely on adaptive software to access electronic information, and use a guide dog for my everyday mobility needs. Today, I live independently, and work in London as a Civil Servant, as Head of Bus and Taxi Accessibility at the Department for Transport. However, reaching this point has been an arduous road for my family and I, and uncertainty about the future progression of my sight and about my ability to adapt to it means that I cannot take my current position for granted. **Education** From the age of five until sixteen I was educated first at a fully mainstream village Primary School, and then at a mainstream Secondary school with specific provision for disabled children. Whilst I was initially provided with one-to-one support this was gradually diluted, and much of my eleven years in mainstream education was marked by frequent battles with the Local Education Authority (LEA) and schools, to ensure that my needs were recognised, relevant support provided, and that appropriate arrangements were made for my transition to Secondary school and sixth form. The LEA's confrontational and

If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	intransigent approach to those transitions had a particularly negative impact on my health and wellbeing, and on that of my immediate family. Following my GCSEs I moved to the Royal National College for the Blind (RNC) to enable me to focus on my A-Levels, confident that appropriate support would be provided, and that I would also have access to mobility and daily living skills vital for independent life. Whilst effectively leaving home at sixteen to attend college was challenging, I am clear that I would not have progressed to University without this step. I then studied History at the University of York. Life as a disabled student could at times be difficult – my mobility, particularly after dark, was poor and I relied heavily on my peers. Perceived deterioration in my sight at this time also made it impossible to keep up with the reading for my course, and I often made do with seminar notes taken by a notetaker when preparing for exams. This contributed to me losing confidence in my own ability, and particularly in speaking in public, I am only now overcoming the latter, some fifteen years on. **Family Life** I have been lucky throughout my life to date to have a family which both challenged me to be the best I could, whilst supporting me when I needed help. I grew up as non-disabled children did, playing in the street with friends and even riding a bicycle, somehow unaware of the consequence of colliding with obstacles unseen around me. I suspect this was difficult for my parents, wanting me to be as “normal” as possible, yet seeing the dangers that I couldn’t. As indicated previously, they fought for me to receive the right education, and in more recent times have always been there when I needed them, to move home at short notice when my guide dog was rejected by a landlord, to help keep the flat clean when my visual impairment made this difficult, or simply to tell me when a suit was worn out or support me when shopping for new clothes. **Employment** Whilst I count myself incredibly lucky to be in the minority of visually impaired people in employment, and to have a supportive employer, my experience has not always been positive. I joined the Civil Service on the Graduate Fast Stream, but found early on that a reliance on networking to identify the best postings, and the reluctance of some line managers to consider me, meant that I could not always access the jobs I wanted. My visual impairment also means that tasks requiring consideration

	of significant amounts of data or presenting information in a particular way can take me substantially longer than colleagues, requiring me to work twelve or more hour days on a regular basis, detrimentally affecting my work life balance. Whilst my employer rightly prides itself on its leadership on equality issues, the workplace can still sometimes be an inaccessible place, always dependent upon the accessibility of IT systems and the willingness of line managers to provide the support I need. A combination of the pressure of continually adapting to meet expectations, and of poor support, has previously contributed to periods of depression. In recent times I have found it increasingly difficult to adapt both to my changing sight and updated IT systems, and I genuinely fear that a time could come when my effectiveness at work is too compromised for me to continue. **Overall** Whilst I know that many will claim that they are not defined by the way in which they are disabled, I feel that it is impossible to separate the person I am, and the experiences I have had, from my visual impairment. Growing up with an evolving eye condition one is acutely aware of the barriers that begin to appear – of a fading interest in visual media as the screen or page becomes less visible, of a creeping anxiety constraining independent mobility, and of compromising venues visited and transport used to avoid the confrontation which remains a regular occurance for guide dog owners. For a fiercely independent, motivated person like me, who still wants to make a difference, to make the most of life and to travel widely, the compromises that visual impairment forces on one are incredibly frustrating. My ability to follow the career I want feels at times to hang in the balance as I attempt to maintain my effectiveness, and my travel horizons are limited by my need to be with others for the majority of trips. Almost every aspect of my life that I can think of is impacted by my sight, from the place I choose to live so as to be close to public transport, to the people I socialise with, the places I go, and the confidence with which I live my life. This is not to infer that visual impairment acts as a constant negative influence. Rather, it is an ever present factor, consciously or unconsciously steering the decisions I take tnd the direction I travel in.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	My first consultant at Moorfields Eye Hospital suggested to my parents that I would likely "go blind" but that whilst there were no proven treatments available at that time, he expected one to be developed within my lifetime. Whilst I was privileged to participate in the Moorfields/UCL RPE65 Gene Therapy trial in 2007, today, there is still no treatment available on the NHS, and neither I nor others in the same position can realistically expect a sustained pause in or reversal of our visual degeneration In 2007 I was the first patient to receive gene therapy treatment for an inherited retinal dystrophy. Until this point the only interventions offered by the NHS were low vision aid assessments, and the prescription of magnifying glasses and monoculars for the viewing of near and far text respectively. I generally found such sessions to be of limited usefulness, particularly given the rather rudimentary aids offered when compared to technological solutions now available.
11. Is there an unmet need for patients with this condition?	Whilst it is fair to say that perspectives on the prospect of a treatment for visual impairments, hitherto viewed as permanent aspects of people's lives differ considerably between affected people, with many, in my experience, indicating contentment with their current position, there clearly is an unmet need to arrest or reverse visual degeneration for many more. Today a person newly diagnosed with LCA can be given little hope of receiving meaningful treatment, still less of recovering lost or maintaining residual vision. The existance of an effective treatment, however constrained in its overall efficacy or the patients who can be treated, could therefore provide that hope that such a diagnosis no longer indicates an inevitable descent into increasing levels of blindness. For the small number who could be treated the impact would clearly depend upon the efficacy of the treatment itself, however any treatment would likely be welcomed by many for a category of impairment for which no other effective treatment currently exists.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the	I have no direct experience of the specific technology under consideration. I understand however that it has been shown to arrest the deterioration of rod cells in the retinas of treated patients. As such I would expect that the chief benefit of the intervention would be a stabilization and potentially reversal of night blindness symptoms. As I highlight later in this statement night blindness is far more than a simple inability to

progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	see clearly between dusk and dawn, but rather affects patients at any point of transition between levels of light, such as on entering a dimly lit meeting room, or walking from a brightly lit station platform into an interior corridor. A change in the level of night blindness experienced could help patients to navigate more safely, confidently and independently at night, but also to approach all mobility tasks with confidence about the consistency of their visual reaction. Such an improvement, and the increase in independent mobility it might support, could also indirectly assist the mental wellbeing of some patients. This effect may belimited however if the patient continues to experience other impacts of the condition, including severely reduced acuity, which are not improved with this technology.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	I address this point below, with reference to a similar technology I have experienced.

Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	Whilst I have no direct experience of the specific technology under consideration I was a subject in the trial of a similar gene therapy technology for treating RPE65 linked LCA in 2007 and can comment from that perspective. In my experience the intervention itself was relatively straightforward. I was treated as an outpatient, with the vitrectomy and sub-retinal injection performed under general anaesthetic, though I understand that it is possible to do this with local anaesthesia. On waking, my treated eye was initially immobilised and I recall experiencing some discomfort at the visual distortion this produced, as well as a high level of light sensitivity. A high dose of steroids, which was tapered off slowly over the following month left me feeling more unwell than the treatment itself, although this was also relatively short-lived. More recently, check-ups have indicated early signs of a cateract in the treated eye. In the longer term I have found that the added uncertainty of the impact of the intervention on my vision has exacerbated existing anxiety at the degeneration of my sight and my continuing ability to adapt to it. That said, the experience of participating in such a significant clinical trial was very positive and I have no regrets about it. Overall, in my view, a less invasive procedure (ie: requiring only a local anaesthetic), less steroidal cover and with a higher degree of certainty about the expected outcome is likely to have fewer disadvantages for patients. The less beneficial impacts of potentially gaining additional vision from such a treatment should also be considered however. Support for visually impaired people is loosely based on visual ability, with higher rates of state benefit, personal tax allowance and other support focused on those with the poorest vision and greatest need for assistance. It is feasible that a modest increase in sight resulting in only limited improvements in independent mobility, could nevertheless reduce an individual's entitlement to support, including their financial income. It might also affect their ability to compete in blind sport, where competitors are categorised by level of sight. Ultimately weighing the pros and cons of treatment would be a matter for individuals or their parents/carers.
Patient population	
15. Are there any groups of patients who might benefit	In my view, there would be considerable benefit in stabilizing or reversing the visual deterioration of school age or younger children, even if the effect was limited in time. Whilst growing up with a visual

more or less from the treatment than others? If so, please describe them and explain why.	impairment, rather than gaining it later in life, allows one to develop coping strategies iteratively, it also places a heavy burden on children, potentially preventing them from fulfilling their potential in the classroom or of participating in sport or social activities alongside their peers. Relieving them of the stress of the constant adaptation which is, in my experience, the hallmark of living with a degenerative eye condition, would allow them to focus their energy on becoming independent, informed adults equipped to achieve their ambitions. ,
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**Personally, I am not aware of any such issues.**
Other issues	
17. Are there any other issues that you would like the committee to consider?	I believe the technology is focused primarily on maintaining or improving the low-light vision of patients. Whilst the impact of night blindness is a significant factor inhibiting the independent mobility of affected patients, potentially contributing to social isolation and constrained horizons, success in education and access to employment are, to my mind, influenced more significantly by visual acuity. I would therefore encourage the committee to understand the potential benefit to patients in the context of the specific visual attributes which could be improved, rather than assuming that any increase in vision would have a uniformly positive impact across areas of a patient's life.

Topic-specific questions	
18. Has the progressive nature of the condition had an effect on you, your family or carers?	I have been lucky that the degeneration in my sight has generally occurred slowly over time and that, until relatively recently, I have been able to adapt my skils to remain independent. That said, at several points in my life, whilst at secondary school and again at University, I perceived faster than usual deterioration in my sight, which was difficult to cope with in practical terms, particularly when in the middle of a reading-heavy degree. More recently I have found it increasingly difficult to adapt to my changing sight. I find it more challenging to access certain technologies, including making the transition between predominantly using vision to interact with a computer, to relying on a screen reader. I am also finding that, despite hitherto being a confident and enthusiastic traveller, I am now more nervous in crowded or unfamiliar locations. My ability to work supports my self-esteem and allows me to contribute to society, yet I fear that in time my ability to adapt to my deteriorating vision will weaken further and that there will come a time when I am insufficiently effective to continue in my current career, and therefore to live the life I want to. Overall the uncertainty about my future sight, and its impact on my ability to live and work as I want to weighs heavily on my mind. I think it is certainly a contributing factor in bouts of depression I have experienced over the past half-decade, and whilst I am generally a positive person, it can cause me to feel quite despondent at times.
19. The company consider nyctalopia (night blindness) a defining characteristic of the condition. Has nyctalopia affected you, your family or carers?	Profound night blindness has been the hallmark of my visual impairment throughout my life. In my early years it was my failure to respond to poorly lit stimuli that first concerned my parents, at University it stopped me leaving campus alone past dusk, and more recently it constrained my horizons and was a strong contributing factor in my decision to apply for a guide dog. In some ways the term “night blindess” does the lived experience of this aspect insufficient justice, as the impact is felt throughout one’s daily life. Walking from a bright street into a shop lit by artificial light, into a crowded meeting room or off a train onto a dim platform I find myself disorientated, confused, sometimes scared. It takes confidence and resilliance to put oneself into such environments knowing that the immediate impact will never change.

	That said, it is my reducing visual acuity and field of vision which has arguably had the greatest impact on my effectiveness at work and my perspective on the future in more recent times. With a guide dog or good long cane skills I can reach many of the places I want to go, but it was my failing visual acuity which, at University, prevented me from reading even a small percentage of the material recommended for my course, and which today threatens my ability to work effectively, and therefore to live my life as I want to. Reducing the effects of night blindness could give patients confidence, improve their safety and prevent isolation, but it will not help them to access written material, to recognise faces and interact naturally with colleagues and stakeholders.

Key messages

20. In up to 5 bullet points, please summarise the key messages of your statement:

-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Voretigene neparvovec for treating inherited retinal dystrophies caused by *RPE65* gene mutations [ID1054]

A Highly Specialised Technology Appraisal

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Date completed	15th April, 2019
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 17/56/05.

Declared competing interests of the authors	Professor Lotery has received payment from Novartis to speak at an educational meeting unrelated to the health technology/comparator under evaluation. He also holds shares in a company unrelated to this evaluation. No further interests.
Rider on responsibility for document	**The views expressed in this report are those of the authors** and not necessarily those of the NHS, the NIHR SER programme or the Department of Health and Social Care**.** **Any errors are the responsibility of the authors.**
This report should be referenced as follows	C. Farmer, A. Bullement, D. Packman, L. Long, S. Robinson, E. Nikram, S. Bello, S. Dodman, M. Rezaei Hemami, A. Churchill, A. Lotery, A. Hatswell, G.J. Melendez-Torres, L. Crathorne. Voretigene neparvovec for inherited retinal dystrophies (*RPE65* mutations) [ID1054]: a Highly Specialised Technology Evaluation. Peninsula Technology Assessment Group (PenTAG), 2019
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Contributions of authors	Caroline Farmer acted as project manager and lead systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Ash Bullement acted as health economic project lead, critiqued the company's economic evaluation and contributed towards writing the report. David Packman acted as modelling lead, critiqued the company's economic evaluation and contributed to the writing of the report. Linda Long acted as systematic reviewer, critiqued the clinical effectiveness evidence and the patient and practitioner contributions, and contributed to the writing of the report. Sophie Robinson acted as lead information scientist on this project, critiqued the literature searches performed by the company, and contributed to the writing of the report. Elham Nikram acted as health economist, critiqued the company's economic evaluation and contributed to the writing of the report. Segun Bello, Sophie Dodman, and Mohsen Rezaei Hemami critically appraised the epidemiological evidence presented by the company and contributed towards writing the report. Amanda Churchill and Andrew Lotery acted as clinical advisors to the evaluation and reviewed the epidemiology and clinical effectiveness sections of the report. Anthony Hatswell critiqued the clinical effectiveness evidence and the company's economic evaluation, contributed to the writing of the report and provided general guidance on the health economics part of the project. G.J. Melendez-Torres critiqued the clinical effectiveness methods and evidence, and contributed towards writing the report. Louise Crathorne critiqued the company's definition of the decision problem, their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

ABBREVIATIONS

AAV	adeno-associated virus
AE	adverse event
AMA	American Medical Association
BCVA	best-corrected visual acuity
BSC	best supportive care
CF	counting fingers
CI	confidence interval
CMO	cystoid macular oedema
CS	company submission
DI	delayed intervention
EED	Economic Evaluation Database
EMA	European Medicines Agency
EOSRD	early-onset severe retinal dystrophy
ERG	Evidence Review Group
FST	full-field light sensitivity
HM	hand motion
HR	hazard ratio
HRQoL	health-related quality of life
HS	health state
HST	highly specialised technology
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
IRBP	interphotoreceptor retinoid-binding protein
IRD	inherited retinal disease
ITT	intention to treat
LCA	leber's congenital amaurosis
logMar	logarithm of the minimum angle of resolution
LP	light perception
LRAT	lecithin retinol acyltransferase
MD	mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	medical subject heading
mITT	modified intention to treat
MLMT	multi-luminance mobility test
NHS	National Health Service
NHSE	National Health Service England
NHx	natural history
NICE	National Institute for Health and Care Excellence
NLP	no light perception
NR	not reported
OCT	optical coherence tomography
OI	original intervention
ONS	Office for National Statistics

PAS	patient access scheme
PLR	pupillary light reflex test
PT	preferred term
QALY	quality-adjusted life year
RCT	randomised controlled trial
RDH8	retinol dehydrogenase 8
RNIB	Royal National Institute for the Blind
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
RPE65	retinal pigment epithelium-specific 65 kDa protein
SAE	serious adverse event
SD	standard deviation
SE	standard error
SECORD	severe early childhood onset retinal dystrophy
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SoC	standard of care
TEAE	treatment emergent adverse event
TP	transition probability
VA	visual acuity
VF	visual function
VFQ	Visual Function Questionnaire
VI	visual impairment
VN	voretigene neparvovec

1 SUMMARY

1.1 Background

Inherited retinal dystrophies (IRD) are a heterogeneous group of rare diseases caused by germline mutations in more than 260 genes, including the *RPE65* gene. The key outcome of *RPE65*-mediated IRD is inexorable and progressive loss of vision, culminating in near or total blindness, though the rate of deterioration varies considerably between patients. The pathophysiology underlying progressive loss of vision relates to the inability to complete the visual cycle because of deficiencies in the *RPE65* enzyme. Deficiencies in this enzyme arrest the molecular pathways that culminate in transmission of signals to the brain. In addition, the accumulation of toxic precursors in the visual cycle leads to apoptosis, or cell death, in photoreceptor cells. IRD is often diagnosed in infancy and adolescence. Night blindness is a common first symptom, but in infants, the 'oculo-digital sign', or eye poking, is a common presentation, though its association with *RPE65*-mediated IRDs is unclear. *RPE65*-mediated IRD is an autosomal recessive-transmitted disorder, including two related disorders; retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA).

The impact of the condition begins in early life, with impacts on child social development arising from poor visual function. Adults may face decreased employment opportunities arising from challenges in accessing education. IRD also impacts carers and household members through increased caring burden, and is associated with an increased risk of depression among patients and their family members. The ERG noted that while evidence presented for these impacts drew from IRD generally, there was no evidence specific to *RPE65*-mediated IRD.

Diagnosis of *RPE65*-mediated IRD includes medical history and genetic testing. The company estimated that only 50% of people with the disease are currently diagnosed. Care for this condition is at present primarily supportive, and few national or expert guidelines exist. For children, visual aids and magnifiers are recommended, as well as supportive resources in school settings (e.g. specially qualified teachers).

While the ERG noted that the evidence related to incidence and prevalence of the condition is scant and thus any estimate is highly uncertain, the company estimated that the prevalence of IRD mediated by the *RPE65* gene would lead to a population of 86 patients in the UK eligible for treatment.

Voretigene neparvovec (VN; Luxturna®; Spark Therapeutics, Inc.) is an adeno-associated virus (AAV) gene therapy treatment which introduces a healthy copy of the defective *RPE65* gene into the retinal cells of patients with *RPE65*-mediated IRD. VN is administered as two subretinal injections (no fewer than six days apart) once per lifetime. Prior to administration (approximately 3 days

before), patients are required to receive an immunomodulatory regimen (such as prednisone), which is expected to be continued for a further 18 and 30 days, depending on the timing of the second administration (i.e. the other eye). The introduction of *RPE65* enables patients to produce functional *RPE65* protein. The subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells. This enables patients to produce functional *RPE65*, resulting in improved functional vision (improved ability to perform vision-related daily activities) and visual function (improved performance of the eyes at the organ level). In order to derive benefit from VN treatment, the company states that patients must have confirmed biallelic (pertaining to both paternal and maternal alleles) *RPE65* mutations and have sufficient viable retinal cells into which healthy copies of the *RPE65* gene can be introduced.

VN is not currently used in the UK for any patient population. The European Medicines Agency (EMA) awarded VN marketing authorisation on 22 November 2018. VN is expected to be used in line with the marketing authorisation for the treatment of individuals with vision loss due to IRD caused by confirmed biallelic *RPE65* mutations.

1.2 Critique of the decision problem submitted by the company

The decision problem included in the company submission broadly adhered to the final NICE scope. The ERG noted that the company restricted the population of patients from those with *RPE65*-mediated IRD to include only those who additionally possessed sufficient viable retinal cells. The ERG regarded that this was clinically justified. The intervention as specified matched the NICE scope, but the ERG noted that comparators, broadly classes as best supportive care, were not defined in the company submission.

Outcomes presented by the company included the multi-luminance mobility test (MLMT), which was not in the scope but described by the company as a clinically relevant test of functional vision. The MLMT was the primary endpoint of the company's pivotal phase 3 trial. While most other scoped outcomes were reported in the CS, the ERG noted that health-related quality of life data were not collected as part of the phase 3 trial, nor were data reported relating to need for cataract surgery.

Finally, the company used an economic perspective in their evaluation in line with the NICE scope.

1.3 Summary of clinical effectiveness evidence submitted by the company

The company presented a systematic review that included evidence from two trials. The pivotal trial for the submission is Study 301/302; an open-label, multi-centre, phase 3 RCT involving 31 patients (Study 301), followed by an optional phase after one year where 9/10 (90%) patients from the control arm received VN (Study 302). Patients were recruited from multiple countries worldwide, and

travelled to sites in the US for treatment administration and follow-up. Study 301/302 is ongoing: data up to and including a four-year follow-up was available for some, though not all, outcomes in this submission. Study 101/102 is an open-label, phase 1, single-arm trial. Study 101 employed a dose-ranging design; with patients receiving either a 'low', 'medium', or 'high' dose of VN in a single (worse, non-preferred) eye. Patients travelled to sites in the US for treatment administration, following which 7/12 (58.3%) were followed up in the US, and 5/12 (41.7%) were followed up in Italy. After a minimum of 1 year, patients from Study 101 were invited to receive VN in the contralateral eye: 11/12 (91.7%) patients from Study 101 were eligible for entry into Study 102. All patients in Study 102 received a 'high' dose of VN in their contralateral (better, preferred) eye.

Primary visual acuity (VA) outcomes in Study 301/302 did not demonstrate a significant difference in changes from baseline to 1 year between VN and BSC (0.16 LogMAR, 95% CI [-0.41, 0.08]; p=0.17). All changes in VA were under the company's definition of a clinically meaningful change (≥0.3 LogMAR). Study 101/102 had similar findings. In contrast, VF improved in VN patients as compared to BSC patients at 1 year in Study 301/302. Improvements in VF were demonstrated by 30 days in the VN arm, and these remained relatively stable until 1 year (assessed by Goldmann III4e, MD 378.7; 95% CI [145.5, 612.0]; post-hoc p = 0.0059). Despite numerical evidence of decline after the 2 year timepoint, clinical advice received by the ERG suggested these changes were clinically meaningful. In Study 301/302, [redacted], but differences at 1 year in photosensitivity were significant albeit below the company's defined threshold for clinical significance (full-field light sensitivity MD -2.11 log units; 95% CI [-3.91, -1.04]; p=0.0004), [redacted]. The company also presented evidence for the MLMT, which suggested [redacted] at 1 year before the BSC arm patients received VN, the mean difference in lux units was 2.0 (95% CI [1.14, 2.85]). Finally, patient-reported outcomes including a modified Visual Function Questionnaire (VFQ) were reported for Study 301/302. [redacted] No health-related quality of life nor cataract surgery data were reported.

With regard to common adverse events attributed by the company to administration procedure, in the short term (one year), [redacted]

[redacted]

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG regarded that the quality of methods used to locate the evidence was reasonable, though the use of unconventional search methods meant that there was a small, albeit unlikely, chance that studies may have been missed.

The pivotal phase 3 trial submitted, Study 301/302, generally matched the decision problem. Though the majority of patients (26/31) in this study were treated in the US, the ERG considered that the setting would generalise to UK practice. Of note is that inclusion and exclusion criteria for Study 301/302 were narrower than included in the NICE scope, given the study's requirement for sufficient viable retinal cells. The ERG considered that this was a clinically relevant consideration. However, the ERG noted that this additional criterion means it likely that there will be some patients included in the population specified in the NICE scope who will be excluded for treatment with VN because they have no viable retina to treat.

The small sample size in Study 301/302 (n=29; following the exclusion of 2 patients following randomisation) introduced uncertainty in the estimation of treatment effect.

[redacted] While age differences were noted between the randomised groups at baseline, clinical advice suggested that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population. Retinal function at baseline was suggested to be a potentially stronger mediator of treatment response, which may be partially correlated with age. However, none of the differences at baseline were considered by the ERG to demonstrate a clear bias in any direction, although it was noted that only a small number of characteristics were reported at baseline.

The ERG regarded that outcome assessment was generally appropriate and clinically relevant in this population, and that statistical methods used to analyse outcome data were acceptable. However, measurement of VA, VF and contrast sensitivity is widely considered to be unreliable, and some imprecision in their measurement should be expected. In addition, the ceiling effect inherent to the MLMT measure may underestimate the treatment effect reported for continuous data. The removal of

HRQoL data from the VFQ suggested to the ERG that the VFQ was not an appropriate measure of HRQoL. No HRQoL data, or PRO data for the carers of patients with IRD, was reported in the CS, which the ERG considered to be an important omission. Finally, while the ERG noted that multiple years of follow-up were presented for multiple outcomes, the inconsistency of follow-up duration across outcomes and the small sample size present uncertainties in estimating duration of effect.

The quality of the submitted evidence was acceptable, though the ERG noted Study 301/302 may be at high risk of bias. The ERG agreed substantially with the company's risk of bias assessment for Study 301/302. Study 301/302 did not include blinding of patients and providers given that the use of sham injections was considered unethical. However, quality of methods used for randomisation and the evaluation of the primary endpoint, MLMT, by a blinded rater were strengths of the trial. The ERG did note, however, that the company did not report co-interventions in sufficient detail. The company did not provide quality assessment for Study 101/102, which the ERG undertook. The ERG concluded that the small sample size of the study was a key limitation. Ambiguities in the trial inclusion criteria relating to LCA vs RP meant that the ERG could not draw a conclusion about the applicability of the evidence base across diagnoses.

More serious risks associated with subretinal administration of VN and concomitant oral corticosteroid use include endophthalmitis, permanent decline in visual acuity, increased intraocular pressure, retinal abnormalities (e.g., retinal tears or breaks), and cataract development and/or progression. The ERG highlight that these might have long term consequences, especially if they were left untreated. With concomitant use of oral corticosteroid (prednisone) at the time of subretinal injection of VN, the ERG agree that the immune response to AAV capsid and *RPE65* appears mild.

Due to the small patient population included in the trials and indeed the small population with the condition, the representativeness of patients with respect to the UK population of patients with inherited retinal dystrophies is difficult to assess. The ERG regarded that no important groups, by age, ethnicity or sex, were unduly excluded from the relevant trials. The small evidence base presented in the submission is reflective of the rare nature of this condition, but does limit the generalisability of the evidence base beyond the included trials. As there is poor understanding of the characteristics that may impact on disease prognosis and treatment efficacy, it is not possible for the ERG to determine whether the populations of the included trials is consistent with the UK population.

1.5 Summary of value for money evidence submitted by the company

The company submission comprised of a *de novo* cost-effectiveness model constructed to assess the cost-effectiveness of voretigene neparvovec versus best supportive care. The model adopted a Markovian state-transition cohort structure, and comprises of five "alive" health states plus a sixth

absorbing health state representing death. The cost-effectiveness model was constructed in line with the anticipated use of voretigene neparvovec in clinical practice. A lifetime horizon was modelled, and annual discount rates of 3.5% for costs and outcomes were used in the company base case.

The cohort model structure was developed primarily to capture the impact of voretigene neparvovec treatment on health-related quality of life outcomes. Five "alive" health states (based on differing degrees of vision impairment) were used such that different utility values could be assigned to these states. The use of these health states was considered necessary in order to reflect clinically-meaningful differences in health-related quality of life following treatment with VN, and as patients experience progression as part of the natural history of the condition.

Patient transitions from baseline to 1 year were informed by the pivotal Study 301/302, whereas long-term transitions were informed by a combination of clinical expert opinion regarding the long-term effect of voretigene neparvovec and a multistate model fitted to natural history data from the *RPE65* NHx study. Outcomes within the model were based on a combination of visual acuity (VA, clarity of vision) and visual field (VF, range of vision), though the primary endpoint of Study 301/302 was the improvement in the multi-luminance mobility test (MLMT).

Health-state utility values were derived through interviews held with clinicians to complete proxy generic health related quality of life questionnaires for each of the health states in the economic model, based on summary descriptions and their experience with patients. Costs were based on published sources, and were inflated where necessary to reflect the 2018 cost year. The included cost categories considered treatment acquisition, surgery, monitoring, medical resource use, resolution of adverse events, and eligibility testing. Medical resource use utilisation was informed through a combination of assumptions made by the company and input from clinical experts. The company also presented additional analyses to ascertain the impact of treatment beyond costs borne by the NHS and PSS.

In the company's base case analysis, voretigene neparvovec was associated with an incremental cost of [redacted] and a QALY gain of 7.06, leading to an incremental cost-effectiveness ratio of [redacted] (including the proposed simple PAS discount for voretigene neparvovec). The company also presented a range of one-way deterministic and multi-way probabilistic sensitivity analyses, which illustrated that the key drivers of cost-effectiveness for voretigene neparvovec are the expected long-term outcomes and the quantification of patient health-related quality of life.

1.6 Summary of the ERG's critique of the value for money evidence submitted

The company's submission has been generally developed in accordance with the requirements stipulated within the NICE reference case, and is broadly aligned with the final scope issues by NICE. The company deviated slightly from the final scope to exclude patients without sufficient retinal cells from the economic analysis, which the ERG agreed was appropriate and aligned with the anticipated use of voretigene neparvovec in clinical practice. While the ERG is generally satisfied that the company's model provides a sufficient basis for decision making, the ERG is concerned with a number of assumptions and settings incorporated within the company's submission which have the capacity to lead to substantially different cost-effectiveness estimates.

The cost-effectiveness model structure makes use of a multistate modelling component which the ERG considered to have been unnecessary to inform the estimation of cost-effectiveness within the context of a rare disease. Furthermore, the company's assumed duration of treatment effect for voretigene neparvovec is not considered by the ERG to be robustly supported by the available data from Studies 101/102 and 301/302. The ERG feels that the combined effect of these two features of the company's modelling approach means that the estimation of the long-term effect of voretigene neparvovec is highly uncertain.

Outside of the quantification of longer-term outcomes for patients with *RPE65*-mediated IRD, the estimation of utility values is an incredibly important aspect of the cost-effectiveness model which has the potential to greatly influence cost-effectiveness estimates. A number of methodological issues were identified with the values produced as part of the elicitation exercise, and so the ERG does not consider these utility values to constitute an appropriate basis for decision making.

The ERG also identified a number of other assumptions made in the model that were not clearly supported by the evidence presented. The company assumed vision impairment was associated with increased mortality, though this was based on the findings of a study conducted in elderly patients without *RPE65*-mediated IRD. Medical resource utilisation estimates were also primarily taken from a non-*RPE65*-mediated IRD population, and adjusted based on a number of assumptions relating to relative use between patients with differing extents of vision impairment, and across age groups.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

The company identified what is likely the only other published cost-effectiveness analysis of voretigene neparvovec, conducted by the Institute for Clinical and Economic Review in the United States. The ERG noted some limitations in the company's systematic review that led to the

identification of this study, but considers it highly unlikely that any other studies would have been identified.

The cost-effectiveness model was constructed in a clear and logical manner, aligns with the NICE reference case, and makes use of the most relevant data to quantify the effect of voretigene neparvovec for patients with *RPE65*-mediated IRD. The choice of modelled health states illustrates the key stages of progression in the condition. The company provided the ERG with comprehensive responses as part of the clarification process, and presented a clear understanding of the key limitations in the evidence base for voretigene neparvovec.

1.7.2 Weaknesses and areas of uncertainty

The primary weaknesses of the company's submission relate to the lack of data to quantify the long-term effect of VN, and the health-related quality of life of patients with *RPE65*-mediated IRD. The treatment effect of VN is unclear both in terms of the level of effect maintained, and the duration for which it will be maintained. The ERG emphasises caution when interpreting the results of the cost-effectiveness analysis, as the results are greatly influenced by assumptions regarding the treatment effect of VN, which is currently unknown.

Within the company's submission, it was noted that there are no data available related to the health-related quality of life of the *RPE65*-mediated IRD population. Consequently, the company's model relies upon the use of questionnaire responses that were used to inform utility values. The ERG does not consider these utility values to be appropriate for decision making, and has therefore provided an alternative set of values to inform the model. Utility values are associated with a profound effect on the cost-effectiveness results, and so the ERG deems the lack of data for the relevant population to constitute a substantial weakness in the company's submission.

In addition to these weaknesses, there is large uncertainty around the modelling of natural history data in the economic model. While the data available comprise a relatively large sample size (in the context of the disease), and provides useful additional information to inform the cost-effectiveness analysis, the approach taken by the company appears overly complex and has not been validated against data or expert opinion. Based on the ERG's understanding of the condition, the company's projections appear to contradict clinical opinion as many patients are estimated to have "moderate vision impairment" for a long period of time.

Study 301/302 provides a within-trial comparison of voretigene neparvovec and best supportive care, though this is based on a comparison of n=20 original intervention patients, and n=9 delayed intervention patients. The ERG understands the limitations associated with recruiting patients to trials

of treatments for rare conditions, though the small sample size of the pivotal study leads to unavoidable uncertainty in the outcomes of the submitted cost-effectiveness model. In addition, it was not possible for the company to produce a cost-effectiveness model based on the primary endpoint of Study 301/302 – it remains uncertain what the cost-effectiveness of voretigene neparvovec would be were the model constructed around the MLMT outcome.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG noted that the key areas of uncertainty are related to the expected long-term treatment effect of VN, the impact of *RPE65*-mediated IRD on patient health-related quality of life, and the modelling of the natural history of the condition. The ERG amended the company's model by changing settings relating to healthcare costs, mortality assumptions, expected treatment effect duration, impacts of *RPE65*-mediated IRD on carers of affected children, model transition probabilities, and utility values.

The ERG's preferred base-case leads to an ICER of [redacted] (including the PAS discount for VN) and £155,750 (excluding the PAS discount for VN). The changes made comprised of the following:

- Amendment of costing of medical appointments, tests, and resource utilisation
- Omission of excess mortality impacts associated with specific health states
- Differing assumptions relating to impact on carer utility
- Use of crossover-based transition probabilities
- Simplification of the treatment effect duration
- Application of published utility values more closely aligned with the NICE reference case

The change associated with the largest impact on the ICER was the use of alternative utility values, which if varied in isolation of all other changes, caused the ICER to increase by approximately [redacted] (with PAS) and £35,659 (without PAS). The ERG's exploratory and sensitivity analyses highlighted the influence of alternative assumptions regarding the expected duration of treatment effect of voretigene neparvovec and the application of utility values. Adoption of a governmental perspective led to a slight decrease in the base-case ICERs.

In light of the evidence available and the remit of this appraisal, the ERG was unable to fully explore and/or resolve issues relating to the specification of the MSM (which the ERG considered to be unnecessarily complex) and the lack of clarity regarding (long-term) outcomes for patients with *RPE65*-mediated IRD (treated with either voretigene neparvovec or best supportive care).

1.9 Conclusions

The evidence presented in the CS, suggests VN appears to offer a sustained but modest improvement in vision, measured using a variety of outcomes. Whilst patients are highly likely to remain with vision impairment, for as long as the treatment effect persists, they are unlikely to decline further. Evidence indicates a good safety profile. While the evidence in the CS is extremely limited, the paucity of evidence is common with rare diseases.

The submitted cost-effectiveness model presents a comprehensive summary of the key stages of vision impairment which are expected to influence patient utility, and therefore affect the estimation of the cost-effectiveness of VN. The company made use of a number of relevant data sources in order to populate the cost-effectiveness model, and identified all relevant evidence in a transparent manner. While relevant to clinical practice, the modelling approach is associated with a range of limitations and relied heavily upon a large volume of clinical expert input in order to produce cost-effectiveness estimates.

Three key aspects of the model were identified as being primary contributors to the overall uncertainty in the model: (1) treatment effect of VN, (2) modelling of long-term natural history outcomes, and (3) utility values. The duration of treatment effect and estimation of utility values required extensive clinical expert input to inform the model base case, and the long-term natural history of *RPE65*-mediated IRD was based on a highly complex MSM which is subject to palpable uncertainty. Consequently, the ERG was unconvinced that the assumptions relating to the long-term effects of VN were supported by the available evidence, and was concerned with the large impact alternative assumptions relating to the estimation of these benefits have on the cost-effectiveness results; should the treatment effect fail to remain at 100% for at least 35 years, the ICER begins to rise alarmingly.

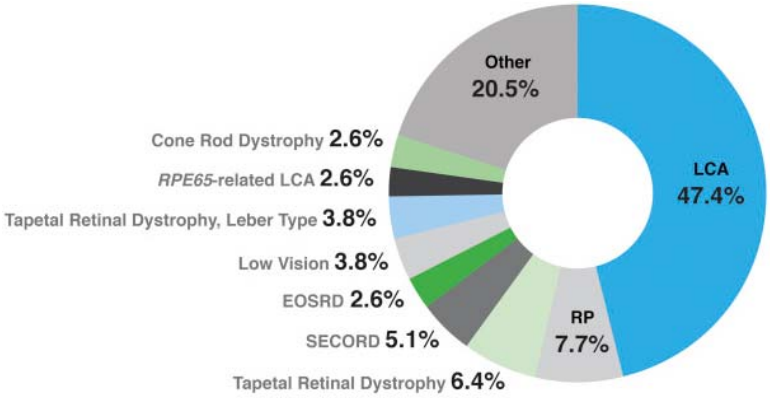
2 BACKGROUND

2.1 Description of health problem

2.1.1 Epidemiology

Inherited retinal dystrophies are a heterogeneous group of rare diseases caused by germline mutations in more than 260 genes, including the *RPE65* gene.[1] Patients are primarily diagnosed with either retinitis pigmentosa (RP) or Leber congenital amaurosis (LCA),[2] the latter of which is more rare. The CS cites a natural history study[3] of *RPE65*-mediated IRD, which reports that 47.4% and 7.7% of patients received a diagnosis of LCA and RP, respectively. However, a total of 24 different diagnoses associated with mutations in the *RPE65* gene were diagnosed in this cohort (Figure 1). *RPE65*-mediated disease has been documented to account for 6-16% of LCA and 2% of RP.[4,5]

Figure 1: Initial clinical diagnosis received by patients with *RPE65*- related IRD.



Source: Chung et al. (2019)[3]
Numbers sum to more than 100, as some patients received multiple diagnoses.

The company conducted an SLR to identify relevant evidence for the prevalence and incidence of RP and LCA, although the methods they used and the number of studies identified were not outlined in the CS. Based on evidence from the SLR, the CS reports a combined prevalence of 12.3-28.8 per 100,000 people for the LCA/RP population based on studies in a few European countries (including the UK), US, and Korea. This is largely consistent with the literature identified by the ERG, although as one study reported a prevalence of RP alone of 30 per 100,000,[6] the upper bound prevalence rate of the combined population could be higher than this.

The CS reported that mutations in the *RPE65* gene accounted for a median of 1.1% (0.8–1.9%) of RP cases and 6.4% (1.0% - 22.2%) of LCA cases. The ERG found the medians reported to be within the

range of values documented in the literature. However, the methods used to arrive at the median values, were unclear.

The CS estimated the prevalence of *RPE65*-mediated IRD in England to be between 57-564 patients. No references were cited for this data, and the ERG could not find evidence to support these numbers. The incidence of RP was estimated in the CS to be between 0.6 – 1.6 per 100,000 people per year. This evidence was derived from Danish, South Korean and American populations.[7-9] No data was found for the incidence of LCA. The incidence data reported in the CS is consistent with evidence identified by the ERG.

The company estimates that the target patient population for VN in the UK is 86 patients. Their calculations, alongside comments from the ERG, are reported in Table 1.

Table 1: Estimated UK Prevalence of *RPE65*-mediated RP and LCA

Parameter	%	N	ERG Comment
Population of England in 2019†	-	56,512,870	Consistent with data from the office for National Statistics
Population of England in 2017 [10]	-	*55,619,400*	Consistent with data from the office for National Statistics
Annual population growth in England [10]	-	*0.8%*	Consistent with data from the office for National Statistics
Prevalence of *RPE65*-mediated IRD‡	0.0003%	180	From the points noted below, the prevalence of *RPE65*-mediated IRD may be higher than 0.0003% but not likely to have important impact on the budget
Prevalence of RP [11]	*0.02%*	*11,402*	The prevalence of RP is consistent with the literature
% of RP that is RPE65-mediated [5,12,13]	*1.3%*	*144*	Unclear how 1.3% was derived but it appears to be the simple average of 0.8% and 1.9% from the cited references
Prevalence of LCA [14,15]	*0.002%*	*1,001*	Prevalence of LCA is consistent with the literature
% of LCA that is RPE65-mediated [16]	*3.4%*	*34*	The 3.4% used is much lower than the median reported in the CS (6.4%) and the majority of values from the literature
% of patients with sufficient viable retinal cells [17]	95%	171	The ERG did not find evidence for the proportion of patients with sufficient viable cells
% of patients who are diagnosed¶	50%	86	One old study conducted in Birmingham in 1978 suggested that up to 50% of patients were derived from sources other than the hospital settings. [11]

Abbreviations: LCA, Leber congenital amaurosis; RP, retinitis pigmentosa.
† Calculated as (2017 population size) x (1 + annual population growth)2
‡ Calculated as (prevalence of RP x % of RP that is *RPE65*-mediated) + (prevalence of LCA x % of LCA that is *RPE65*-mediated)
¶ Clinical experts estimated that between 33% and 50% of patients have been diagnosed with an *RPE65* mutation; given that diagnosis rates may be expected to increase following the availability of voretigene neparvovec, the upper end of this range was used.
Source: company submission pg. 42

ERG comment:

The ERG recognises that there is limited evidence within this patient population group to inform estimates of the disease prevalence and incidence. Therefore there is likely to be some uncertainty about the accuracy of the data available. The evidence used by the company was derived from international studies, which may create uncertainty in the applicability to the UK settings given that population estimates have been found to vary between different ethnicities.

The CS did not report the SLR methods the company used to identify epidemiology data. In clarification, the company provided copies of the literature search strategies for the systematic review. The ERG considered that the searches used were not comprehensive, and that it is therefore possible that relevant papers may have been missed.

The CS estimates that 50% of patients with *RPE65*-mediated IRD in the UK are not currently diagnosed. This evidence was stated to be informed by clinical expert opinion, although data from a UK study[11] conducted in the 1980s was consistent with this estimation. This study was however conducted four decades ago, and may therefore not reflect contemporary practice. Clinical experts to the ERG advised that, compared to the time this study was conducted, genetic eye clinics and testing are now more available to patients, and methods of gene testing are more accurate. The ERG therefore considered that the patient population in the UK diagnosed with *RPE65* IRD is likely to be greater than estimated in the CS, which may have implications for the potential budget impact of VN (see Section 7.3).

The CS did not elaborate on the factors that may explain variations in the distribution of population estimates for IRD. The ERG noted that the prevalence of RP can vary widely, depending on factors such as the degree of homogeneity in ethnicity, geographical location and cultural behaviours.[18] Prevalence is estimated globally at between 1/4500 (0.02%) – 1/3000 (0.03%), but may be much higher in communities with a high rate of consanguinity.[11,18] For example, the prevalence reported among young Muslim population in a UK population study in Birmingham city in 1978 was 0.06% despite being 0.02% for the whole city[11]. This was attributed to the high rate of consanguineous parents among the population.

2.1.2 Aetiology

The CS reports that *RPE65*-mediated IRD is caused by mutations in the *RPE65* gene which causes a deficiency of the functional *RPE65* enzyme involved in the regeneration of the visual cycle.

RPE65-mediated IRD is an autosomal recessive disease;[19] affected individuals carry pathogenic genetic variants in both copies of the *RPE65* gene. Homozygous individuals, carry the same

pathogenic variant on both chromosomes, while compound heterozygous individuals carry two different pathogenic variants in the *RPE65* alleles.[2] Studies investigating the pathogenic variants in homozygous or compound-heterozygous individuals with *RPE65*-mediated IRD have identified missense and nonsense single nucleotide variants, insertions, deletions and splice defects in *RPE65*.[2,19]

ERG comment:

The CS reports that *RPE65* mutations are responsible for *RPE65*-mediated IRD however, no further detail regarding the genetic basis of this disease was reported in the CS.

2.1.3 Pathology

In the visual cycle, signalling is controlled by photosensitive rhodopsin molecules inside the retina.[20] In the absence of light, the 11-*cis*-retinal molecule is covalently bonded to an inactive, opsin signalling protein, this complex is termed rhodopsin.[20] Upon light activation the isomerisation of 11-*cis*-retinal into all-*trans*-retinal causes a conformational change in the opsin signalling protein which triggers a nerve impulse that transmits this signal to the brain.[20]

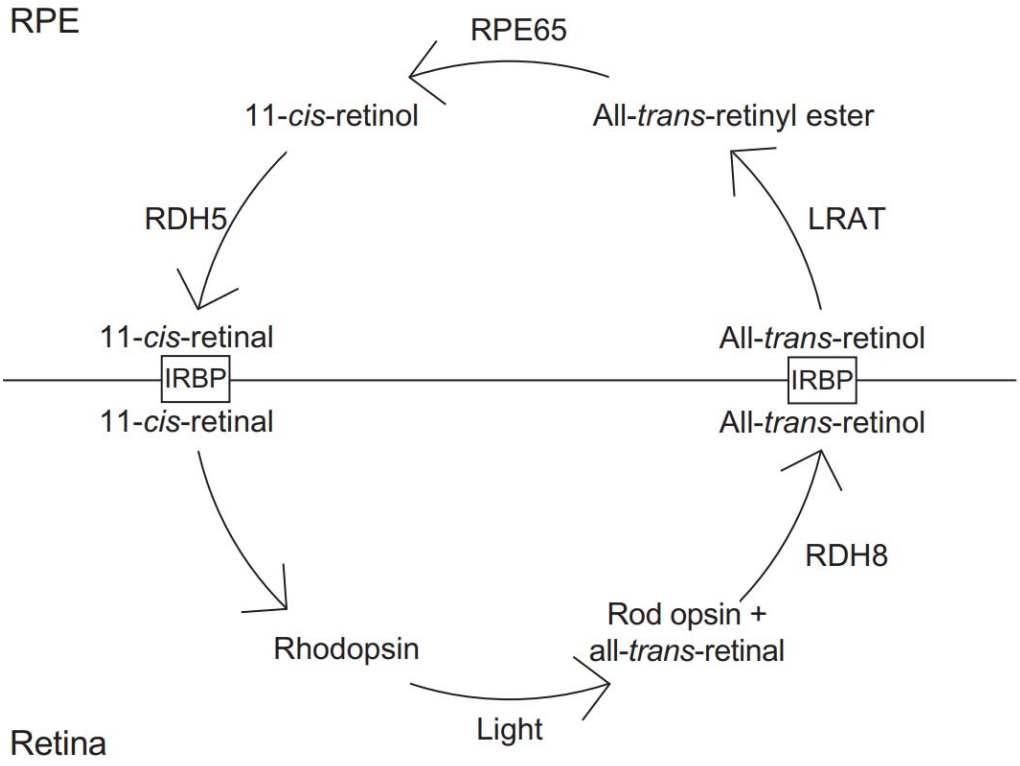
The visual cycle requires the regeneration of 11-*cis*-retinal from all-*trans*-retinal to allow the cycle to continue, as shown in Figure 2. All-*trans*-retinal is reduced to all-*trans*-retinol and is transferred across the interphotoreceptor matrix into the retinal pigment epithelium (RPE).[20] Once inside the RPE, all-*trans*-retinol is converted into all-*trans*-retinyl ester.[20] The *RPE65* enzyme is responsible for the conversion of all-*trans*-retinyl ester into 11-*cis*-retinol which is subsequently oxidised to 11-*cis*-retinal.[2] The 11-*cis*-retinal molecule travels back into the photoreceptor to regenerate the rhodopsin complex allowing continuation of the visual cycle.[20]

Mutations in the *RPE65* gene result in deficiency of functional *RPE65*, arresting the visual cycle.[2] Additionally, the accumulation of toxic precursors results in photoreceptor cell apoptosis.[2]

ERG comment:

The disease pathology description concurs with descriptions published in the literature.

Figure 2: The biochemistry of the visual cycle



Source: CS (page 38); original source Wright 2015[21]

Abbreviations: IRBP, interphotoreceptor retinoid-binding protein; LRAT, lecithin retinol acyltransferase; RDH5, retinol dehydrogenase 5; RDH8, retinol dehydrogenase 8; RPE, retinal pigment epithelium; *RPE65*, retinal pigment epithelium 65kDa protein.

2.1.4 Clinical features

The CS reports that individuals with *RPE65*-mediated disease can present at a range of ages between infancy and adolescence. The submission states that nyctalopia (night-blindness) is the first symptom of this disease. The ERG agreed that nyctalopia is typically considered the first symptoms of *RPE65*-mediated IRD,[22] however notes that not all affected patients experience this symptom.[19] The CS reports that infants frequently present with the 'oculo-digital sign' or eye poking. This symptom is a common feature of LCA[23] however, based on the literature it is unclear how frequently this symptom presents in those with *RPE65*-mediated IRD. Evidence suggests that involuntary eye movement, termed nystagmus, is often observed within this population however this was not reported in the CS.[3,19,24]

The CS describes the degenerative nature of the condition and reports that both VF and VA deteriorate over time, accompanied by a loss of retinal sensitivity. It is also stated that there is no

evidence of spontaneous improvements in VA or VF. The evidence in the literature supports these conclusions.

Regarding the visual field, the submission reports that the merging of peripheral blind spots and loss of central vision in the later stages of disease lead to complete blindness, this statement is based on studies investigating RP. The ERG found no evidence to support this statement in studies investigating only *RPE65*-mediated IRD. The submission also states that patients tend to lose 50% of their remaining vision every five years, this was also based on evidence from a study investigating RP and no evidence specific to *RPE65*-mediated IRD population was found to support this statement.

The company states that visual acuity is usually no higher than 20/400, with 1/3 of infants having no perception of light at all however, reference supporting this statement is a study investigating LCA. The CS also states that the natural history study investigating *RPE65*-mediated IRD reported that by age 18, more than half of the patients had a VA lower than 6/60 in one eye.

An additional clinical feature of disease not reported in the CS is poor performance on electroretinogram assessment; at a young age rod ERGs are frequently undetectable and cone ERGs severely diminished.[19] Additionally, although performance on Optical Coherence Tomography (OCT) assessments for some patients are in the normal range, in some cases preservation of the central macular area is surrounded by a ring of retinal thinning.[22]

ERG comment:

The ERG broadly agreed with the CS description of the clinical features of *RPE65*-mediated IRD, however notes that some of the detail is based on studies investigating either RP or LCA. Several studies have investigated the phenotypic presentation of *RPE65*-mediated IRD, therefore it would have been preferable for the CS to focus on these studies, as some features observed in patients with LCA/RP will not be applicable to the population of interest.

2.1.5 Diagnosis

The CS did not report details of the way in which *RPE65* IRD is diagnosed in practice in the UK. The ERG identified that diagnosis usually involves a comprehensive assessment of medical history, clinical symptoms, and analysis of family history prior to genetic screening.[23] Multigene panel testing or whole exome/genome sequencing may then be used.[23] Multipanel gene testing screens an individual for potentially pathogenic variants in several genes known to be associated with the disease.[23] The genes analysed by this method may vary between laboratories and in some cases may be selected at the clinicians' discretion.[23] Multigene panel analysis can perform sequence analyses,

deletion/duplication analyses and/ or other non-sequence based analyses, and is therefore able to detect several of the different types of variants implicated in *RPE65*-mediated IRD.[23]

The CS reports that RPE54 IRD is currently undiagnosed, with only 50% of people with the disease expected to be diagnosed (CS, p. 42). The company suggest this may be due to the lack of available treatment options undermining the needs for a diagnosis (CS, p.15).

The company note that differentiation of LCA and RP IRD is unreliable, with a minority of patients having received both diagnoses. LCA and RP are typically differentiated by clinical presentation and family history, with LCA presenting earlier and having a more aggressive prognosis (CS, p.36). Clinical experts to the ERG advised that LCA is typically diagnosed shortly after birth, while RP is typically diagnosed in late childhood or early adulthood.

ERG comment:

Standard practice for the diagnosis of *RPE65*-mediated IRD was not reported in the company submission. As discussed in Section 2.1.1, it's unclear whether a 50% diagnosis rate is representative of current practice in the UK; however, the ERG agreed with the company that it is likely that diagnosis rates will increase following the availability of a suitable treatment. The ERG also recognised that diagnosis of the subtypes of LCA and RP IRD may be unreliable.

2.1.6 Prognosis

The CS discussed the degenerative nature of the disease, which eventually culminates in complete/ near-total blindness.[22] Furthermore, the CS states that there is no evidence of spontaneous sustained improvements in either VA or VF.

The rate at which vision deteriorates in patients with this disease varies considerably, this is briefly acknowledged in the CS. The ERG found evidence which suggests that in some patients vision deteriorates rapidly, while some individuals retain some vision into the second and third decades of life, and others maintain central vision until the end of life.[25-27] Conversely, a cohort study of 70 individuals diagnosed with biallelic *RPE65*-mediated IRD reported that more than half of the cohort were blind by age 18, defined as VA<20/200.[3] This study reported that VA was impaired but stable up until age 15, rapid deterioration was reported between the ages of 15-20, followed by more accelerated deterioration after the age of 20.[3] Overall, this evidence suggests that the prognosis for individuals with *RPE65*-mediated IRD is heterogenous.

The company also discusses the complications associated with IRDs such as cataracts and macular oedema. The ERG was unable to find evidence in the literature regarding the incidence of cataracts or macular oedema in those with *RPE65*-mediated IRD.

ERG comment:

The CS discussed the progressive nature of the disease and reports that there is no evidence of spontaneous improvements. In the literature, the number of studies reporting the prognosis for individuals diagnosed with *RPE65*-mediated IRD is relatively low, however the evidence suggests that the rate at which vision deteriorates in individuals diagnosed with this condition varies considerably.

2.1.7 Disease burden and impact

The CS did not elaborate on the disease burden of *RPE65*-mediated IRD. The ERG found evidence that hereditary retinal disorders constitute 20% of the causes of severe sight impairment among working age adults in England and Wales, and accounted for 83 hospital admissions in England between 2014 and 2015.[28,29]

The CS reports that IRD impacts on the visual function of patients early in life. The subsequent social impact of the disease on the patient and the carer may be considerable, and results from the patients' reduced capacity to perform activities such as walking around and driving, especially in dim light. Patients may have to live a significant part of their lives with reduced capacity.

Children's social development could also be affected early in life. The ability to relate and interact well within the household which is important for the child's developmental milestones, is reduced. Thus, children affected by the condition may require special education.[30] The ERG found evidence that self-reported quality of life of children with the condition is worse than that of their siblings, and that of children with chronic systemic disorders.[31]

Employment opportunities are also more likely to be reduced amongst patients, and they are more likely to be earning lower incomes than the general population. Patients are also less likely to have a higher education, less likely to be married, and more likely to retire earlier.[32] These difficulties place both a greater emotional as well as economic burden on the patient, their carers, and other members of the household. An increased risk of depression among the patients, their caregivers and spouses, has also been documented.[33-35]

ERG comment:

There is no evidence specific for the disease burden of *RPE65*-mediated IRD. The CS provides a comprehensive description about different aspects of the effect of IRD on the health-related quality of life (HRQoL) of patients, including the impact on their early lives and education, employment and productivity, mobility, mental health, sleep and driving. The CS reports that patients with IRD experience a gradual deterioration of vision; this has an impact on patients' early life and education, mobility due to night blindness, and mental health. The CS also provides information for the economic and health burden of IRD on caregivers. Other evidence about the impact of IRD on quality of life is based on evidence from other populations with visual impairment. Due to similarity between IRD clinical signs and symptoms and affected population with visual impairment, this evidence is useful but cannot necessarily be accurately generalised due to differences between groups (not least, age). For non-newborn patients the effect of gradual deterioration of vision on quality of life should be captured as well as effect of visual impairment.

The ERG noted that the CS did not report evidence on the quality of life of the carers of the patients; however the ERG were unable to find any evidence for this.

2.2 Current service provision

There are currently no curative or disease modifying treatments available for IRDs, including RP and leber congenital amaurosis (LCA).[36] The Argus II Retinal Prosthesis System, an implanted device, is approved in the United States under a Humanitarian Device Exemption (HDE). The device is indicated for use in patients 25 years of age and older with severe to profound retinitis pigmentosa (bare light or no light perception in both eyes) by providing electrical stimulation of the retina to induce visual perception. Voretigene Neparvovec gained FDA approval in December 2017 and EMA approval in November 2018 (Section 2.3).

In the UK, current management is focused on accurate diagnosis, specialised genetic counselling, strategies to improve the use of residual vision, social and educational support, and is best provided as part of specialised multidisciplinary services.[37] Treatment options are limited and focus on optimising remaining vision, including the use of low vision aids, specialised computer software and mobility training.[37,38] A statement on the clinical assessment of patients with inherited retinal degenerations has been published by the American Academy of Opthalmology.[39] There are, however, very few UK or expert guidelines. The National Institute for Health and Care Excellence (NICE) interventional procedures guidance on the use of subretinal (IPG537) and epiretinal (IPG519) prostheses for RP, each recommend that the devices are only used in the context of research.[40,41]

Current UK guidelines published by the *British Medical Journal* for the management of patients with RP recommend the use of visual aids such as glasses and magnifiers. Adjuncts to these approaches include vitamin A supplementation, fish oils, and lutein, with the aim of slowing retinal degeneration,[42] although clinical advisors to the UK suggest that some of these adjuncts are rarely used in the UK; E.g. vitamin A supplementation. Surgery and carbonic anhydrase inhibitor are recommended for treating posterior subcapsular cataracts and cystoid macular oedema (CMO), respectively, which are common complications.[42] Additionally, children with visual impairment are eligible for learning support provided by a qualified teacher specialised in supporting individuals with vision impairment.[43] For affected adults, treatment is also supportive between clinical care, employers and social services. Genetic counselling is provided via medical genetic services to affected families.

The CS provides a summary of the current clinical pathway of care for *RPE65*-mediated inherited retinal dystrophies (refer to the CS, Section 8.2, Figure 2, p. 52). Most people will typically visit their GP or optometrist in the first instance: symptoms in adults included difficult seeing in dim light or at night, and in babies and young children symptoms noticed by parents include nystagmus, light-seeking behaviours and eye rubbing. If IRD is suspected, referral is made from primary care to a secondary care outpatient ophthalmology service, usually a nearby specialised paediatric ophthalmology centre commissioned nationally by NHS England (NHSE).

Genetic testing is required to detect the presence of pathogenic(s) variants in the *RPE65* gene. It is also commissioned nationally by NHSE, although access varies by region. Once a confirmed diagnosis is made, patients should be referred to a low-vision consultant who can help them to obtain visual aids. The number of tests used varies between centres but all patients should have visual field (VF) tests and an electroretinogram performed.

ERG comment:

The CS reports that current standard of care involves the use of vision aids and learning support for children with visual impairment and states that there are currently no available therapies for *RPE65*-mediated IRD. The CS acknowledges that prostheses are currently only available in the context of research. The ERG concurs with the CS description of current standard of care.

2.3 Description of the technology under assessment

Voretigene neparvovec (VN; Luxturna®; Spark Therapeutics, Inc.) is an adeno-associated virus (AAV) gene therapy treatment which introduces a healthy copy of the defective *RPE65* gene into the retinal cells of patients with *RPE65*-mediated IRD.[44] VN is administered as two subretinal injections (no fewer than six days apart) once per lifetime. Prior to administration (approximately 3 days

before), patients are required to receive an immunomodulatory regimen (such as prednisone), which is expected to be continued for a further 18 and 30 days, depending on the timing of the second administration (i.e. the other eye).

The European Medicines Agency (EMA) awarded VN marketing authorisation on 22 November 2018.[45] VN is expected to be used in line with the marketing authorisation for the treatment of individuals with vision loss due to leber's congenital amaurosa (LCA) or retinitis pigmentosa (RP) inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations. Orphan status was maintained at the time of marketing authorisation:[46] the two previous orphan designations for the "treatment of LCA" and "treatment of RP" were merged to "treatment of IRDs".

The introduction of *RPE65* enables patients to produce functional *RPE65* protein. The subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells.[44] This enables patients to produce functional *RPE65*, resulting in improved functional vision (improved ability to perform vision-related daily activities) and visual function (improved performance of the eyes at the organ level). In order to derive benefit from VN treatment, the company states that patients must have confirmed biallelic (pertaining to both paternal and maternal alleles) *RPE65* mutations and have sufficient viable retinal cells into which healthy copies of the *RPE65* gene can be introduced.

ERG comment:

The CS provides a relatively short description of VN. *RPE65* was noted by the clinical experts as crucial in the visual (retinoid) cycle, and is located in the retinal pigment epithelial cells (discussed further in Section 2.1). Successful introduction of a healthy copy of the *RPE65* gene is expected to lead to long-term improvements in visual function (and consequently, functional vision), though it was noted by the ERG's clinical experts that there is currently no evidence to suggest that introduction may stop degeneration entirely or cause regeneration. The ERG's clinical experts also noted the importance of having sufficient retinal cells in order to benefit from VN – some patients with *RPE65*-mediated IRD may have irreversible retinal deterioration and therefore would be highly unlikely to be able to benefit from treatment.

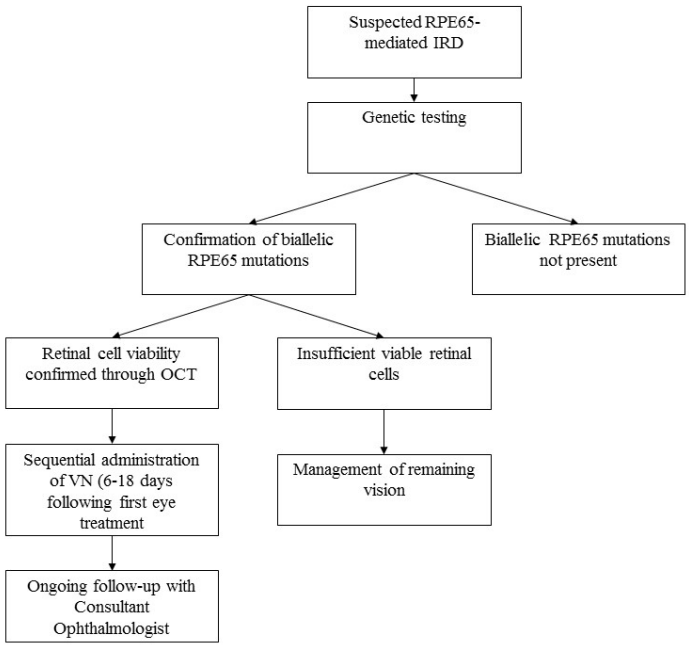
2.4 Current usage in the NHS

Voretigene neparvovec (VN) is not currently used in the UK for any patient population. VN is the first gene therapy to be approved for a retinal disease.

In the CS, the company proposed that treatment is offered to patients with confirmed biallelic *RPE65* mutations with sufficient viable retinal cells (Figure 3). Genetic testing will therefore be required to determine eligibility for treatment. In the clinical trials of VN, patients were deemed to have sufficient

viable retinal cells if they had an area of retina within the posterior pole of >100 micron thickness, as estimated by OCT. In clinical practice, OCT examinations are more likely to be qualitative, and supplemented by tests of VA and VF. Treatment will be initiated by a consultant in retinal degeneration and administered by a retinal surgeon experienced in performing macular surgery. A single dose will be administered to each eye within a close interval between six and 18 days apart.

Figure 3: Proposed pathway of care incorporating VN



Key: IRD, inherited retinal disease; OCT, optical coherence tomography; *RPE65*, retinal pigment epithelium-specific 65 kDa protein; VN, voretigene neparvovec

NHS England currently directly commissions specialised ophthalmology services including the treatment of ocular genetic disorders. These are best managed by specialist networks which provide multidisciplinary services including diagnosis, testing, counselling and imaging as well as treatment. It is anticipated that the treatment would be used in this clinical setting and implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services. The company anticipate that VN gene therapy will fit a specialised centre model, with diagnosis, counselling, treatment and follow-up performed at a few centres nationally. Treatment centres will need to meet EMA risk management plan criteria.

The company note that genetic testing and counselling will need to be available to patients who might benefit from treatment (CS, Section 8.7). In current practice, the frequency of monitoring varies dependent on disease severity and complications. The company note that, other than increased

frequency, monitoring requirements will not change (CS, Section 8.4.3). Monitoring will take place every three to six months following administration and then annually once the patient is stable.

Treatment will be initiated by a consultant in retinal degeneration and administered by a retinal surgeon experienced in performing macular surgery. The company note that surgeons will be required to attend a four to five hour session at a preclinical clinical research organisation in Denmark or France, and pharmacists a two to three hour onsite session. The cost of these education sessions will be covered by the company. The focus of the training will be to provide education on the EMA risk management program as well as specific surgical and pharmacy handling techniques outlined in the Summary of Product Characteristics (SmPC).

The company also note that to reduce the risk of an immunomodulatory response, prednisone (or equivalent) should be initiated, starting three days prior to administration and lasting between 18 and 30 days. One course of prednisone (or equivalent) treatment will be sufficient to cover the fellow eye administration as this is expected to be planned six to 18 days following the first eye administration (CS, Section 8.7.2, Table 5).

Facilities will be required by the pharmacy handling the product to keep it at the required storage temperature (≤65C) and quarantine level. Pharmacies will require a Laminar Flow Cabinet for the preparation of the syringes for subretinal injection. The ERG was advised by clinicians that such facilities would be available in all centres likely to administer the treatment. For this reason, no special arrangements or changes to existing practices are likely to be needed.

ERG comment:

The ERG generally agreed with the proposed use of VN in the clinical pathway.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Introduction

The objective of this section is to critique to what extent the CS adheres to the final NICE scope. The scope aimed to evaluate the benefits and costs of VN within its marketing authorisation for treating inherited retinal dystrophies caused by *RPE65* gene mutation. The critique will consider the intervention, population, comparators, outcomes, nature of the condition, impact of the new technology and the cost to the NHS and Personal Social Services (PSS) addressed in the CS.

3.2 Adherence to the decision problem

Table 2 presents a summary of the decision problem as set out in the NICE and some comments from the ERG considering the CS.

Table 2: Adherence of the CS to the decision problem

	Final Scope	Deviation of CS from final scope
Population	People with inherited retinal dystrophies caused by *RPE65* mutations	The population is broader than specified in the scope, but is in line with the licensed indication; i.e. Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells
Intervention	Voretigene neparvovec	The intervention is in line with scope
Comparator(s)	Best supportive care	The comparator is in line with scope
Outcomes	• Best corrected visual acuity (both eyes) • Visual field • Contrast sensitivity • Photosensitivity • Need for cataract surgery • Adverse effects of treatment • Health-related quality of life (for patients and carers)	The outcomes assessed are broadly in line with the scope. Of note, the multi-luminance mobility test (MLMT) is also considered as an outcome measure in the CS. This outcome is the primary measure considered in the pivotal clinical trial. The ERG also noted that data for contrast sensitivity and the need of cataract surgery were not reported in the CS; and no health-related quality of life data was presented. No data for the impact of treatment on carers was presented.
Subgroups to be considered	None specified	Not applicable

Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	The nature of the condition is broadly in line with scope. However, the ERG noted the absence of data on the impact of the disease on carer's quality of life.
Clinical effectiveness	• Overall magnitude of health benefits to patients, and when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	Treatment continuation rules are not considered as VN is a one-time treatment. Heterogeneity of health benefits could not be evaluated, as no subgroups were prespecified in the clinical trials due to the small sample size.
Cost to the NHS and PSS, and Value for Money	• Cost-effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	The cost to the NHS and PSS, and value for money were in line with scope.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Where there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services. The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	The impact of the technology beyond direct health benefits and on the delivery of the specialised service were in line with scope

Other considerations	• Guidance will only be issued in accordance with the marketing authorisation • Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye • Guidance will take into account any managed access arrangements	The CS defines health states based on the average of the two eyes. The CS gives the rationale as established symmetry between the eyes for IRDs and the difference in results between modelling the average eye and the best-seeing eye is negligible

Source: CS, p. 20-21

3.3 Population

The population in the CS was aligned with the EMA MAA and the population in the pivotal trial (Study 301/302 and Study 101 and Study 102); i.e. paediatric and adult patients with vision loss due to IRD caused by biallelic *RPE65* mutations and who have sufficient viable retinal cells.

Inherited retinal dystrophies (IRDs) are a heterogeneous group of rare diseases caused by germline mutations in more than 260 genes, including the *RPE65* gene.[1] Patients are primarily diagnosed with either retinitis pigmentosa (RP) or leber congenital amaurosis (LCA) (refer to Section 2.1).[2] The ERG noted that the population inclusion criteria for the pivotal trial specifies the inclusion of patients with LCA (a specific subtype of *RPE65*-related IRD). The recruitment of patients to the trials presented in the CS is unclear, but appears to have favoured the inclusion of patients with LCA. Patients with LCA represent a minority of patients with *RPE65*-mediated IRD, and have a worse prognosis. While the ERG were unaware of evidence to suggest that the treatment effect was likely to differ dependent on a diagnosis of LCA or RP, it noted that this may impact on the generalisability of absolute data (such as speed of visual deterioration).

The requirement for patients to have sufficient retinal cells was defined in the CS per the definition in Study 301/302: an area of retina within the posterior pole of >100 μm thickness shown on OCT; ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole or remaining visual field within 30-degrees of fixation. In clinical practice, the company note that this evaluation may be more qualitative, and supplemented by tests of VA and VF (CS, p. 54). Clinical advice indicated that the presence of sufficient viable retinal cells is necessary to facilitate the treatment mechanism of VN, and it is feasible for this criterion to be assessed in practice.

These factors are discussed in more detail in Section 4.2.2.2 of the ERG report.

ERG Comment:

In summary, given the population characteristics of the evidence base, the ERG considered the population informing the decision problem to be narrower than that outlined in the NICE final scope but note that it is aligned with the marketing authorisation for VN. However, the ERG considered the population from which evidence is derived to predominantly reflect the population most likely to be treated with VN and to be relevant to the decision problem.

3.4 Intervention

The intervention included within the CS is VN (Luxturna®) in line with its licensed indication (refer to Section 2.4). There is no variation between the technology as described in the CS and in the NICE scope.

A single dose of 1.5×10^{11} vector genomes in each eye, is delivered into the subretinal space in a total volume of 0.3 mL (refer to the CS, Section 2, pages 24 to 25). Injections are usually given at least six days apart. An immunomodulatory regimen should be initiated, starting three days prior to administration and lasting between 18 and 30 days, depending on the timing of administration to the second eye. The dose is given once per lifetime. The ERG noted that no further information was provided about background care received by patients during the trials.

The dose and administration of VN used in Study 301/302 is consistent with its licensed indications and how the treatment is expected to be used in practice. The ERG highlight the extended duration between treatments in Study 101/102 but clinical advice indicated that the impact was unlikely to be significant.

For more details on the intervention refer to Section 4.2.2.3 of the ERG report.

ERG Comment:

In summary, the ERG considered the intervention for which evidence is presented in the CS to be consistent with the NICE final scope.

3.5 Comparators

The comparator is described in the CS is best supportive care (BSC); however, no definition of BSC is provided in the CS.

There is no licenced medical product for *RPE65* mediated sight loss and treatment options are limited and focus on visual rehabilitation, including the use of low vision aid, specialised computer software and mobility training. Surgical devices are available; however, these are only recommended in research (refer to Section 2.1.7 of the ERG report).

ERG Comment:

In summary, given the population for which evidence has been submitted, the ERG and its clinical advisors agreed with the company that BSC is the most relevant comparator in the setting of IRDs caused by *RPE65* gene mutations.

3.6 Outcomes

The company state that no treatments are currently available for *RPE65*-mediated IRD, and therefore no precedents exist for endpoints to assess the therapeutic benefits of products for this unique group of diseases. The measurement of visual acuity (VA), VF and contrast sensitivity are generally well accepted as the best visual predictors of mobility performance. For people with low vision, orientation and mobility are more affected by spatial contrast sensitivity and VF than by VA, although these parameters vary widely. The measurement of VA, VF and contrast sensitivity to be clinically relevant in the population in this assessment, and is consistent with the evaluation of visual impairment across other populations. However, these endpoints are challenging to measure in the population considered in this assessment because baseline visual function is poor, and they do not capture characteristic features of the condition; e.g., night blindness, reduced light sensitivity, and nystagmus. These measures are also difficult to use in paediatric populations.

In context of these condition-specific features the company designed and validated the multi-luminance mobility test (MLMT).[47] The MLMT measures changes in functional vision, as assessed by the ability of a subject to navigate a course accurately at a reasonable pace at different levels of environmental illumination. Change in MLMT from baseline to one year was the primary endpoint of the company's pivotal Phase 3 clinical trial (Study 301/302). Although the ERG noted that these data are not used in the economic model.

The ERG noted that no data was reported for the need of cataract surgery following treatment. Safety data indicate that patients receiving VN are at a higher risk of cataracts, and the proportion of patients who would require cataract surgery was estimated in the company's economic model, although the basis for this estimation is unknown.

Finally, no health-related quality of life (HRQoL) was reported in the CS. Rather, the company present the impact of treatment with VN on visual function using a patient-reported outcome (PRO). However, this evidence does not capture the possible impact of treatment on the broader HRQoL of patients. Further, no evidence was presented on the impact of treatment on the carers of patients with *RPE65* IRD.

For more details on outcomes and appropriateness of outcome measures refer to Section 4.2.2.4 of the ERG report.

ERG Comment:

In summary, the ERG considered the outcomes presented in the CS to be clinically relevant to the decision problem and to be aligned with the final scope issued by NICE, however, the ERG also noted the absence of outcomes from the CS that are clinically relevant; for example, the need for cataract and most importantly the absence of HRQoL data.

3.7 Costs to the NHS and PSS, and value for money

As specified in the NICE scope, the economic impact of VN was compared with BSC was analysed by the company in terms of its budget impact in the NHS and personal social services (PSS), and included costing and budget impact information. Outcomes were assessed over a lifetime horizon. The ERG's critique of the company's economic analysis is given in detail in Section 5.

3.8 Other relevant factors

In the CS, the company highlights that the population considered in the submission (visual impairment resulting from *RPE65* mutation) is a protected group under the Equality Act 2010. The company notes that there is a non-uniform distribution of *RPE65* mutations between different ethnic groups with prevalence highest in South Asian population and note that clinical advice has suggested that prevalence is highest among South Asian populations living in the UK due to consanguinity (CS, Section 5.1).

The company also highlight that access to genetic testing in regions of the UK is variable and the absence of available treatment options to date.

ERG Comment:

In general, the ERG considered the equality issues raised in the CS to be reasonable.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company presented a literature search protocol to support its review of clinical effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy, and a search of conference websites. The literature search was carried out in March 2018 and updated in January 2019.

The bibliographic database searching used a search strategy that took the following form:

(controlled index terms for retinal dystrophy/leber congenital amaurosis) OR
(free-text terms for retinal dystrophy/leber congenital amaurosis) AND
(controlled index terms OR free text terms for *RPE65* gene) AND
(search results limited to humans in Medline and Embase).

The search strategy was applied in the following bibliographic databases: Medline and Embase (Elsevier at Embase.com), Medline-in-Process (OvidSP), and The Cochrane Library (OvidSP).

A number of relevant conference websites were searched. Clinicaltrials.gov was searched for ongoing and recently completed trials

The literature searching for clinical effectiveness studies was conducted in an unusual manner. A very narrow population search was carried out (for patients with *RPE65* gene mutation only) and no intervention search was carried out. Usual practice would be to search for a broader population (retinal dystrophies more generally) in combination with the intervention in question (VN).

When a more suitable structured search was trialed in Ovid Medline only (March 2019 - broader population plus intervention – results of the search compared to the results of the company search using NOT) we identified a further 1,447 papers which had not been found by the company searches. A paper may not necessarily specifically mention *RPE65* gene mutation in its title or abstract, even if it is mentioned in the full text of the article, therefore it is possible that the narrow search conducted by the company could have excluded relevant articles. We did not screen the 1,447 additional papers retrieved, but some may potentially have been relevant.

We do not have access to Embase.com so are unable to test the searches but the value of searching Medline and Embase simultaneously with one strategy is debatable since these databases use different indexing terms (Emtree for Embase and MeSH for Medline).

Cochrane Library searches were carried out in EBMR (Ovid) not in The Cochrane Library database itself. Since EBMR is only updated quarterly it is possible that some more recent studies might have been missed.

ERG Comment:

Although the clinical effectiveness searches were not conducted in the most comprehensive way, this is not likely to have had a significant impact on the review in this case as it is likely that the company is already aware of the significant literature and trials in this area.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the Company's SLR of clinical effectiveness of evidence are summarised in Table 3.

Table 3: SLR of Clinical Effectiveness Evidence Inclusion Criteria

Inclusion criteria	
Population	Patients with inherited retinal dystrophies caused by *RPE65* gene mutations
Interventions	Voretigene neparvovec (AAV2-h*RPE65*v2)
Outcomes	Clinical efficacy: • Multi-luminance mobility test • Full-field light sensitivity threshold • Visual acuity • Visual field Safety†: • Treatment emergent adverse events (TEAEs) • Serious adverse events • Administration related TEAEs
Study design	• Randomised controlled trials • Phase 1/2 studies
Language restrictions	English
Search dates	From inception of database to 8th March 2018 (initial search) and to 11th January 2019 (update search)
Exclusion criteria	
Population	Patients with inherited retinal dystrophies caused by gene mutations other than *RPE65*
Interventions	• Gene therapy using other vectors (e.g. rAAV2-CBSB-h*RPE65*, tgAAG76, rAAV2-CB-h*RPE65*, rAAV2/4.h*RPE65*, rAAV2-h*RPE65*) • Other oral preventive drugs (e.g. QLT091001, oral synthetic cis-retinoid)
Outcomes	None
Study design	• Reviews • Editorials • Notes

Inclusion criteria	
	• Opinions • Case reports
Language restrictions	None
Search dates	None

Abbreviations: *RPE65*, retinal pigment epithelium 65 kDa protein; TEAE, treatment emergent adverse event.

Notes:

† These outcomes were included to capture studies relevant to Section 9.7.1 and Appendix 2 on adverse events. Source: CS, p. 5-6

ERG Comment:

The ERG found that the inclusion and exclusion criteria for the SLR were broadly appropriate. The population matched the decision problem, as did included interventions. Exclusion of other gene therapy interventions posed the risk that studies that could have contributed to a network meta-analysis might have been missed; however, the ERG's further work on searching (Section 4.1.1) suggested this possibility was very small. Of note is that a comparator was not specified, leaving open the question of how this was included in study selection.

Outcomes included were a subset of those described in the decision problem; specifically, need for cataract surgery and HRQoL were not included in the criteria. While it would have been preferable to describe all relevant outcomes as part of inclusion criteria, it is again unlikely that with such a small evidence base studies would have been missed.

Given the size of the patient population included in this disease, the decision to include phase 1 and 2 studies alongside randomised trials was appropriate. Restriction of language to English may have missed some studies, though the small evidence base generally makes this possibility unlikely.

4.1.3 Data extraction

Details of screening and data extraction are provided in CS (17.1.7; Appendix 1). A two-stage screening process was adopted, with a first-pass screening based on titles and abstracts followed by a second-pass screening for full-text publications. Screening was undertaken in duplicate and independently, with recourse to a third reviewer. In the CS, numbers of studies excluded by reason were provided, but these numbers did not tally in the included PRISMA diagram for the update search. The company provided an updated diagram in response to clarification. In addition, a list of excluded studies was not provided as part of the CS. This was also provided in response to clarification.

Data from included studies were extracted by one reviewer and checked by a second independent reviewer, with reconciliation of any differences carried out by a third independent reviewer. Details of the extraction form were not provided.

ERG Comment:

The ERG judged that the process on study selection followed appropriate methodological practice. The table of excluded studies provided offered a study-level description of reasons for exclusion and increased confidence in the appropriateness of decisions taken. The ERG also judged that the procedure for data extraction described in the CS fulfilled minimum accepted methodological practice, though details of data extraction grids used would have increased confidence in the process.

4.1.4 Evidence synthesis

In the CS (section 9.8.2; p. 130), the company describes that no meta-analysis was undertaken because only one comparative study was included. The ERG regarded that this was an appropriate decision.

4.1.5 Quality assessment

The quality assessment strategy for Study 301/302 used an adapted version of the York Centre for Reviews and Dissemination checklist (CS section 9.5.1, p. 95). The number of reviewers involved and whether judgments were checked or undertaken in duplicate was not stated. Moreover, neither a strategy for appraisal, nor the results thereof, were presented for Study 101/102 despite this study's inclusion throughout the CS.

ERG Comment:

The CS included an appropriate quality assessment tool and provided judgements to support ratings. However, lack of detail on how the appraisal was carried out and the absence of appraisal of Study 101/102 decrease confidence in the quality assessment strategy used. The ERG replicated the appraisal (Section 4.2.5) to remedy these issues.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Excluded Studies

In clarification, the company provided the table of excluded studies for this systematic review. This is clearly presented with most studies being excluded on publication type, population or outcome. It was

not possible for the ERG to review whether the reasons for excluding studies were justifiable, therefore cannot rule out the possibility that relevant data may have been excluded. However given the size of the evidence base in this patient group, this was judged to be unlikely.

4.2.2 Included Studies

The company included 22 publications in their review. These publications reported data from 2 trials (Studies 101 and 301), each followed by an extension period (Studies 102 and 302, respectively). Due to an overlap in participants and methodology between the original and extension trial phases, the company refers to the trials as Study 101/102 and Study 301/302 (although note that the company highlight a partial change in methodology between Studies 101 and 102; see Sections 4.2.2.1 - 4.2.2.4). Evidence for the four trials were reported in 10 published records and 12 unpublished records (see Table 4 below).

Table 4: List of Trial Publications

Study name (NCT ID)	Study Design	Primary Study Reference	Secondary Study References [publication type]
Study 101 (NCT00516477)	Phase 1 open-label, single arm safety evaluation	Maguire et al. (2009)[48]	Maguire et al. (2008)[49] [oral presentation] Simonelli et al. (2010)[50] Testa et al. (2013)[51] Ashtari et al. (2011)[52] Study 101 CSR[53]
Study 102 (NCT01208389)	Crossover phase of Study 101	Bennett et al. (2016)[54]	Ashtari et al. (2017)[55] Bennett et al. (2012)[56] Maguire et al. (2017)[49] [oral presentation] Study 102 CSR[57]
Study 301 (NCT00999609)	Open-label RCT (VN vs. BSC)	Russell et al. (2017)[58]	Hui et al. (2016) [short report] Chung et al. (2017) [abstract] Leroy et al. (2016) [abstract] Leroy et al. (2018) [abstract] Study 301 CSR[59]

Study name (NCT ID)	Study Design	Primary Study Reference	Secondary Study References [publication type]
Study 302 (NCT reference includes follow up of patients across all trials: NCT03602820) (	Crossover/continuation phase of Study 301	(not published)	Maguire et al. (2017)[60] [slide desk] Russell et al. (2017)[61] [poster presentation] Russell et al. (2018)[62] [abstract] Leroy et al. (2018)[63] [abstract] Maguire et al. (2018)[64] [abstract]

Key: BSC, best supportive care; RCT, randomised controlled trial; VN, voretigene neparvovec

4.2.2.1 Study Design

Table 5 provides an overview of the study designs of the three studies evaluating VN; all included trials were consistent with the decision problem and the scope issued by NICE. The pivotal trial for the submission is Study 301/302; an open-label, multi-centre, phase 3 RCT involving 31 patients (Study 301), followed by an optional phase after one year where 9/10 (90%) patients from the control arm received VN (Study 302). Patients were recruited from multiple countries worldwide, and travelled to sites in the US for treatment administration and follow-up. Study 301/302 is ongoing: data up to and including a four-year follow-up was available for some, though not all, outcomes in this submission. Patients will ultimately be followed-up for 15 years. An infographic of the design of Study 301/302 is presented in Figure 4.

Study 101/102 is an open-label, phase 1, single-arm trial. Study 101 employed a dose-ranging design; with patients receiving either a 'low', 'medium', or 'high' dose of VN in a single (worse, non-preferred) eye. Patients travelled to sites in the US for treatment administration, following which 7/12 (58.3%) were followed up in the US, and 5/12 (41.7%) were followed up in Italy. After a minimum of 1 year, patients from Study 101 were invited to receive VN in the contralateral eye: 11/12 (91.7%) patients from Study 101 were eligible for entry into Study 102. All patients in Study 102 received a 'high' dose of VN in their contralateral (better, preferred) eye.

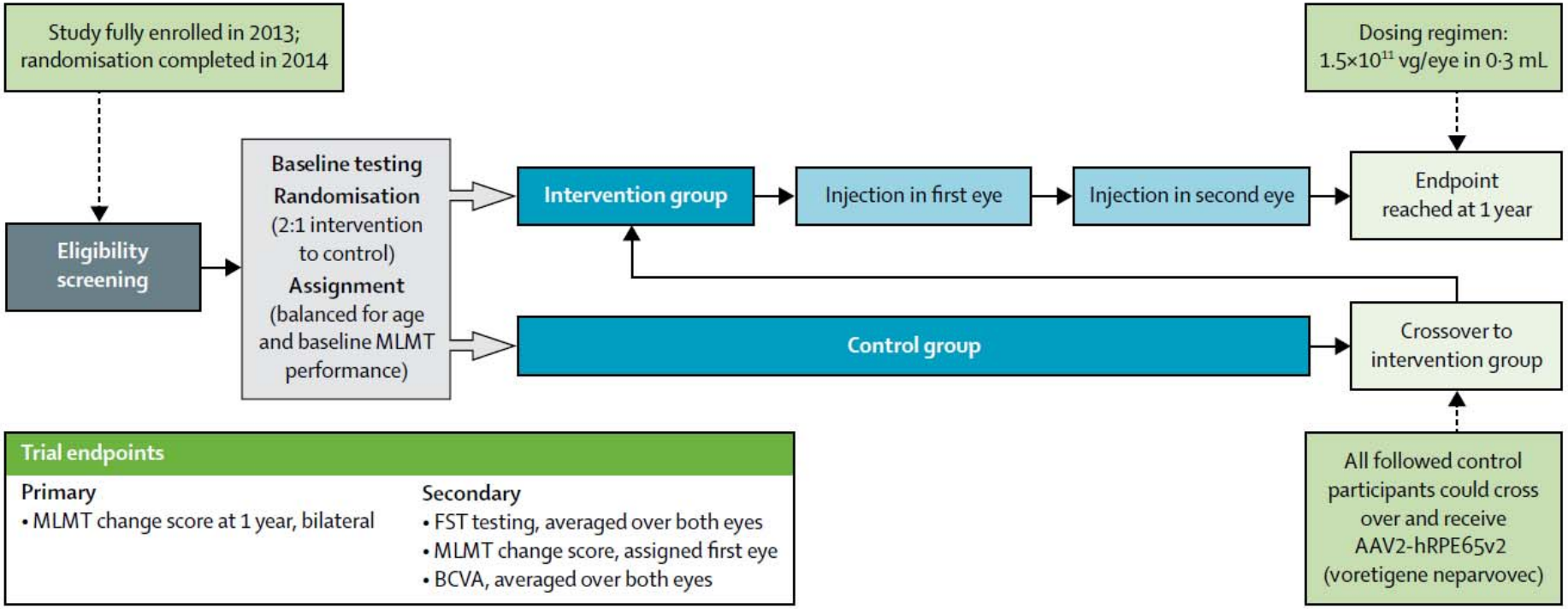
Table 5: Study Designs of the Trials of the Technology of Interest

	Study 101	Study 102	Study 301/302
Sample size	12	11	31
Randomisation status	Non-randomised phase 1 safety study	Non-randomised Follow-on safety study	Randomised Phase 3 RCT
Multi-centre trial?	Yes, multi-centre trial in USA and Italy	No. Single-centre trial in USA	Yes, multi-centre trial in USA
Blinding	Open label	Open label	Open label

	Study 101	**Study 102**	**Study 301/302**
Intervention	Sub-retinal injection of 1.5 x 10^{10} vg (low dose), 4.8 x 10^{10} vg (middle dose) or 1.5 x 10^{11} vg (high dose) of AAV2-h*RPE65*v2 into patients' worse, non-preferred eye.	Subretinal injection of 1.5 x 10^{11} vg of AAV2-h*RPE65*v2 into the previously uninjected, contralateral eye	Sub-retinal injection of 1.5 x 10^{11} vg AAV2-h*RPE65*v2 (voretigene neparvovec) in each eye.
Control	N/A (single arm)	N/A (single arm)	Untreated for at least one year from baseline. After one year control patients were eligible to receive the intervention.
Follow-up	15 years	15 year	15 years

Source:CS p.28-30

Figure 4: Infographic of Study 301/302 Design



Abbreviations: BCVA, best-corrected visual acuity; FST, full-field light sensitivity threshold; MLMT, multi-luminance mobility test; vg, vector genomes.

Source: CS Figure 5, p. 70. Original source Russell 2017[58]

The key objectives for the three studies are summarised below in Table 6, Table 7, and Table 8. The objectives of Study 101/102 were primarily to evaluate the safety and tolerability of VN in human patients. After establishing acceptable safety of VN at a high dose in Study 101/102, Study 301/302 was intended to establish the impact of VN on clinical outcomes.

Table 6: Study 101 Primary and Secondary Objectives

Primary Objectives	To determine the safety and tolerability of subretinal administration of voretigene neparvovec to patients with LCA due to *RPE65* mutations
Exploratory Objectives	To assess the objective clinical measures of efficacy in human patients

Table 7: Study 102 Primary and Secondary Objectives

Primary Objectives	To assess the safety and tolerability of non-simultaneous, bilateral subretinal administration of voretigene neparvovec
Exploratory Objectives	To evaluate the efficacy of contralateral eye administration of voretigene neparvovec, using pre-injection measurements of the eye to be injected as a control

Table 8: Study 301/302 Primary and Secondary Objectives

Primary Objectives	To determine whether non-simultaneous, bilateral sub-retinal administration of AAV2-h*RPE65*v2 improved the ability to navigate (as measured by mobility testing) in adults and children, three years of age or older, with LCA due to *RPE65* mutations
Secondary Objectives	To continue to assess the safety and tolerability of AAV2-h*RPE65*v2 administrations

ERG Comment:

The evidence base for VN in this patient population consists of two small trials, each with an optional phase to extend treatment to the contralateral eye. These trials include one small, Phase 1, single arm trial (Study 101/102) to establish the safety of VN in human populations, and one small Phase 3 RCT (Study 301/302) to compare the clinical efficacy of VN in comparison to best supportive care. In total, the trials are comprised of 43 patients with biallelic *RPE65* IRD. The small evidence base for VN is representative of the rare nature of this condition, but does provide limited evidence of the effectiveness of VN beyond the limits of the research settings and study designs.

The study designs are appropriate to the research aims and objectives, and the long-term follow-up employed by both trials may provide useful data on the long-term effect and safety of VN. At present, follow-up data is available up to 4 years following administration, which the ERG judged to be acceptable for determining the safety of VN (given that many adverse events of treatment were expected to be related to the administration of VN). The company claim that VN will have a lifetime

impact on the sight of patients with biallelic *RPE65* IRD. This can evidently not be demonstrated from the current treatment follow-up; however the ERG judged that a four year follow-up is acceptable for determining whether VN may result in some clinical benefit for patients.

For the majority of patients (26/31; 83.9%), treatment was administered at centres in the US. However, feedback from clinical experts for the ERG was that the settings of the evidence base can be generalised to UK practice.

4.2.2.2 Population

The key inclusion and exclusion criteria reported in the CS for both studies are summarised below in Table 9.

The ERG noted that the population characteristics used in the included trials for the technology of interest (VN) and best supportive care (BSC) were consistent with licensing authorisation; i.e. adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations who have sufficient viable retinal cells. The ERG noted that the population characteristics included in all three studies were narrower than those specified in the NICE scope for this appraisal; however, the ERG judged the change to be appropriate. Expert advisors to the ERG suggested that the requirement for patients to have a sufficient number of viable retinal cells is necessary to facilitate the treatment mechanism of VN. The ERG noted that patients are excluded from the included trials if they have a retina less than 100 microns (equivalent to more than half of a normal retina's thickness). Expert advisors to the ERG acknowledged that while 100 microns seems to be an arbitrary number (and apparently being used as a proxy for the health of the photoreceptors), if VN is injected into a retina with thickness of less than 100 microns, it seems reasonable to assume that there would be fewer viable retinal cells and hence improvements would be less likely. Given the localised action of gene therapy, and the need for safe administration of VN to sufficient retinal cells to ensure there are grounds for improvement, the ERG agreed that it seems reasonable to limit the trial population to people with retina thickness of more than 100 microns at the site of injection. However, the ERG noted that this additional criterion would mean it likely that some patients included in the population specified in the NICE scope would be excluded for treatment with VN because they have no viable retina to treat. In practice, it's unclear whether this threshold of retinal thickness would be strictly used: the company state (CS, p.54) that they expect OCT tests in practice to be more qualitative, and to be supplemented by tests of VA and VF. Clinical advisors to the ERG suggested that this may result in a similar population identified for treatment, as patients who demonstrate visual function using VA and/or VF tests may be assumed to have sufficient retinal cells to experience some treatment benefit.

The ERG also noted that population inclusion criteria for Studies 101/102 and 301/302, as described in the CS and trial CSRs, specify the inclusion of patients with a specific subtype of *RPE65* related IRD, Leber's congenital amaurosis (LCA). However a footnote to the inclusion criteria (CS Table 9, p. 71-74; CS Table 11, p. 84-87) adds that patients were eligible if they had a "molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations… regardless of clinical diagnosis". This presumably permits the inclusion of patients with RP IRD. However if this is the case, the ERG are unclear why trial inclusion criteria primarily specify patients with LCA only, and whether this means that patients with LCA were favoured in recruitment strategies for the trials, or constituted a higher proportion of patients in the trial samples. The CS did not provide a breakdown of the proportion of patients diagnosed with LCA vs. RP IRD, and the ERG were unable to find this information in the respective CSRs. While the ERG acknowledge some overlap in the diagnostic criteria for RP and LCA, typically patients with LCA are rarer and exhibit a more aggressive prognosis.[65] Clinical advisors to the ERG were unaware of evidence that would prevent generalising evidence from patients with LCA to those with RP, and suggested that the treatment effect is likely to be unaffected by diagnosis. However, the ERG noted that absolute data (such as the speed of visual deterioration) may not be comparable between LCA and RP patients. Nevertheless, as it is not clear from the CS whether trial samples involved a greater proportion of LCA patients, it is not possible to draw a conclusion about whether this could affect the applicability of the evidence base.

Patient populations and eligibility criteria were broadly similar between the Phase 1 and Phase 3 trials, although three changes in inclusion criteria for Study 301/302 are notable. Firstly, trial inclusion criteria for Study 301/302 was extended to include younger children between the ages of 3 and 7 years. Age is thought to influence the potential treatment effect of VN, due to the potential benefits of administering VN prior to further retinal degeneration. Criteria for Study 301 were further restricted to include those with more severe deficits in VA (from VA of 20/160 in Study 101/102 to 20/60 in Study 301/302), although as baseline VA was not reported in the CS for Study 101/102, it was not possible for the ERG to determine if the change in inclusion criteria resulted in worse VA at baseline in Study 301/302. Clinical experts to the ERG advised that both age and baseline VA may have an impact on treatment outcome, and therefore differences may be expected in the treatment outcome between Study 101/102 and Study 301/302; although the direction and magnitude of any difference is not yet understood. Ultimately as Study 101/102 is under-powered to evaluate clinical effectiveness of VN and is non-comparative in design, emphasis on clinical efficacy outcomes should be given to data from Study 301/302.

Changes in eligibility criteria were included for patients in Study 102 following their participation in Study 101; these were intended to ensure that patients had VA equal to or greater than light perception

(and had therefore not deteriorated below this since participation in Study 101), and more stringent criteria were introduced for Studies 102/301/302 for determining the number of viable retinal cells (≥3 disc areas of retina in Studies 102/301/302 compared to Study 101).

Table 9: Studies 301/302 and 101/102 Key Population Inclusion Criteria

	Study 301/302	**Study 101/102**
Inclusion criteria	• Adults and children (aged ≥3 years) diagnosed with LCA≠. • Molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations • BCVA worse than 20/60 (both eyes) and/or visual field less than 20^0 in any meridian (both eyes) • Sufficient viable retinal cells as defined by: o an area of retina within the posterior pole of > 100 µm thickness as shown on OCT; o ≥ 3 disc areas of retina without atrophy of pigmentary degeneration within the posterior pole based on ophthalmoscopy; or o remaining visual field within 30^0 of fixation. • Ability to perform mobility testing (primary efficacy endpoint) at Screening within the luminance range evaluated in the study: o by receiving an accuracy score of ≤ 1 at 400 lux (maximum light level); and o by being unable to pass	• Adults and children (aged ≥8 years) diagnosed with LCA. • Molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations • Visual acuity ≤ 20/160 or visual field less than 20° in the eye to be injected. • Sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy:

	Study 301/302	**Study 101/102**
	mobility testing at 1 lux (minimum light level).	
Key Exclusion criteria	• Prior participation in a study in which a gene therapy vector was administered • Use of high-dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months • Prior intraocular surgery within six months • Sensitivity to medications planned for use in the peri-operative period • Pre-existing eye conditions or complicating systemic diseases (in which the disease itself or treatment of it could alter ocular function) that would preclude the planned surgery or interfere with study interpretations • Pregnancy or unwillingness to use effective contraception for four months following vector administration • Inability to perform mobility testing (primary efficacy endpoint) for reasons other than poor vision, including physical and attentional limitations	• Participation in a clinical study with an investigational drug in the past six months • Prior intraocular surgery within six months • Sensitivity to medications planned for use in the peri-operative period • Pre-existing eye conditions that would preclude the planned surgery or interfere with interpretation of study endpoints • Pregnancy or unwillingness to use effective contraception for the duration of the study • Presence of neutralising antibodies to AAV2 above 1:1000

Note that key inclusion criteria only have been included in this table; the full list of inclusion/exclusion criteria reported is available in the CS, p. 71-72; 84-85; 87-88

≠ The following footnote was added to the inclusion criteria specified in the CS: "Although LCA is mentioned, patients were eligible if they had molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations i.e. regardless of clinical diagnosis."

Study 301/302

Demographic information for patients included in Study 301, as provided in the CS, is summarised in Table 10. Demographic information is not presented separately for the 9 patients in the control arm (90%) who crossed over to VN in Study 302, although will likely be highly similar.

The company report that population demographics were generally well matched between arms. [redacted] On the basis of the evidence, therefore, it is not possible to determine whether patients in the VN arm had improved vision at baseline. However, the lack of adjustment of baseline data adds uncertainty to the validity of the estimated treatment effect.

Clinical advisors to the ERG were not aware of evidence of variation in disease burden or treatment effect according to race, ethnicity, or patient nationality. The CS notes that the prevalence rate of *RPE65*-related IRD is higher amongst patients of South Asian descent (p.34), however it is not yet known whether patients also experience differential prognosis. The ERG noted a higher proportion of Black/African American patients in the VN arm (2/21; 9.5%) compared to the BSC arm (0/10; 0%), and a greater number of Hispanic/Latino patients (5/21; 24% vs. 1/10; 10%). Further, the nationality of patients in either arm was found to vary: in the VN arm, 85% of patients were from North America and 4.8% from Europe; compared to 60% and 40% in the BSC arm, respectively. However, it is not clear whether these differences will have impacted on the treatment effect.

Table 10: Study 301 Trial Population (ITT population)

Category	VN (N=21)	BSC (N=10)	Total (N=31)
Age at Randomisation (years)			
Mean (SD)	14.7 (11.8)	15.9 (9.5)	15.1 (10.9)
Range (min, max)	4 - 44	4 - 31	4 - 44
Male, n (%)	9 (43%)	4 (40%)	13 (42%)
Race, n (%)			
White	14 (67%)	7 (70%)	21 (68%)
Asian	3 (14%)	2 (20%)	5 (16%)

Category	VN (N=21)	BSC (N=10)	Total (N=31)
Native American Indian or Alaska	2 (10%)	1 (10%)	3 (10%)
Black or African American	2 (10%)	0	2 (6%)
Ethnicity, n (%)			
Not Hispanic or Latino	16 (76%)	9 (90%)	25 (81%)
Hispanic or Latino	5 (24%)	1 (10%)	6 (19%)
Country, n (%)			
United States	17 (81%)	6 (60%)	23 (74%)
Netherlands	1 (5%)	2 (20%)	3 (10%)
Belgium	0	1 (10%)	1 (3%)
Canada	1 (5%)	0	1 (3%)
India	1 (5%)	0	1 (3%)
Italy	0	1 (10%)	1 (3%)
Mexico	1 (5%)	0	1 (3%)
Baseline visual outcomes			
[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	-
[redacted]	[redacted]	[redacted]	-

Abbreviations: BSC, best supportive care; FST, full-field light sensitivity; MLMT, multi-luminance mobility test; SD, standard deviation; SE, standard error; VA, visual acuity; VF, visual field; VN, voretigene neparvovec

Source: CSR, p. 42, Appendix 6, Table 3; and data provided at clarification

≠ Holladay scale

∞ mITT population

*Hand calculated by the ERG based on data supplied by the company at clarification

Table 11: Study 301 MLMT Performance at Baseline (ITT population; proportions represent the final pass rate at each light level)

Lux level, n (%)	Intervention (N=21)	Control (N=10)	Total (N=31)
1	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]
125	[redacted]	[redacted]	[redacted]
250	[redacted]	[redacted]	[redacted]
400	[redacted]	[redacted]	[redacted]
> 400	[redacted]	[redacted]	[redacted]

Source: CSR, Appendix 6, Table 4

Study 101/102

Population characteristics for patients in Study 101/102, as reported in the CS, are summarised in Table 12.

As expected for the low sample size within each dosing arm, [redacted]. There is an absence of evidence for the role of gender in treatment prognosis for this patient group, however as noted above, clinical advisors to the ERG advised that age at baseline may impact on the likely treatment effect, with treatment at a younger age being potentially more beneficial. Baseline visual performance was not reported in the CS, although consistent with procedures for favouring the worst, non-preferred eye for injection in Study 101, [redacted] (Study 101 CSR, p. 59).

Table 12: Study 101/102 Patient Demographics (all patients)

		Study 101				Study 102
Parameter		**Low Dose (N=3)**	**Middle Dose (N=6)**	**High Dose (N=3)**	**Total (N=12)**	**Total (N=11)**
Gender, n (%)	Male	1 (33%)	4 (67%)	2 (67%)	7 (58%)	6 (55%)
	Female	2 (67%)	2 (33%)	1 (33%)	5 (42%)	5 (46%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years	Mean (SD)	23.7 (4.0)	14.7 (6.6)	30.3 (17.2)	20.8 (11.2)	22.8 (10.26)
	Median (IQR)	26.0 (7.0)	13.5 (11.0)	36.0 (33.0)	19.5 (15.5)	23.0 (15.0)
	Min, Max	(19,26)	(8,24)	(11,44)	(8,44)	(11,46)

Source: CSR, Appendix 6, Table 1

ERG Comment:

There are several differences in population characteristics between the VN and BSC arms in Study 301. Given the small size of the trial, the ERG considered a number of differences between arms to be inevitable and to not necessarily represent a violation in randomisation. None of the differences at baseline were considered by the ERG to demonstrate a clear bias in any direction, although it was noted that only a small number of characteristics were reported at baseline.

While age differences were noted between the randomised groups at baseline, clinical advice suggested that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population. Retinal function at baseline was suggested to be a potentially stronger mediator of treatment response, which may be partially correlated with age.

Due to the small sample size of the studies it was not possible for the company to adjust for baseline visual performance. As differences in MLMT, VA and VF were noted at baseline of Study 301/302, and as these outcomes represent the key clinical data underpinning this appraisal, this contributes to uncertainty in the effect estimate for these outcomes. However, as there is no evidence to support how visual performance at baseline could affect the treatment effect, the ERG is unable to comment on the potential impact this may have.

Due to the paucity of evidence for this population group, there is uncertainty over additional population characteristics that may be associated with treatment prognosis, and therefore whether the trial populations may be more or less representative of the intended treatment group or whether differences between the trial arms are present. Given the small size of both studies, it is likely that there are unknown differences in population characteristics at baseline between studies and trial arms.

It is unclear why the company specify the inclusion of patients with LCA in their trial inclusion criteria for Studies 101/102 and 301/302, and whether this means that the study sample is more representative of patients with LCA, who have a worse prognosis than those with RP. There is no evidence that treatment is likely to be more or less effective in patients with LCA than RP, although the ERG noted that this may impact on the generalisability of absolute data (such as speed of visual deterioration).

Inclusion criteria that were changed between Study 101/102 and study 301/302 were judged by the ERG to be appropriate for evaluating VN in this patient population, although the ERG noted that this may have resulted in some differences between study samples.

4.2.2.3 Intervention and Comparator

The intervention characteristics used in the trials evaluating VN, as detailed in the CS, are summarised in Table 13 below.

VN was administered as a one-off treatment for each eye, delivered into the subretinal space in a total volume of 0.3mL. Study 101 evaluated three doses of VN; a low (1.5×10^{10} vg), middle (4.8×10^{10} vg), and high dose (1.5×10^{11} vg). The high dose of VN was subsequently used exclusively in Study 102 and Study 301/302, and is the dose at which VN is licensed for use in this population. Following Study 101/102, where the minimum time between treating each eye permitted by the trial design was

1 year, the manufacturers introduced guidance that there should be between 6 – 18 days between administering VN to each eye. Patients treated with VN also require treatment with immunomodulatory agents, starting 3 days prior to administration and lasting between 18 – 30 days, depending on the timing of administration to the second eye.

The ERG noted that no further information was provided about background care received by patients during the trials. The ERG considered it likely that patients receiving VN would also receive BSC, since this would not be contraindicated and does not form part of the exclusion criteria for any of the studies. As such, the ERG considered the intervention could be described as VN plus BSC. The comparator intervention for Study 301, stated to be BSC, is not described in the CS. The ERG understands that BSC in the UK may include monitoring, psychological support, visual rehabilitation, and wearing sunglasses. More invasive therapy (such as the use of retinal prostheses) is used in the US, and also for research purposes in the UK. The ERG assumed that these were not permitted during the trials (although this is not stated clearly in the CS).

Table 13: Studies 301/302 and 101/102 Intervention Characteristics

Treatment	**Study 101**	**Study 102**	**Study 301/302**	
	N=10	N=9	VN: N=21	BSC: N=10
Intervention	Sub-retinal injection of 1.5 x 10^{10} vg (low dose), 4.8 X 10^{10} vg (middle dose) or 1.5 x 10^{11} vg (high dose) of AAV2-h*RPE65*v2 into one eye	Sub-retinal injection of 1.5 x 10^{11} vg of AAV2-h*RPE65*v2 into the contralateral eye not injected in Study 101 (min time between treatments = 1 year; mean/variance not reported)	Sub-retinal injection of 1.5 x 1011 vg of AAV2-h*RPE65*v2 in each eye. Mean time between treatments = 8.8 days (variance not reported)	Not described; assumed to be the same as Study 301
Background care	Prednisone at 40 mg/day for the first 10 days and 20 mg/day for an additional 7 days.	Prednisone at 1 mg/kg/day for 10 days (max dose 40 mg/day) followed by 0.5 mg/kg/day for an additional 7 days (max dose 20 mg/day). Prednisone was started 3 days before treatment.	Prednisone at 1 mg/kg/day for 7 days (max dose 40 mg/day), beginning 3 days before first injection). Prednisone was tapered until 3 days before injection of the second eye, when the steroid regimen was repeated.	Not described

Source: CS pages 72, 85 and 88. Russell et al. (2017)[58] Study 101 CSR Table 9.6

ERG Comment:

The ERG considered it likely that patients in the VN arm of Study 301/302 received BSC as background care, and therefore the treatment evaluated in this trial may be considered to be VN + BSC. There is limited detail about the nature of BSC received by patients in the control arm of Study 301, and in the background of treatment arms in the three studies. The comparator is therefore unclear. As some BSC interventions may be associated with improvements in visual function, such as the use of visual aids, the presence or absence of such interventions in the control arm of Study 301 would aid interpretation of the reported effect size.

The dose and administration of VN used in Study 301/302 is consistent with its licensed indications and how the treatment is expected to be used in practice. The extended duration between treatments in Study 101/102 may result in increased deterioration of the retina in the contralateral eye, although clinical experts to the ERG did not believe significant change to occur within 1 year.

Due to the small sample size of Study 101/102, the company did not plan subgroup analyses, such as might investigate whether a dose effect occurs for VN, although given the sample size of this study and the presence of other confounding factors, it would not be possible to identify a dose effect from this evidence.

4.2.2.4 Outcome Assessment

An overview of the outcomes evaluated in the included studies is provided in Table 14; further details of the outcomes assessed, their measurement and analysis are reported in Table 15.

Table 14: Studies 301/302 and 101/102 - Overview of Outcomes Reported

Outcome	Study 101	Study 102	Study 301	Study 302
Visual Acuity	✓	✓	✓	✓
Visual Field	✓	✓	✓	✓
Contrast Sensitivity	✗	✗	✓	✓
Photo sensitivity	✓	✓	✓	✓
Need for cataract surgery	✗	✗	✗	✗
MLMT	✗	✓	✓	✓
Modified-VFQ	✗	✗	✓	✓
Health related quality of life	✗	✗	✗	✗
Safety	✓	✓	✓	✓

Abbreviations: MLMT, Multi-luminance mobility test; VFQ, visual function questionnaire

The ITT population (all patients randomised) was stated to be prioritised for clinical outcomes, while the mITT/safety population (excluding 2 patients who dropped out of the study prior to knowing treatment allocation) is reported for AE data and for some outcomes, which was judged by the ERG to be appropriate.

Several limitations in outcome assessment were noted as important. Firstly, while randomisation was stratified by age (</≥ 10 years), it was not feasible for the company to adjust outcome data for baseline characteristics, due to the small sample size of both trials. It is unclear how this limitation may impact on the treatment outcome; based on the limited data provided and the evidence known about prognostic markers in this population, there is no consistent pattern in either amplifying or reducing the potential treatment effect.

Secondly, as noted in the CS, scoring for the MLMT exhibits a ceiling effect inherent to the design of the task. As the test does not allow for testing at light levels lower than 1 lux (equivalent to a moonless summer night or an indoor night light; CS p. 78), change scores will be capped at this light setting. The ERG agreed with the company's assertion that this may underestimate the mean change in patient scores on the test, which may result in an underestimation of the treatment effect. This will be applicable to continuous data only (mean final/change scores), but will not impact on the proportion of patients who achieved a change greater than 1 light level, which is also reported in the CS, as all patients were at least 1 light level away from the ceiling at baseline.

Thirdly, while VA and VF are the only two outcome measures that have been used successfully to approve new drugs for retinal application, there are known limitations with the reliability of their measurement. Natural variability in VA between assessments means that obtaining a representative estimate may require multiple tests. In Study 301/302, VA was assessed as the average BCVA of each eye (rather than bilaterally). The company state that this may underestimate the clinically useful vision that is achieved with both eyes open (CS, p. 136). Further, many patients with IRD have such poor vision or fixation that VF testing cannot be performed reliably; while VF testing is clinically relevant as a loss of visual field is a key and early symptom of the condition, this very feature can lead to indeterminate test results (CS, p. 82), and is likely only possible in children over 7 or 8 years of age. Further, it should be noted that available measures of contrast sensitivity rely on knowledge of the alphabet, and are therefore not suitable for use in children unable to recognise letters.

Fourthly, the ERG do not consider the VFQ to be an appropriate replacement for a measure of HRQoL. The VFQ, which has been used extensively to evaluate vision-related functioning in patients with age-related macular degeneration, and demonstrates good reliability and construct validity[66], was modified for use in Study 301/302. The CS does not report details about the way in which the measure

was modified, however a report of the psychometric properties of the measure provided by the company describes the modifications as 'substantial' (p.10).[67] These modifications are stated to have been made to better assess functional vision in patients with *RPE65* IRD, and clinical advisors to the ERG advised that the modifications were appropriate. Psychometric data for the tool also indicates that it demonstrates good reliability and validity. However, the ERG noted that in this process items related to HRQoL were removed from the tool, and therefore this outcome is considered by the ERG to be appropriate for evaluating visual function in this patient population, but cannot be used to evaluate HRQoL.

Finally, it should be noted that the objective of Study 101/102 was to evaluate the safety of VN, and while clinical efficacy endpoints were evaluated (including VA, VF, FST, contrast sensitivity, and mobility assessment), the study was not powered to evaluate change in these outcomes.

ERG Comment:

The measurement of VA, VF, and contrast sensitivity was clinically relevant in this patient population, and is consistent with evaluation of visual impairment across other populations. However, their measurement is widely considered to be unreliable, due to inter-test variability in this population requiring greater improvements from baseline to demonstrate a treatment benefit. MIDs for these outcomes are derived in considered of inter-test variability.

The ERG agreed that the ceiling effect inherent to the MLMT measure may underestimate the treatment effect reported for continuous data. The ERG considered this to be an important outcome for evaluating the impact of visual impairment on functioning; however a clinical advisor to the ERG suggested that the current scoring (change in the light level under which patients could complete the course) may be less sensitive to assessing functional vision than a change in the time it takes patients to complete. The ERG also considered there to be uncertainty in the validity of the company's threshold for a clinically meaningful change (1 lux).

The modified VFQ should be considered an appropriate measure of functional vision in these patients, and has acceptable psychometric properties. However, items related to HRQoL from the original tool were removed, and the ERG did not consider this measure to measure HRQoL following treatment with VN. No HRQoL data, or PRO data to evaluate the burden of *RPE65*-mediated IRD for carers, was reported in the CS, which the ERG considered to be an important omission.

Table 15: Studies 301/302 and 101/102 Outcome Assessment

Endpoint		Study 101	Study 102	Study 301/302
Visual acuity (VA) testing	**Definition**	The ability to identify images presented as shapes/letters of different size; measured as BCVA. Measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) in adults and the HOTV test in children. Lower scores = better acuity. Clinically meaningful improvement defined as a change in LogMAR ≥0.3.	The ability to identify images presented as shapes/letters of different size; measured as BCVA. Measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) in adults and the HOTV test in children. Lower scores = better acuity Clinically meaningful improvement defined as a change in LogMAR ≥0.3.	The ability to identify images presented as shapes/letters of different size; measured as BCVA. Measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) in adults and the HOTV test in children. Lower scores = better acuity Clinically meaningful improvement defined as a change in LogMAR ≥0.3.
	Time-points outcome reported	Baseline and yr1	Assessed but not reported	Baseline, d1, d30, d90, d180, yr1, yr2, yr3, yr4
	Statistical methods	The level of central visual resolution was converted to a visual angle score [Logarithm of the Minimum Angle of Resolution (LogMAR)] for comparison purposes. Comparison of the injected and uninjected eyes at baseline and Year 1 visits. Missing values were treated as missing without any imputation	N/A	Change in (LogMAR) bilateral visual acuity at Year 1 as compared to baseline Change in (LogMAR) VA. Off-chart LogMAR assignments were using the Holladay scale. Sensitivity analyses for VA used the scale proposed by Lange 2009
	Analysis population	PP	N/A	ITT and mITT

Endpoint		Study 101	Study 102	Study 301/302
Visual Field (VF)	**Definition**	Function of different regions of the retina determined by manual kinetic photopic visual fields (pre- and post-injection). Measured according to the Goldmann perimetry test. Higher scores = greater visual field Clinically meaningful change: 20% change from baseline score	Function of different regions of the retina. Kinetic fields to be measured with Goldman perimetry; static fields measured with Humphrey computerised testing. Higher scores = greater visual field Clinically meaningful change: 20% change from baseline score	Function of different regions of the retina. Kinetic fields to be measured with Goldman perimetry; static fields measured with Humphrey computerised testing. Higher scores = greater visual field Clinically meaningful change: 20% change from baseline score
	Time-points outcome reported	Assessed but not reported	Assessed but not reported	Baseline, d30, d90, d180, yr1, yr2, yr3
	Statistical methods	N/A	N/A	Change from baseline; final values at each time point.
	Analysis population	N/A	N/A	mITT
Contrast sensitivity	**Definition**	Subject's ability to discern targets presented at varying levels of contrast. Testing was carried out using best-corrected visual acuity. Higher scores = better contrast sensitivity. Change of 0.3 log units is clinically meaningful (CS p.110)	Subject's ability to discern targets presented at varying levels of contrast. Change following injection to the contralateral eye; evaluated using pre-injection, follow-on baseline evaluations as a control. Higher scores = better contrast sensitivity	Subject's ability to discern targets presented at varying levels of contrast. Assessed using the Pelli-Robson Change of 0.3 log units is clinically meaningful (CS p.110) Higher scores = better contrast sensitivity

Endpoint		Study 101	Study 102	Study 301/302
			Change of 0.3 log units is clinically meaningful (CS p.110)	
	Time-points outcome reported	Assessed but not reported	Assessed but not reported	Baseline, d30, d90, d180, yr1
	Statistical methods	N/A	N/A	Change from baseline and score at each timepoint, transformed into log units. Note that this test is not suitable for young children, although missing data not reported.
	Analysis population	N/A	N/A	PP
Full field light sensitivity threshold testing (FST)	**Definition**	The threshold of light brightness that can be seen. Lower thresholds = better sensitivity Clinically meaningful change: 10 dB or 1 log.	The threshold of light brightness that can be seen. Lower thresholds = better sensitivity Clinically meaningful change: 10 dB or 1 log.	FST reflects underlying physiological function by measuring light sensitivity of the entire visual field. Lower thresholds = better sensitivity Clinically meaningful change: 10 dB or 1 log.
	Time-points outcome reported	Baseline, d14, d30, d60, d90, d180, d270, yr1	Baseline, yr1.5, yr2, yr3, yr3.5 yr4, yr4.5, yr5, yr5.5, yr6.5 and yr7.5	Baseline, d30, d90, d180, yr1, yr2 and yr3.

Endpoint		Study 101	Study 102	Study 301/302
	Statistical methods	Change in full-field light sensitivity before and after injection FST data were not available for all patients/timepoints as the equipment was not available at the start of the trial (CS, p. 116). Missing values were treated as missing without any imputation	Change in FST following injection to the contralateral eye evaluated using pre-injection, follow-on baseline evaluations as a control.	Change in white light FST averaged over both eyes at year 1 relative to baseline
	Analysis population	PP	ITT	ITT and mITT
MLMT	**Definition**	Subject's ability to navigate a short obstacle course with both eyes open (except for some cases where either the injected eye or the uninjected eye was occluded) and varying light levels. Lower scores = better performance Change ≥1 lux levels indicates a clinically meaningful improvement	Subject's ability to navigate a short obstacle course with both eyes open and varying light levels. Lower scores = better performance Change ≥1 lux levels indicates a clinically meaningful improvement	Subject's ability to navigate a short obstacle course with both eyes open. Lower scores = better performance Change ≥1 lux levels indicates a clinically meaningful improvement
	Time-points outcome reported	N/A	Baseline, d60, d90, yr1, yr2, yr3 and yr4	Baseline, d30, d90, d180, yr1, yr2, yr3 and yr4
	Statistical methods	ITT population Monocular assessment: evaluated in first treated eye.	ITT population. Monocular and bilateral assessment. Change in MLMT following injection to the contralateral eye evaluated using pre-injection, follow-on baseline evaluations as a control	ITT [primary] and mITT [secondary] Monocular and bilateral assessment. Change in bilateral mobility test performance relative to baseline. Bilateral performance on the MT as measured by a change score.

Endpoint		Study 101	Study 102	Study 301/302
	Analysis population	N/A	ITT	ITT [primary] and mITT [secondary]
HRQoL	**Definition**	[redacted]	N/A	No measures of HRQoL were evaluated in the included trials. The CS reports results of the modified-Visual function questionnaire, which consists of 25 questions pertaining to perceived difficulty of ADL that are dependent upon vision or have a vision component Scale 0-10; higher = improved visual function [redacted]
	Time-points outcome reported	N/A	N/A	Baseline, d30, d90, d180, yr1,
	Statistical methods	NR	N/A	Change from baseline and score at each time point
	Analysis population	NR	N/A	mITT
Adverse events (AEs)	**Definition**	Incidence of adverse events listed as treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in response to unilateral (one eye) injection with low dose, middle dose and high dose VN	Incidence of adverse events listed as treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in response to injection with low dose, middle dose and high dose VN following non-simultaneous bilateral subretinal administration of VN	Incidence of adverse events listed as treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in response to injection with high dose VN in both eyes

Endpoint		Study 101	Study 102	Study 301/302
	Time-points outcome reported	Baseline and yr7	Baseline and yr4	Baseline and yr1
	Statistical methods	Adverse events analysed by relatedness to study drug and to administration procedure.	Adverse events analysed by relatedness to study drug and to administration procedure.	Adverse events analysed by relatedness to study drug and to administration procedure.
	Analysis population	mITT	mITT	mITT

Abbreviations: AE, adverse events; ADL, activities of daily living; ITT, intention to treat; mITT, modified ITT; N/A, not applicable; NR, not reported; PP, per protocol; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Source: CS; additional information identified from: Study 101 CSR, Table 9.3,[53] Study 102 CSR 102,[57] Study 301 CSR[59]

4.2.3 Clinical Effectiveness

4.2.3.1 Clinical outcomes

The CS reported data for most, though not all, of the outcomes known to have been assessed in the trials: data were not reported for contrast sensitivity for patients in Study 101/102, and no data on the need for cataract surgery was reported for either trial. There was some variation in the timepoints reported for each outcome, the reasons for which are unclear: the longest follow-up data in Study 301/302 was only reported in the CS for VA and MLMT, and FST in Study 101/102. At clarification, longer follow-up data for patients in Study 301/302 was reported for VF.

The NICE scope specifies that clinical effectiveness should be demonstrated with consideration of (i) the overall magnitude of health benefits to patients/carers; and (ii) the heterogeneity of health benefits within the population. The company reported MIDs in the CS for most outcomes: VA (CS p. 116), CS (CS, p.110), FST (CS, p. 116), and MLMT (CS, p.103). The ERG identified an MID for the modified VFQ from their company's psychometric report,[67] although note that this has not been externally validated. Clinical advisors to the ERG further provided a MID for VF, which is based on estimates of between-test variability in VF.[68] All MIDs used in this appraisal are reported in Table 15. The company state that they were unable to evaluate heterogeneity in the treatment effect, due to the size of the trial samples precluding satisfactory subgroup analyses. However, at the request of the ERG, the company provided one subgroup analysis evaluating the treatment effect across age groups (see Section 4.2.3.1.6).

4.2.3.1.1 Visual Acuity (VA)

Visual acuity (VA) was evaluated in all included trials as BCVA. Unless specified otherwise, data for VA are reported as the average performance of each eye. The proportion of patients whose vision changed so as to no longer meet the criteria for blindness in the UK was not reported nor calculable from the data provided in the CS.

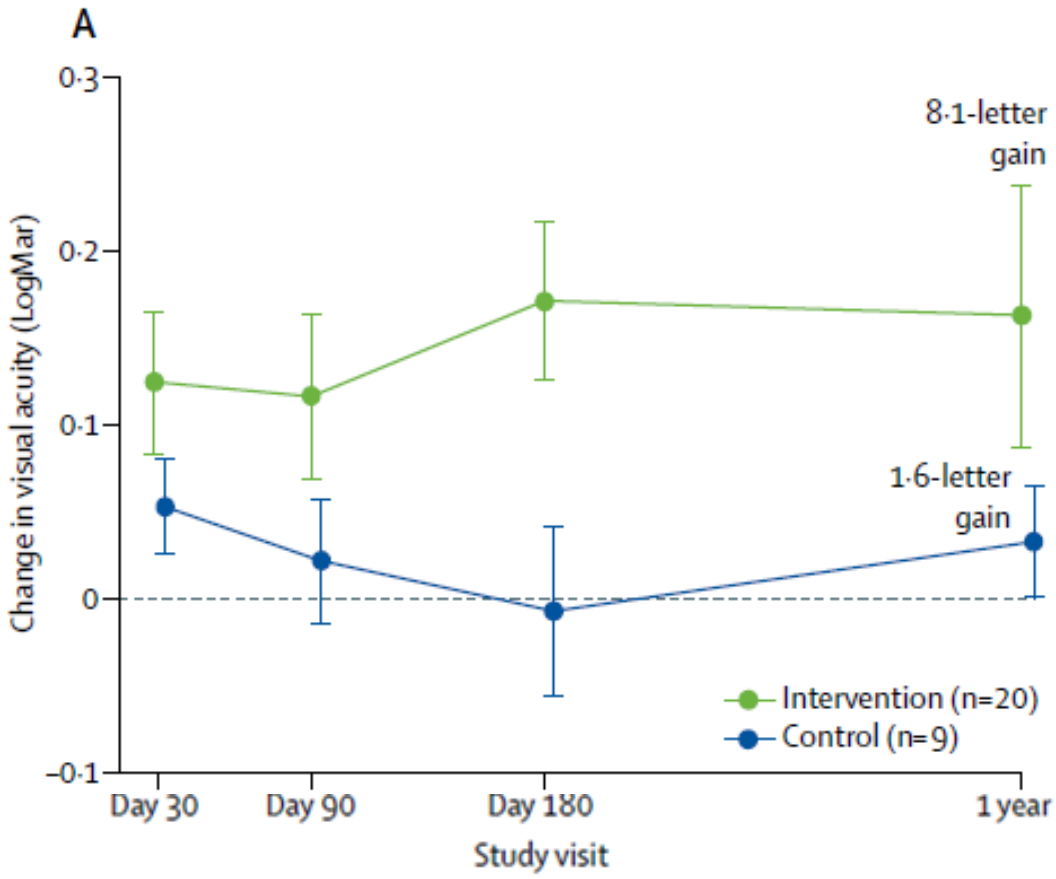
Details of the measurement of VA in the included trials is summarised in Section 4.2.2.4.

Study 301/302

According to measurements using the Holladay scale, there was no statistically significant difference in the change in VA between baseline and 1 year between patients in the VN and BSC arms (CS p. 99, 104, 107). In the ITT population, there was a numerical difference of 0.16 LogMAR in change of VA between VN and BSC (95%CI -0.41, 0.08; p=0.17), which indicates a small improvement in VA in the VN arm compared to BSC. There was no change in mean VA of patients in the BSC arm (mean

0.1; SE = 0.10), but an improvement of 0.16 in the VN arm (SE = 0.07). Results were comparable in the mITT population (p.105): mean change in VA was reported as -0.16 in the VA arm compared to -0.03 in the BSC arm (MD not reported; 95%CI -0.37, 0.11; p = 0.27). This was reported to be equivalent to a mean change in each group as 8.1 letters for VN and 1.6 letters for BSC (no variance reported; see Figure 5). All changes in VA were under the company's definition of a clinically meaningful change (≥0.3 LogMAR).

Figure 5: Study 301 Mean change in VA between 30 days and 1 year (Holladay scale; mITT population)



Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; mITT, modified intention-to-treat.

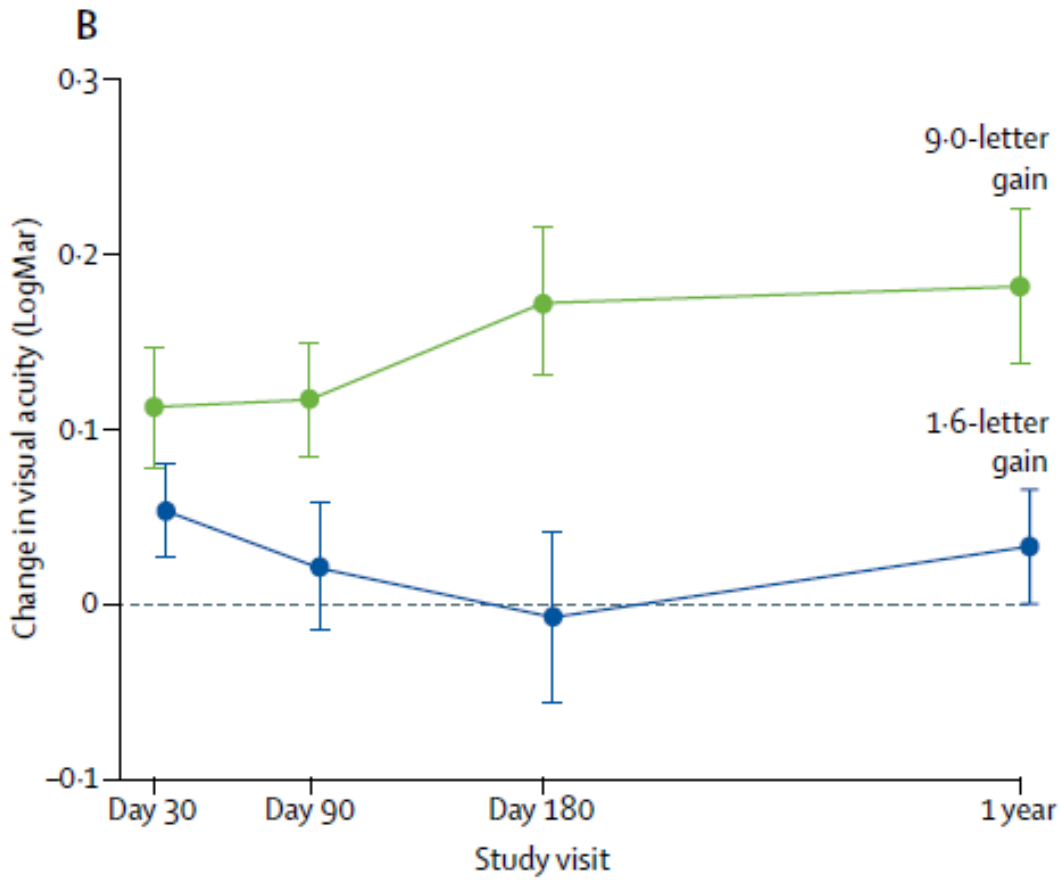
Notes: Green line represents VN arm; blue line represents BSC arm. Error bars represent standard errors.

Source: Russell 2017[61]

A post-hoc analysis of VA according to the Lange scale demonstrated a marginally statistically significant difference in mean VA between VN and BSC at 1 year. In the ITT population, a mean difference of -0.15 was reported (95%CI -0.29, 0.00; p = 0.047), corresponding to a 7.5 letter difference between VN and BSC arms. There was a mean improvement of 9 letters in the VN arm,

compared to 1.6 letters in the BSC arm (mITT population; MD not reported; 95%CI 0.1, 14.6; p = 0.0469). Data for this population at 1 year is reported in a plot (see Figure 6), which appears to show a numerical difference in VA at 30 days, and at all timepoints up to and including 1 year. However, this change did not meet the company's definition of a clinically meaningful change. Data is not reported for the ITT population at 1 year in the CS.

Figure 6: Study 301 Mean change in VA between 30 days and 1 year (Lange scale; mITT population)

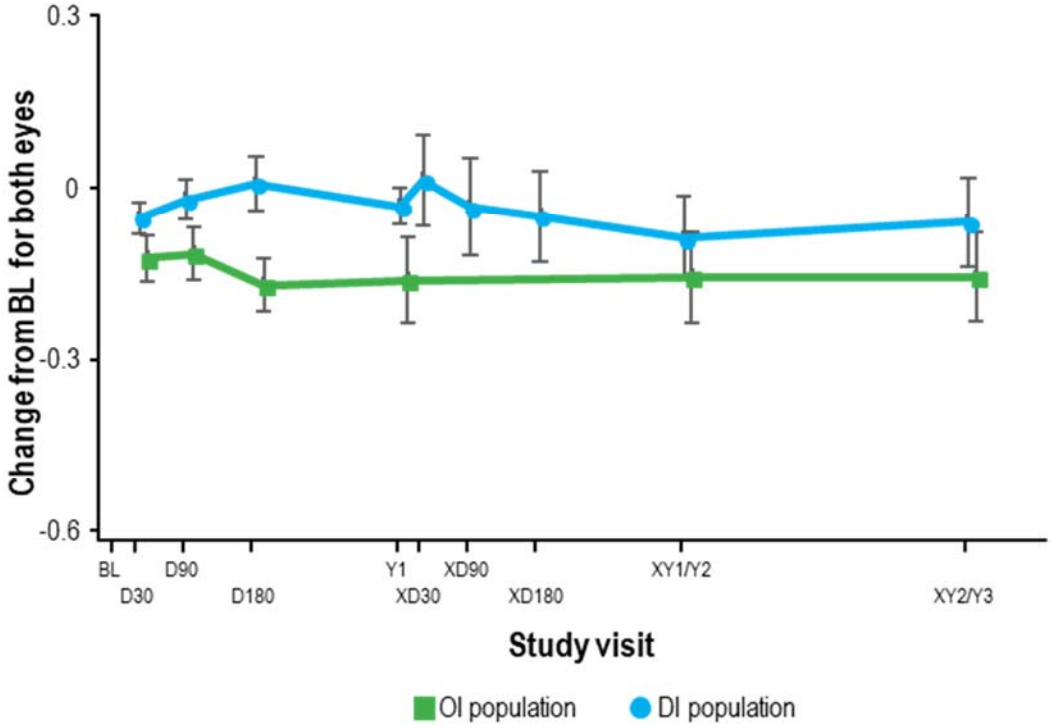


Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; mITT, modified intention-to-treat. Source: Russell 2017[58]. Green line represents VN arm; blue line represents BSC arm. Error bars represent standard errors.

Data from Study 302 reported in the CS appears to show no change in VA between baseline and 3 years for patients treated with VN in the original and delayed arms (see Figure 7). [redacted]

[redacted]

Figure 7: Study 302 Mean change in VA between baseline and 3 years (Holladay scale; ITT population)



Abbreviations: BL, baseline; DI, delayed intervention; OI, original intervention; VA, visual acuity.

Source: Maguire 2017[60].Error bars represent standard errors.

[redacted] 8

Visual Acuity (LogMAR) Using Holladay Off-chart, both Eyes	Original intervention (n=20)		Control/Intervention (n=9)		Total (n=29)	
	Value	Change (Visit-BL)	Value	Change (Visit-BL)	Value	Change (Visit-BL)
Injection baseline (BL)						
N	20		9		29	
Mean (SD)	1.14 (0.37)		0.95 (0.33)		1.08 (0.36)	
Range (min, max)	0.72, 2.06		0.52, 1.63		0.52, 2.06	
Quartiles (25th, median, 75th)	0.89, 1.03, 1.21		0.81, 0.85, 1.11		0.84, 0.99, 1.19	
Year 1B						
N	20	20	9	9	29	29
Mean (SD)	0.97 (0.54)	-0.16 (0.34)	0.87 (0.26)	-0.09 (0.22)	0.94 (0.47)	-0.14 (0.30)
Range (min, max)	0.43, 2.94	-0.61, 1.07	0.46, 1.15	-0.48, 0.27	0.43, 2.94	-0.61, 1.07
Quartiles (25th, median, 75th)	0.67, 0.84, 1.03	-0.29, -0.17, -0.11	0.69, 0.78, 1.13	-0.20, -0.08, -0.04	0.69, 0.81, 1.13	-0.27, -0.15, -0.08
Year 2B						
N	20	20	9	9	29	29
Mean (SD)	0.98 (0.55)	-0.16 (0.36)	0.89 (0.27)	-0.06 (0.23)	0.95 (0.47)	-0.13 (0.32)
Range (min, max)	0.44, 2.96	-0.79, 1.10	0.41, 1.22	-0.43, 0.36	0.41, 2.96	-0.79, 1.10
Quartiles (25th, median, 75th)	0.70, 0.85, 1.03	-0.29, -0.16, -0.08	0.73, 0.82, 1.18	-0.11, -0.09, -0.03	0.73, 0.85, 1.11	-0.27, -0.12, -0.05
Year 3B						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quartiles (25th, median, 75th)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4B						
N	[redacted]	[redacted]	0	0	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Quartiles (25th, median, 75th)	[redacted]	[redacted]	-	-	[redacted]	[redacted]

[redacted]

Study 101/102

The CS reports that there was no statistically significant difference in change of VA between injected and uninjected eyes from baseline to one year. Using the Holladay scale, a change in LogMAR units was reported to be -0.4233 in injected eyes and -0.1525 in uninjected eyes (p = 0.1019). The change in VA in injected eyes from baseline to one year was statistically significant (p = 0.0003, post-hoc analysis), indicating an overall improvement in VA in the VN arm at 1 year. The change in uninjected eyes was not statistically significant (p = 0.1927). Of 12 patients included in the analysis, nine patients (75%) demonstrated an improvement of VA, which was clinically meaningful (≥0.3 LogMAR) in 7 patients (58.3%). No VA data is reported for patients in Study 101 at final follow-up, or for any patients in Study 102.

ERG Comment:

Changes in VA reported in the CS up to 4 years following treatment are under the company's definition of a clinically meaningful change. [redacted]

Evidence from Study 101 indicates that 58% of patients exhibited a clinically meaningful improvement in VA at 1 year; however, no further follow-up data is reported, and as this study is under-powered and not an RCT, overall the ERG considered the evidence from Study 301/302 to be more compelling.

4.2.3.1.2 Visual Field (VF)

Details of the measurement of VF in the included trials is summarised in Section 4.2.2.4.

Study 301/302

The CS reports a statistically significant difference in VF between VN and BSC at 1 year. As assessed using Goldmann (III4e), patients in the VN arm demonstrated an improvement in VF (baseline 332.9; mean change 302.1; variance not reported), while there was a numerical reduction in VF in the BSC arm (baseline 427.1; mean change -76.7, variance not reported; MD 378.7; 95%CIs 145.5, 612.0; post-hoc p = 0.0059). According to *** [redacted]9, below, improvements in VF were demonstrated by 30 days in the VN arm, and these remained relatively stable until 1 year.

[redacted]9

[redacted]

[redacted]

VF data for Study 302 and at follow-ups later than 1 year for Study 301 were not reported in the CS, however at clarification the company provided

**[redacted]10, which appears to show that patients in the delayed intervention arm in Study 302 exhibited the same improvement in VF between baseline and 30 days, following which VF remained relatively stable until 3 years.

[redacted]

[redacted]

10

[redacted]

[redacted]

Using the Humphrey VF test, the CS also reports a statistically significant difference in macular sensitivity threshold between VN and BSC at 1 year; there was a mean difference of 7.9 dB (95%CI 3.5, 12.2, post-hoc p = 0.0005). An increase in VF was reported in the VN arm (baseline 16.1 dB; 1 year 24.0 db; mean change and variance not reported), while there was stated to be no change in the BSC arm (data not reported). The CS provides ***[redacted]11, which indicates that improvements in Humphrey VF in the VN arm were demonstrated by 30 days, and sustained until 1 year. Advisors to the ERG suggested that these changes would be clinically significant in improving patient mobility and navigational vision.

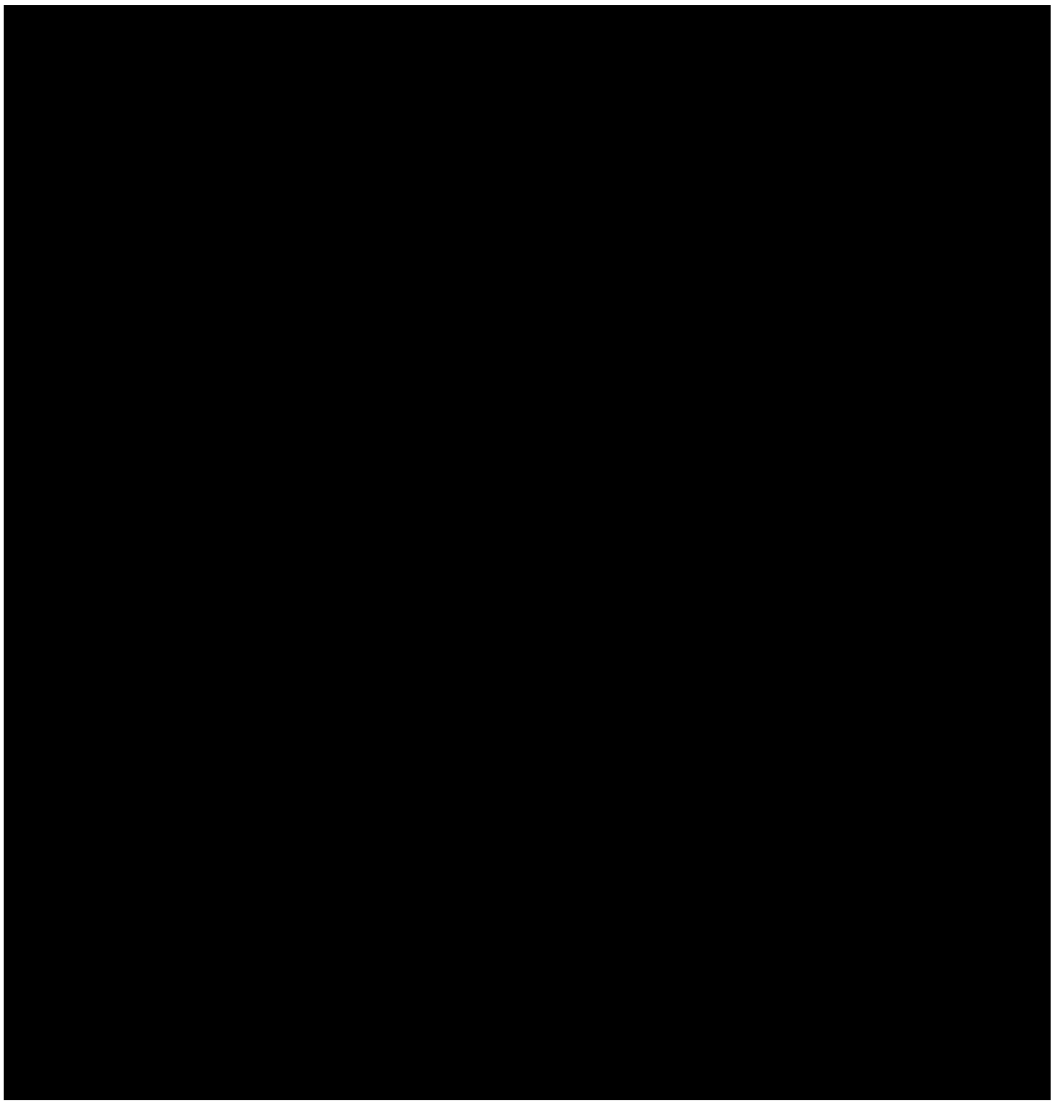
[redacted]11[redacted]

[redacted]

Again, data for Study 302 and at longer follow-up for Study 301 were not reported in the CS, however the ERG identified some data from the trial CSR.[59]

[redacted]

[redacted] **12**



The CS reports that there was no statistically significant difference between VN and BSC with Humphrey foveal sensitivity threshold at Year 1 (mean difference 0.04; 95% CI -7.1, 7.2; post-hoc p = 0.18). [redacted].

[redacted]

Study 101/102

VF was stated to be a secondary outcome in the research protocols for Study 101/102, and no data was reported in the CS for the impact of VN on VF for patients in either study. For patients in Study 101, the company noted that all 12 patients experienced "an improvement" in VF, although that there was "substantial variation" in the effect (CS; p. 116).

ERG Comment:

The results of Study 301/302 demonstrate a clinically meaningful impact of VN on VF, which can be seen at the 30 day timepoint following treatment, and which remain above a clinically meaningful threshold up to 4 years later. Findings as assessed according to the Humphrey VF mean macula threshold method at 1 year are also consistent.

[redacted]

[redacted]

4.2.3.1.3 Contrast Sensitivity

Details of the measurement of contrast sensitivity in the included trials is summarised in Section 4.2.2.4.

Study 301/302

[redacted]

[redacted]14[redacted]

[redacted]

[redacted]No data were reported in the CS with regards to contrast sensitivity for patients in Study 101/102.

ERG comment:

[redacted]

4.2.3.1.4 Photosensitivity

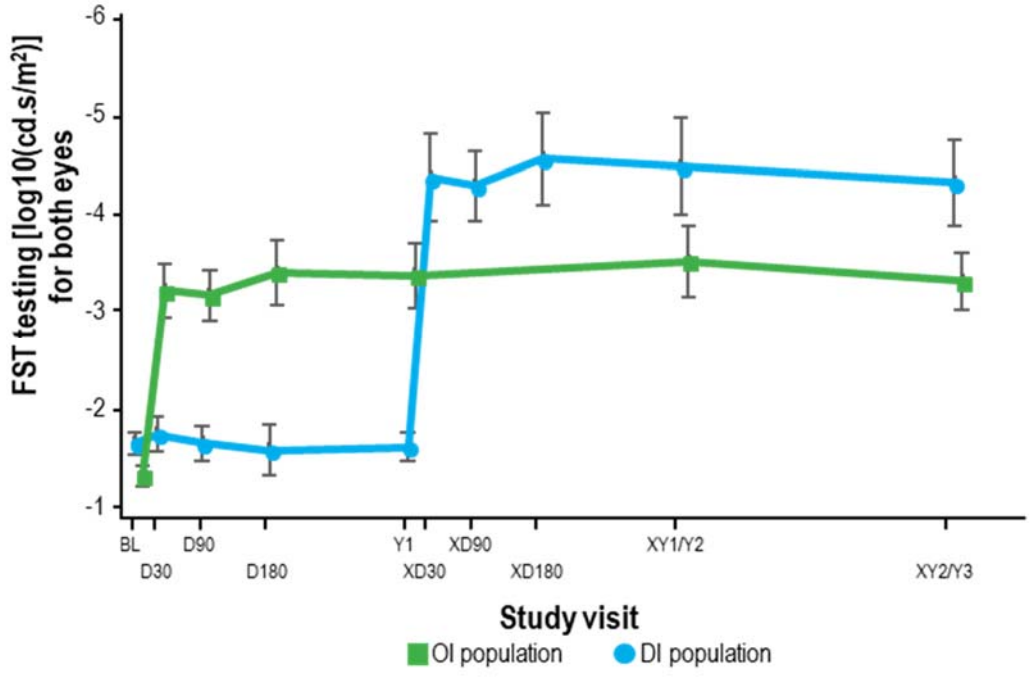
Details of the measurement of photosensitivity in the included trials is summarised in Section 4.2.2.4.

Study 301/302

A statistically significant difference in full-field light sensitivity (FST) threshold was reported at 1 year (MD -2.11 log units; 95%CI -3.91, -1.04; p=0.0004; ITT population). Patients in the VN arm exhibited a mean improvement in FST of -2.08 (SE 0.29), while no change was exhibited by patients receiving BSC (mean change 0.04; SE 0.44).

At 3-year follow- up, the effect of VN on FST was maintained in the original intervention arm (mean change -2.04; SD 1.43; N=19), as well as in those who crossed over from the BSC arm (mean change -2.69; SD 4.41; N=9; see Figure 15). These changes were below the company's defined threshold for clinical significance (≥10dB).

Figure 15: Study 302 Full-Field Light Sensitivity Threshold at one year



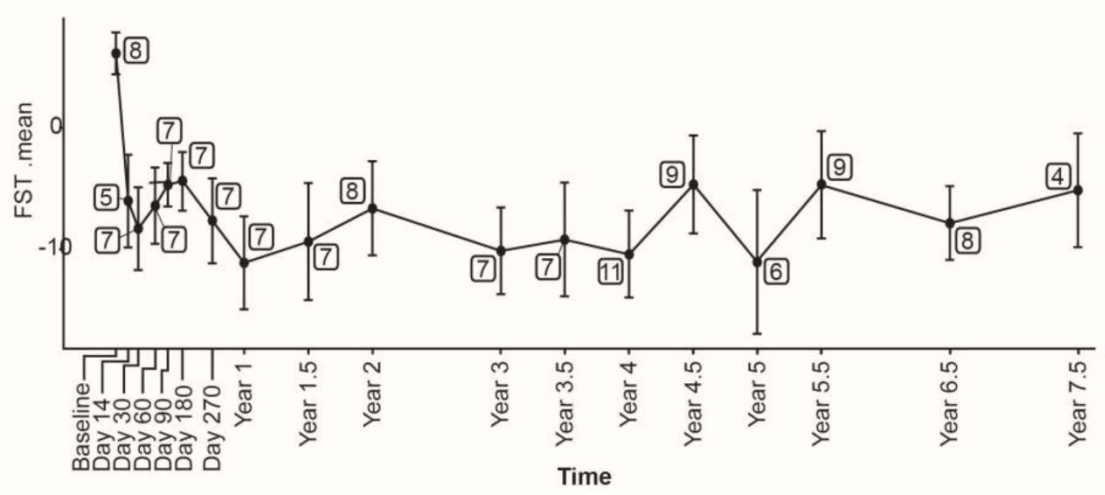
Abbreviations: DI, delayed intervention; OI, original intervention

Error bars represent standard errors Source: Maguire 2017[60]

Study 101/102

The company report that not all patients included in Study 101/102 were assessed for full-field light sensitivity (FST) as the equipment required was not available at the start of the trial. In Study 101, it was stated that 57% of patients assessed exhibited a clinically meaningful improvement in FST (a decrease ≥10dB), although the data, and the sample size, is not reported. A graph is provided (Figure 16) that appears to indicate an improvement in FST occurs in a subsample of patients, although it's unclear from the y axis whether this occurs from baseline or at an early follow-up. The size of the improvement is also not clear. After this initial improvement, FST remains relatively stable until final follow-up at 7.5 years, although only a small minority of patients are available for follow-up (four patients available at 7.5 years). It is also unclear from the findings whether there is variation in the effect on FST between doses of VN.

Figure 16: Study 101 Mean (+/- SE) FST over time in the first injected eye



Notes:

The numbers within the boxes represent the number of patients at each time point; time points with fewer than three observations and without baseline data were excluded from the analysis.

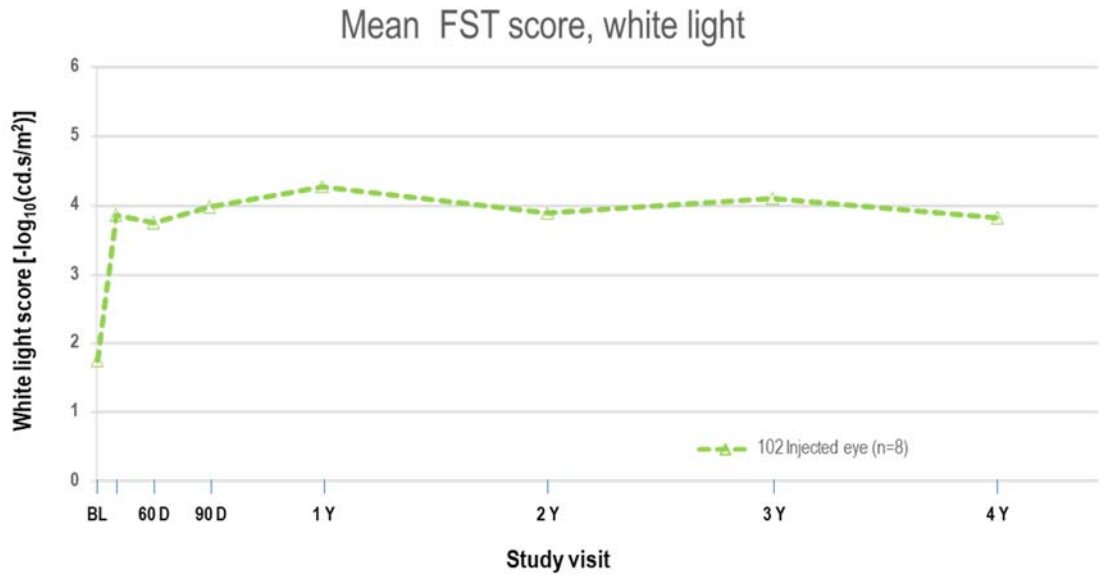
Data pooled across the 3 different doses: 1.5x1010, 4.8x1010 and 1.5x1011 vg. Abbreviations: FST, full-field light sensitivity threshold; SE, standard error; vg, vector genomes.

Source: Chung 2019[71]

In Study 102, the CS reports that patients exhibited a mean improvement in FST of 18.04 (variation not reported; p<.0001; post-hoc; n=8). The CS also notes that there was a statistically significant difference in FST in eyes injected in Study 102 compared to those injected in Study 101, with eyes in Study 102 exhibiting a bigger improvement (MD 14.06, variation not reported, p=0.0067, post hoc).

Eyes in Study 102 were better functioning at baseline, and all received a high dose of VN. The company provide a graph (Figure 17), which appears to show an improvement in FST from baseline, which is then maintained at four years (N=8).

Figure 17: Study 102 FST Mean Score for Eyes injected at 4 years



Abbreviations: FST, full-field light sensitivity threshold

Source: Maguire 2017[49]

ERG Comment:

The evidence from Study 301 suggests that VN has a small, statistically significant effect on FST at 1 year. However, this effect is below thresholds for a clinically meaningful difference, and approximate to estimates of measurement error in this population (3.90 dB; Roman et al, 2005).[72] While the effect was seen consistently across follow-up, wide error bars around the effect were noted. No further data for FST is reported for study 301/302, and therefore it is not possible for the ERG to determine if the effect was maintained, or altered, after 1 year.

Evidence from Study 101 indicates a possible numerical improvement in FST following VN, which was shown consistently across follow-up, but again below the threshold for a clinically meaningful difference. A large effect on FST was reported in Study 102, however only 8 patients were included, and no variation data was reported.

4.2.3.1.5 Need for Cataract Surgery

Need for cataract surgery was listed as an outcome in the NICE scope for this submission, however data for this outcome is not reported in the CS. The proportion of patients who experienced cataracts is reported to be 3/20 (15%; see Section 4.2.3.3, Table 19). In the trial publication,[58] 2 of these patients were reported to be still experiencing cataract(s) at 1 year, while 1 had been resolved following extraction. Based on the evidence available to the ERG, the risk of cataracts appears to be higher in the VN arm compared to BSC, but there is insufficient evidence in the CS to determine whether treatment with VN increases the risk for cataract surgery.

4.2.3.1.6 Additional Outcomes: Multi-luminance mobility test (MLMT)

Details of the measurement of MLMT in the included trials is summarised in Section 4.2.2.4.

Study 301/302

MLMT data (the primary outcome of this trial) at 1 year is reported in Table 16 below. At 1 year, patients in the VN arm experienced an improvement in MLMT scores (mean across both eyes 1.8; SD 1.1), while there was no improvement in the BSC arm (mean across both eyes 0.1; SD 0.7). This difference was statistically significant (MD 2.0; 95%CI 1.14, 2.85). The same pattern of results was observed when each eye was assessed individually. At 1 year, none of the patients in the BSC arm (0/10) were able to pass the test at 1 lux, compared to 63.2% of those in the VN arm (12/19; note that this excludes one patient who passed the MLMT at 1 lux at baseline, in a protocol violation[61]).

Table 16: Study 301 MLMT scores at Year 1 compared to baseline (ITT Population)

	Intervention	Control	Difference (95% CI)	Permutation test p value
Baseline MLMT				
Patients ≥125lux	9/21 (48%)≠	6/10 (60%)	-0.17 (-0.54, 0.20)≠	0.364
Both eyes				
Mean change (SD)	1.8 (1.1)	0.2 (1.0)	1.6 (0.72, 2.41)	0.0013
Range	0 to 4	-1 to 2	-	-
Median (IQR)	2 (1 to 3)	0 (-1 to 1)	-	-
First eye				
Baseline (SD)	2.2 (1.8)	2.4 (1.5)	-	-
Mean (SD)	4.1 (2.7)	2.6 (1.7)	-	-
Mean change (SD)	1.9 (1.2)	0.2 (0.6)	1.7 (0.89, 2.52)	0.0005
Range	0 to 4	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-

	Intervention	Control	Difference (95% CI)	Permutation test p value
Second eye				
Mean change(SD)	2.1 (1.2)	0.1 (0.7)	2.0 (1.14, 2.85)	0.0001
Range	0 to 5	-1 to 1	-	-
Median (IQR)	2 (1 to 3)	0 (0 to 1)	-	-

Abbreviations: CI, confidence interval; IQR, interquartile range; ITT, intention to treat; MLMT, multi-luminance mobility test; SD, standard deviation

Note that the First eye is the worst, non-preferred eye.

Source: Russell 2017; CS p.100 and p.107

≠ Calculated by the ERG

Individual performance on the MLMT is presented in ***[redacted]18. This figure is able to depict the ceiling effect inherent to the MLMT, where the test is unable to assess performance under a lux 1 level of light (see Section 4.2.2.4).

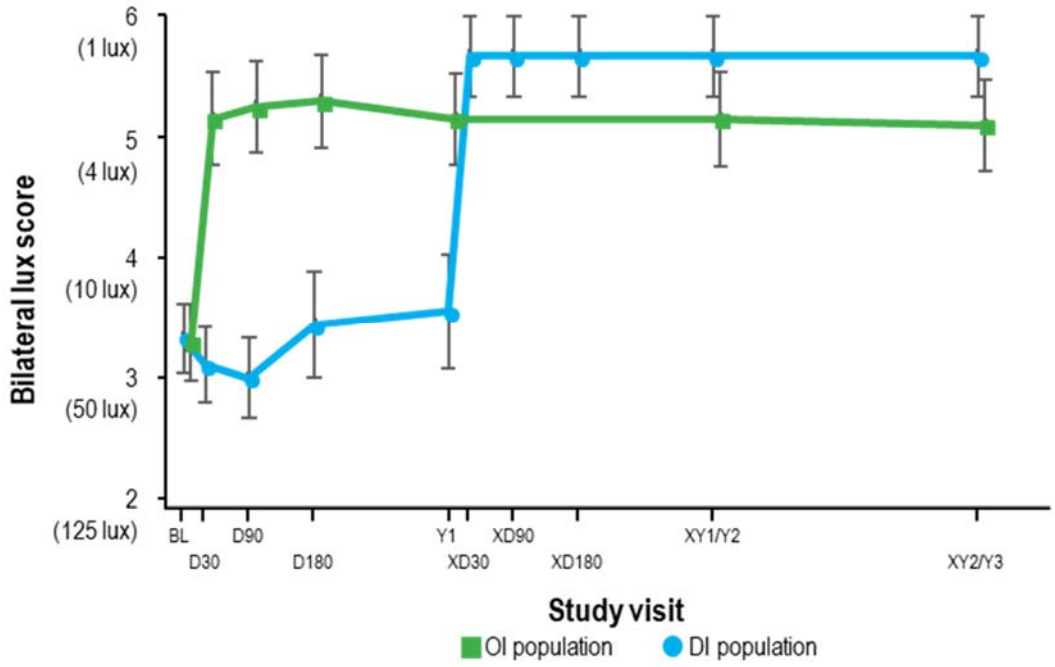
18

[redacted]

MLMT scores reported at follow-up timepoints in Study 302 are presented in Figure 19 and ***[redacted]17, below. Figure 19 depicts a sharp improvement in MLMT scores following administration of VN in both the original and delayed arm. Improvements in MLMT then appear to remain steady until the follow-up timepoint at 3 years (2 year follow-up for those in the delayed arm). Mean MLMT scores at 3 years were not provided in the CS, however the ERG were able to identify mean change scores from the trial CSR (***[redacted]17):

[redacted] According to the CS, at 3 years (2 years in the delayed arm), 60% (12/20) of the original VN arm and 89% (8/9) of the delayed arm were able to pass the MLMT at 1 lux

Figure 19: Study 301/302 Year 3 MLMT Results



Abbreviations: DI, delayed intervention; OI, original intervention.

Error bars represent standard errors.

Source: Maguire 2017.[60]

[redacted] 17 [redacted]

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Trial CSR,[59] p. 27

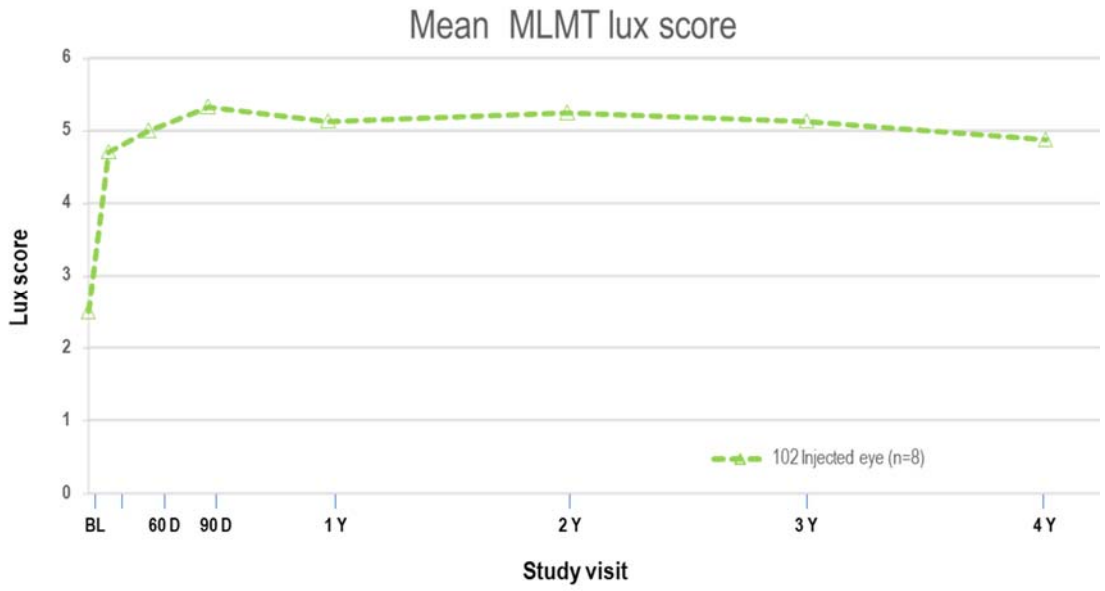
At clarification, the ERG requested if the company had found a difference in treatment effect between children (<18 years) and adult (≥18 years) patients.

[redacted]

Study 101/102

In Study 102, 8/11 (72.7%) patients were evaluated using a mobility test (which subsequently became the MLMT). The CS reports that all 8 patients demonstrated a clinically significant improvement of >1 lux with their second (better, preferred) eye, and 5/8 (63%) patients passed the MLMT at the lowest level (1 lux). This data is presented in Figure 20 below. This figure demonstrates a sharp improvement in mean MLMT following administration of VN, which is maintained until follow-up at 4 years. Mean change in MLMT score was 2.6 (SD 0.56) at 1 year follow-up, and 2.4 (SD 0.46). These 8 patients were all stated to meet inclusion criteria for Study 301/302.

Figure 20: Study 102 MLMT Mean Score at 4 years



Abbreviations: MLMT, multi-luminance mobility test

Source: Maguire 2017.[49]

ERG Comment:

The evidence from Study 301/302 indicates that treatment with VN was associated with a statistically significant improvement in MLMT, which is clinically significant according to the company's chosen clinically meaningful threshold (change ≥1 light level). Based on this threshold, all patients who received VN in the included trials exhibited a clinically meaningful change in MLMT score. This improvement was also shown to be maintained until follow-up at 4 years (3 years in delayed arm).

4.2.3.2 Patient-Reported Outcomes/Health-Related Quality of Life

Details of the measurement of visual function in the included trials is summarised in Section 4.2.2.4.

Study 301/302

Mean scores for the modified Visual Function Questionnaire (VFQ) at 1 year are presented in [redacted]18[redacted]

[redacted].

No generic instruments were included in the company studies

[redacted] 18 [redacted]

[redacted]	[redacted]				[redacted]					
	[redacted]		[redacted]		[redacted]		[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] 21 [redacted]

[redacted]

Data for the modified VFQ is not presented in the CS for timepoints later than 1 year, and for patients in the crossover arm of Study 301/302. However, the ERG were able to identify some further data from the trial CSR.[59] [redacted]

ERG Comment:

Preliminary data in Study 301 suggests that treatment with VN has a statistically significant effect on VFQ scores, as reported by patients and parents, compared to BSC. [redacted]

It is interesting that – according to the distribution method of deriving MIDs[67] – [redacted]. Clinical advisors to the ERG advised that patients are likely to adapt to their surroundings over time, which may explain a proportion of the change in HRQoL in both arms. [redacted].However [redacted]

As with several of the other outcomes included here, evidence for the impact of VN on VFQ scores is based on one small RCT only, with no follow-up data. [redacted].

Finally, the ERG noted that the absence of HRQoL data in the trial adds an additional uncertainty to the economic evaluation. This is explored in depth in Section 5.2.7 below.

4.2.3.3 Safety data

The CS reports that no deaths were reported in any of the included trials. Safety data was reported as treatment-emergent AEs (TEAEs; Section 4.2.3.3.1); serious AEs (SAEs; Section 4.2.3.3.2); drug-related AEs (Section 4.2.3.3.3) and administration-related AEs (Section 4.2.3.3.4).

Details of the measurement of adverse events in the included trials is available here.

4.2.3.3.1 Treatment-emergent adverse events

The company did not report their definition of TEAE in the CS; however the ERG assumed that a general definition of TEAE was used, i.e. any AE occurring following administration of treatment, irrespective of the frequency or whether this was deemed to be related to the study drug. A breakdown of TEAEs according to whether these were deemed to be SAEs, drug- or administration-related is provided in Sections 4.2.3.3.2 - 4.2.3.3.4.

Study 301/302

The proportion of all TEAEs reported for patients in Study 301 were not reported in the CS; however, the ERG identified the proportion of non-SAEs experienced by ≥5% of patients in the VN and BSC arms (Table 19) from clinicaltrials.gov. These AEs were reported in 13/20 (65%) of patients in the VN arm, and 1/9 (11.1%) of patients in the BSC arm. All AEs reported were eye disorders.

Table 19: Study 301 Non-Serious Adverse Events Experienced by ≥5% of Patients between baseline and 1 year

	VN		BSC	
	Affected / at Risk (%)	**# Events**	**Affected / at Risk (%)**	**# Events**
Total	13/20 (65.00%)		1/9 (11.11%)	
Eye disorders				
Cataract	3/20 (15.00%)	4	0/9 (0.00%)	0
Elevated intraocular pressure	4/20 (20.00%)	5	0/9 (0.00%)	0
Retinal tear	2/20 (10.00%)	2	0/9 (0.00%)	0
Eye inflammation	2/20 (10.00%)	6	0/9 (0.00%)	0
Conjunctival cyst	1/20 (5.00%)	1	0/9 (0.00%)	0
Conjunctivitis viral	1/20 (5.00%)	1	0/9 (0.00%)	0
Eye irritation	1/20 (5.00%)	1	0/9 (0.00%)	0
Eye pain	1/20 (5.00%)	1	0/9 (0.00%)	0
Eye pruritus	1/20 (5.00%)	1	0/9 (0.00%)	0
Eye swelling	1/20 (5.00%)	1	0/9 (0.00%)	0
Foreign body sensation in eyes	1/20 (5.00%)	1	0/9 (0.00%)	0
Iritis	1/20 (5.00%)	1	0/9 (0.00%)	0
Macular hole/degeneration[1]	1/20 (5.00%)	2	0/9 (0.00%)	0
Maculopathy/epiretinal membrane	1/20 (5.00%)	2	0/9 (0.00%)	0
Pseudopapilledema	1/20 (5.00%)	1	0/9 (0.00%)	0
Retinal hemorrhage	1/20 (5.00%)	1	0/9 (0.00%)	0
Photopsia	0/20 (0.00%)	0	1/9 (11.11%)	1

Notes:

[1] Same eye of a single subjects, a full-thickness macular hole spontaneously resolved (with sequelae) to thinning, which subsequently resolved (without sequelae). Classified as two adverse events, but occurred in the same clinical course of events

Source: Clinicaltrials.gov

[redacted]

Study 101

A total of [redacted] TEAEs were reported by participants (N=12) between baseline and 7-year follow-up. Of these, [redacted] were reported by patients in the low dose group (n=3); [redacted] were reported by patients in the medium dose group (n=6); and [redacted] were reported by patients in the high dose group (n=3). The proportion of patients who experienced one or more TEAEs was not reported in the CS, although the trial CSR[53] [redacted].

[redacted] The company state that there were no apparent effects of VN dose on TEAE incidence, although the ERG noted that it is hard to draw conclusions on this given the small sample size.

Study 102

Between baseline and follow-up at 4 years,

[redacted]

The proportion of patients who experienced one or more TEAE was not reported in the CS, although the trial CSR[57] reports that [redacted]

4.2.3.3.2 Serious adverse events

Study 301/302

SAE data for patients receiving VN and BSC during Study 301 was not reported in the CS; however the ERG were able to identify this from the trial CSR[59]; this is summarised in [redacted] below. The data indicates that

[redacted].

[redacted] 20 [redacted]

	VN		BSC	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted] 21 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted].

Source: CS Table 22, p. 125

Study 101

[redacted] was recorded in Study 101, [redacted]

Study 102

[redacted]

4.2.3.3.3 Drug-related adverse events

The CS reports that

[redacted]

4.2.3.3.4 Administration procedure-related adverse events

Study 301/302

The proportion of administration-related AEs were not reported separately for patients in Study 101; i.e. the first year after treatment for patients in the Original VN arm of Study 302. These AEs are incorporated into follow-up data for Study 102.

The company provides a summary table of administration procedure-related TEAEs reported by patients in Study 302 from baseline to final follow-up ([redacted]22). In total, [redacted] patients receiving VN exhibited a total of [redacted] that were considered by the company to be related to the administration procedure: [redacted] patients in the Original arm and [redacted] in the Delayed arm. In total, [redacted] patients experienced an eye disorder related to administration:

[redacted] although the company's criteria for determining this was not reported.

[redacted] 22 [redacted])

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: CS Table 21, p.124

Study 101

The company provide a summary table of administration-related TEAEs reported between baseline and 7 year follow-up ([redacted]). This shows that [redacted] experienced TEAEs that the company determined to be related to the administration of VN.

[redacted]

[redacted] 23 [redacted]

[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[redacted]

Source: CS Table 12.4, p. 128

Study 102

The company provide a summary table of administration-related TEAEs between baseline and 4 years (***[redacted] 24). The company state that [redacted] reported TEAEs considered to be related to the administration procedure. [redacted]

[redacted] 24 [redacted]

[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: CS Table 23, p. 126

ERG Comment:

Overall, the evidence indicates that VN is associated with an acceptable safety profile. No deaths were recorded during the trials, and no AEs were thought to be related to VN itself. The administration of VN, however, is associated [redacted]

4.2.4 Meta-analysis

Only 1 comparative study (Study 301/302)[61] has been conducted to evaluate the relative effectiveness of VN to treat IRD. As such, no meta-analysis of clinical effectiveness was provided, or expected.

4.2.5 Quality assessment of the included evidence

The company conducted quality assessment of Study 301/302; quality assessment judgements reported by the company are reported in Table 25, alongside ERG comments. No quality assessment was reported for Study 101/102, but was conducted by the ERG (Table 26).

Table 25: Study 301/302 Quality Appraisal

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
Was randomisation carried out appropriately?	Yes	A randomisation list was generated under the direction of the independent party biostatistician using a permuted block design, stratified by age (<10 years and ≥ 10 years) and baseline mobility testing passing level	Yes	The ERG agree that there is a low risk of selection bias associated with the randomisation procedure. Randomisation was determined by order of enrolment, verification of study eligibility, and the participant's randomisation stratum. Subjects were randomised in a

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
				2:1 ratio to the Intervention or Control group, stratified by Screening age (≥ 10 years or < 10 years) and mobility testing category (≥ 125 lux or < 125 lux). Within each stratum, randomised blocks (block size of 3) governed the allocation to treatment group.
Was the concealment of treatment allocation adequate?	No	The use of sham injections in the control group was considered unethical, so participants and investigators were aware of study group assignment	Yes	The ERG believe that in fact the trial had adequate allocation concealment. The trial's concealment of allocation was accomplished by generation of a randomisation list by an independent biostatistician. The ERG submit that the interpretation of this question was inaccurate, as the company's response relates to whether participants and investigators were blind to treatment allocation, not whether the sequence of allocation was concealed appropriately.
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	No	The groups were similar in age and sex at screening; baseline MLMT passing level was not completely balanced between the two groups due to the small number of participants	No	Due to the paucity of evidence for this patient group, it is unclear whether differences in baseline age and gender between intervention and control groups may introduce a risk of bias. However, the ERG note an imbalance at baseline MLMT performance following assignment to treatment/control group that the ERG considers to introduce a high risk of bias.
Were the care providers, patients and outcome assessors blind to treatment allocation? If	Partial	Open label allocation Graders assessing MLMT were affiliated with an independent reading centre, and were masked to treatment group by providing video files to them as coded files that did not	Partial	The ERG agree that sufficient steps have been taken to ensure appropriate blinding of outcome assessment of the primary outcome measure (MLMT) and judge that there is low risk of detection bias for this outcome.

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		reference data or assignment group Orientation and mobility assessors were also masked to treatment group		However, the ERG considers that while the company state that orientation and mobility assessors were masked, there is insufficient detail provided in the CS to judge if adequate blinding of outcome assessment has been performed for all secondary outcome measures e.g. VF and VA.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	Analyses for primary and secondary efficacy endpoints included prespecified summaries on the full ITT and mITT populations Adverse event summaries used mITT population	Yes	The ERG agree that while there were unexpected dropouts, these were accounted for appropriately. There was a 10% drop out rate in the control group compared to 5% drop out rate in the intervention group. Explanations for discontinuation were unrelated to treatment with VN, and included severe retinal atrophy precluding participation and personal reasons. Because an ITT analysis was performed taking these dropouts into account, the ERG agree there is low risk of attrition bias for efficacy endpoints using these analyses. The mITT population was appropriately used for assessments of adverse events, but is not as probative as the ITT analysis for clinical outcomes.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes mentioned in the protocol are reported	Unclear	The ERG consider the risk of selective reporting to be unclear. The ERG agree that there is low risk of selective reporting bias based on the trial registry NCT00999609. However, the company were requested by the ERG to provide additional information relating to the protocol (Appendix 16.1.1 of the original CSR) but this appendix was not provided by the company. The ERG note that in study 301/302 CSR, the

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
				company state that the original primary efficacy endpoint stipulated in the protocol was changed from pupillary light reflex (PLR) testing to mobility testing.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	•Analyses for primary and secondary efficacy endpoints included prespecified summaries on the full ITT and mITT populations •Adverse event summaries used mITT population	Yes	The ERG consider appropriate intention-to-treat analysis was performed for both primary and secondary outcome measures, comparing VN and control group outcomes according to the initial random allocation. The ERG consider appropriate intention-to-treat analysis was performed for adverse events.

Abbreviations: ITT, intention to treat; mITT, modified intention to treat; MLMT, multi-luminance mobility test

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care[74]

Source: Adapted from CS Table 14, p. 94

Table 26: Study 101/102 ERG Quality Appraisal

Study question	ERG response	ERG comments
Was the study question or objective clearly stated?	Yes	The study's goal was to examine the safety of VN in humans (CS, p. 115).
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	The study was registered at ClinicalTrials.gov (NCT00516477), with criteria provided.
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Given the small sample size (n=12), the generalisability and representativeness cannot be determined.
Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	The CONSORT chart provided in response to clarification question A19 suggests that all eligible patients were included.
Was the sample size sufficiently large to provide confidence in the findings?	No	Given the rarity of the disease of interest, a small sample size is unsurprising.
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Included doses were clearly described for Study 101/102 (see CS table 19, p. 115).
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	The study primarily aimed to understand the safety of VN.

		Visual acuity was a secondary outcome.
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	This was not a comparative study.
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	One patient did not progress to Study 102 due to glaucomatous changes in one eye (CS section 9.4.6, p. 94).
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Mixed-effects models were used to estimate effectiveness on visual acuity outcomes (CS table 19, p. 115). Safety outcomes were assessed descriptively.
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	A baseline assessment was taken. Patients in Study 101/102 continue to be followed up.
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Not relevant	This was not a group-level intervention.

Based on National Heart, Lung and Blood Institute study quality appraisal tools[75]

ERG Comment:

The company used an appraisal tool based on the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare for Study 301/302.[74] This was an appropriate tool. The ERG assessment of risk of bias in Study 301/302 matched the company's assessment in the main. The ERG noted that an incorrect interpretation of one of the checklist questions meant that low, rather than high, risk of bias was associated with one of the questions. Moreover, risk of bias was not reported separately for each outcome. This is important because risk of bias arising from assessment differs by outcome. For example, the ERG considered there to be a low risk of detection bias due to adequate blinding of assessment of the primary outcome MLMT, with outcome assessors being independent and blinded to treatment group through the provision of coded video files that did not reference assignment group. In contrast, while the ERG noted that the company states that orientation and mobility assessors were masked to treatment group, no further details of blinding for secondary outcome measures were given in the CS. In the published trial report,[58] authors clarify that functional home-based assessments were conducted and evaluated by orientation and mobility specialists independent from the study teams and the sponsor. These functional home-based assessments were designed to document the functional visual abilities of the participants in each of the following domains: self-report, functional visual field, basic visual skills, illumination, orientation and mobility. The ERG noted that this lack of detail in the CS and relevant trial publication mean that it is unclear if assessors of the main secondary outcome measures of visual function, visual acuity and visual field

were blinded. Finally, the ERG considered that the CS does not report co-intervention details in sufficient detail. These risk of bias judgments collectively suggest that Study 301/302 may be at high risk of bias.

The company did not present quality appraisal of Study 101/102. The ERG regard this as a serious omission given the limited evidence base available to inform this appraisal and the relevance of these data for understanding safety. The ERG undertook its own appraisal of Study 101/102, presented above, and found that there were several potential threats to study quality.

4.3 Additional work on clinical effectiveness undertaken by the ERG

No additional work was conducted by the ERG.

4.4 Conclusions of the clinical effectiveness section

The ERG has conducted a detailed review of the clinical effectiveness evidence presented by the company for VN. Overall, the SLR conducted by the company is broadly consistent with the NICE scope, appears to be methodologically sound, and the ERG expect that all relevant evidence has been captured. Notable deviations from the NICE scope included the restriction of the trial populations to those with sufficient viable retinal cells, which was judged to be clinically appropriate, and the omission of evidence for HRQoL in both patients and carers, and for need for cataract surgery.

Overall, there is a small evidence base for the clinical effectiveness of VN, with a total population of 43 patients with *RPE65*-mediated IRD across the included trials. One of these trials, Study 101/102, is a Phase 1 clinical trial designed primarily to evaluate the safety of VN, and was under-powered to evaluate clinical efficacy outcomes. The availability of evidence from a RCT in this patient population is notable, and provides a stronger evidence base from which to evaluate the efficacy of VN. However, due to the small sample sizes involved, and as both trials have been appraised as at a high risk of bias, the evidence should be interpreted with caution.

The evidence provided by the company indicates that in comparison with BSC, treatment with VN may be associated with clinically meaningful improvements in functional vision. [redacted]. These outcomes pertain to the ability of patients to navigate their surroundings and engage with everyday activities, and the ERG considered that these outcomes are important to considering the impact of visual impairments on the lives of patients. Clinical advisors to the ERG also suggested that these outcomes may be better suited to evaluating visual impairments in this patient group compared to traditional measures of visual performance (e.g. VA, VF), which may be

unreliable due to natural variations in visual function between tests. Nevertheless, there is some uncertainty over the validity of MIDs for both the MLMT and the modified-VFQ; both are new outcomes with limited validation. Furthermore, as no HRQoL data was reported, it is not possible for the ERG to conclude on whether improvements in visual function translate to broader improvements in patients' HRQoL.

The ERG noted that numerical improvements in visual function were exhibited by patients receiving VN; including VF, VA, FST, and [redacted]. These improvements exceeded MIDs for VF and FST. While improvements in VA and [redacted], these were nevertheless demonstrated consistently across follow-up timepoints, suggesting a potential minor effect of VN on these outcomes, beyond the natural variation that would be expected in these outcomes.

The evidence suggests that VN demonstrates an acceptable safety profile. No AEs were considered to be due to VN, and no deaths were recorded in the included trials. The administration of VN is associated with [redacted]; [redacted]. However, as per the current license for VN, these risks would be limited to a single administration.

4.4.1 Key areas of uncertainty

The ERG noted that a small sample of patients available at later follow-up for Study 301 exhibit [redacted]; however the potential of VN for longer-term gains in visual performance and function remains unclear until longer follow-up data is available.

The small evidence base presented in the submission is reflective of the rare nature of this condition, but does limit the generalisability of the evidence base beyond the included trials. As there is poor understanding of the characteristics that may impact on disease prognosis and treatment efficacy, it is not possible for the ERG to determine whether the populations of the included trials are consistent with the UK population.

[redacted]

[redacted] While age differences were noted between the randomised groups at baseline, clinical advice suggested that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population. Retinal function at baseline was suggested to be a potentially stronger mediator of treatment response, which may be partially correlated with age. However, none of the differences at baseline were considered by the ERG to demonstrate a clear bias in any direction, although it was noted that only a small number of characteristics were reported at baseline.

5 VALUE FOR MONEY FOR THE NHS AND PSS

5.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic review to identify studies regarding the cost-effectiveness of VN versus BSC for treating *RPE65*-mediated IRD. The company initially ran searches on 8 March 2018, and updated the searches on 11 January 2019. The company provided the search strategy, including terms, databases searched and details of supplementary searching within an appendix to the submission dossier. Inclusion and exclusion criteria for screening were also provided.

The company searched Medline and Embase (Elsevier at Embase.com), Medline-in-Process (OvidSP), and The Cochrane Library (OvidSP) to identify relevant cost-effectiveness studies. The company conducted supplementary searches to identify other potentially-relevant material, including unpublished research and grey literature. The cost-effectiveness search strategy is identical to the strategy employed for the clinical evidence review (discussed further in Section 4.1.1).

In addition to the searches for previous cost-effectiveness studies, the company conducted separate searches to identify evidence regarding healthcare resource use and health-related quality of life. The company stated that both these reviews provided no relevant data for the *RPE65*-mediated IRD population under analysis.

The company's cost effectiveness review identified one relevant study – the findings of a health technology assessment conducted by the Institute for Clinical and Economic Review in the United States, which compared VN and best supportive care (BSC) for vision loss associated with biallelic (pertaining to both alleles [paternal and maternal]) *RPE65*-mediated IRD.[76]

ERG Comment:

The search strategy for cost effectiveness was the same as that used for clinical effectiveness. The ERG considered this to be an acceptable approach, since the clinical effectiveness searches were not limited by study type, as long as appropriate screening and data extraction methods are used. Separate searches were also carried out for resources (Appendix 4) and utilities (Appendix 5). These were generally well conducted and reported.

The ERG previously noted several reservations regarding the clinical effectiveness searches (see Section 4.1.1). A very narrow population search was carried out (for patients with *RPE65* gene mutation only) and it is possible that the narrow search conducted by the company would not have identified all relevant papers.

The searches for resource use and utilities, would have benefited from a search filter such as the McMaster University filter for costs,[77] and the Canadian Agency for Drugs and Technologies in Health filter for utilities.[78] However, the population element for both these searches is well constructed.

A summary of the study inclusion and exclusion criteria is provided in Table 27, alongside comments from the ERG. The ERG agreed that the screening criteria are aligned with the final scope issued by NICE. However, the exclusion of interventions not considered BSC (such as other oral preventative drugs [e.g. oral synthetic cis-retinoid]) may have led to the omission of cost-effectiveness studies of potential relevance.

Table 27: Inclusion/exclusion criteria used in the company's cost-effectiveness review

Feature	Inclusion	Exclusion	ERG comment
Population	Patients with IRD caused by *RPE65* gene mutations	IRD due to gene mutations other than *RPE65*	None
Interventions	Voretigene neparvovec, best supportive care	Gene therapy using other vectors (e.g. rAAV2-CBSB-h*RPE65*, tgAAG76, rAAV2-CB-h*RPE65*, rAAV2/4. h*RPE65*, rAAV2-h*RPE65*), other oral preventive drugs (e.g. QLT091001, oral synthetic cis-retinoid)	Given the broad definition of best supportive care, the ERG considered that it may have been more appropriate to not exclude any comparator intervention (for the purpose of the cost-effectiveness review)
Outcomes	Direct costs, utilities, ICER, LYs, QALYs	None	The ERG would have expected to see the inclusion of outcomes expressed in natural units (e.g. cost per letter improvement)
Study design	Economic evaluation alongside clinical trials, economic evaluation modelling studies	Reviews, editorials, notes, opinions, case reports	None
Language restrictions	English	Languages other than English	None
Search dates	From inception of database to 8th March 2018 (original search) and 11th January 2019 (updated search)	None	None

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IRD, inherited retinal dystrophies; LY, life year; QALY, quality-adjusted life year.

The ERG has highlighted a number of concerns with the cost-effectiveness review (including the exclusion of studies based on comparator treatment). However, the ERG was generally satisfied that the company's cost-effectiveness review has identified all previous relevant cost-effectiveness studies of VN versus BSC for treating *RPE65*-mediated IRD.

The CS does not contain a clear summary of the findings of the review (including how the ICER study may have helped inform the cost-effectiveness model submitted to inform this appraisal). In clarification, the company provided the table of excluded studies for this systematic review. This is clearly presented with most studies being excluded on publication type, population or outcome. The company also provided the tables of excluded studies for the resources and health utilities reviews (almost all were excluded on outcome).

While not necessarily a summary of the findings of the review, the CS provides a comparison of outcomes between the company model and the study identified by the literature review, as well as where assumptions and/or analytical methods differed. Discussion of the identified cost-effectiveness study is presented in Section 11.2 of the CS (p. 158-159).

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 28: NICE reference case checklist

Element of health technology assessment	Comments with reference to the scope	Issues arising	Section providing details
Defining the decision problem	The company's description of the decision problem builds on the scope definition. The population is broader than specified in the scope, but is in line with the licensed indication.	None.	**3.2 & 5.2.3**
Comparator(s)	The comparator described in the CS is BSC, which is in accordance with the final scope.	A formal definition for BSC is not provided. VN in the cost-effectiveness analysis might be equivalent to VN+BSC.	**5.2.4**
Perspective on outcomes	The list of the outcomes in the CS includes all those listed in the final scope, as well as MLMT, the primary measure in the pivotal clinical trial. Some of these, including MLMT, are not used in the economic evaluation due to a lack of related cost and utility data. Health states in the economic evaluation are defined by VA and VF.	It is written in section 9.4.1.1.1 of the CS that VA and VF do not capture all of the features of the condition, and hence some direct health effects may not be accounted for in the economic evaluation.	**3.6 & 5.2.2**
Perspective on costs	The company consider costs from the perspective of the NHS and PSS.	None.	**5.2.5**
Type of economic evaluation	A cost-utility analysis with outcomes reported as ICERs in cost per QALY gained.	None.	**5.2.2**
Time horizon	A lifetime horizon has been adopted, which means that patients have been followed until maximum age of 100 years.	None.	**5.2.5**

Element of health technology assessment	Comments with reference to the scope	Issues arising	Section providing details
	The baseline age of patients starting in the model is 15.1 years.		
Synthesis of evidence on health effects	The SLR conducted for the synthesis of evidence of health effects is not comprehensive, but it is unlikely that a relevant study has been missed.	None.	**4.1 & 5.1**
Measuring and valuing health effects	Health effects in the economic evaluation are expressed in QALYs. Utility values are based on the HUI-3 since this measure contains a visual component, unlike EQ-5D.	No data were collected as part of the clinical study program for VN on patient or carer HRQoL using a validated preference-based measure.	**5.2.7**
Source of data for measurement of health-related quality of life	Vignettes for health states based on VA and VF were developed using testimonials from five patients and parents and the descriptions given by an advisory board of twelve general specialists.	Utility values from the customised questionnaire administered to patients within the pivotal clinical trial could not be used, due to the lack of a mapping function.	**5.2.7**
Source of preference data for valuation of changes in health-related quality of life	Six clinicians were asked to complete proxy generic HRQoL questionnaires for each of the health states in the economic model, based on summary descriptions and their experience with patients.	The proxy elicitation exercise suffers from severe methodological and face validity issues, as well as being subject to a number of biases.	**5.2.7**
Equity considerations	QALYs gained are of equal weight, irrespective of patient characteristics.	None.	**5.2.7**
Evidence on resource use and costs	Unit costs were largely drawn from standard sources, with a cost year of 2017-18.	The costs of health care resource utilisation are based on a number of assumptions and could be revised.	**5.2.9**
Discounting	Annual 3.5% discount applied to costs and QALYs.	None.	**5.2.5**

Abbreviations: HRQoL, health-related quality of life; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; MLMT, multi-luminance mobility test; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years; SLR, systematic literature review; VA, visual acuity; VF, visual field.

5.2.2 Model structure

The company constructed a de novo cost-effectiveness model in Microsoft Excel. The model adopts a Markovian state-transition cohort structure, and comprises of five "alive" health states plus a sixth absorbing health state representing death. The company chose to use a cohort structure (as opposed to an individual-level model) as *RPE65*-mediated IRD affects both eyes with relative symmetry and therefore there is no need to model each eye separately (as has been done in several ophthalmology appraisals), and the lack of data to appropriately generate statistical relationships. The company note however that a scenario analysis was developed to explore the impact of considering the impact on

results if the change in vision within in the best-seeing eye was considered (as opposed to the average change across both eyes).

The health states included within the model are based on the worst of either visual acuity (VA, measured using LogMAR where a higher value indicates poorer vision) or visual field (VF, where a higher value indicates better vision). Health states were based on VA and VF instead of the primary outcome of Study 301/302 (improvement in the MLMT) as *"no data are available linking this outcome to costs, utilities or mortality, and no data are available on the long-term change in this outcome."* (refer to the CS Section 12.1.6.). A description of the health states included within the company's model is presented in Table 29.

Table 29: Health state descriptions included within the company model

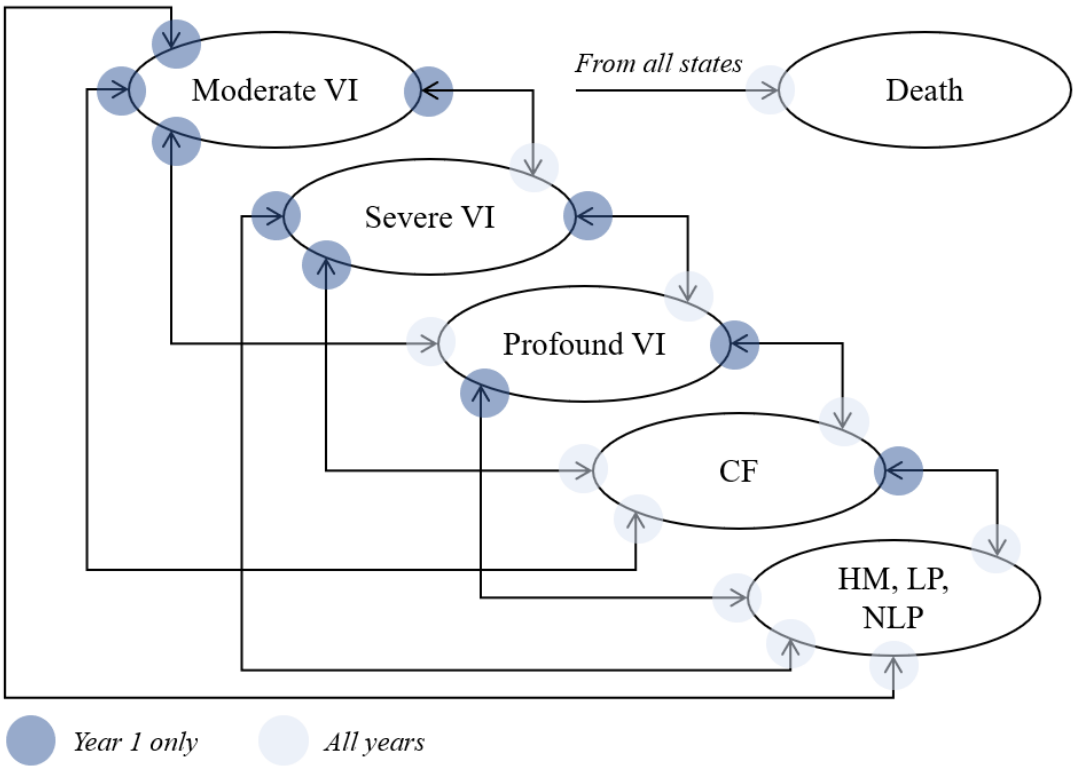
Health state	Description	Worst of	
		VA (LogMAR)	VF (degrees, □)
HS1	Moderate VI	VA >1.0	240 < VF ≤ 360
HS2	Severe VI	1.0 ≤ VA < 1.4	144 < VF ≤ 240
HS3	Profound VI	1.4 ≤ VA < 1.8	48 < VF ≤ 144
HS4	CF	1.8 ≤ VA ≤ 3.0	0 < VF ≤ 48
HS5	HM, LP, NLP	VA < 3.0 or an indication of HM, LP, or NLP	-

Key: CF, counting fingers; HM, hand motion; HS, health state; LP, light perception; NLP, no light perception; VA, visual acuity; VF, visual field; VI, visual impairment.

The model comprises two phases; an initial phase (from baseline to Year 1), and a long-term phase (from Year 1 onwards). Model transitions for the initial phase are derived via data from the pivotal Study 301/302, and long-term phase transitions are based on the *RPE65* NHx natural history study. In the initial phase, both forward (worsening vision) and backward (improving vision) transitions are permitted; however, in the long-term phase only forward (worsening transitions) are permitted. The company justify this by noting that both forward and backward transitions were observed within the first year of Study 301/302, and that clinical expert opinion suggests that without further intervention, VA and VF would only worsen over time.

A schematic of the submitted model is presented in Figure 22 (re-drawn by the ERG for clarity). Transitions permitted only in the first year (initial phase only) are highlighted with a dark circle, whereas transitions permitted from any model cycle (initial and long-term phases) are highlighted with a light circle. The derivation of the transition probabilities is discussed in further detail within Section 5.2.6.

Figure 22: Model schematic (re-drawn by the ERG)



Key: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment.

ERG Comment:

The model has been constructed to a good standard, with model code and sheets presented in a logical and clear manner. The ERG agreed with the choice to adopt a cohort model, in light of the evidence available and the bilateral nature of the disease. The ERG also agreed that the use of average vision across both eyes is aligned with the anticipated impact of treatment with VN, and the impact of disease progression.

Despite being a break from convention, the decision to utilise a model structure wherein health states are based on a combination of VA and VF is consistent with available evidence to inform the estimation of costs and outcomes for cost-effectiveness models constructed to assess retinal interventions. However, it should be noted that improvement in VA or VF was not the primary outcome of Study 301/302, and there are several issues in using these outcomes that are discussed in further detail below.

The company's decision to choose five "alive" model health states for vision was based on American Medical Association (AMA) guidelines. The ERG acknowledged the existence of such guidelines

serves as a reasonable basis for the selection of clinically-relevant health states; however, the use of a relatively large number of health states versus the sample size in Study 301/302 will inevitably preclude the estimation of all possible health state transitions. This is clearly evident for the BSC population, wherein there were nine patients who were treated and a total of 20 possible movements (excluding death). A smaller number of health states would have led to a more robust estimation of transitions, at the cost of omitting smaller changes in vision from consideration in the analysis.

The ERG agreed with the company's approach to splitting the model into initial and long-term phases, and the modelling assumption that after one year only forwards (worsening vision) transitions are permitted. The ERG noted that the re-drawn model schematic (Figure 22) has been provided for two reasons: (1) to clarify which transitions are permitted at relevant points in time, and (2) to confirm that some transitions that were mistakenly omitted from the company's original model schematic are indeed possible (the revised diagram represents the company's model, and does not constitute any amends to the company's model calculations).

The ERG was unclear why the company chose to "twelfth-cycle" correct the first model cycle instead of using transitions from baseline to Day 30 in combination with transitions from Day 30 to Year 1. The "twelfth-cycle" correction is discussed further in Section 5.2.5. The ERG was also not convinced that it was necessary for the company to specify a complex modelling approach in order to predict longer-term outcomes for patients with *RPE65*-mediated IRD. Further discussion of health state transitions, including the modelling approach, is discussed in Section 5.2.6.

5.2.2.1 Evidence used to inform the company's model parameters

To inform the model, the company consider data from a range of different sources. These sources are described alongside any associated modelling assumptions in Table 30. Further details of these data sources may be found in the relevant section(s) of the ERG report (provided alongside each parameter category in Table 30).

Table 30: Summary of key evidence and assumptions within the company model

Category	Data source(s) and key assumptions	Section
Baseline patient characteristics	The distribution of baseline patient characteristics utilised by the cost-effectiveness model (age, sex, and health state occupancy) are based on the ITT population of Study 301/302.	**5.2.3**
Incorporation of treatments	The use of VN is incorporated per its use in Study 301/302, which was validated by clinical experts	**5.2.4**
Analysis settings	The model has been constructed according to the NICE reference case. A lifetime horizon has been adopted, with an NHS and PSS perspective in the model base case. Annual discount rates of 3.5% for costs and outcomes are applied.	**5.2.5**

Efficacy of VN *vs.* BSC	Estimates of the efficacy of VN and BSC were derived from Study 301/302 directly from baseline to Year 1. For BSC, after Year 1 the natural history component of the model is followed. For VN, it is assumed (based on clinical expert opinion) that the treatment effect of VN will persist for a period of 40 years (during which the only permitted transitions are to the "death" state). After 40 years, it is assumed that there is a 10-year waning period over which the long-term efficacy of VN (that is, maintenance of the effects observed at Year 1) decreases from 100% to 25% (where loss of treatment effect translates to patients following the natural history model projections).	**5.2.6**
Natural history of *RPE65*-mediated IRD	The natural history of the disease is based on data from the *RPE65* NHx study.	**5.2.6**
Mortality	Data from a study by Christ *et al.* are applied to background mortality estimates from the ONS Life Tables.	**5.2.6**
HRQoL	Utility values within the model were derived via an expert elicitation exercise conducted by the company (Acaster and Lloyd, 2018)	**5.2.7**
Cost of VN	The cost of VN is applied per the list price provided by the company (currently commercial-in-confidence)	**5.2.8**
Other direct costs	Unit costs taken from published sources, with resource use estimates informed by a combination of published literature and clinical expert opinion	**5.2.8**

Abbrev: BSC, best supportive care; HRQoL, health-related quality of life; IRD, inherited retinal dystrophy; ITT, intention-to-treat; ONS, Office for National Statistics; VN, Voretigene neparvovec.

5.2.3 Population

The CS states that the population considered within the cost-effectiveness analysis is *"patients with RPE65-mediated IRD who have sufficient viable retinal cells"*, per the population considered within Study 301/302, and the European Marketing Authorisation for VN. However, the ERG noted that the final scope issued by NICE does not explicitly exclude patients without sufficient retinal cells (discussed further in Section 0). As discussed in Section 2.1, *RPE65*-mediated IRD is used to describe two specific forms of IRD: (1) retinitis pigmentosa (RP), and (2) Leber's congenital amaurosis (LCA). Patients who have sufficient viable retinal cells were defined by the company per the description adopted in Study 301, which was based on patients meeting any one of the following three criteria:

1) an area of retina within the posterior pole of > 100 micron thickness as shown on OCT;
2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy; or
3) remaining visual field within 30□ of fixation.

Within the cost-effectiveness model, data from Study 301/302 were used to inform the baseline patient characteristics. At baseline, the cohort had a mean age of 15.1 years (based on the intention-to-

treat [ITT] population), of which 42% were male. The distribution of patients residing within each of the modelled health states at baseline was derived based on the ITT population, as shown in Table 31.

Table 31: Baseline distribution of patients by health state (Study 301/302)

Health state	ITT (n=31)	BSC (n=10)	VN (n=21)
HS1 (Moderate VI)	23% (n=7)	30% (n=3)	19% (n=4)
HS2 (Severe VI)	32% (n=10)	40% (n=4)	29% (n=6)
HS3 (Profound VI)	23% (n=7)	10% (n=1)	29% (n=6)
HS4 (CF)	19% (n=6)	10% (n=1)	24% (n=5)
HS5 (HM, LP, NLP)	3% (n=1)	10% (n=1)	0% (n=0)

Key: BSC, best supportive care; CF, counting fingers; HM, hand motion; ITT, intention-to-treat; LP, light perception; NLP, no light perception; VI, visual impairment; VN, voretigene neparvovec.

The company state that the population of Study 301/302 is considered broadly representative of the UK population, for on two key reasons:

(1) the non-restrictive inclusion/exclusion criteria (of the 36 screened subjects, n=5 were screening failures)

(2) the recruiting centres are expected to be broadly representative of real-world treatment centres (given the expectation of VN to be administered at a small number of specialist centres)

To inform longer-term extrapolation, the company use data from a natural history study (*RPE65* NHx). The company suggest that this study may be considered representative of the UK population as it is a retrospective chart review and therefore reflects a real-world population. The company also provides a scenario analysis wherein the baseline characteristics of this population are used to inform the cost-effectiveness model. The mean age of patients in *RPE65* NHx was 15.0 years and 40% were male, with the distribution of patients residing within each of the modelled health states at baseline shown in Table 32.

Table 32: Baseline distribution of patients by health state (*RPE65* NHx, CS Table 47)

Health state	Proportion of patients
HS1 (Moderate VI)	57% (n=39)
HS2 (Severe VI)	29% (n=20)
HS3 (Profound VI)	6% (n=4)
HS4 (CF)	4% (n=3)
HS5 (HM, LP, NLP)	3% (n=2)
Total	*100% (n=68)*

Abbrev: CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; VI, visual impairment.

ERG Comment:

The ERG was generally satisfied that the cost-effectiveness model reflects the patient population specified within the final NICE scope, which is aligned with the 301/302 study and the European Marketing Authorisation. The ERG acknowledged that studies of rare diseases are often fraught with issues relating to sample sizes, generalisability and non-standard clinical study design. The decision to deviate from the scope in regards to the population of patients with insufficient retinal cells is aligned with the expected use of VN in clinical practice.

Clinical expert opinion sought by the ERG confirmed that it was appropriate for the two conditions (RP and LCA) to be grouped for the purpose of assessing the clinical- and cost-effectiveness of VN. However, it should be noted that only patients with LCA were enrolled within the clinical studies of VN, and therefore there is no clinical evidence pertaining to the use of VN in an RP-specific population.

Within the company's cost-effectiveness model, the distribution of patients at baseline by health state is based upon the pooled estimate across both treatment arms of Study 301/302. Due to the small sample size, the proportions of patients within each treatment arm differ to the pooled estimate (as shown in Table 31). Furthermore, the natural history study (*RPE65* NHx) comprises of a less severe population (87% of patients reside within HS1 or HS2 at baseline, versus approximately 55% of the ITT population within Study 301/302 [based on Table 31 and Table 32]).

The ERG noted that a total of n=70 patients were considered "eligible" in the *RPE65* NHx study. However, in Table 32 the total number of patients sums to 68. Further to this, within Section 12.1.8.3.3 of the CS, it is stated that *"67 patients were included in the analysis"*. The ERG requested clarity from the company regarding the baseline characteristics of patients in the *RPE65* NHx study, and were referred to the original study report which unfortunately does not provide information regarding health state allocation, or specific reasons why some patients may have been excluded.

For the purpose of the ERG report, a total of n=68 patients are assumed to be relevant to the analysis (based on the outputted log file from the statistical analysis discussed in Section 5.2.6).

The differences in characteristics between treatment arms extends to the average age of the cohort. The mean age for patients treated with VN is 14.8 years, versus 15.9 years for patients receiving BSC. Clinical advice provided to the ERG suggested that treatment may be given at any age, and that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population.

Within NICE HST7 (strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency, a different gene therapy),[79] it was stated that *"age is a factor that may*

determine suitability and success of gene therapy" (ERG report Section 5.2.3). Similarly a study by Pierce and Bennet regarding *RPE65* gene therapy trials stated that *"In aggregate, the reported results suggest that the response to treatment is at least in part age dependent".*[80] The age differences between the randomised groups and the associated impact this may have on treatment outcomes should be noted as an uncertainty in the evidence base for VN.

Two patients within Study 301/302 (one in each treatment arm) did not receive treatment after randomisation – one due to physician decision, and the other due to personal reasons. The ERG noted that small differences in the baseline proportions of patients may have an impact on the estimation of cost-effectiveness (especially when combined with other model adjustments), yet acknowledge that this issue is somewhat unavoidable within the context of studies in rare diseases.

Based on the limitations present within the company's cost-effectiveness model stated above, the ERG has undertaken additional analyses to explore the impact of alternative assumptions in relation to the patient population on cost-effectiveness results. The results of these analyses are presented in Section 6. The ERG's preferred base case makes use of a pooled average of patient characteristics based on data from Study 301/302 (ITT, Table 31) and the *RPE65* NHx study (Table 32), as combining baseline health state occupancy based on a larger sample size is expected to align more closely to the patient population seen in clinical practice.

5.2.4 Interventions and comparators

The intervention considered within the cost-effectiveness analysis is VN (Luxturna®). VN is administered as two subretinal injections (one injection into each eye) on two separate occasions, which are usually at least six days apart. Prior to each injection, patients will receive a regimen of oral prednisone. The company states that *"treatment will be initiated by a consultant in retinal degeneration and administered by a retinal surgeon experienced in performing macular surgery."* (refer to the CS Section 8.4.2), and expect that diagnosis, counselling, treatment and follow-up for patients who may be eligible for VN will be performed at only a few specialist centres nationally.

The comparator included within the cost-effectiveness analysis is best supportive care (BSC). While no formal definition for BSC is provided within the company submission, in practice BSC comprises various disease-management measures, such as low-vision aids (e.g. magnifiers) and subretinal or epiretinal prostheses (though are only recommended in research by NICE). Within the submitted cost-effectiveness model, no costs are assumed to be related to BSC specifically outside the costs assigned to healthcare resource use associated with each model health state. Resources and costs are discussed further in Section 5.2.9.

ERG Comment:

The ERG agreed with the application of the intervention and comparator within the cost-effectiveness model submitted by the company, though an explicit description of BSC is not provided in the CS. Clinical advice provided to the ERG noted the lack of current treatment options available for patients with *RPE65*-mediated IRD, and suggested that BSC comprises of general lifestyle advice (such as protection against the sun and dietary recommendations) in addition to providing access to visual aids.

The application of VN within the cost-effectiveness model is aligned with the protocol of Study 301/302, and the EMA. However, the ERG noted that the intervention arm may be considered as VN + BSC (given that there is no evidence that it would be inappropriate for patients treated with VN to receive BSC as well).

5.2.5 Perspective, time horizon and discounting

In the base case analysis, the company takes the perspective of the National Health Service and Personal Social Services (NHS and PSS), per the NICE reference case. Alternative perspectives were considered within scenario analyses. The company model adopts a lifetime horizon - equivalent to following patients until a maximum age of 100 years, which corresponds to a time horizon of 85 years in the base case analysis.

A cycle length of one year is applied within the model, which the company defends by stating that this reflects the relatively slow rate of visual decline in the *RPE65*-mediated IRD population. The model includes adjustments to "twelfth-cycle" correct relevant costs and outcomes within the first year after administration of VN (or initiating BSC). The "twelfth-cycle" correction was justified by the company based on the improvement in VA/VF observed within Study 301/302 at approximately one month. To apply the "twelfth-cycle" correction, the company used the following formula:

$$Occupancy_{First\ cycle} = \frac{1 \times Occupancy_{Baseline} + 11 \times Occupancy_{Year\ 1}}{12}$$

After the first year, the company included adjustments to "half-cycle" correct relevant costs and outcomes thereafter.

Discount rates of 3.5% for costs and outcomes (QALYs) were applied in the company base-case analysis. The company provide a scenario where the discount rates are set to 1.5% in line with NICE guidance which states that these rates may be considered by the NICE appraisal committee if: *"… it is highly likely that, on the basis of the evidence presented, long-term health benefits (normally at least 30 years) are likely to be achieved and that the technology does not commit the NHS to significant irrecoverable costs"*.[81]

ERG Comment:

The ERG considered that the lifetime horizon (equivalent to 85 years) is appropriate within the context of this inherited, chronic disease. The base case perspective of the NHS and PSS is aligned with the NICE reference case, though other perspectives may be appropriate to consider within the context of *RPE65*-mediated IRD due to the substantial costs that fall on other government services. The use of annual discount rates of 3.5% for costs and outcomes is also aligned with the NICE reference case. Discount rates of 1.5% may be appropriate to consider (given the anticipation of benefits extending beyond 30 years), however these remain unproven and VN comprises a technology that does commit the NHS to significant, irrecoverable costs as VN is a 'one-off' gene therapy with uncertain long term effectiveness.

5.2.6 Treatment effectiveness and extrapolation

The company's model comprises of two phases – an initial phase (baseline to Year 1) and a long-term phase (from Year 1 onwards). For both phases, the company incorporates mortality data from external sources as no deaths were observed in the clinical studies of VN, or the natural history study. The methods employed by the company to account for treatment effectiveness and outcome extrapolation are discussed below.

5.2.6.1 Initial phase

Health state transitions from baseline to Year 1 were derived using transition matrices based on observed patient numbers residing within each health state from Study 301/302. In the company's base case, transitions were based on the original intervention arm of Study 301/302 only, using a combination of VA and VF, taking an average across both eyes (reflecting the bilateral nature of the condition). Sensitivity analyses were explored wherein the crossover data (i.e. delayed intervention) arm transitions were also included, health states were based on VF only and/or the best-seeing eye.

The transition matrices used in the model base case are based on the exact transitions observed within Study 301/302. However, the company note that no patients resided within HS5 (hand motion, light perception, no light perception) at baseline for those treated with VN or BSC. Therefore, it was necessary to make an assumption regarding how patients may transition from this health state within the first year. Two options were presented by the company:

(1) Patients in health states with no transition data move the same number of health states as those patients in the next least severe health state (e.g. if no transitions were observed for patients in HS5 at baseline, and 100% of patients in HS4 moved to HS3, this option would assume that 100% of patients in HS5 at baseline would move to HS4)

(2) Patients in health states with no transition data remain in the same state at Year 1 (i.e. no improvement and no worsening versus baseline)

Option (1) was applied in the company's base case, as the company noted that while these transitions were not observed within the clinical trial, they would still be possible in clinical practice. Option (2) was considered as a sensitivity analysis.

The model base case transition matrices for the initial phase of the model are presented in Table 33. Forward (worsening vision) transitions are presented with a solid background, whereas backward transitions (improving vision) transitions are presented within a dashed background. An overview of the change in health state occupancy (non-half-cycle corrected) between baseline and Year 1 is presented in Figure 27. It can be seen from the table and figure that the transitions for patients treated with VN led to higher occupancy of HS1 at Year 1, and reduced occupancy of all other "alive" health states. For BSC, there is a less clear pattern of transitions, with a small increase in occupancy of HS1 and HS3, and lower occupancy of HS2, HS4 and HS5.

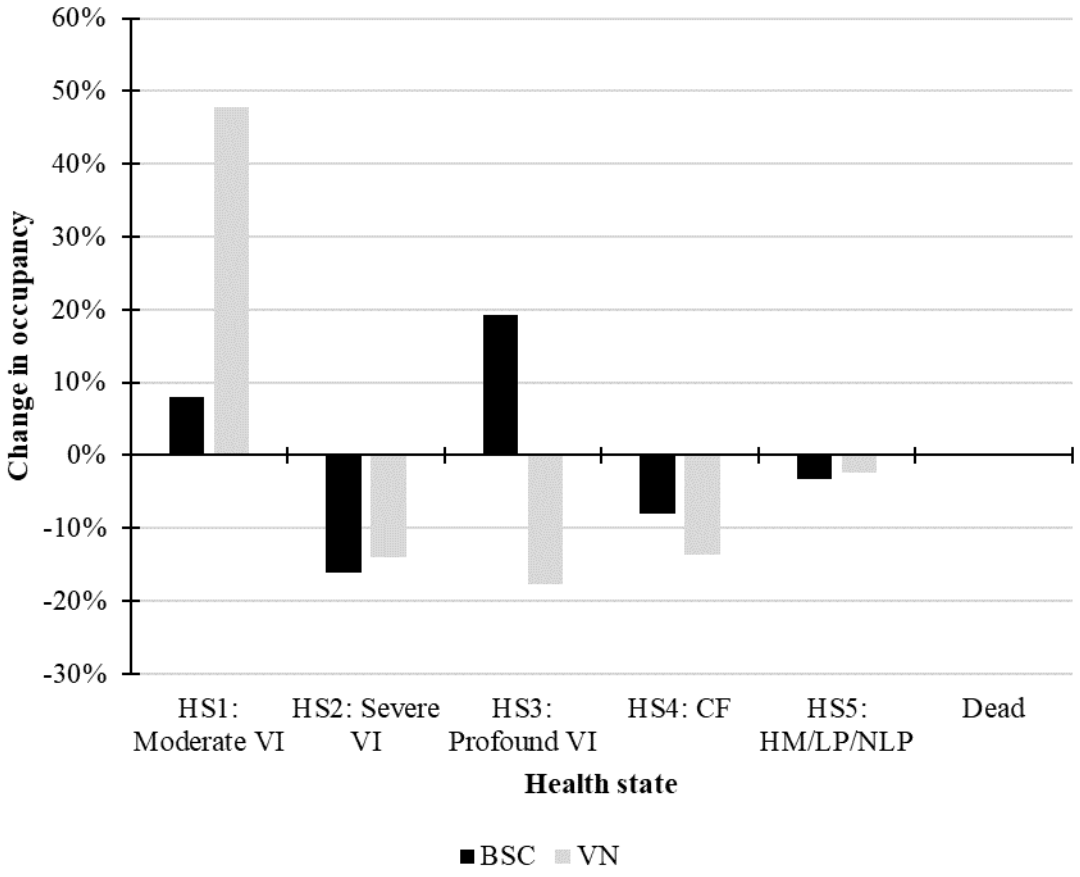
Table 33: Base case transition matrices for initial phase of the model

VN							BSC						
	To							To					
From		HS1	HS2	HS3	HS4	HS5	From		HS1	HS2	HS3	HS4	HS5
	HS1	100%	0%	0%	0%	0%		HS1	100%	0%	0%	0%	0%
	HS2	83%	17%	0%	0%	0%		HS2	25%	50%	0%	25%	0%
	HS3	50%	50%	0%	0%	0%		HS3	0%	0%	100%	0%	0%
	HS4	50%	0%	25%	25%	0%		HS4	0%	0%	100%	0%	0%
	HS5	0%	50%	0%	25%	25%		HS5	0%	0%	0%	100%	0%

Key: BSC, best supportive care; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception; VN, voretigene neparvovec.

Sources: Table 39 and Table 40 of the CS.

Figure 23: Change in health state occupancy from baseline to Year 1 (initial phase, produced by the ERG)



Key: BSC, best supportive care; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception; VN, voretigene neparvovec.

In addition to the base-case transition matrices which were based on the observed transitions (termed the *"Exact TP"* approach), the company provided alternative scenarios (referred to as an *"adjusted TP"* approach). The company posits that following the same logic as per the lack of observed transitions from HS5 within the *"Exact TP"* approach, it should be noted that some of the other transitions are associated with zero probabilities despite being possible in clinical practice – for example, VN patients cannot transition from HS4 to HS2 in the model base case.

To address this limitation, the company considered two alternative applications of the *"state-dependent"* approach to estimate transition probabilities: (1) a *"state-dependent adjusted TP" analysis*, and (2) a *"state-independent adjusted TP"* analysis. These are described below:

- In both analyses, transitions into HS1 were unchanged (as these transitions were deemed to be *"relatively well populated"* with the *"Exact TP"* approach)

- Transitions into other states were categorised as either an improvement (movement to a better state) or a deterioration (movement to a poorer state)
- In the *"state-dependent adjusted TP"* analysis, improvements were apportioned evenly across all possible improvement health states, and the same approach was applied for deteriorations. Non-transitions (i.e. patients remaining in the same state) were unchanged compared with the *"exact TP"* approach.
- In the *"state-independent adjusted TP"* analysis, all improvements, deteriorations and non-transitions were grouped across all original health states and used to apportion the transitions (i.e. it is assumed that all improvements and deteriorations can be considered equivalent, combined and then applied across each starting health state which *"allows for the use of limited available data to be maximised"*)

The resultant transition probabilities for each of these analyses are presented in Table 34. The ERG noted that the company state that the results of these scenarios (and in particular the *"state-independent adjusted TP"* analysis) should be interpreted with caution.

Table 34: Base case and sensitivity analysis transition matrices for initial phase of the model

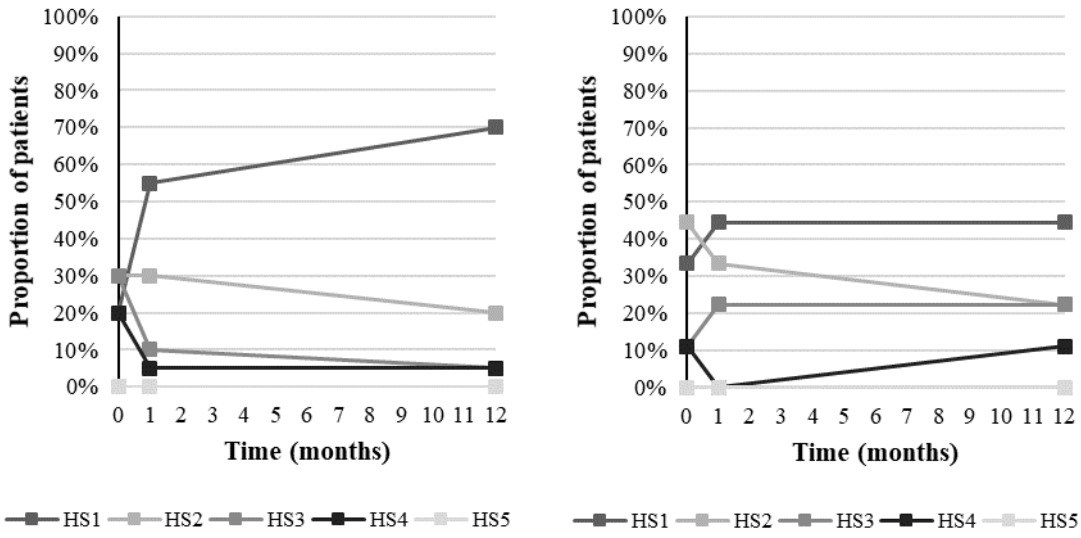
		VN							BSC					
Base case		**To**							**To**					
	From		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**	**From**		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**
		HS1	100%	0%	0%	0%	0%		**HS1**	100%	0%	0%	0%	0%
		HS2	83%	17%	0%	0%	0%		**HS2**	25%	50%	0%	25%	0%
		HS3	50%	50%	0%	0%	0%		**HS3**	0%	0%	100%	0%	0%
		HS4	50%	0%	25%	25%	0%		**HS4**	0%	0%	100%	0%	0%
		HS5	0%	50%	0%	25%	25%		**HS5**	0%	0%	0%	100%	0%
SA1 (dep)		**To**							**To**					
	From		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**	**From**		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**
		HS1	100%	0%	0%	0%	0%		**HS1**	100%	0%	0%	0%	0%
		HS2	83%	17%	0%	0%	0%		**HS2**	25%	50%	8%	8%	8%
		HS3	50%	50%	0%	0%	0%		**HS3**	0%	0%	100%	0%	0%
		HS4	50%	13%	13%	25%	0%		**HS4**	0%	50%	50%	0%	0%
		HS5	0%	25%	25%	25%	25%		**HS5**	0%	33%	33%	33%	0%
SA2 (ind)		**To**							**To**					
	From		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**	**From**		**HS1**	**HS2**	**HS3**	**HS4**	**HS5**
		HS1	100%	0%	0%	0%	0%		**HS1**	100%	0%	0%	0%	0%
		HS2	83%	17%	0%	0%	0%		**HS2**	25%	60%	5%	5%	5%
		HS3	50%	33%	17%	0%	0%		**HS3**	0%	20%	60%	10%	10%
		HS4	50%	17%	17%	17%	0%		**HS4**	0%	10%	10%	60%	20%
		HS5	0%	22%	22%	22%	33%		**HS5**	0%	7%	7%	7%	80%

Abbrev: BSC, best supportive care; dep, state-dependent; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception; indep; state-independent; SA, sensitivity analysis; VN, voretigene neparvovec.

Sources: Tables 39-40, 43-46 of the CS.

At clarification stage, the company provided data regarding health state allocation of patients at baseline, 30 days, and 1 year in Study 301/302. A visual representation of this is provided in Figure 24. For the BSC arm, occupancy at Day 30 and Year 1 were identical for 8 of the 9 patients. For the VN arm, occupancy at Day 30 and Year 1 were identical for 16 of the 20 patients. For 3 of the 4 patients who transitioned between health states from Day 30 to Year 1, this was a movement from HS2 to HS1 (hence the diagonal lines shown for these health states in Figure 24).

Figure 24: Health state occupancy within Study 301/302 at baseline, 30 days, and 1 year (left: VN, right: BSC; plots produced by ERG)



Key: BSC, best supportive care; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception; VN, voretigene neparvovec.

ERG Comment:

The ERG agreed with the company's base case approach to using the observed transitions from Study 301/302. However, the ERG considered that it would have been more appropriate to utilise data from both the original and delayed intervention to inform the cost-effectiveness model for a number of reasons, including:

- The larger sample size (versus the original intervention arm only)
- The ability to inform a larger number of transitions (some of which were unpopulated if only the original intervention patients were used)
- The impact of crossover (e.g. given the lack of a formal washout period) is not expected to

affect the estimation of outcomes for the delayed intervention group

As previously stated, the ERG was unclear why the company considered it necessary to adjust outcomes at 1 year such that the treatment effect was fully realised at 1 month (using the "twelfth-cycle correction"), given that data are available at 1 month to inform this directly. Receipt of data provided by the company at clarification showed that while some transitions occurred between 30 days and 1 year, these were relatively small in number and so the company's modelling assumption is not expected to have a large impact on the model results.

The company did not include any further data from later years of the study, but noted in their submission that at least one subject treated with VN was observed to transition between health states during Years 2 and 3. The ERG asked the company for clarification regarding the number of patients who transitioned after Year 1. [redacted] The company noted that Study 101/102 was based on a small sample of patients who did not necessarily receive the licensed dose of VN and may not have had sufficient retinal cells such that they would have been eligible for enrolment within Study 301/302 (or treated in practice). This remains a key uncertainty in the expected treatment effect of VN.

5.2.6.2 Long-term phase (natural history)

Transitions after Year 1 are based on a combination of assumptions regarding the duration of VN treatment effect and the application of a parametric multi-state model (MSM). The MSM approach involves the specification of a statistical model that simultaneously estimates the probabilities of patients moving between the five "alive" health states over time.

The MSM was fitted to data from the "Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the *RPE65* Gene (*RPE65* NHx)" study [3]. *RPE65* NHx is a retrospective chart review of 70 patients with *RPE65*-mediated IRD who would be eligible to receive VN. Patients had a mean age of 15 years at the start of data collection, and were followed up for a mean duration of 7.28 years. The company noted that previous analyses of the data found a statistically significant relationship between age and VA ($p<0.001$).

The company specified an MSM in line with the methodology proposed by Crowther and Lambert [82] The company summarise the benefits of adopting an MSM approach based on the following:

"A multistate survival model allows for the risk of moving between health states to vary over time, as may be expected in clinical practice. Multiple alternative survival distributions can be tested to determine the most plausible extrapolation of observed data, including the assumption of constant risk (i.e. the exponential distribution). In addition, by parameterising the risks of moving between health states, this approach allows for parameters determining the long-term health state distribution to be tested in univariate and probabilistic sensitivity analysis." (CS, Section 12.1.8.3.2, page 185)

In line with clinical expert opinion, the company specified the MSM as *"progressive only"*, such that the only permitted transitions were those to "poorer" health states (i.e. it was not possible for patients to experience an improvement in health state beyond Year 1). The company also highlighted that the implementation of a progressive only MSM is less complex to implement within the cost-effectiveness model (versus an unrestricted MSM). Transitions to the "dead" health state were not captured by the MSM, as no death events were observed within the *RPE65* NHx study.

A parametric multistate (five state) Markov MSM was fitted by the company. Within the context of the MSM approach, the Markov assumption implies that the probability of movement to another state is independent of the time spent in the current state, instead the probability of movement to another state is dependent on the time since model entry. The ERG noted that it is important to flag that the Markov assumption within the context of an MSM differs to the traditional definition used to describe a Markov cost-effectiveness model wherein transitions may be considered Markovian (memoryless) if they are independent of time, such as in the case of an exponential distribution.

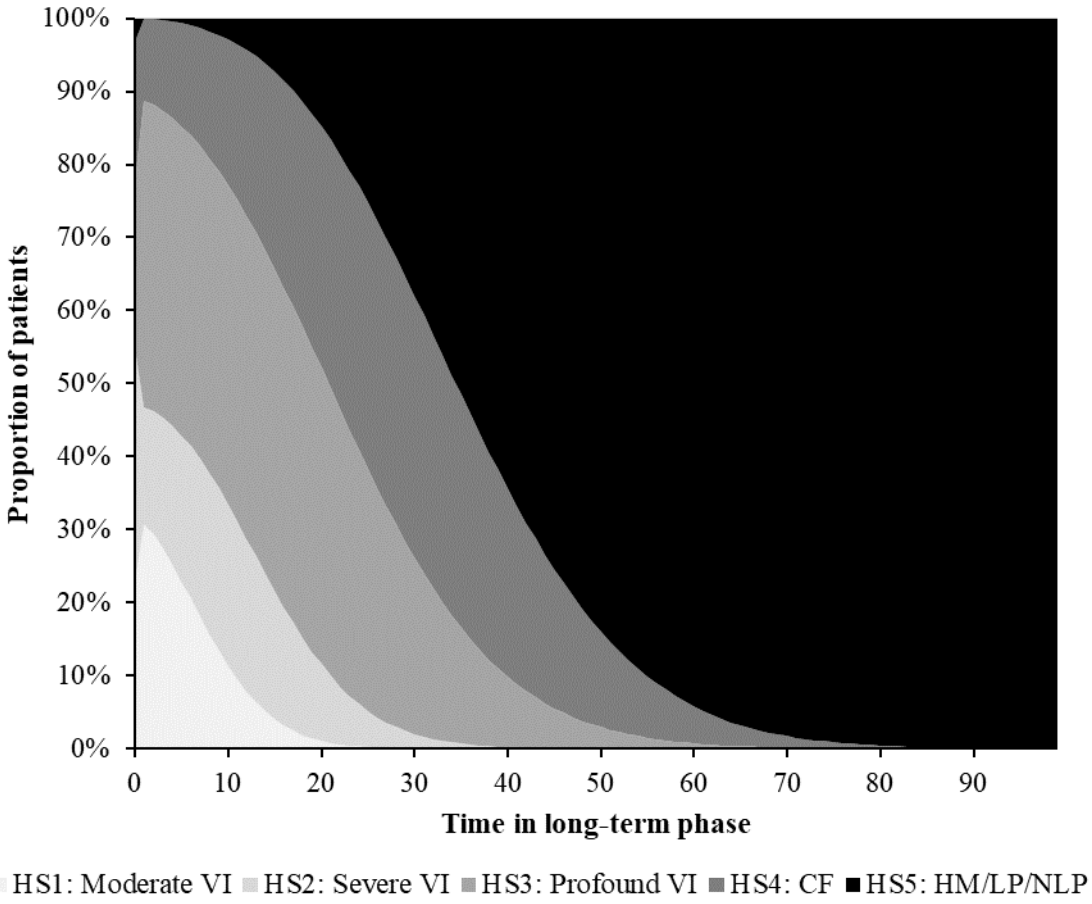
The company fitted the MSM using the Stata software package *MULTISTATE* [82]. The company successfully fitted a total of 5 MSMs, based on the following statistical distributions: exponential, Weibull, Gompertz, log-logistic, and log-normal. A generalised gamma MSM was also attempted, though the company noted that this model did not converge. The MSM fits were specified assuming proportionality between baseline hazard functions and the transition intensities within the same distributional model.

The statistical fits of the models were compared using Akaike and Bayesian information criteria (AIC and BIC, respectively), in addition to an analysis of Cox-Snell residual plots. The ERG requested further information regarding the Cox-Snell residual plots provided within the CS at clarification stage. The company provided some data used to inform the Cox-Snell residual plots, but did not provide as explanation as to what exactly they were intended to illustrate.

The Weibull MSM was selected to inform the company's base case, and was selected according to both statistical fit (lowest AIC and BIC) and *"visual inspection"*. To illustrate the base-case projections of the MSM component of the model, a plot is presented in Figure 25 which shows

estimated health state occupancy within the company's model for the BSC arm upon entry into the long-term phase of the model. The impact of mortality was removed to inform the diagram.

Figure 25: Long-term projections of the base-case MSM component of the company's model (for the BSC arm, removing the impact of mortality)



Key: BSC, best supportive care; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

The company note that the *MULTISTATE* Stata package provides outputs for the MSM that are transition rates. The cost-effectiveness model requires the derivation of transition probabilities, though the standard formula for converting rates to probabilities (the probability of an event per unit time is equal to 1 minus the exponent of the negative rate multiple by the time interval) is not applicable in the context of competing risks (which features within the MSM).

To convert the rates to probabilities, the company state that there are two alternative methods:

1) Generating probabilities within a statistical software package (such as Stata); or

2) Apply matrix algebra logic based on a procedure detailed by Jones *et al* to present a *"straightforward implementation of PSA and for increased model transparency"*[83].

The company opted to use the latter approach, and used the computer algebra system wxMaxima to determine the calculations required in order to convert the MSM parameters to transition probabilities that changed over time.

At clarification stage, the company noted an error in their original MSM analysis. The company found that they were no longer able to re-produce the MSM in the originally-submitted cost-effectiveness model, and that this was because of differences in a constructed dataset between executions of the code. This was believed to have been the result of an error in the merge command in the statistical software package STATA. In an addendum to the clarification response, the company provided updated cost-effectiveness results and an updated cost-effectiveness model. This model was used to inform the ERG's critique.

ERG Comment:

The ERG agreed with the use of the natural history study to inform the long-term outcomes for patients with *RPE65*-mediated IRD receiving BSC. The study provides data for a relatively large number of patients collected as part of a retrospective chart review. The ERG noted that a small number of the eligible patients (n=2) were omitted from the analysis, yet no explanation for this was provided within the CS. While there are some differences in baseline patient characteristics (e.g. distribution of health state allocation, shown in Table 31 and Table 32), and limitations associated with the retrospective study design (e.g. changes in clinical practice over time), the ERG was satisfied that the use of data from this study is appropriate to inform the cost-effectiveness model.

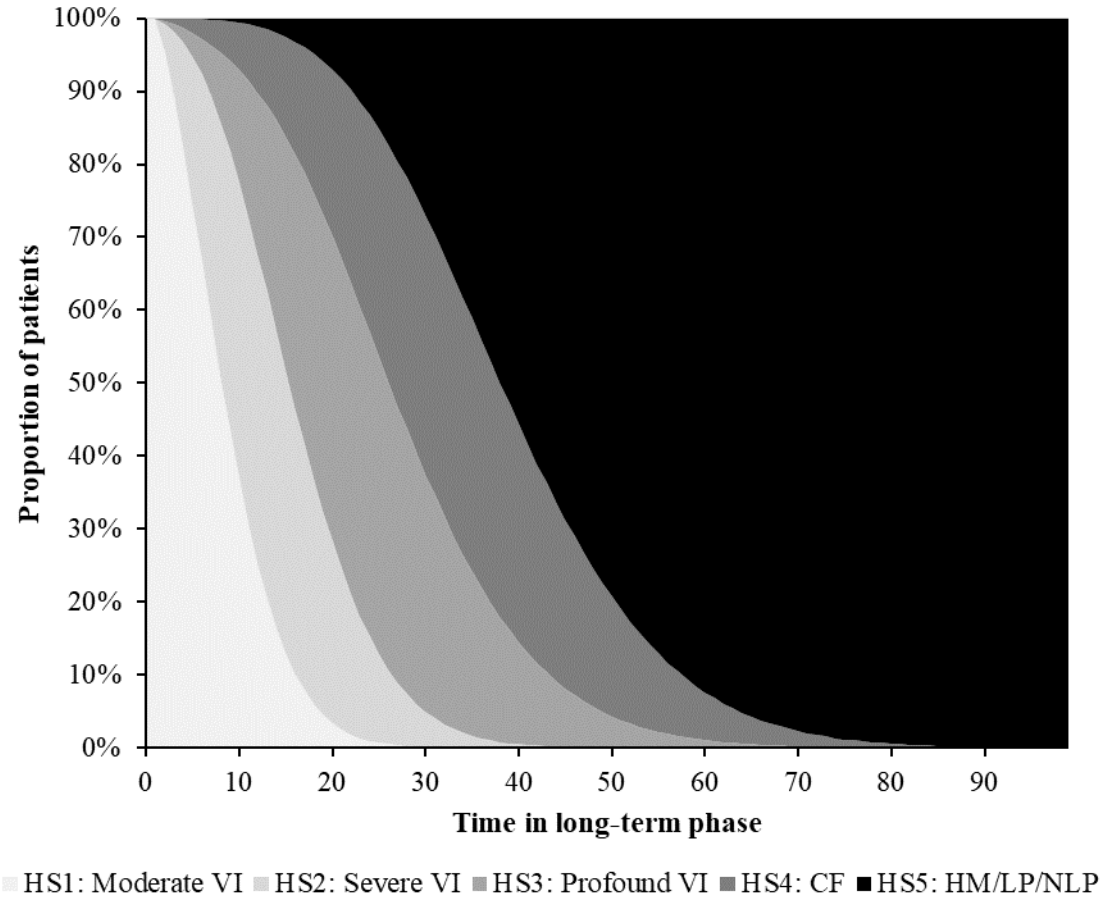
The company's decision to apply an MSM to extrapolate longer-term outcomes was based on the intention of including the ability for transition probabilities to change over time. However, this decision does not appear to be well justified in light of the evidence available from the *RPE65* NHx study. As previously stated, data are available for a total of n=68 patients, and as stated within the addendum supplied to the ERG at clarification stage there were a total of n=35 transitions between the five "alive" health states. The company's base-case analysis (a Weibull MSM) requires the estimation of 11 parameters. Consequently, the Weibull MSM was fitted based on an average of 3.2 transitions (events) per parameter (n=35 transitions for 11 parameters), or 6.2 patients per parameter (n=68 patients for 11 parameters). It is the ERG's opinion that the specification of such a model is overly complex and likely *"over fits"* the available data from the *RPE65* NHx study.

The ERG also highlighted a number of further issues with the MSM approach. The Cox-Snell residual plots provided for each MSM parameterisation do not provide clear evidence of which model (of those fitted) may be expected to yield the best fit to the data, as it is unclear what the cumulative hazard is intended to represent. The ERG expects that these plots show the estimated fit of the MSM, with no specific consideration given to the type(s) of transition (e.g. an event is defined as any transition); however, it remains unclear how this analysis would deal with multiple events for a given patient, or if considered all transitions in a blended plot is particularly meaningful.

The specification of a Markov MSM is based on assumption, which the company fails to justify within their submission, though the ERG acknowledges that providing evidence to defend the Markov assumption would be very difficult with the limited sample size available. At clarification stage, the company noted that they performed an informal test as described within the Crowther and Lambert paper [82]. The test suggested the Markov assumption may not hold, though the company stated that the Markov assumption was assumed to hold based on the design of the *RPE65* NHx study (which was not designed to allow this to be tested formally) and the availability of data to inform individual transitions.

Beyond the duration of follow-up from *RPE65* NHx, the extrapolations have not been validated based on clinical plausibility and appear to conflict with the company's statements on long-term natural history outcomes. The company did not provide an illustration of the observed proportions by health state occupation versus the Weibull MSM predictions, nor did they provide evidence of validating these estimates with clinical experts. The CS states that *"RPE65-mediated [IRDs] cause progressive vision loss, leading to near-total blindness as early as preschool years or as late as the third decade of life."* (CS executive summary). However, the company's Weibull MSM suggests that many patients continue to reside in the less severe health states far beyond the third decade of life. To illustrate this further, Figure 26 shows the estimated proportion of patients residing in each model health state assuming (1) all patients at baseline are in HS1, and (2) the impact of mortality is removed.

Figure 26: Long-term projections of the base-case MSM component of the company's model (for the BSC arm, all in HS1 at baseline, removing the impact of mortality) from time=0 when patients are aged 15



Key: BSC, best supportive care; HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.

Figure 26 shows that by 15 years, approximately 10% of patients who reside in HS1 at baseline have not experienced disease progression to the extent that they would transition to HS2 or beyond (given that backward transitions are not permitted within the Weibull MSM specified by the company). Given that average age at baseline is approximately 15 years, this means that the model estimates a substantial proportion of patients who do not appear to have *"near-total blindness"* by the third decade of life (i.e. age 30 years = 15 years at baseline + 15 years extrapolation).

The ERG acknowledges that the MSM has been implemented correctly, including the use of the method by Jones *et al.* to convert the outputted parameters to transition probabilities. However, the use of the MSM to project longer-term outcomes remains a key limitation of the company's model.

5.2.6.3 Long-term treatment effect

The effect of VN may be described in relation to four key time points following treatment:

- **1 month:** the effect of VN is assumed to fully apply
- **1 year:** full effect of VN as measured in Study 301/302
- **41 years:** full effect of VN ceases to apply, treatment effect starts to wane
- **51 years:** 'waning' period ends, residual treatment effect applied henceforth

The assumptions relating to the treatment effect within the first 12 months have been discussed earlier in this section, and within Sections 5.2.2 (discussion of the model structure) and 5.2.5 (discussion of the twelfth-cycle correction) of this report. The remainder of this section is focused on the long-term extrapolation of the VN treatment effect.

The company state that the assumptions relating to the application of the long-term treatment effect of VN were based primarily on consultation with UK clinical experts. At clarification stage, the ERG requested further information regarding the elicitation of clinical expert opinion to inform these model assumptions. The company provided meeting notes that summarised the nature of the conversations had with the experts, though no formal transcript was recorded.

ERG Comment:

The ERG's clinical experts stated that the plausibility of a long-term treatment effect is aligned with the currently-evidence available for VN, but it remains unknown (and unknowable) whether or not this treatment effect will truly persist over the lifetime of patients.

[redacted] Consequently, the experts consulted were unable to validate the assumptions used by the company in their submission. The ERG's clinical experts noted that a study by Bainbridge *et al.* of a different gene therapy did provide evidence that treatment effects are not necessarily lifelong for all patients.[84]

[redacted] However, some longer-term data from Study 301/302 (and the earlier phase Study 101/102) suggest VA/VF may decline in future years (though these analyses are associated with a number of caveats, including the reliance on last-observation-carried forward).

The validation of the treatment effect of VN is understood to be a very difficult question to answer, and that based on the evidence available a long-term treatment effect is expected. However, the ERG was unconvinced that the company's base case assumptions were plausible. More specifically, the ERG believed that a constant treatment effect of 40 years is not defended by the evidence available to data. Further to this, a 10-year treatment waning period from 100% to 25% does not appear to be based on any biological rationale for why this pattern of reduction in treatment effect would be expected to occur. The company also stated that the value of 25% is entirely arbitrary, and therefore the ERG had little basis from which to provide its critique of this assumption.

In the ERG's base case, the assumption around treatment effect duration has been simplified to the choice of a single number to capture the expected duration over which VN is expected to delay vision deterioration. The 40-year treatment effect assumption is maintained in the base case, but the ERG stresses that this is only maintained given the absence of an alternative assumption to include within the model. However, the ERG conducted a threshold analysis to ascertain how long the treatment duration would need to be such that the ICER falls within an acceptable range.

In a separate analysis, the ERG considered the base-case assumption used to incorporate the duration of treatment effect within the analysis undertaken by the Institute for Clinical and Economic Review.[76] This is described in further detail within Sections 9.2.8 and 10.3 of their report (with the findings presented in Section 10.3).

5.2.6.4 Mortality

To account for mortality, the company used general population life tables for England and Wales, available from the Office for National Statistics (ONS). The probability of death for each model cycle was assumed to be based on the mean baseline characteristics (age and sex), and a health state-specific mortality effect (in the form of a hazard ratio [HR]) applied using data derived from a study by Christ *et al.*[85] The mortality multipliers (HRs) used for each health state are presented in Table 35.

Table 35: Company applied HRs in each model health state (versus general population)

Health state	Hazard ratio applied	Description
HS1 (Moderate VI)	1.08	Baseline LogMAR = 0.6
HS2 (Severe VI)	1.18	Baseline LogMAR = 1.0
HS3 (Profound VI)		
HS4 (CF)		
HS5 (HM, LP, NLP)		

Key: CF, counting fingers; HM, hand motion; HR, hazard ratio; ITT, intention-to-treat; LogMAR, Logarithm of the Minimum Angle of Resolution; LP, light perception; NLP, no light perception; VI, visual impairment.

Source: CS, p. 190-191

The company notes a number of limitations of the Christ *et al.* study, including that it is based on a population of patients aged 65 to 84 years, and was conducted between 1993 and 2003. Furthermore, the HRs are based on a comparison to a population with 20/20 vision (i.e. "perfect" VA, where at a distance of 20 feet patients are able to clearly see what should normally be considered possible to see at this distance). Finally, the company note the lack of disaggregation of the results reported means that it is not possible to distinguish between HS2, HS3, HS4 and HS5. In spite of these limitations, the company apply the mortality multipliers in their base case and explore the removal of them within sensitivity analysis.

ERG Comment:

The ERG agree with the company's approach to capturing mortality within the model structure separate to the transitions between the living health states. However, the ERG does not agree with the company's assumption that the model health states are associated with an increased risk of death. The ERG observed that within all of the studies presented by the company (including the retrospective chart review), no death events have occurred. Furthermore, the study referenced considers a substantially different population of patients to the scope of this appraisal, who have lost their sight for different reasons, at a different age, which may have a number of comorbidities that may affect the risk of death that were simply coded as either "no conditions", "one condition", and "two or more conditions". Within the ERG's base case, the mortality hazard ratio is therefore not included.

5.2.6.5 Other clinical outcomes

Within the company's model, the average MLMT and FST scores by health state were calculated and used to provide an illustration of how the average score for the cohort changed over the modelled time horizon. To do this, the company made two explicit assumption: (1) all observations for VN-treated patients (crossover patients) were assumed to be representative of the VN arm, and (2) all observations for non-VN-treated patients (including baseline observations prior to treatment) were assumed to be representative of the BSC arm.

ERG Comment:

While the ERG understands this analysis was presented for illustrative purposes, there are a number of concerns associated with the presentation of such graphs. The values for BSC are based on relatively earlier observations than those for VN (as observations for BSC are capped at 1 year); hence, *ceteris paribus*, the observations for the VN arm may be lower than those for the BSC arm. The ERG noted that no explicit adjustments to account for repeated measures within patient groups

will be accounted for within the analysis, and that patients randomised to BSC are included in both groups at various time points.

5.2.7 Health related quality of life

5.2.7.1 Health state utility values

As part of the clinical study program for VN, no data were collected regarding patient or carer HRQoL using a validated preference-based measure (such as the EQ-5D). Furthermore, no data were identified regarding the HRQoL of patients with *RPE65*-mediated IRD by the company through their systematic review of the literature.

In Study 301/302, a customised visual function questionnaire was administered to patients, which differs from other widely-used instruments in visual disorders, such as the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25). The NEI VFQ-25 (and other instruments) were stated to be unable to capture the full patient experience of *RPE65* mediated IRD, which includes low light vision limitations.

Due to the lack of published data in *RPE65*-mediated IRD and the lack of a mapping function to elicit utility values based on the questionnaire administered within the study, the company asked six clinicians to complete proxy generic health related quality of life questionnaires for each of the health states in the economic model, based on summary descriptions and their experience with patients. The results of this elicitation exercise are presented in Table 36, with the HUI3 results preferred by the company as the HUI3 contains a vision component (the EQ-5D does not).

Table 36: Utility values from company's elicitation exercise

Health state	Utility value	
	HUI3, mean (SD)	EQ-5D-5L, mean (SD)
HS1 (Moderate VI)	0.52 (0.16)	0.71 (0.09)
HS2 (Severe VI)	0.36 (0.11)	0.62 (0.04)
HS3 (Profound VI)	0.22 (0.10)	0.52 (0.07)
HS4 (CF)	0.14 (0.09)	0.35 (0.06)
HS5 (HM, LP, NLP)	-0.04 (0.07)	0.15 (0.11)

Abbreviations**:** CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; SD, standard deviation; VI, visual impairment.

Source: CS, p. 147

ERG Comment:

The lack of patient-reported values for patients treated with VN is a key limitation of the evidence base provided by the company, and introduces considerable uncertainty to the economic evaluation. This uncertainty relates to both the ERG's assessment of the clinical-effectiveness of VN, as the impact of treatment on patient HRQoL is unclear due to the lack of a validated patient-reported outcome measure, and in terms of the economic evaluation, as it is unclear which utility values are the most appropriate for use.

The proxy elicitation exercise that was conducted by the company suffers from severe methodological and face validity issues, as well as being subject to a number of biases. These include the use of proxies (clinicians in this case) for patient values, which have been seen in multiple instances to be a poor surrogate of patient values, and the questions being asked over the telephone by researchers, as opposed to completed by the clinicians without interaction. Methodologically, the ERG is concerned that as clinicians will be focused primarily on vision-related issues faced by patients (the health state descriptions are vivid in their descriptions of limitations), and that this will introduce a 'framing' effect wherein clinicians are unlikely to take into account the broad range of activities patients can perform that are unrelated to vision loss. The use of only 6 respondents (not taken from the general public), also limits the generalisability of the results and is not aligned with the NICE reference case.

At clarification stage, the ERG asked the company to confirm which order questions were asked in, as this may also influence the responses provided. The company provided a further report detailing the design of the elicitation exercise, but unfortunately this did not explicitly state the order the questions were asked. However, given the order of the report, it appears that clinicians were asked to first complete the questionnaires for the 'best' health state, and then subsequently the questionnaires for deteriorating health states. This ordering is likely to have impacted results by 'capping' the utilities of each state by the previous one. Were the order of the health states reversed and HS5 (hand motion, light perception, no light perception) valued first, the results may have been substantially different. A clear example of the effect of ordering can be seen in the Czoski-Murray et al (2009) study referenced by the company [86]. In the study members of the public were given vision altering contact lenses to simulate different levels of vision impairment - their valuation of the states however varied depending on the order in which they received the contact lenses (Table 2 of the paper).

The lack of face validity is due to two related issues: firstly, the absolute values given by clinicians not appearing to match with the patient experience described by the ERG's clinical advisors, and secondly, the negative value for HS5. When asked to describe the HRQoL of patients, the ERG's clinical advisors stated that patients had restrictions imposed by their vision, but in general did not

have other health problems. As the patients had always experienced vision problems, they did not experience a sense of 'loss' from otherwise average vision, and continued to perform their usual activities, modifying these over time – for instance taking up disability sport (possibly to high levels). Even with extremely poor vision, patients were described as leading meaningful lives with high levels of enjoyment. The description given of patient's lives did not correspond to the utility values provided by the company. When asked specifically about the value for HS5 (for which a negative value is indicative of a health state *"worse than death"*), this was not recognised by clinicians for patients in this indication, and did not appear to be representative of the patient population residing in this health state.

To investigate the apparent lack of face validity, the ERG reviewed all previous NICE submissions involving vision loss to gain a broader understanding of the utility values used to inform previous appraisals. While there have been no specific submissions in *RPE65*-mediated IRD, nearly all appraisals incorporated health states based on vision loss. The results of this review are reported in Table 37.

Table 37: Summary of range of utility values in previous NICE TAs

Number	Category	Lowest and highest utilities
TA155	Macular degeneration	0.40 and 0.89
TA229	Macular oedema and retinal vein occlusion	0.548 and 0.750
TA274	Macular oedema and retinal vein occlusion	0.353 and 0.869
TA283	Macular oedema and retinal vein occlusion	0.314 and 0.869
TA294	Macular degeneration	0.31 and 0.920
TA297	Eye conditions: general and other	0.314 and 0.8280
TA298	Refractive errors including astigmatism, myopia and presbyopia	0.353 and 0.991
TA301	Macular oedema and retinal vein occlusion	0.245 and 0.920
TA305	Macular oedema and retinal vein occlusion	0.469 and 0.828
TA346	Macular oedema and retinal vein occlusion	0.26 and 0.86
TA349	Macular oedema and retinal vein occlusion	Not reported
TA369	Eye conditions: general and other	Not relevant
TA409	Macular oedema and retinal vein occlusion	0.29 and 0.83
TA460	Eye conditions: general and other	0.353 and 0.869
TA467	Corneal conditions	Not relevant
TA486	Refractive errors including astigmatism, myopia and presbyopia	Not reported
TA532	Corneal conditions	Not relevant

Abbreviations**:** TA, Technology Appraisal.

The results of this review demonstrate that in all previous appraisals, the lowest utility values were between 0.26 and 0.548, though at least some of these were based on alternative definitions of blindness – for example, the value of 0.548 was for patients with "≤ 38 letters". A value of 0.31 was used in TA294 for the health state "blindness", which was equivalent to patients with "< 36 letters". The ERG noted that the majority of these previous STAs consider health states described as "blind" that may cover a number of the health states provided as part of the CS (including some of the 'best' health states).

Many of the aforementioned studies referenced three published studies regarding the HRQoL of patients with vision loss, noted also within the CS: Czoski-Murray et al (2009), Brown et al (1999) and Brown et al (2000) [86-88]. The CS notes that the study by Czoski-Murray *et al.* is associated with "some limitations" which are not stated. The ERG considers the primary limitation of this study (in relation to the decision problem at hand) is the inability to compare the health states included in the company's model and those reported within the Czoski-Murray study. Henceforth, only the values reported by Brown *et al.* are considered, and are provided in Table 38.

Table 38: Comparison of published utility scores for CF, HM, LP, and NLP with CS

CS (HUI3 proxies)		Brown (1999)		Brown (2000)	
CF	0.14	CF	0.520	CF - LP	0.400
HM, LP, NLP	-0.04	LP	0.350		

Abbreviations**:** CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; SD, standard deviation; VI, visual impairment.

The values available for the worst health states in each of the studies by Brown are all positive, and are notably higher than that proposed by the company for HS5 (as would be the worst health state valued in Czoski-Murray et al.. Given the patients are younger in this indication (and thus would not be expected to have as many comorbidities), the ERG noted that the values presented in the literature for an older population may be lower than the equivalent values for the *RPE65*-mediated population. However, the ERG understands that the experience of *RPE65*-mediated IRD is not restricted to the impact on VA alone.

As the values proposed by the company were inappropriate in multiple respects, the ERG sought alternative values from the literature which would not have been captured by the company's systematic literature review (due to differences in patient population from the scope of this appraisal). Searching identified a time trade off study by Rentz et al. [89] to develop a scoring system for the NEI VFQ-25. In the study 607 members of the general public (in Australia, Canada, the UK, and US) were asked to perform time-trade-off for eight health states with varying degrees of vision problems. The

results ranged from means of 0.956 (health state 111111; no problems) to 0.343 (555555; the worst health state with substantial limitations due to lack of vision).

Using the study by Rentz et al., the descriptions of health states given by the company were compared to those used in the health state valuation exercise. To avoid missing the severity of the condition, HS5 (described in Appendix 9 of the CS) was assumed to be equivalent to the worst health in the Rentz et al. study (555555, described in supplementary materials to the publication). HS1 was assumed to be nearest to health state 333322, which had a valuation of 0.717. The company's description of HS1 and the description given in Rentz et al. for the state 333322 are shown in Table 39.

Table 39: Comparison of company description of HS1 and Rentz et al. description of VFQ-25 health state 333322

Company description of Moderate visual impairment (Health State 1)	VFQ-25 Health State 333322
• The person has *RPE65* mediated inherited retinal disease. The condition causes degeneration of the retina with associated vision loss. The person has no other significant comorbidities. They have moderate visual impairment. They can read words on a page and can cross a street safely. They may rely on a person's shape/ hair colour or voice in order recognise them. • The person does not need to use visual aids or a cane, but may rely on a flashlight. Young people can struggle to adapt to their progressive sight loss. It can be difficult for people to accept that they cannot drive. • The person has difficulty with seeing at night time and during the transition (early evening). This makes it difficult to go out independently during those times. Navigating outside on their own at night can be extremely challenging, especially as they walk through areas of different light levels. • The person can navigate through their own home with little difficulty. Going to the bathroom at night may lead them to bump into things. They may rely on additional lighting. • The person can see the TV, but may not always recognise characters on the TV until they hear them speak. • Navigating areas with depth – such as stairs or steps can be challenging. Near work is easier than far work, especially supported by visual aids. Cell phones/ tablets and computers can be used with little or no adaptation. • The person has a range of career options available to them, especially if their employer offers flexibility. • Sight loss can be extremely challenging, very difficult to come to terms with. Some people feel socially isolated partly because they find it hard to meet new people. They may be reliant on friends or services like Uber to take them to social events. They may fail to recognise someone when they walk past them. The person may live independently or may still live with parents. • Social activities in the evening such as going to a restaurant or to the cinema can be very challenging. This may limit the enjoyment people feel from such events. • The person can physically do sports, especially with assistance, but will struggle with sports in the evening or with sports where the ball is small. Running, swimming or gym work is possible, especially with assistance. Eye protection maybe worn to prevent accidental injury. • The person may sometimes feel low, but at other times is accepting of their vision loss. They may worry about the future.	• I have moderate difficulty doing work or hobbies that require seeing well up close, such as cooking, sewing, fixing things around the house, or using hand tools • Because of my eyesight I have moderate difficulty seeing how people react to things I say • Because of my eyesight I have moderate difficulty going out to see movies, plays, or sports events • I am limited in how long I can work or do other activities some of the time because of my vision • I stay at home some of the time because of my eyesight • I worry some of the time about doing things that will embarrass me or others because of my eyesight

Abbreviations**:** *RPE65*, Retinal pigment epithelium-specific 65 kDa protein; TV, television; VFQ, visual-function questionnaire.

For HS2, HS3, and HS4, values were derived by linear interpolation between the scores for HS1 and HS5. The resulting values are presented in the table below. Two sensitivity analyses are also presented, one using only the values derived from the UK population in the study (n=152/607), and one using the same overall values, but assuming the worst health state is the penultimate state

presented in Rentz et al. (433354). The resulting values used in the ERG's analysis are presented in Table 40.

Table 40: ERG analysis utility values

Health state	Values based on value from Rentz et al.	Values based on value from Rentz et al. (UK only)	Values using health state 433354 for Health State 5
HS1 (Moderate VI)	0.717	0.687	0.717
HS2 (Severe VI)	*0.624*	*0.581*	*0.638*
HS3 (Profound VI)	*0.530*	*0.476*	*0.560*
HS4 (CF)	*0.437*	*0.370*	*0.481*
HS5 (HM, LP, NLP)	0.343	0.264	0.402

Abbreviations**:** CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; SD, standard deviation; VI, visual impairment.
Note**:** Interpolated values shown in *italics*.

The values produced in the analysis based on the study by Rentz *et al*.[89] are clearly imperfect, however a strength of the study is that the descriptions (shown above for 333322) are described via the functional impact of vision problems, as opposed to being linked to VA alone as in many other conditions. This study was not identified in the company's systematic literature review, as the review was targeted specifically at *RPE65* mediated vision loss. Importantly however when valued by 600 members of the general public, the results indicated a poor but plausible utility for blindness (0.343 for all patients, 0.2644 for UK patients), as opposed to a 'worse than death' health state.

5.2.7.2 Adverse event disutilities

The company submission includes disutilities for three adverse events; cataract (-0.14 for 1 month), eye inflammation (-0.30 for 3.6 months), and increased intraocular pressure (-0.10 for 1 month). Both cataract and eye inflammation were referenced to previous macular degeneration submissions, with a reference to the literature for increased intraocular pressure.

ERG Comment:

The company's approach to accounting for the impact of adverse events on HRQoL appears broadly acceptable, though the disutility for eye inflammation appears to be particularly large, especially when patients already have relatively low health-state utilities (versus the general population). Nevertheless, the ERG maintains this assumption in the preferred base case, given the lack of an alternative value that may instead be used.

5.2.7.3 Carer disutility

In addition to the impact of *RPE65*-mediated IRD on patient HRQoL, the CS also includes the disutility experienced by carers. The value used for this is taken from a systematic review by Wittenberg *et al* (2013) [90] which demonstrated a lower utility for the parents of children with activity limitations (a reduction of 0.08). This value was applied by the company to the four most severe health states for school age children, and half this value assumed to apply for patients of working and retirement age.

ERG Comment:

The ERG reviewed the company's approach to carer disutility, and while there is palpable uncertainty around the estimates employed to inform the CS, the ERG broadly agreed with the approach taken by the company. However, the ERG noted that a school age child would typically have more than one caregiver, so in the ERG's preferred base case the disutility for carers is multiplied by 1.78 (the mean number of parents in a household) [91].

The study selected by the company to inform the disutility value is not the primary source for the value of 0.08. This value is reported within a 2010 US study by Kuhlthau et al. (2010) [92]. An update to the systematic review referenced by the company was recently published (Wittenberg et al., 2019) [93], which the ERG was aware of (and was unlikely to have been published during the time the company were preparing their submission). Included in this updated review was a value from a UK study by Al-Janabi (2016) [94], which presented a matched-pair analysis of caregiver utilities versus non caregivers, finding a disutility of 0.041. This value is applied within the ERG's preferred base case, as it is aligned with the NICE reference case and exhibits improved generalisability versus the US study. Nevertheless, the ERG accepts the net result of the aforementioned changes yields a close to zero impact on the ICER when compared to the CS.

Furthermore, the ERG does not agree with the company's base-case assumption that the disutility for carers would be halved for HS1 versus all other health states. The carer disutility is applied in all modelled health states in the ERG's preferred base case. The ERG acknowledges that the disutility for carers is expected to vary according to health state, but in the absence of data to appropriately capture this the ERG considers it inappropriate to select an arbitrary percentage.

5.2.8 Model validation and face validity check

In regards to model validation, the CS states that the model was verified by its developers as well as by health economists who were not involved in its construction. No specific checklists or checks were detailed by the company. Instead, the company states that a cell-by-cell check of the model logic and

consistency was performed, alongside a logical test of the model outputs. The company state that it was not possible to validate the model outputs due to the lack of long-term data available for patients with *RPE65*-mediated IRD.

A comparison to the study identified as part of the review of cost-effectiveness evidence was provided within the CS. This study was conducted by the Institute for Health and Economic Review (ICER) in the US, and compared VN with "standard of care" (SoC), which was assumed to be comparable to BSC in the UK setting [76]. Details of this study are provided in Table 41, alongside additional comments from the ERG. Within the CS, the findings of a quality assessment of the study were also presented (Table 31 of the CS).

Table 41: Relevant studies identified by the company's cost-effectiveness review

Feature	Description provided by company	ERG additional comments
Study name and year	Institute for Health and Economic Review (2018)	None
Location of study	US	None
Summary of model and comparators	VN *vs.* SoC	ERG note that SoC may be considered equivalent to BSC. The model assumes no impact of mortality for presence of biallelic *RPE65*-mediated IRD or exposure to VN. The model also assumes a 10-year treatment effect, following by a 10-year waning period.
Patient population	Reflects the Study 301 trial population. Assumed mean age of 15 years and 43% male. An alternative population was modelled with a mean age of three years.	None
Costs	Direct medical costs as well as direct nonmedical costs and indirect costs for education, productivity loss, informal care, and nursing home care.	None
Patient outcomes	Utility values were based on visual ability in terms of VA or VF (i.e. health states). VN provided patients with an additional 1.3-2.1 QALYs if treated at age 15, and 2.7-4.4 additional QALYs if treated at age 3.	Utility values sourced from a publication by Lloyd *et al.*, (2005) [95] based on patients with diabetic retinopathy.
Results	Incremental cost per QALY: • Age 15: $228,000 - $644,000 • Age 3: $16,000 - $288,000	None

Abbreviations**:** BSC, best supportive care; ERG, Evidence Review Group; IRD, inherited retinal dystrophies; QALY, quality-adjusted life year; SoC, standard of care; US, United States; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

Within section 12.8.1 of the CS, a description of the outcomes of the Institute for Health and Economic Review (2018) study is provided within the context of the company's cost-effectiveness

model. The company note that because of the differences in currencies, health care resource and acquisition costs, a difference in costs is expected. The company do not comment further on the cost differences.

The company note within their submission that the key driver of differences in the estimation of QALYs between the analyses is due to differing assumptions around utility values. The following rationale is then provided by the company in regards to why their application of utility values is more appropriate to inform their model: (1) the utility values were derived from a diabetic retinopathy population (considered to *"differ substantially"* from an *RPE65*-mediated IRD population); (2) the model considers only three health states, which would not reflect any differences for patients who are considered "blind"; and (3) the model required assumptions to made in regards to the changes in VA and VF over time as patient-level data were unavailable to the authors.

ERG Comment:

With no explicit evidence provided, it is not possible for the ERG to assess the quality of the model validation process undertaken by the company. Nevertheless, following the ERG's independent quality control the model was found to be logically laid out, and constructed to a good standard with only small errors identified (discussed further in Sections 5.3 and 6). The ERG disagrees with the company's assertion that it was not possible to validate the model outputs against long-term data sources. It would have been useful to validate the extrapolations provided by the cost-effectiveness model against the observed transitions seen within the natural history study. The ERG acknowledges that these data are used to inform the cost-effectiveness model, and therefore this validation task does not constitute an assessment of the external validity of the cost-effectiveness model, which the ERG agrees would not be possible as no other long-term data are available.

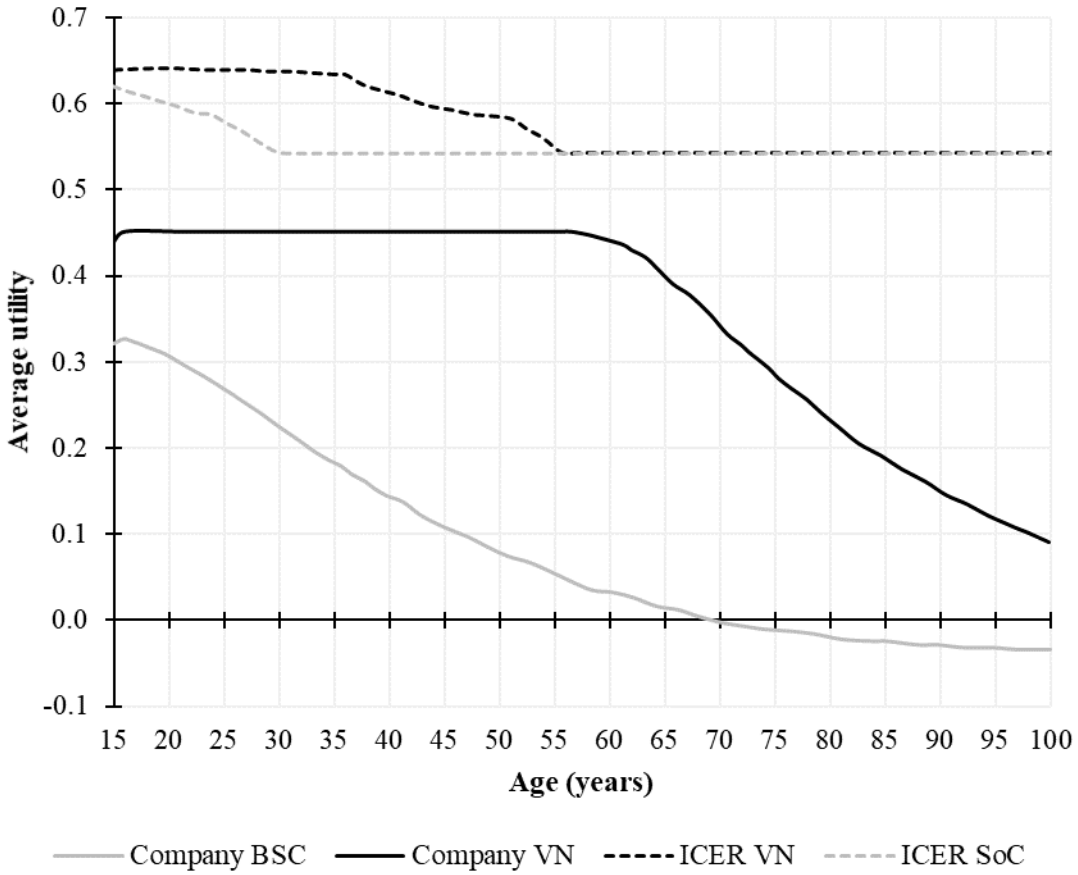
In regards to the analysis undertaken by ICER, the company state that the key reason for differences in the incremental QALY gains was due to the application of utility values. The ERG disagrees that this is the sole reason for the difference in QALYs gained, as a combination of at least three distinct factors cause this: (1) the utility values used; (2) the assumed duration of treatment effect; and (3) the estimation of long-term health-state occupancy. A plot of average utility values for the living cohort in each of the two models is presented in Figure 27 which provides a means of illustrating these key differences:

1. Based on the relative heights of the two sets of curves, it can be seen that the health-state utility values in the company's analysis (solid lines) are considerably lower than the Institute for Health and Economic Review analysis (dashed lines)
1. The length of the flat sections in each of the darker lines ("Company VN" and "ICER VN") is

indicative of the difference in the duration of treatment effect assumed by each analysis (company: 40-year duration, 10-year waning period, 25% of effect is maintained indefinitely; Institute for Health and Economic Review: 10-year duration, 10-year waning period, 0% of effect persists after this period)

2. The longer-term differences between the two sets of curves shows that the Institute for Clinical and Economic Review analysis (dashed lines) eventually lead to all patients residing in the worst health state (VF = 0°, utility = 0.5410) by age 56. Conversely, the CS shows that BSC patients continue to experience a reduction in their utility over the entire modelled time horizon. The former of these analyses relied upon aggregate-level data to incorporate a decline in VA and VF over time, which may in part explain this finding. However, a clear difference in the projection of long-term outcomes for patients with *RPE65*-mediated IRD is noted between the analyses. The CS implies some patients may still have LP for more than 50 years, despite stating elsewhere that "progressive vision loss leads to near-total blindness as early as preschool years or as late as the third decade of life." (CS Section 6.1). These key differences in the estimated outcomes for *RPE65*-mediated IRD patients contribute to markedly different estimates of the incremental QALY gain attributable to VN.

Figure 27: Comparison of utility values used in CS and ICER analysis (derived via digitisation of Figures 45 and 46 of the CS)



Abbreviations**:** BSC, best supportive care; ICER, Institute for Health and Economic Review; SoC, standard of care; VN, voretigene neparvovec.

5.2.9 Resources and costs

5.2.9.1 General approach

Within the company's cost-effectiveness model, costs fall into two categories. The first category consists of one-off costs that are implemented during the first model cycle. These costs include the administration of VN (including acquisition, surgery, immunomodulatory regimen and OCT costs), eligibility tests (to ensure patients would be eligible for treatment with VN) and the resolution of adverse events. The second category comprises longer-term resource utilisation, covering both healthcare and non-healthcare costs, primarily related to the management of severe vision impairment and blindness.

The second category of costs are calculated based on different age groups across health states – for example, residential and community care for elderly patients. Other than those associated with the

administration of VN, all costs are applied across both treatment arms over the entire modelled time horizon with respect to percentage of the patients residing within different health states. The non-healthcare costs (e.g. carer's allowances and productivity losses) are not considered in the company's base case, but are considered within a number of scenario analyses. All costs are discounted at 3.5% per year.

ERG Comment:

In general, the ERG agrees with the company's approach to including costs within the cost-effectiveness model. Specific comments pertaining to individual cost items are provided below.

5.2.9.2 VN acquisition cost

The list price of VN is £613,410 per patient for both eyes. A [redacted] PAS discount is also implemented in the company's base case which reduces the price to [redacted].

5.2.9.3 Surgery

VN administration requires two surgeries. The surgeries are subretinal injections which are administrated on separate occasions. The cost for each surgery in the CS is taken from the NHS National Schedule of Reference Costs 2017/2018 [96] and is based on a weighted average of the codes for "complex and very complex, vitreous retinal procedures" for children (18 years and under) and adults (see Table 42). The distribution of adults and children was taken from Study 301/302, which comprises of 35% adults and 65% children. Consequently, the total cost per surgery is calculated to be £2,269.80.

Table 42: Currency codes for complex and very complex vitreous retinal procedures

Currency code	Currency description	Unit cost
BZ81B	Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1	£1,771.37
BZ82Z	Very Complex or Complex, Vitreous Retinal Procedures, 18 years and under	£2,537.64

ERG Comment:

The ERG noted that the company did not account for the cost code for very complex procedures in adults (BZ80B: Very Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1); and the company have considered the overall cost associated with the currency code across all settings (e.g. inpatient, outpatient, day case). It is the ERG's understanding that VN would be administered in a day case setting, and that there is no clear reason why a "very complex" procedure for adults (with

CC Scores of 0, 1, or 2) would be inappropriate for consideration. Therefore, the ERG has adjusted the company's administration cost based on currency codes BZ80A, BZ80B, BZ81A, BZ81B, and BZ82Z; described in Table 43. This gives a (reduced) cost per administration of £1,959.90.

Table 43: ERG's preferred administration cost

Currency code	Currency description	Activity	Unit cost
BZ80A	Very Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 2+	1,727	£2,002.25
BZ80B	Very Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1	2,863	£1,980.04
BZ81A	Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 2+	3,282	£1,678.79
BZ81B	Complex Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1	8,123	£1,643.90
Weighted average of BZ80A to BZ81B (day case, based on activity)		-	*£1,749.92*
BZ82Z	Very Complex or Complex, Vitreous Retinal Procedures, 18 years and under	252	£2,072.96
Weighted average for children and adults (based on Study 301/302)		-	*£1,959.90*

Abbreviations**:** CC, complications and comorbidities.

5.2.9.4 Immunomodulatory regimen

The immunomodulatory regimen using prednisone (or an equivalent glucocorticoid) is initiated 3 days prior to the first administration and lasts between 18 to 30 days depending on the timing of the administration to the second eye. Table 44 describes the necessary doses of prednisone for the pre- and post-operative periods.

Table 44: Pre- and post-operative immunomodulatory regimen

Period	Duration	Treatment
Pre-operative	3 days prior to VN administration	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
Post-operative	4 days (including the day of administration)	Prednisone (or equivalent) 1 mg/kg/day (maximum of 40 mg/day)
	Followed by up to 5 days, or until the beginning of second eye regimen, for the first eye or 5 days for the second eye	Prednisone (or equivalent) 0.5 mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day for the first eye only	Prednisone (or equivalent) 0.5 mg/kg every other day (maximum of 20mg/day)

Abbreviations: kg, kilogram; mg, milligram; VN, voretigene neparvovec.

The dose cost of prednisone is taken from the British National Formulary (BNF) [97], with a unit cost of £0.89. Table 45 contains the required dosage and assumed duration of prednisone administration for patients treated with VN.

Table 45: Prednisone resource use and total costs

Dose	Units/day†	Number of days	Total cost
1 mg/kg/day	11	14	£137.06
0.5 mg/kg/day	6	6.8	£36.31
Total	-	-	£173.37

Abbreviations**:** kg, kilogram; mg, milligram.

ERG Comment:

The ERG is broadly satisfied with the company's application of the costs associated with the immunomodulatory regimen required for VN treatment. However, assumptions such as the average weight of the population and the number of the days between surgeries are taken from Study 301/302, which may not be entirely representative of the UK population. As the final ICER is not sensitive to the costing application of prednisone, and that this is a very small cost compared with the acquisition of VN, the ERG considers the company's approach is acceptable.

It was noted at clarification stage that the ERG was unable to verify the cost of oral prednisone from the BNF. The company proceeded to contact the BNF for further comment, though as noted above the cost of prednisone is not associated with a large impact on the ICER.

5.2.9.5 Monitoring

In the first year following VN treatment, four monitoring visits including optimal coherence tomography (OCT) are required. The cost is the weighted average of the retinal tomography currency codes in the NHS National Schedule of Reference Costs 2017-18, based on the activity recorded in each currency code [96]. While not explicitly stated, it is assumed that these relate to the overall currency code, rather than a specific setting.

Table 46: Currency codes of the retinal tomography

Currency code	Currency description	Activity	Unit cost
BZ88A	Retinal Tomography, 19 years and over	1,435,110	£114.03
BZ88B	Retinal Tomography, 18 years and under	19,341	£145.90
-	Weighted average (per visit)	-	£114.46
-	Total (first year)	-	£457.83

ERG Comment:

Although based on clinical expert opinion alone, the ERG is satisfied that four monitoring visits in the first year is reflective of the expected frequency of monitoring for patients following VN treatment. However, it is unclear to the ERG whether this code accounts for consultation with patients (for example, discussion regarding any issues they may have experienced following treatment).

The ERG also noted several minor issues in the application of the cost for OCT. Firstly, the company weighted the costs according to the activity level, rather than the distribution of age in Study 301/302. Secondly, the company used the overall currency code, whereas in reality these monitoring visits would be expected to be performed in an outpatient setting (however, the values for the overall currency code and only those for outpatient appointments are near-identical). The ERG's preferred base case makes use of a value of £134.65, based on a weighted average of outpatient appointments based on the split of adults and children in Study 301/302.

5.2.9.6 Eligibility test

The eligibility tests included within the model are genetic testing (to identify patients with an affected *RPE65* gene) and the retinal cell assessment (to ensure patients have sufficient retinal cells in order for VN treatment to be appropriate). The cost of genetic testing is applied to both arms within a scenario analysis.

Retinal cell assessment is considered only for patients in the VN arm, since sufficient viable retinal cells are critical for the success of VN treatment and it would not be administered to patients treated with BSC. Testing for sufficient viable retinal cells is conducted using OCT. The cost per test is estimated to be £114.46 based on the weighted average of codes of BZ88A and BZ88B in NHS National Schedule of Reference Costs 2017/2018 [96].

Based on the clinical expert opinion it is expected that 95% of tested individuals will have sufficient viable retinal cells. The company therefore calculated the average cost incurred by patients in the model of £120.48, based on £114.46 ÷ 95%.

ERG Comment:

The ERG agrees that the exclusion of genetic testing costs in the base case analysis is appropriate, based on clinical expert feedback provided to the ERG which noted that genetic testing is expected to become standard in NHS practice. The company's application is based on clinical expert opinion, rather than the proportion of patients who were considered eligible in the trial (n=31/36, ~86.1%). The ERG did not amend this in the preferred base case as the value of 95% may be deemed more reflective of UK

practice, and the value from the trial may be affected by patients who were enrolled in other clinical trials and/or previously received VN in Study 101/102.

For the cost of an outpatient ophthalmologist appointment, the company does not specify that this is expected to be a consultant-led appointment. Therefore, the ERG's preferred base case includes the unit cost for an outpatient ophthalmologist appointment of £101.83 (taken using the same code per the company's submission, but using the cost for "consultant-led" appointments).

The ERG also agrees with the company's application of testing for sufficient retinal cells, as testing would only be necessarily should VN be recommended. However, the previously raised concerns regarding the cost of OCT for monitoring within the first year after VN treatment also apply here.

5.2.9.7 Adverse events costs

The adverse events associated with VN treatment include cataracts, eye inflammation and increased intraocular pressure. Table 47 contains each type of adverse events, the proportion of patients who experienced the events (based on data from Study 301/302), and the estimated cost of resolution.

Table 47: Adverse event proportions and estimated resolution costs

Adverse event	Items	Proportion of patients	Value	Reference
Cataract	Hospital costs	15%	£896.65	NHS Reference Costs 2017-18: Weighted average of non-elective short stay and day case codes for Phacoemulsification Cataract Extraction and Lens Implant: BZ34A, BZ34B and BZ34C [96]
Eye inflammation	GP visit†	10%	£37.00	Unit Costs of Health and Social Care 2018: Cost per GP visit lasting 9.22 minutes (including direct care staff costs, with qualification costs) [98]
Increased IOP	GP visit†	20%	£37.00	Unit Costs of Health and Social Care 2018: Cost per GP visit lasting 9.22 minutes (including direct care staff costs, with qualification costs) [98]

Abbreviations**:** GP, general practitioner; IOP, increased intraocular pressure; NHS, National Health Service.
Note**:** † Given that adverse events associated with eye inflammation and increased IOP are expected to be relatively minor, the cost of one GP visit is assumed.

The total costs associated with treatment-related adverse events is captured within the model as £160.50 applied within the first modelled cycle.

ERG Comment:

The ERG agrees with the company's application of adverse events within the model (incurred within the first cycle of the model only). Clinical expert advice sought by the ERG suggested that it would be

expected that minor issues that may arise through the administration of VN would typically be resolved as part of the surgery itself.

The ERG noted that the estimated cost for the adverse events are based on the proportion of patients affected, rather than the proportion of eyes affected. Therefore, it may be that the total cost for adverse events should be higher. However, the total cost of resolving adverse events is small, and so increasing this (for example, by doubling the costs) would have a negligible effect on the ICER.

The ERG also noted that the costs for resolving two of the adverse events (eye inflammation and increased IOP) are associated with a GP appointment. It is the ERG's opinion that these costs are likely underestimates, within the context of patients having received a gene therapy associated with a high acquisition cost. In the ERG's base case, these costs are changed to reflect the cost of a consultant-led outpatient appointment with an ophthalmologist (the same cost as would be used to inform eligibility testing, reported within Section 5.2.9.6).

5.2.9.8 Healthcare resource utilisation

The cost of healthcare resource utilisation is calculated for each health state within the company's model. The company included all cost categories expected to be affected by the extent to which patients are visually impaired. Patients are divided to three distinct age groups consisting of school-age (< 18 years old), working-age (between age 18 and 65 years) and retirement-age (>65 years). The healthcare categories for school-age and working age groups are hospitalisation, low vision rehabilitation, low vision aids and depression. For the retirement-age group, the aforementioned categories were included, as well as residential and community care.

The cost of health states for each category is calculated annually and applied for all alive health states. For patients residing in HS2, HS3, HS4, or HS5; the costs are based on medical resource utilisation of patients who are blind according to RNIB guidelines. For patients residing in HS1, each cost category is assumed to be half of the values for the other health states, as an unknown proportion of the patients in HS1 are not considered blind per the RNIB guidelines. The costs associated with depression for non-retirement age patients are assumed to be half of those for patients of school- or working-age. Table 48 contains the healthcare resources for each modelled health state by age-group.

Table 48: Healthcare resource use categories and their cost for health state 2

Healthcare resource	Annual cost					
	School age		Working age		Retirement age	
	HS1	HS2-5	HS1	HS2-5	HS1	HS2-5
Hospitalisation	[redacted]	£32.06	[redacted]	£32.06	[redacted]	£32.06
Low vision rehabilitation	[redacted]	£13.44	[redacted]	£13.44	[redacted]	£13.44

Healthcare resource	Annual cost					
	School age		Working age		Retirement age	
	HS1	HS2-5	HS1	HS2-5	HS1	HS2-5
Low vision aids	[redacted]	£61.19	[redacted]	£61.19	[redacted]	£61.19
Depression	[redacted]	£489.68	[redacted]	£489.68	[redacted]	£979.36
Residential care	-	-	-	-	[redacted]	£13,759.20
Community care	-	-	-	-	[redacted]	£546.37

Note: Highlighted values are based on assumption

ERG Comment:

The ERG understands that the identification of medical resource utilisation for patients with *RPE65*-mediated IRD is difficult, and that the company therefore has relied upon a range of different studies to populate resource estimates within the model. However, many of these estimates are based on assumption (for example, the cost associated with depression for patients of school age residing in HS1 is assumed to be 25% of the cost for patients of retirement age residing in HS2–5 with no evidence provided).

It is the ERG's opinion that in the absence of clear evidence of differences by health state, cost adjustments should not be included within the model. Therefore, the ERG's preferred analysis considers costs that are referenceable to the published literature, with no adjustments based on arbitrary percentages. In addition, the costs associated with depression have been removed, as it is the ERG's opinion that these costs are unlikely to be reflective for the *RPE65*-mediated IRD population, whom are expected to be legally blind from a relatively early age compared with other visual conditions. A further sensitivity analysis is conducted wherein all medical resource use costs are omitted to ascertain the influence of including these costs on the ICER.

5.2.10 Cost effectiveness results

Summary results of the company's deterministic base case analysis are presented below, based on the VN list price and with the proposed simple PAS discount in Table 49 and Table 50. In the company's model, a lower hazard ratio is applied to the mortality rates from the general population life tables for patients with moderate visual impairment than that applied for those with more advanced visual impairment (see Section 5.2.6.4 for details), but, since the relative difference between the hazard ratios is small (and the low risk early in the model), the difference in life years gained between the strategies over the time horizon is minimal (0.07). However, the model does suggest a difference of 7.06 quality adjusted life years between the strategies over the time horizon, due to the substantial differences among the health states in assigned utility values (see Section 5.2.7.1). The total cost of the VN strategy is much higher than that of BSC, with a difference in costs of £612,013 based on the

VN list price and of [redacted] with the proposed PAS, due to the acquisition cost of VN. Hence, the deterministic ICER for VN versus BSC was £86,635 per QALY based on the VN list price and [redacted] with the PAS.

Table 49: Base case results of the deterministic analysis (list price)

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	£46,473	25.46	3.64	-	-	-	-
VN	**£658,486**	25.50	10.70	**£612,013**	0.04	7.06	**£86,635**

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years; VN, voretigene neparvovec

Source: Based on Table 1, section 1.1.1 of CS addendum results section. Data extracted from CS model.

Table 50: Base case results of the deterministic analysis (PAS price)

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	£46,473	25.46	3.64	-	-	-	-
VN	[redacted]	25.50	10.70	[redacted]	0.04	7.06	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality adjusted life years; VN, voretigene neparvovec

Source: Based on Table 1, section 1.1.1 of CS addendum results section. Data extracted from CS model.

Life years and QALYs gained and costs incurred with and without the PAS over the time horizon for each strategy, disaggregated by category and health states, are presented in Table 51, Table 50 and Table 53 respectively.

Table 51: Summary of discounted LY and QALY gain by health state

Health State	LYs (BSC)	LYs (VN)	Incremental LYs	QALYs (BSC)	QALYs (VN)	Incremental QALYs	% Absolute QALY increment
HS1: Moderate VI	2.22	16.67	14.45	1.15	8.65	7.50	68%
HS2: Severe VI	3.02	5.00	1.98	1.10	1.81	0.72	6%
HS3: Profound VI	8.11	1.77	-6.34	1.81	0.40	-1.41	13%
HS4: CF	5.76	1.72	-4.04	0.81	0.24	-0.57	5%
HS5: HM, LP, NLP	6.35	0.34	-6.01	-0.25	-0.01	0.23	2%
AE disutility	-	-	-	0.00	-0.01	-0.01	0%
Carer disutility	-	-	-	-0.99	-0.38	0.61	5%
Total	25.46	25.50	0.04	3.64	10.70	7.06	100%

Abbreviations: AE, adverse event; BSC, best supportive care; HS, health state; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality adjusted life year; VI, visual impairment; VN, voretigene neparvovec

Source: Based on Tables 5 & 6, sections 1.1.5-1.1.6 of CS addendum results section. Data extracted from CS model.

Table 52: Summary of estimated resource use cost per patient (list price)

Resource use	Cost (£) (BSC)	Cost (£) (VN)	Incremental costs (£)	Absolute cost increment (£)	% Absolute increment
Acquisition, administration and monitoring	£0	**£618,571**	**£618,571**	**£618,571**	**99%**
AEs	£0	£146	£146	£146	**0%**
Total healthcare resource use	£46,300	£37,917	-£8,383	£8,383	**1%**
HS1: Moderate VI	£661	£7,810	£7,149	-	-
HS2: Severe VI	£1,804	£12,686	£10,882	-	-
HS3: Profound VI	£5,248	£10,032	£4,785	-	-
HS4: CF	£5,715	£6,712	£997	-	-
HS5: HM, LP, NLP	£33,046	£2,408	-£30,638	-	-
Total	£46,300	£656,754	£610,454	£627,100	100%

Abbreviations: AE, adverse event; BSC, best supportive care; HS, health state; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality adjusted life years; VI, visual impairment; VN, voretigene neparvovec

Source: Based on Tables 8 & 9, sections 1.1.8-1.1.9 of CS addendum results section.

Table 53: Summary of estimated resource use cost per patient (PAS price)

Resource use	Cost (£) (BSC)	Cost (£) (VN)	Incremental costs (£)	Absolute cost increment (£)	% Absolute increment
Acquisition, administration and monitoring	£0	[redacted]	[redacted]	[redacted]	[redacted]
AEs	£0	£146	£146	£146	[redacted]
Total healthcare resource use	£46,300	£37,917	-£8,383	£8,383	[redacted]
HS1: Moderate VI	£661	£7,810	£7,149	-	-
HS2: Severe VI	£1,804	£12,686	£10,882	-	-
HS3: Profound VI	£5,248	£10,032	£4,785	-	-
HS4: CF	£5,715	£6,712	£997	-	-
HS5: HM, LP, NLP	£33,046	£2,408	-£30,638	-	-
Total	£46,300	[redacted]	[redacted]	[redacted]	100%

Abbreviations: AE, adverse event; BSC, best supportive care; HS, health state; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; VI, visual impairment; VN, voretigene neparvovec

Source: Based on Tables 7 & 9, sections 1.1.8-1.1.9 of CS addendum results section.

ERG Comment:

The ERG agrees with the way in which the company's deterministic base case results have been calculated.

5.2.11 Sensitivity analyses

5.2.11.1 Univariate sensitivity analyses

The company conducted univariate deterministic sensitivity analyses to explore the impact on the ICER of varying the model parameters individually. With the exception of the value of the parameter being varied, the company's base case settings were used: this involved, for example, a Weibull multi-state model fitted to stacked data for the long-term phase (see Section 5.2.6.2), with health states defined based on the worst of VA and VF for the average eye (Section 5.2.2), with associated utility values from the elicitation exercise by Acaster and Lloyd, using the Health Utilities Index Mark 3 (Section 5.2.7.1).

Each of the ten model parameters that have the greatest impact on the ICER when varied individually is either a Weibull distribution parameter for the long-term phase of the model or a health state utility value. The former are assumed to be normally distributed and the latter are assumed to follow Beta distributions, with the lower and upper bounds of the 95% confidence intervals used in the univariate sensitivity analysis. The effects on the ICER are presented in [redacted]54 and depicted graphically with tornado diagrams in Figure 28 and ***[redacted]29.

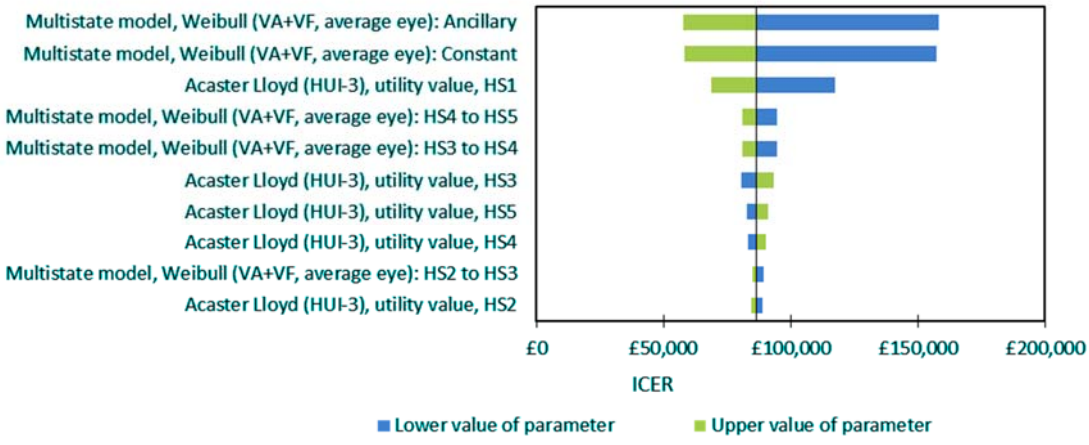
[redacted] 54

Model parameter	List price ICER (£/QALY)			PAS price ICER (£/QALY)		
	Lower bound	Upper bound	Absolute difference	Lower bound	Upper bound	Absolute difference
Weibull MSM parameter: ancillary	£158,320	£57,969	£100,351	[redacted]	[redacted]	[redacted]
Weibull MSM parameter: constant	£157,427	£58,092	£99,335	[redacted]	[redacted]	[redacted]
HS1 utility value	£117,376	£68,654	£48,722	[redacted]	[redacted]	[redacted]
Weibull MSM parameter: HS4 → HS5 transition	£94,458	£80,961	£13,497	[redacted]	[redacted]	[redacted]
Weibull MSM parameter: HS3 → HS4 transition	£94,525	£81,074	£13,451	[redacted]	[redacted]	[redacted]
HS3 utility value	£80,723	£93,480	£12,757	[redacted]	[redacted]	[redacted]
HS5 utility value	£82,748	£90,904	£8,156	[redacted]	[redacted]	[redacted]
HS4 utility value	£83,135	£90,442	£7,307	[redacted]	[redacted]	[redacted]
Weibull MSM parameter: HS2 → HS3 transition	£89,299	£84,775	£4,524	[redacted]	[redacted]	[redacted]
HS2 utility value	£88,863	£84,516	£4,347	[redacted]	[redacted]	[redacted]

Abbreviations: HS, health state; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; MSM, multi-state model; PAS, patient access scheme; QALYs, quality adjusted life years.

Source: Based on Tables 11 & 12, section 1.1.11 of CS addendum results section. Data extracted from CS model

Figure 28: Tornado diagram from the univariate sensitivity analysis (list price)



Abbreviations: BSC, best supportive care; HS, health state; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; VA, visual acuity; VF, visual field.

Source: Reproduction of Figure 6, section 1.1.11 of CS addendum results section.

[redacted]29

Abbreviations: BSC, best supportive care; HS, health state; HUI-3, Health Utilities Index Mark 3; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; VA, visual acuity; VF, visual field.

Source: Reproduction of Figure 5, section 1.1.11 of CS addendum results section.

In the univariate analysis, an arbitrary range of ± 15% is used to determine the upper and lower bounds of parameters that are varied according to a Gamma distribution in the probabilistic sensitivity analysis, as well as for a few other parameters (the probability of AEs, the proportion of individuals with sufficient viable retinal cells and the frequency of detecting the *RPE65* gene) varied according to a Beta distribution but for which standard errors were unavailable.

5.2.11.2 Probabilistic sensitivity analyses

The company carried out a probabilistic sensitivity analysis using Monte Carlo simulation. A summary of the average results of 10,000 simulations, based on the VN list price and with the proposed simple PAS discount, are presented in Table 55 and Table 56. The estimated incremental QALYs and incremental costs, based on the VN list price and with the PAS, are depicted graphically in cost-effectiveness planes in Figure 30 and ***[redacted]31.

Table 55: Results of the probabilistic sensitivity analysis (list price)

Comparison	Number of simulations	Average incremental costs (£)	Average incremental QALYs	ICER (£/QALY)
VN vs BSC	10,000	**£612,018**	6.8	**£89,878**

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; VN, voretigene neparvovec

Source: Based on section 1.1.13 of CS addendum results section.

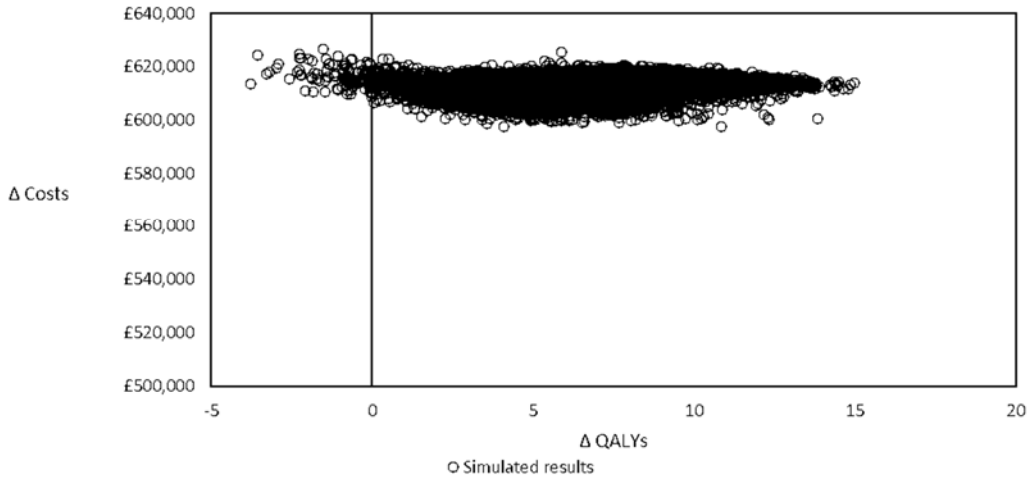
Table 56: Average results of the probabilistic sensitivity analysis (PAS price)

Comparison	Number of simulations	Average incremental costs (£)	Average incremental QALYs	ICER (£/QALY)
VN vs BSC	10,000	[redacted]	6.8	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; VN, voretigene neparvovec

Source: Based on section 1.1.13 of CS addendum results section.

Figure 30: PSA cost-effectiveness plane (list price)



Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years.

Source: Reproduction of Figure 8, section 1.1.13 of CS addendum results section.

[redacted]31[redacted])

[redacted]

Abbreviations: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years.

Source: Reproduction of Figure 7, section 1.1.13 of CS addendum results section.

ERG Comment:

The choices of distribution chosen for varying the parameters in the sensitivity analyses have not been justified, but seem to be appropriate. It is noted in section 12.5.14 of the company's report that the effects on the ICER of varying the Weibull distribution parameters in the univariate sensitivity analysis should be interpreted with caution since these parameters are highly correlated, a result of the stacked data approach to the multi-state model. This is also true of the probabilistic sensitivity analysis, in which the model parameters are varied concurrently but independently.

The health state utility values are also interrelated, at least in so far as being ordered parameters: a utility value should not improve if moving to a health state defined by worse VA and VF. Though the ranking is maintained in the univariate sensitivity analyses, this is not necessary the case with the probabilistic simulations. An alternative approach for sampling the utility values could have been taken in the probabilistic sensitivity analysis, such as that detailed by *Ren et al.*[99]

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of exploratory and sensitivity analyses to establish the impact of alternative assumptions and settings on the cost-effectiveness results. The cost-effectiveness results associated with each of these analyses are provided within Section 6 of this report. A description of the exploratory and sensitivity analyses performed is provided below, and may also make reference to the ERG's preferred base case which is presented in full within Section 6 of this report.

5.3.1 Duration of treatment effect

It is noted that the duration of treatment effect is highly influential on cost-effectiveness results. To explore the impact of alternative assumptions regarding the expected duration of treatment effect for VN, the ERG performed a number of scenario analyses.

Scenario #1: Threshold analysis of treatment effect duration

The first of these was a threshold analysis to ascertain the relationship between the duration of treatment effect for VN and the ICER, with the aim of identifying how long this needs to be in order for the ICER to be £100,000 or less.

Scenario #2: Institute for Clinical and Economic Review duration of treatment effect settings

In addition to this analysis, the ERG considered the base-case assumptions regarding the duration of treatment effect used to inform the analysis conducted by the Institute for Clinical and Economic

Review.[76] In this analysis, a 10-year duration of treatment effect, followed by a 10-year waning period with 0% residual treatment effect was applied in the base case.

5.3.2 Medical resource use

The medical resource use estimates used by the company to inform healthcare costs are based on a population of patients who do not necessarily have *RPE65*-mediated IRD, and indeed appear to be quite different patients. Adaptability is expected to play a role in the volume of healthcare resource use required for patients with *RPE65*-mediated IRD.

Scenario #3: Remove all healthcare resource use costs

It is the ERG's opinion that several of these resource use estimates are likely to be over-estimated for the *RPE65*-mediated IRD population, as the majority of patients are expected to be considered legally blind from the early years of life. To explore the influence of medical resource use costs on the total costs incurred, the ERG removed all healthcare resource use costs in this scenario.

Scenario #4: Use company-preferred healthcare resource use costs

To understand the difference in results if the medical resource use costs were unchanged, the ERG conducted an additional analysis wherein all healthcare resource use costs were applied per the company base case.

By considering both scenarios, an ICER range may be established (as the ERG considers Scenario #3 to represent the "lower bound" of resource use, and Scenario #4 to represent an upper bound).

5.3.3 Utility values

Table 40 presents the ERG's preferred base-case utility values, derived from a study by Rentz *et al.*[89] The ERG's base case values were chosen based on the following:

- HS5 (described in Appendix 9 of the CS) was assumed to be equivalent to the worst health in the Rentz et al. study (555555, described in supplementary materials to the publication)
- HS1 was assumed to be nearest to health state 333322, which had a valuation of 0.717
- For HS2, HS3, and HS4, values were derived by linear interpolation between the scores for HS1 and HS5

In addition to the base-case utility values the ERG considered two scenarios, described in turn below.

Two sensitivity analyses are also presented using the same study; one using only the values derived from the UK population in the study (n=152/607), and one using the same overall values, but assuming the worst health state is the penultimate state presented in Rentz et al. (433354).

Scenario #5: Use UK utility values (based on Rentz et al.)

The ERG's base case makes use of the total population in the Rentz *et al.* study (n=607). While a smaller sample size, it is possible to consider the UK population only in their valuation of health states (n=152). The ERG therefore conducted a scenario analysis to explore the impact of using these values to inform the model.

Scenario #6: Use alternative (higher) utility values (based on Rentz et al.)

The ERG's base case assumes the worst health state in the company's model (HS5) is aligned with the worst health state in the Rentz *et al.* study. However, by definition of the health state provided by the company, HS5 includes patients with varying vision impairment (i.e. those with hand motion as well as those with no light perception). The ERG therefore conducted a scenario analysis to explore the impact of assuming that the utility value for HS5 is based on the second-worst health state provided within the Rentz *et al.* study (433354).

5.3.4 Baseline characteristics

In the ERG's base case, the baseline health state occupancy is assumed to be made up of a naïvely-pooled average of health state occupancy from Study 301/302 and the *RPE65* NHx study (the CS uses only Study 301/302). By using data from both studies, the largest sample size may be used to establish the likely spread of patients by health state occupancy at baseline in what is a rare disease.

The ERG noted however that it may be important to consider the impact on the cost-effectiveness results were this to be based on alterative values. Therefore, the following scenarios were performed to establish the influence of baseline health state occupancy on the cost-effectiveness results:

- *Scenario #7: ITT population from Study 301/302* (n=31)
- *Scenario #8: RPE65 NHx population* (n=68)

These scenarios were presented in the company's submission, but are considered again here in combination with the ERG's preferred base-case assumptions for completeness.

5.3.5 Analysis perspective

In addition to the above, the ERG considers it important to consider a governmental perspective within the context of an intervention that has a clear impact on vision impairment, which is directly

linked to state support in a number of areas. This perspective is already possible to consider within the company's model, and so the ERG presents analyses adopting this perspective within Section 6 of this report.

5.4 Conclusions of the cost effectiveness section

The ERG has performed a detailed review of the evidence available to quantify the cost-effectiveness of VN for the treatment of *RPE65*-mediated IRD. The ERG noted that the company's model has been constructed in a clear and logical manner, with only a small number of technical errors identified (none of which substantially impact the ICER). The company's submission is therefore sufficiently aligned with the scope of this appraisal. Nevertheless, within the context of a rare, genetic disorder there is substantial uncertainty within the cost-effectiveness results including notable evidence gaps.

5.4.1 Key areas of uncertainty

The ERG noted the key areas of uncertainty are related to the expected long-term treatment effect of VN, the impact of *RPE65*-mediated IRD on patient health-related quality of life, and the modelling of the natural history of the condition.

Long-term treatment effect of VN

The treatment effect of VN has, to date, only been assessed within the context of Studies 101/102 and 301/302. These studies are currently associated with a maximum follow-up period of approximately 7.5 years, and consequently the effect of VN beyond this period is unknown. The company assumes a 40-year duration of treatment effect based on clinical expert opinion. However, the ERG is unconvinced that the company's base case assumptions are plausible. More specifically, the ERG believes that a constant treatment effect of 40 years is not defended by the evidence available to date; including gene therapies more broadly. Nevertheless, this assumption is maintained in the ERG's base case (Section 10), and explored through a range of sensitivity analyses due to the lack of a more plausible estimate.

Health-related quality of life

The lack of patient-reported values for patients treated with VN is a key limitation of the evidence base provided by the company, and introduces considerable uncertainty to the economic evaluation. This uncertainty relates to both the ERG's assessment of the clinical-effectiveness of VN, as the impact of treatment on patient HRQoL is unclear due to the lack of a validated patient-reported outcome measure; and in terms of the economic evaluation - while the values in the CS are entirely unsuitable, it is unclear which utility values are most appropriate for use.

Natural history of RPE65-mediated IRD

The ERG agrees with the use of the natural history study to inform the long-term outcomes for patients with *RPE65*-mediated IRD receiving BSC. The study provides data for a relatively large number of patients collected as part of a retrospective chart review. However, the company's decision to apply an MSM does not appear to be well justified in light of the evidence available from the *RPE65* NHx study. The company's base-case analysis (a Weibull MSM) requires the estimation of 11 parameters for n=35 transitions observed for n=68 patients. It is the ERG's opinion that the specification of such a model is overly complex and likely "over fits" the available data from the *RPE65* NHx study while also imposing a strict framework on the data. The results from the model have also not been assessed for face validity, given the expectation that *RPE65*-mediated IRD is expected to lead to near-total blindness by the third decade of life (which is not mirrored in the economic modelling).

The ERG has made a number of changes to the company's model to address some of these concerns, and where possible conducted analyses to illustrate the associated impact on the cost-effectiveness results. The results of these analyses are provided within Section 6.

5.4.2 Outstanding issues

In light of the evidence available and the remit of this appraisal, the ERG was unable to fully explore and/or resolve the following outstanding issues with the company's model:

Specification of the complex MSM

The company's decision to specify an MSM to predict the natural history of *RPE65*-mediated IRD does not appear to be justified by the evidence base available. The ERG would have preferred to see a simplified approach to capturing the natural history of the condition, which would have been possible to consider within a state-transition or partitioned-survival framework (given the progressive nature of the condition).

Further to this, the ERG has unanswered questions regarding the clinical plausibility of the MSM projections, as many patients are predicted to remain within HS1 for several decades following diagnosis. If the model was adjusted to reflect the situation wherein all patients are expected to reside within HS5 after 20-30 years (for example), this may lead to a reduction in the ICER.

Lack of clarity regarding (long-term) outcomes for patients treated with VN

The ERG appreciates the issues associated with quantifying the expected benefit of treatments which may (or may not) have lifelong effects for some or all patients treated. However, the ERG is unable to

truly determine the likely duration of treatment effect associated with VN, nor is it able to fully confirm how generalisable the findings of the studies that inform the company's model may be to the UK population (given that the population size is very small).

The company provided further data at clarification stage regarding endpoints of the clinical trial programme for VN which potentially show some evidence of a reduced treatment effect of VN over time. This however is subject to several major caveats, including the reliance of using last-observation-carried-forward and unlicensed doses of VN within Study 101/102.

Notwithstanding the issues with the MSM and estimation of the long-term treatment effect of VN, the ERG considers the company's model to constitute a sufficient basis to inform decision making and appreciate the willingness of the company to engage with the issues raised by the ERG as a part of the clarifications process.

The ERG's corrections, preferred settings and assumptions are presented in Section 6 of this report.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

This section provides the results of the ERG's additional analyses within the company's model. The analyses are considered in the following components:

- Corrections made to the company's model to reflect computational errors and/or flawed application of data
- The ERG's preferred base-case analysis
- Additional exploratory and sensitivity analyses undertaken by the ERG

The findings of these analyses are presented in the sub-sections below.

6.1 Corrections made to the company's model

The company's model has been constructed to a good standard, and so the ERG did not identify many modelling errors. Following clarification, the company provided a corrected MSM which features both within the company's and ERG's preferred base case. Details of the corrections made to the model are provided in Section 5.2.6, and summarised in an addendum to this report. In addition to this, the ERG made the following amends to the application of costs in the company's model:

- Surgery changed from £2,269.80 to £1,959.90 (Section 5.2.9.3)
- Retinal tomography changed from £114.46 to £134.65 (Section 5.2.9.5)
- Ophthalmologist outpatient consultation changed from £97.94 to £101.83 (Section 5.2.9.6)

Finally, the ERG also corrected the following minor errors within the company's model which do not affect the base-case results:

- Sheet "Engine_VN", range "CN12 to CN111": erroneous application of the half-cycle correction to the total costs incurred per model cycle
- Correct implementation of the light sensitivity scenario analysis (which by default originally selected a value of 0 if enabled)

6.2 ERG's preferred base case

The ERG's preferred base-case analysis is described in Table 57, which also includes the corrections made to the company's model described in Section 6.1.

Table 57: Summary of the ERG's preferred base case

Category	Company's base case	ERG's base case	Rationale for change
Cost of resolving AEs	• GP appointment for eye inflammation and increased IOP	• Outpatient ophthalmologist for eye inflammation and increased IOP	• Not expected to be seen by a GP given specialist nature and high cost of therapy, added to potential risks • Suggest an outpatient ophthalmologist cost as a minimum
Medical resource use costs	• Taken from published sources. For missing values, assume 50% for children or working age adults, and assume 50% for HS1	• Remove depression costs • Set HS1 costs to be the same as HS2 to HS5	• Depression costs are based on sight loss in later life, as opposed to lifelong sight loss • No clear rationale for why HS1 costs should be substantially lower than costs for HS2 to HS5 as no source for 50% multiplier is provided
Mortality	• Apply mortality multipliers for HS2 to HS5 based on Christ (2014)	• Remove mortality multipliers	• Mortality multipliers derived based on a substantially dissimilar population (elderly patients who exhibited later life sight loss) • No deaths observed in all studies of VN and the *RPE65* NHx study, conflicting with the assumption of notable levels of mortality
Carer disutility	• Disutility from Kuhlthau (2010) • Assumes 1 carer per patient • Applied for children and 50% of adults • Applied for 50% of patients in HS1	• Disutility from Al Janabi (2016) • Multiply disutility by average number of carers per child (1.78) • Remove carer disutility for adults • Applied for all patients in HS1	• Amended source reflects UK population • Adjusts disutility to account for multiple carers per child • Remove carer disutility for adults • Per medical resource use, no clear rationale for why HS1 carer disutility should be substantially lower than those for HS2 to HS5 as no source for 50% multiplier

Category	Company's base case	ERG's base case	Rationale for change
Baseline health state occupancy	• ITT population of Study 301/302	• Naïvely pooled populations of Study 301/302 and *RPE65* NHx	• Makes use of largest possible sample size • No reason why values would differ substantially between studies
Transitions	• Exact TP • Average eye • For missing data, assume movement per previous state • OI arm only ("no crossover")	• Exact TP • Average eye • For missing data, assume movement per previous state • OI and DI arms ("crossover")	• Makes use of largest possible sample size • Provides a means of informing otherwise "unobserved" transitions • No clear rationale for difference in treatment effect for OI and DI patients
Duration of treatment effect	• Duration of treatment effect (40 years) • Waning period (10 years) • Residual effect (25%)	• Duration of treatment effect (40 years) • Remove waning period and residual effect (waning period = 0 years, residual effect = 0%)	• Specification of three components for the treatment effect is unnecessarily complex • No clear evidence for why company's approach is more appropriate than a simple duration
Utility values	• Based on vignette study by Acaster and Lloyd	• Based on published study by Rentz (2014)	• Company values lack face validity • Multiple issues with the study design • Does not meet the NICE reference case

Abbreviations**:** AE, adverse event; BSC, best supportive care; DI, delayed intervention; GP, general practitioner; HS1, moderate visual impairment; HS2, severe visual impairment; HS5, hand motion, light perception to no light perception; IOP, intraocular pressure; ITT, intention to treat; OI, original intervention; TP, transition probabilities; VN, voretigene neparvovec.

The impact of these changes on the ICER is presented in the following tables:

- Table 58 (including the PAS discount for VN, with each change varied independently)
- Table 59 (including the PAS discount for VN, with all changes varied in combination)
- Table 60 (excluding the PAS discount for VN, with each change varied independently)
- Table 61 (excluding the PAS discount for VN, with all changes varied in combination)

Table 58: Summary of the ERG's preferred base case (independent, including PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Error corrections						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Change application of medical resource use (remove depression, equal across health states)						
BSC	£33,608	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Remove mortality multipliers						
BSC	£48,699	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
Amend application of carer disutilities						
BSC	£46,473	4.5				
VN	[redacted]	10.9	[redacted]	6.5	[redacted]	[redacted]
Pooled baseline health state occupancy						
BSC	£46,034	4.5				
VN	[redacted]	11.5	[redacted]	7.0	[redacted]	[redacted]
Use of crossover transition probabilities						
BSC	£46,473	3.6				
VN	[redacted]	10.2	[redacted]	6.6	[redacted]	[redacted]
Removal of waning period and residual treatment effect						
BSC	£46,473	3.6				
VN	[redacted]	10.5	[redacted]	6.9	[redacted]	[redacted]
Alternative utility values						
BSC	£46,473	11.5				
VN	[redacted]	16.5	[redacted]	5.0	[redacted]	[redacted]
ERG's preferred base case (all changes combined)						
BSC	£35,731	12.9				
VN	[redacted]	16.9	[redacted]	4.0	[redacted]	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 59: Summary of the ERG's preferred base case (cumulative, including PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
As above + error corrections						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
As above + cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£46,473	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
As above + change application of medical resource use (remove depression, equal across health states)						
BSC	£33,608	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
As above + remove mortality multipliers						
BSC	£35,667	3.6				
VN	[redacted]	10.7	[redacted]	7.1	[redacted]	[redacted]
As above + amend application of carer disutilities						
BSC	£35,667	4.5				
VN	[redacted]	11.0	[redacted]	6.5	[redacted]	[redacted]
As above + pooled baseline health state occupancy						
BSC	£35,731	5.2				
VN	[redacted]	11.6	[redacted]	6.4	[redacted]	[redacted]
As above + use of crossover transition probabilities						
BSC	£35,731	5.2				
VN	[redacted]	11.2	[redacted]	6.0	[redacted]	[redacted]
As above + removal of waning period and residual treatment effect						
BSC	£35,731	5.2				
VN	[redacted]	11.0	[redacted]	5.8	[redacted]	[redacted]
As above + alternative utility values						
BSC	£35,731	12.9				
VN	[redacted]	16.9	[redacted]	4.0	[redacted]	[redacted]
ERG's preferred base case (all changes combined)						
BSC	£35,731	12.9				
VN	[redacted]	16.9	[redacted]	4.0	[redacted]	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 60: Summary of the ERG's preferred base case (independent, excluding PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£46,473	3.6				
VN	£658,486	10.7	£612,013	7.1	£86,635	-
Error corrections						
BSC	£46,473	3.6				
VN	£657,978	10.7	£611,505	7.1	£86,563	-£72
Cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£46,473	3.6				
VN	£658,504	10.7	£612,031	7.1	£86,637	+£3
Change application of medical resource use (remove depression, equal across health states)						
BSC	£33,608	3.6				
VN	£652,740	10.7	£619,132	7.1	£87,642	+£1,008
Remove mortality multipliers						
BSC	£48,699	3.6				
VN	£660,344	10.7	£611,645	7.1	£86,087	-£548
Amend application of carer disutilities						
BSC	£46,473	4.5				
VN	£658,486	10.9	£612,013	6.5	£94,785	+£8,151
Pooled baseline health state occupancy						
BSC	£46,034	4.5				
VN	£657,338	11.5	£611,304	7.0	£87,252	+£617
Use of crossover transition probabilities						
BSC	£46,473	3.6				
VN	£659,593	10.2	£613,120	6.6	£93,165	+£6,531
Removal of waning period and residual treatment effect						
BSC	£46,473	3.6				
VN	£659,930	10.5	£613,457	6.9	£88,901	+£2,266
Alternative utility values						
BSC	£46,473	11.5				
VN	£658,486	16.5	£612,013	5.0	£122,293	+£35,659
ERG's preferred base case (all changes combined)						
BSC	£35,731	12.9				
VN	£654,079	16.9	£618,348	4.0	£155,750	+£77,799

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 61: Summary of the ERG's preferred base case (cumulative, excluding PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£46,473	3.6				
VN	£658,486	10.7	£612,013	7.1	£86,635	-
As above + error corrections						
BSC	£46,473	3.6				
VN	£657,978	10.7	£611,505	7.1	£86,563	-£72
As above + cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£46,473	3.6				
VN	£657,997	10.7	£611,524	7.1	£86,565	-£69
As above + change application of medical resource use (remove depression, equal across health states)						
BSC	£33,608	3.6				
VN	£652,251	10.7	£618,643	7.1	£87,573	+£938
As above + remove mortality multipliers						
BSC	£35,667	3.6				
VN	£654,016	10.7	£618,348	7.1	£87,030	+£395
As above + amend application of carer disutilities						
BSC	£35,667	4.5				
VN	£654,016	11.0	£618,348	6.5	£95,203	+£8,569
As above + pooled baseline health state occupancy						
BSC	£35,731	5.2				
VN	£654,079	11.6	£618,348	6.4	£96,531	+£9,896
As above + use of crossover transition probabilities						
BSC	£35,731	5.2				
VN	£654,079	11.2	£618,348	6.0	£103,924	+£17,289
As above + removal of waning period and residual treatment effect						
BSC	£35,731	5.2				
VN	£654,079	11.0	£618,348	5.8	£106,712	+£20,077
As above + alternative utility values						
BSC	£35,731	12.9				
VN	£654,079	16.9	£618,348	4.0	£155,750	+£69,116
ERG's preferred base case (all changes combined)						
BSC	£35,731	12.9				
VN	£654,079	16.9	£618,348	4.0	£155,750	+£77,799

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

The ERG's preferred base-case leads to an ICER of [redacted] (including the PAS discount for VN) and £155,750 (excluding the PAS discount for VN). The change associated with the largest impact on the ICER was the use of utility values based on the study by Rentz *et al.*, which if varied in isolation

of all other changes, caused the ICER to increase by approximately [redacted] (with PAS) and £35,659 (without PAS).

6.3 Additional analyses undertaken by the ERG

A brief summary of the additional analyses performed by the ERG is presented in Table 62.

Table 62: Summary of the ERG's exploratory and sensitivity analyses

#	Label	Description of analysis and rationale
1	Threshold analysis of treatment effect duration	Calculate the ICER associated with each plausible duration of treatment effect, varied from 10 to 99 years. Results presented in a plot of ICER against duration of treatment effect. Analysis performed to establish how long the treatment effect would need to be in order for the ICER to be less than £100,000 per QALY gained.
2	Institute for Clinical and Economic Review duration of treatment effect settings	Set duration of treatment effect to 10 years, duration of waning period to 10 years, and residual treatment effect of 0%. Analysis conducted to compare findings of current appraisal to the published analysis by the Institute for Clinical and Economic Review.
3	Remove all healthcare resource use costs	Remove all healthcare resource use costs, as reported in Table 48 of this report. Analysis performed to establish influence of these costs on total costs incurred by patients.
4	Use company-preferred resource use costs	Use healthcare resource use costs as reported in Table 48 of this report. Analysis performed to establish influence of these costs on the ICER.
5	Use UK utility values (based on Rentz et al.)	Use utility values for UK respondents based on study by Rentz *et al.* Impacts values for HS1 to HS5. Analysis performed to establish impact of alternative utility values on ICER, particularly if there is much difference between values from UK respondents versus all respondents.
6	Use alternative (higher) utility values (based on Rentz et al.)	Use utility values based on study by Rentz *et al.* but change the value for HS5 to be slightly higher. Consequently, this affects the linear interpolation of values for HS2, HS3, and HS4. Analysis performed to establish impact of alternative utility values on ICER, particularly if the value for HS5 is higher.
7	Use ITT population from Study 301/302	Set baseline characteristics per Study 301/302. Analysis conducted to establish influence on ICER if baseline characteristics were different.
8	Use *RPE65* NHx population	Set baseline characteristics per the *RPE65* NHx study. Analysis conducted to establish influence on ICER if baseline characteristics were different.

Abbreviations**:** HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; QALY, quality-adjusted life year.

The impact of each analysis on the ICER is presented in the following tables and figures:

- Scenario #1
  - [redacted]32 (threshold analysis, including the PAS discount for VN)
  - Figure 33 (threshold analysis, excluding the PAS discount for VN)
- Scenarios #2-8
  - Table 63 (individual analyses, including the PAS discount for VN)

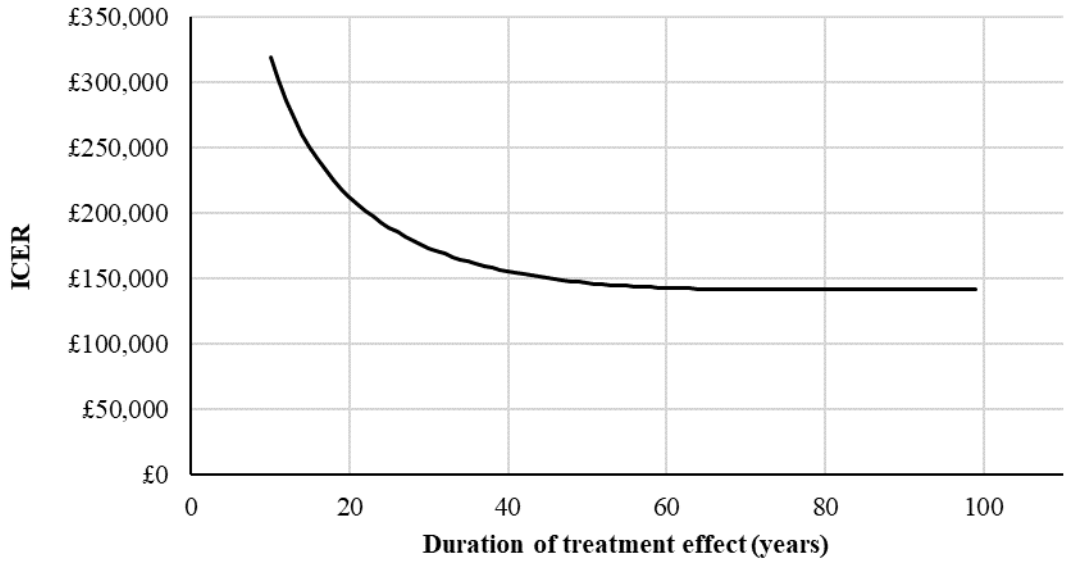
- Table 64 (individual analyses, excluding the PAS discount for VN)

These additional analyses were performed in conjunction with the ERG's preferred base-case settings and assumptions, described in Section 6.2.

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio.

Figure 33: Threshold analysis conducted by ERG (excluding PAS)



Abbreviations: ICER, incremental cost-effectiveness ratio.

Table 63: Summary of the ERG's exploratory and sensitivity analyses (including PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£35,731	12.9			
VN	[redacted]	15.0	[redacted]	2.1	[redacted]
Remove all healthcare resource use costs					
BSC	£0	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Use company-preferred healthcare resource use costs					
BSC	£48,254	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
UK utility values (based on Rentz et al.)					
BSC	£35,731	11.4			
VN	[redacted]	15.9	[redacted]	4.5	[redacted]
Alternative (higher) utility values (based on Rentz et al.)					
BSC	£35,731	13.8			
VN	[redacted]	17.1	[redacted]	3.3	[redacted]
Baseline characteristics derived from Study 301/302					
BSC	£35,667	12.4			
VN	[redacted]	16.5	[redacted]	4.1	[redacted]
Baseline characteristics derived from RPE65 NHx					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 64: Summary of the ERG's exploratory and sensitivity analyses (excluding PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£35,731	12.9			
VN	£654,079	16.9	£618,348	4.0	£155,750
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£35,731	12.9			
VN	£654,079	15.0	£618,348	2.1	£293,582
Remove all healthcare resource use costs					
BSC	£0	12.9			
VN	£618,348	16.9	£618,348	4.0	£155,750
Apply original healthcare resource use costs					
BSC	£48,254	12.9			
VN	£661,562	16.9	£613,309	4.0	£154,481
UK utility values (based on Rentz et al.)					
BSC	£35,731	11.4			
VN	£654,079	15.9	£618,348	4.5	£137,752
Alternative (higher) utility values (based on Rentz et al.)					
BSC	£35,731	13.8			
VN	£654,079	17.1	£618,348	3.3	£185,212
Baseline characteristics derived from Study 301/302					
BSC	£35,667	12.4			
VN	£654,016	16.5	£618,348	4.1	£150,996
Baseline characteristics derived from RPE65 NHx					
BSC	£35,773	13.1			
VN	£654,121	17.0	£618,348	3.9	£158,017

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

The ERG's exploratory and sensitivity analyses highlighted the following:

- Duration of treatment effect:
    - There is no plausible duration of treatment effect that yields an ICER of less than £100,000 using the ERG's preferred base-case settings and assumptions
    - Use of the same duration of treatment effect assumptions as per the analysis by the Institute for Clinical and Economic Review leads to a large reduction in QALYs gained (approximately half the predicted QALY gain in the ERG's base case)
- Medical resource use:
    - Removing all medical resource use in this scenario leads to no change in the ICER (as expected, as the only application within medical resource use that would have an impact on the ICER is the difference in costs for HS1 and other health states)

  - Using the company's preferred medical resource use settings, the ICER decreases marginally based on a reduction in incremental costs in the region of £5,000. The ERG noted that the small increase in the ICER is due to this reduction in incremental costs being relatively small when compared to the acquisition cost of VN. A change in incremental costs of £5,000 within the context of a different appraisal may lead to markedly different estimates of the ICER
- Utility values
  - Use of the UK values leads to a reduction in the ICER, as each health state utility value is smaller versus the whole population of respondents considered in the study by Rentz *et al.* The ERG noted that it is unclear whether this is a result of differing preferences or due to the smaller sample size
  - When considering the alternative utility values where HS5 is based on a slightly less severe health state, the ICER increases (as expected). This analysis illustrates the relationship between the utility values and the ICER – a large difference between utility values across all health states leads to the increased capacity for the benefit of VN to lead to a lower ICER
- Baseline characteristics
  - The baseline distribution in Study 301/302 includes a relatively larger proportion of patients in HS3, HS4, and HS5 versus the RPE NHx study. As such, the total QALYs accrued in the analysis with baseline characteristics based on Study 301/302 is lower than the analysis based on the *RPE65* NHx study

The ERG also conducted an assessment of the ICER were a governmental perspective to be adopted. The findings of this analysis are presented in Table 65. If a governmental perspective is considered, the ICER decreases slightly from [redacted] to [redacted] (including the PAS discount).

Table 65: Summary of ERG's base-case cost-effectiveness results

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (NHS and PSS perspective, including PAS discount)					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
ERG's preferred base case (NHS and PSS perspective, excluding PAS discount)					
BSC	£35,731	12.9			
VN	£654,079	16.9	£618,348	4.0	£155,750
ERG's preferred base case (UK government perspective, including PAS discount)					
BSC	£93,518	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
ERG's preferred base case (UK government perspective, excluding PAS discount)					
BSC	£93,518	12.9			
VN	£698,483	16.9	£604,965	4.0	£152,380

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year; VN, voretigene neparvovec.

7 IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

7.1 Summary of cost savings estimated within the CS

In addition to the administration of the technology, the company present the costs borne by patients and carers, governmental departments outside the NHS, and productivity losses in their submission and economic model. To implement the costs, an assumption is made by the company that for Health States 2 to 5, patients would incur the full costs, whereas in Health State 1, only half the cost would be incurred – this assumption is used throughout the non-NHS costs. The main cost categories are listed below.

7.1.1 Costs to patients and carers

Several costs were highlighted by the company, including the cost of home adaptations, additional educational costs due to vision impairment, and time taken to care for patients. None of these costs are included in the economic modelling.

7.1.2 Governmental costs

Due to the nature of vision loss, the CS highlights that patients are likely to incur substantial additional costs due to social security benefits (carers' allowance, personal independence payments, various employment allowances, and education costs).

To incorporate these costs in the modelling, the company have summed each of the costs likely to be incurred, stratified by the life stage of patients; prior to school leaving age (aged 18 in the model), working age (18 to 65), and following retirement.

- At school age the average annual cost assumed is £8,938.73, consisting of education cost, carer's allowance, and Personal Independence Payment
- This decreases to £2,026.95 at working age - education costs removed, employment and support allowance added, universal credit added, blind person's tax allowance added
- The cost then decreases again in retirement (to £1,956.40) due to the removal of employment and support allowance, universal credit, and blind person's tax allowance, though with the addition of attendance allowance and pension credit

7.1.3 Productivity losses

The CS and model include scenarios where productivity losses are included in the model; included in two ways – as caregiver productivity losses, and as patient productivity losses. Caregiver losses are applied in all three stages of life, with productivity losses only applied at working age.

Caregiver productivity losses are estimated based on two sources, a Portuguese study that reported 39.6% of respondents using informal care, and a US study reporting a mean of 4.3 hours of care per day given to blind patients. These two sources are combined to give a mean of 11.9 hours per week of care, which is costed at approximately £7,000 per year and varies slightly in at different stages of life.

Productivity losses are also estimated for working age patients (aged 18-65 years) – using data from the RNIB the company estimate the impact of blindness to be a 50% reduction in the employment rate (75% versus 25% for blind patients). This is then given as a cost per year of approximately £13,000 in Health States 2 to 5 (and half this in Health State 1) – linked to the UK average weekly earnings.

ERG Comment:

The company highlight that patients with vision loss are likely to be recipients of substantial governmental spending. Whilst not a part of the reference case, a sensitivity analysis of the ERG base case is provided including the impact of government spending (see Section 10.3), noting that the results are highly uncertain, and thus while the results are likely to be directionally similar, there is a lack of evidence on what level of support patients would actually receive in each health state.

The productivity losses estimated by the company however appear overstated. The first reason for this is that earnings are assumed to increase, though no corresponding reduction is made in means tested benefits (for example, universal credit). Secondly, the assumed increase in the employment rate is

based solely on observational data the whole blind population in the UK (which is unlikely to be representative of patients with *RPE65*-mediated IRD). Finally, the source used for estimating the number of hours of caregiving details the number of hours spent caring, and not the additional number of hours (for instance, parents of children without vision problems will also spend a substantial amount of time caring for their children). In addition, this study does not appear comparable to the specific challenges of the *RPE65*-mediated IRD group in the UK, as it contains a mixed cohort in the US, of whom 45% were caring for a spouse, with 55% of patients also having a chronic condition.

Should data become available, other relevant costs that would appear to be omitted from the model include the costs to patients themselves (increased cost of living due to having to rely on alternative transport, such as taxis – highlighted by the company), as well as the cost of medical devices and third sector costs (such as guide dogs).

7.2 Staffing and infrastructure requirements associated with the use of the technology

The technology would be indicated for a low number of patients so is unlikely to constitute a large burden on healthcare staffing or services. This is particularly the case due to the nature of the technology requiring 'one off' administration.

In terms of infrastructure, the technology is required to be stored until close to administration (at -65 degrees Celsius), however the ERG was advised by clinicians that such facilities would be available in all centres likely to administer the treatment. For this reason, no special arrangements or changes to existing practices are likely to be needed.

7.3 Budget impact

The company assume that as BSC is the only treatment option at present, VN will receive a 100% market share, with all existing patients being treated in the first 5 years of VN availability, shown in Table 84 of the CS (reproduced below in Table 66).

Table 66: Company estimated market share

Year	% of existing patients treated per year
Year 1	3%
Year 2	29%
Year 3	29%
Year 4	29%
Year 5	10%

Based on clinical advice provided to the ERG, it seems unlikely that a large number of existing patients (the company estimates there are 78 existing eligible patients) would wait several years before being treated when (according to the CS), their vision would be expected to deteriorate substantially within this time.

Higher numbers of patients treated earlier on would cause VN to exceed £20 million of sales in its first year of availability; at the PAS price this would be [redacted] patients per year. This could occur either through patients being treated in the first years of availability, or if the number of incident/prevalent patients proves to be an underestimate (this may be the case, given that epidemiology data suggests that the rate of diagnosis may be higher than estimated in the CS, and there is substantial uncertainty in estimates of both incidence and prevalence). Epidemiology estimates and input from clinical advisors to the ERG suggested that ultimately, given the rarity of the condition and requirements for treatment, there is substantial uncertainty in how many patients would be eligible for treatment with VN. [redacted]

8 SUBMISSIONS FROM PRACTITIONER AND PATIENT GROUPS

This section presents a summary of additional submissions received from patients, patient organisations, clinicians and NHS England.

8.1 Clinician and NHS England perspective

The first section presents a summary of the submission from clinical experts from NHS England and the Royal College of Ophthalmologists

8.1.1 Patients eligible for VN

Moorfields is a specialist centre which has been the centre of trials in the UK. Consequently, the cohort of patients living with *RPE65* and registered with this centre might nearly include the whole cohort from England. A clinician from the Royal College of Ophthalmologists reported that there are 39 patients currently registered with this condition on the Moorfields database, with potentially more patients recently diagnosed through another study.

NHS England stated that patient selection based on a molecular diagnosis for this treatment will need to be considered by clinicians with expertise in this area to enable patients who benefit from treatment to be identified and informed consent for treatment to be gained from patients.

*8.1.2 **Current management of RP***

NHS England reported that because there are no specific genetic treatments available in England, current management for affected patients is supportive and involves ensuring good liaison between clinical and educational care together with low vision aids as appropriate for children. For affected adults, treatment is also supportive between clinical care, employers and social services. Low visual aids are provided for adults. Genetic counselling is provided via medical genetic services to affected families.

8.1.3 VN

NHS England stated that treatment with VN would provide the first treatment option for patients with the aim of stabilising vision and preventing further visual loss. The impact would be to improve mobility and independence for those patients very poor vision. In addition if treatment with VN is given earlier in the course of the disease, NHS England stated there is the potential to preserve central vision. A clinician from the Royal College of Ophthalmologists expressed a view that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Expert advisors to the ERG are in agreement with this view. A clinician from the Royal College of Ophthalmologists expressed the view that side-effects were unlikely to be a barrier to adoption of the treatment, again a view endorsed by clinical advisors to the ERG. Both the clinician from Royal College of Ophthalmologists and clinical advisors to the ERG consider that adverse reactions caused by a short course of steroids administered post-operatively (e.g. red eye, transient blurred vision, etc.) would be no more than expected or from a similar eye operation.

*8.1.3.1 **Subgroups***

A clinician from the Royal College of Ophthalmologists stated that while all patients with RP and some retained retinal structure might benefit from treatment with VN to some extent irrespective of age, there are a subgroup of patients with a dominant allele giving rise to a very different phenotype that may have a different prognosis from the typical patient.[100] Similarly, there are a subgroup of patients with hypomorphic alleles giving a later less severe recessive phenotype who may have a different prognosis from the typical patient.[101]

*8.1.4 **Changes to service delivery and resources required if VN is recommended***

NHS England stated that because genetic networks are in place across England, patients with known molecular diagnoses who could benefit from treatment can be identified. A clinician from the Royal

College of Ophthalmologists reported that diagnosis and monitoring uses technology that is standard in specialist clinics (imaging, psychophysics, and electrophysiology).

NHS England currently directly commissions specialised ophthalmology services including the treatment of ocular genetic disorders. NHS England state that these are best managed by specialist networks which provide multidisciplinary services including diagnosis, testing, counselling and imaging as well as treatment. NHS England anticipate that the treatment with VN can be implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services. This view is endorsed by a clinician from the Royal College of Ophthalmologists who reported that the surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units. The clinician stated that impact of VA on delivery will be limited as the number of patients affected is small and the treatment is relatively quick; i.e. it is a single treatment given to each eye in an operation that takes about one hour.

8.1.5 ***Conclusion***

There are no specific treatments currently available in England for this small patient group and current management for affected patients is supportive. Treatment with VN would provide the first treatment option for patients with this condition with the aim of stabilising vision and preventing further visual loss and with the potential to preserve central vision if given early.

Clinical experts, both from the Royal College of Ophthalmologists and advisors to the ERG, agree that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Furthermore, all the clinical experts agree that side-effects are unlikely to be a barrier to adoption of the treatment and that adverse reactions caused by a short course of steroids administered post-operatively (e.g. red eye, transient blurred vision, etc.) would be no more than expected or from a similar eye operation.

NHS England anticipate that the treatment with VN can be implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services. This view is endorsed by a clinician from the Royal College of Ophthalmologists who reported that the surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

8.2 ***Patient support group and patient submissions***

Submissions were received from the Fight for Sight charity and a patient expert with the condition nominated by the Fight for Sight charity. The patient expert's statement was in keeping with the

patient support group submission, which is summarised below and which has been illustrated with relevant examples from the patient expert's experience as detailed in his statement.

8.2.1 ***Summary of VN UK Support Group submission***

The Fight for Sight charity is the UK's largest eye research funding charity dedicated to helping patients with eye disease. Fight for Sight receives no government funding and relies on donations from the public as well as corporate support to fund its work.

The Fight for Sight charity provided an overview of the challenges faced by people living with the condition as well as the views of clinical experts supporting patients with this condition. The patient community spoken to by the charity reported a feeling of extreme anxiety and worry when they started to notice changes within their vision, which the charity state can lead to depression and other mental health issues. This link between the condition and poorer mental health was endorsed by expert advisors to the ERG. The patient expert stated that uncertainty about his future sight is a contributing factor in bouts of depression he has experienced in the past 5 years.

The charity reported that people living with the condition stated the condition robs them of opportunities in education, the labour market e.g. getting a job and/or job security, and in day to day life that others with normal vision take for granted such as socialising at night or driving. The patient expert illustrated the challenges he experienced as a child ensuring his needs were recognised and relevant support provided while being educated in a mainstream school. Later at university the patient expert described how deterioration in his eyesight affected his mobility, particularly after dark, and ability to take lecture notes, making him dependent on peers and affecting his confidence, particularly in public speaking.

The patient community also reported that inherited retinal dystrophies often have a substantial effect on parents, carers and loved ones of people living with the condition. Specific examples cited by various patients, including the patient expert, included the profound impact of diagnosis on a patient's parents e.g. the fear of having another child in case they were disabled. Other example include and huge reliance on partners and other family members for assistance, even with assistance of a guide dog.

The charity stated that improving the ability to navigate in the dark will be of huge benefit to patients living with *RPE65*. The patient expert emphasised that night blindness is far more than a simple inability to see clearly between dusk and dawn, but rather affects patients at any point of transition between levels of light throughout one's daily life, such as walking from a bright street into a shop lit by artificial light; or on entering a dimly lit meeting room, or walking from a brightly lit station

platform into an interior corridor. A change in the level of night blindness experienced could help patients to navigate more safely, confidently and independently at night, but also to approach all mobility tasks with confidence about the consistency of their visual reaction.

The charity reported that there is a huge unmet need for people living with *RPE65* as there are currently no treatments for people with this condition available on the NHS. The charity acknowledged that patients with advanced disease where there has been loss of all photoreceptors, will not benefit from this gene therapy approach, as there needs to be viable photoreceptors for the therapy to be effective. However, the charity stated that with improvements in diagnosis patients could be diagnosed at an early age, allowing them to be good candidates for this therapy. The patient expert expressed the view that there would be considerable benefit in stabilizing or reversing the visual deterioration of school age or younger children, even if the effect was limited in time. He expressed the view that growing up with a visual impairment, rather than gaining it later in life, allows one to develop coping strategies iteratively, it also places a heavy burden on children, potentially preventing them from fulfilling their potential in the classroom or of participating in sport or social activities alongside their peers. Relieving them of the stress of the constant adaptation would allow them to focus their energy on becoming independent, informed adults equipped to achieve their ambitions.

The patient expert states that whilst, in his opinion the impact of night blindness is a significant factor inhibiting the independent mobility of affected patients, potentially contributing to social isolation and constrained horizons, success in education and access to employment are, in his view, influenced more significantly by visual acuity which, at University, prevented him from reading even a small percentage of the material recommended for his course, and which today threatens his ability to work effectively, and therefore to live his life as he would wish.

8.2.2 ***Conclusion***

The patient community spoken to by the Fight for Sight charity reported a feeling of extreme anxiety and worry when they started to notice changes within their vision, which the charity state can lead to depression and other mental health issues. This link between the condition and poorer mental health was cited by the patient expert and endorsed by expert advisors to the ERG.

The charity reported that people living with the condition stated the condition robs them of opportunities in education, the labour market e.g. getting a job and/or job security, and in day to day life that others with normal vision take for granted such as socialising at night or driving. The patient expert illustrated the challenges he experienced as a child ensuring his needs were recognised and relevant support provided while being educated in a mainstream school. Later at university the patient

expert described how deterioration in his eyesight affected his mobility, particularly after dark, and ability to take lecture notes, making him dependent on peers and affecting his confidence, particularly in public speaking.

The patient community also reported that inherited retinal dystrophies often have a substantial effect on parents, carers and loved ones of people living with the condition.

In line with the patient expert's view, potential benefits to patients may be best viewed in the context of the specific visual attributes which could be improved, rather than assuming that any increase in vision would have a uniformly positive impact across areas of a patient's life. Reducing the effects of night blindness could give patients confidence, improve their safety and prevent isolation, but it will not help them to access written material, to recognise faces and interact naturally with colleagues and stakeholders which would benefit from improved visual acuity.

9 OVERALL CONCLUSIONS

The ERG has performed a detailed review of the evidence presented in the CS to quantify the clinical- and cost-effectiveness of VN for the treatment of *RPE65*-mediated IRD. In terms of the clinical benefit, VN appears to offer a sustained but modest improvement in vision, measured over a variety of outcomes. Whilst patients are highly likely to remain with vision impairment, for as long as the treatment effect persists, they are unlikely to decline further. VN is also associated with a short administration procedure, and good safety profile. Whilst the evidence provided is extremely limited (and indeed more could be done with the evidence available), this should be seen in the context of a rare disease, with the company's conduct of an RCT being extremely helpful in interpreting the treatment effect.

The submitted cost-effectiveness model presents a comprehensive summary of the key stages of vision impairment which are expected to influence patient utility, and therefore affect the estimation of the cost-effectiveness of VN. The company made use of a number of relevant data sources in order to populate the cost-effectiveness model, and identified all relevant evidence in a transparent manner. While relevant to clinical practice, the modelling approach is associated with a range of limitations relies heavily upon a large volume of clinical expert input in order to produce cost-effectiveness estimates.

Three key aspects of the model were identified as being primary contributors to the overall uncertainty in the model: (1) treatment effect of VN, (2) modelling of long-term natural history outcomes, and (3) utility values. The duration of treatment effect and estimation of utility values required extensive clinical expert input to inform the model base case, and the long-term natural

history of *RPE65*-mediated IRD was based on a highly complex MSM which is subject to palpable uncertainty. Consequently, the ERG remains unconvinced that the assumptions relating to the long-term effects of VN are supported by available evidence, and is concerned with the large impact alternative assumptions relating to the estimation of these benefits have on the cost-effectiveness results; should the treatment effect fail to remain at 100% for at least 35 years, the ICER begins to rise alarmingly.

9.1 Implications for research

In Sections 8.5.2 (p. 57) and 14.6 of the CS (p. 266), the company states that VN has the potential 'to advance the broader field of gene therapy'. This is possibly due to a) the first-in-class nature of this drug as a licensed gene therapy for retinal disease, and potential insights to be gained for onward gene therapy and treatment development. The CS also notes (refer to the CS, Section 8.5.3, p. 57) that the evidence presented represents the first Phase 3 randomised trial of gene therapy for an inherited disease. While the ERG could not find evidence of other gene therapy trials for this condition, how the proposed benefits for research will be realised remains unclear. In addition, while monitoring arrangements agreed as part of European regulatory requirements include patients who participated in Studies 101/102 and 301/302 (refer to the CS Section 15, p. 269), it remains unclear how these data might inform ongoing research, especially as monitoring arrangements do not extend to patients receiving VN in NHS settings.

REFERENCES

1. Farrar GJ CM, Dockery A et al. Toward an elucidation of the molecular genetics of inherited retinal degenerations. Human Molecular Genetics. 2017;26(R1).
2. Cai X, Conley SM, Naash MI. RPE65: role in the visual cycle, human retinal disease, and gene therapy. Ophthalmic genetics. 2009;30(2):57-62.
3. Chung DC, Bertelsen M, Lorenz B, Pennesi ME, Leroy BP, Hamel CP, et al. The Natural History of Inherited Retinal Dystrophy Due to Biallelic Mutations in the RPE65 Gene. American Journal of Ophthalmology. 2019;199:58-70.
4. Gu SM, Thompson DA, Srikumari CR, Lorenz B, Finckh U, Nicoletti A, et al. Mutations in RPE65 cause autosomal recessive childhood-onset severe retinal dystrophy. Nature genetics. 1997;17(2):194-7.
5. Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or Leber congenital amaurosis. Proceedings of the National Academy of Sciences. 1998;95:3088-93.
6. Pagon RA. Retinitis pigmentosa. Surv Ophthalmol. 1988;33(3):137-77.
7. Bunker CH, Berson EL, Bromley WC, Hayes RP, Roderick TH. Prevalence of retinitis pigmentosa in Maine. American Journal of Ophthalmology. 1984;97(3):357-65.
8. Haim M. Epidemiology of retinitis pigmentosa in Denmark. Acta Ophthalmologica Scandinavica Supplement. 2002:1-34.
9. Rim TH, Park HW, Kim DW, Chung EJ. Four-year nationwide incidence of retinitis pigmentosa in South Korea: a population-based retrospective study from 2011 to 2014. BMJ open. 2017;7(5):e015531.
10. Office for National Statistics. England population mid-year estimate. Available from: https://www.ons.gov.uk/.
11. Bundey S, Crews SJ. A study of retinitis pigmentosa in the City of Birmingham. I Prevalence. Journal of Medical Genetics. 1984;21:417-20.
12. Wang F, Wang H, Tuan H-F, Nguyen DH, Sun V, Keser V, et al. Next generation sequencing-based molecular diagnosis of retinitis pigmentosa: identification of a novel genotype-phenotype correlation and clinical refinements. Human genetics. 2014;133(3):331-45.
13. Bocquet B, Marzouka NAD, Hebrard M, Manes G, Sénéchal A, Meunier I, et al. Homozygosity mapping in autosomal recessive retinitis pigmentosa families detects novel mutations. Molecular Vision. 2013;19:2487-500.
14. Bertelsen M, Jensen H, Bregnhøj JF, Rosenberg T. Prevalence of generalized retinal dystrophy in Denmark. Ophthalmic Epidemiology. 2014;21(4):217-23.
15. Stone EM. Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture. American Journal of Ophthalmology. 2007;144(6):791-811.
16. Henderson RH, Waseem N, Searle R, van der Spuy J, Russell-Eggitt I, Bhattacharya SS, et al. An assessment of the apex microarray technology in genotyping patients with Leber congenital amaurosis and early-onset severe retinal dystrophy. Investigative Ophthalmology & Visual Science. 2007;48(12):5684-9.
17. Novartis. Data on file: Clinical expert interview transcripts. 2019.
18. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet (London, England). 2006;368(9549):1795-809.

19. Thompson DA, Gyürüs Pt, Fleischer LL, Bingham EL, McHenry CL, Apfelstedt–Sylla E, et al. Genetics and Phenotypes of RPE65 Mutations in Inherited Retinal Degeneration. Investigative Ophthalmology & Visual Science. 2000;41(13):4293-9.
20. Tsin A, Betts-Obregon B, Grigsby J. Visual cycle proteins: Structure, function, and roles in human retinal disease. The Journal of biological chemistry. 2018;293(34):13016-21.
21. Wright CB, Redmond TM, Nickerson JM. A History of the Classical Visual Cycle. Progress in molecular biology and translational science. 2015;134:433-48.
22. Kumaran N, Moore AT, Weleber RG, Michaelides M. Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions. British Journal of Ophthalmology. 2017;101(9):1147.
23. Kumaran N, Pennesi M, Yang P, al e. Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531510/.
24. Lorenz B, Gyürüs P, Preising M, Bremser D, Gu S, Andrassi M, et al. Early-Onset Severe Rod–Cone Dystrophy in Young Children with RPE65 Mutations. Investigative Ophthalmology & Visual Science. 2000;41(9):2735-42.
25. Hamel PC. Retinitis pigmentosa. Available from: https://www.orpha.net.
26. Lorenz B, Preising M. Leber congenital amaurosis. Available from: https://www.orpha.net/.
27. Lorenz B, Preising M. Severe early-childhood-onset retinal dystrophy. Available from: https://www.orpha.net/.
28. Health & Social Care Information Centre. Hospital episode statistics for England. Admitted patient care, 201-15.
29. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. BMJ Open. 2014;4(2):e004015.
30. RNIB. Children and young people in England: RNIB Evidence-based review. 2016 2016.
31. Hamblion EL, Moore AT, Rahi JS. The health-related quality of life of children with hereditary retinal disorders and the psychosocial impact on their families. Invest Ophthalmol Vis Sci. 2011;52(11):7981-6.
32. Bertelsen M, Linneberg A, Rosenberg T. Socio-economic characteristics of patients with generalized retinal dystrophy in Denmark. Acta Ophthalmol. 2015;93(2):134-40.
33. Braich PS, Jackson M, Knohl SJ, Bhoiwala D, Gandham SB, Almeida D. Burden and Depression in Caregivers of Blind Patients in New York State. Ophthalmic Epidemiology. 2016;23:162-70.
34. Chaumet-Riffaud AE, Chaumet-Riffaud P, Cariou A, Devisme C, Audo I, Sahel J-A, et al. Impact of Retinitis Pigmentosa on Quality of Life, Mental Health, and Employment Among Young Adults. American Journal of Ophthalmology. 2017;177:169-74.
35. Strawbridge WJ, Wallhagen MI, Shema SJ. Impact of spouse vision impairment on partner health and well-being: a longitudinal analysis of couples. The Journals of Gerontology Series B, Psychological Sciences and Social Sciences. 2007;62:S315-22.
36. Jacobson SG, Cideciyan AV, Aguirre GD, Roman AJ, Sumaroka A, Hauswirth WW, et al. Improvement in vision: a new goal for treatment of hereditary retinal degenerations. Expert Opin Orphan Drugs. 2015;3(5):563-75.
37. Smith J, Ward D, Michaelides M, Moore AT, Simpson S. New and emerging technologies for the treatment of inherited retinal diseases: a horizon scanning review. Eye (Lond). 2015;29(9):1131-40.

38. Thompson DA, Ali RR, Banin E, Branham KE, Flannery JG, Gamm DM, et al. Advancing therapeutic strategies for inherited retinal degeneration: recommendations from the Monaciano Symposium. Invest Ophthalmol Vis Sci. 2015;56(2):918-31.
39. American Academy of Opthalmology. Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations AAO Quality of Care Secretariat, Hoskins Center for Quality Eye Care. 2016.
40. National Institute for Health and Care Excellence. Insertion of a subretinal prosthesis system for retinitis pigmentosa | Guidance and guidelines | NICE.
41. National Institute for Health and Care Excellence. Insertion of an epiretinal prosthesis for retinitis pigmentosa | Guidance and guidelines | NICE.
42. Pennesi M, Weleber R, Yang P. BMJ Best Practice - Retinitis pigmentosa. 2018.
43. RNIB. Factsheet: the Role of a Qualified Teacher of learners with Vision Impairment (QTVI). 2016.
44. European Medicines Agency. Luxturna: EPAR - Product Information. 2019.
45. European Medicines Agency. Luxturna: EPAR - Medicine overview. 2019.
46. European Medicines Agency. Luxturna: Orphan Maintenance Assessment Report. 2019.
47. Chung DC, McCague S, Yu Z-F, Thill S, DiStefano-Pappas J, Bennett J, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clinical & Experimental Ophthalmology. 2018;46:247-59.
48. Maguire AM, High KA, Auricchio A, Wright JF, Pierce EA, Testa F, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. The Lancet. 2009;374:1597-605.
49. Maguire AM, Wellman J, Chung DC, Fraser Wright J, McCague S, Marshall KA, et al. Year 4 Results for a Phase 1 Trial of Voretigene Neparvovec in Biallelic RPE65-Mediated Inherited Retinal Disease [oral presentation]. The American Society of Retina Specialists 35th Annual Meeting 2017; Boston, MA, USA2017.
50. Simonelli F, Maguire AM, Testa F, Pierce EA, Mingozzi F, Bennicelli JL, et al. Gene Therapy for Leber's Congenital Amaurosis is Safe and Effective Through 1.5 Years After Vector Administration. Molecular Therapy. 2010;18(3):643-50.
51. Testa F, Maguire AM, Rossi S, Pierce EA, Melillo P, Marshall K, et al. Three Year Follow-Up after Unilateral Subretinal Delivery of Adeno-Associated Virus in Patients with Leber Congenital Amaurosis Type 2. Ophthalmology. 2013;120(6):1283-91.
52. Ashtari M, Cyckowski LL, Monroe JF, Marshall KA, Chung DC, Auricchio A, et al. The human visual cortex responds to gene therapy-mediated recovery of retinal function. The Journal of Clinical Investigation. 2011;121(6):2160-8.
53. Spark Therapeutics. Clinical Study Report (Study 101): A Phase 1 Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium (RPE). 2015.
54. Bennett J, Wellman J, Marshall KA, McCague S, Ashtari M, DiStefano-Pappas J, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. The Lancet. 2016;388:661-72.
55. Ashtari M, Nikonova ES, Marshall KA, Young GJ, Aravand P, Pan W, et al. The Role of the Human Visual Cortex in Assessment of the Long-Term Durability of Retinal Gene Therapy in Follow-on RPE65 Clinical Trial Patients. Ophthalmology. 2017;124(6):873-83.
56. Bennett J, Ashtari M, Wellman J, Marshall KA, Cyckowski LL, Chung DC, et al. AAV2 gene therapy readministration in three adults with congenital blindness. Science Translational Medicine. 2012;4(120):120ra15.

57. Spark Therapeutics. Clinical Study Report (Study 102): A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects with Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study. 2015.
58. Russell S, Bennett J, Wellman JA, Chung DC, Yu Z-F, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. The Lancet. 2017;390:849-60.
59. Spark Therapeutics. Clinical Study Report (Study 301): A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE). 2017.
60. Maguire AM, Bennett J, Wellman J, Chung DC, High KA, Yu Z-F, et al. Phase 3 trial update of voretigene neparvovec in biallelic RPE65 mutation-associated inherited retinal disease [oral presentation]. The American Academy of Ophthalmology (AAO) Annual Meeting 2017; New Orleans, LA, USA2017.
61. Russell S, Bennett J, Wellman J, Chung DC, High KA, Yu Z-F, et al. Two-Year Results for a Phase 3 Trial of Voretigene Neparvovec in Biallelic RPE65-mediated Inherited Retinal Disease [poster]. The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting 2017; Baltimore, MD, USA2017.
62. Russell S, editor Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65mutation–associated inherited retinal disease. Association of Research in Vision and Ophthalmology (ARVO) annual meeting; 2018.
63. Leroy BP, Russell S, Wellman J, Chung DC, High K, Yu Z-F, et al. Year 3 Results and Age-Stratified Analyses for a Phase 3 Trial of Voretigene Neparvovec in RPE65 Mutation–Associated Inherited Retinal Disease. 18th EURETINA Congress, 20–23 September 2018, Vienna, Austria2018.
64. Maguire AM, editor PA074 Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial. American Academy of Ophthalmology annual meeting; 2018.
65. Orphanet. Leber congenital amaurosis. 2015.
66. Revicki DA, Rentz AM, Harnam N, Thomas VS, Lanzetta P. Reliability and validity of the National Eye Institute Visual Function Questionnaire-25 in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010;51(2):712-7.
67. Novartis. (Draft) Psychometric evaluation of the modified Visual Function Questionnaire (VFQ-25) using data from AAV2-hRPE65v2-301 (voretigene neparvovec) phase III trial. 2019.
68. Bittner AK, Iftikhar MH, Dagnelie G. Test-Retest, Within-Visit Variability of Goldmann Visual Fields in Retinitis Pigmentosa. Investigative Ophthalmology & Visual Science. 2011;52(11):8042-6.
69. Roman AJ, Cideciyan AV, Schwartz SB, Olivares MB, Heon E, Jacobson SG. Intervisit variability of visual parameters in Leber congenital amaurosis caused by RPE65 mutations. Invest Ophthalmol Vis Sci. 2013;54(2):1378-83.
70. Pelli DG, Bex P. Measuring contrast sensitivity. Vision research. 2013;90:10-4.
71. Chung DC, Lee K, Reape KZ, High K, Lacey S, Viriato D. Long-term effect of voretigene neparvovec on the full-field light sensitivity threshold test of patients with RPE65 mutation-associated inherited retinal dystrophy: post-hoc analysis of Phase I trial data. Abstract submitted to ARVO 2019 Annual Meeting2019.
72. Roman AJ, Schwartz SB, Aleman TS, Cideciyan AV, Chico JD, Windsor EA, et al. Quantifying rod photoreceptor-mediated vision in retinal degenerations: dark-adapted thresholds as outcome measures. Exp Eye Res. 2005;80(2):259-72.

73. Novartis. (Draft) Summary of Product Characteristics - Luxturna. 2018.
74. Centre for Reviews and Dissemination. Systematic Reviews. CRD's guidance for undertaking reviews in health care. University of York; 2008. Report No.: ISBN 978-1-900640-47-3.
75. National Heart Blood and Lung Institute. Background: Development and Use of Study Quality Assessment Tools.
76. Institute for Clinical and Economic Review (ICER). Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. 2018:128.
77. Health Information Research Unit (HIRU). Search Filters for MEDLINE in Ovid Syntax and the PubMed translation. Available from: https://hiru.mcmaster.ca/hiru/hiru_hedges_medline_strategies.aspx.
78. Canadian Agency for Drugs and Technologies in Health (CADTH). Strings Attached: CADTH's Database Search Filters. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters.
79. National Institute for Health and Care Excellence (NICE). Highly Specialised Technology Evaluation of strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency [ID926]: Evaluation Report. Available from: https://www.nice.org.uk/guidance/hst7/documents/committee-papers.
80. Pierce EA, Bennett J. The Status of RPE65 Gene Therapy Trials: Safety and Efficacy. Cold Spring Harbor perspectives in medicine. 2015;5(9):a017285.
81. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013 2013.
82. Crowther MJ, Lambert PC. Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Statistics in Medicine. 2017;36(29):4719-42.
83. Jones E, Epstein D, García-Mochón L. A Procedure for Deriving Formulas to Convert Transition Rates to Probabilities for Multistate Markov Models. Medical Decision Making: An International Journal of the Society for Medical Decision Making. 2017;37(7):779-89.
84. Bainbridge JW, Mehat MS, Sundaram V, Robbie SJ, Barker SE, Ripamonti C, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. N Engl J Med. 2015;372(20):1887-97.
85. Christ SL, Zheng DD, Swenor BK, Lam BL, West SK, Tannenbaum SL, et al. Longitudinal relationships among visual acuity, daily functional status, and mortality: the Salisbury Eye Evaluation Study. JAMA Ophthalmol. 2014;132(12):1400-6.
86. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12(5):793-9.
87. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. American Journal of Ophthalmology. 1999;128(3):324-30.
88. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. Archives of ophthalmology (Chicago, Ill : 1960). 2000;118(1):47-51.
89. Rentz AM, Kowalski JW, Walt JG, Hays RD, Brazier JE, Yu R, et al. Development of a preference-based index from the National Eye Institute Visual Function Questionnaire-25. JAMA Ophthalmol. 2014;132(3):310-8.
90. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics. 2013;31(6):489-500.
91. Office for National Statistics (ONS). Families and Households: 2017. Available from: https://www.ons.gov.uk/.

92. Kuhlthau K, Kahn R, Hill KS, Gnanasekaran S, Ettner SL. The well-being of parental caregivers of children with activity limitations. Maternal and child health journal. 2010;14(2):155-63.
93. Wittenberg E, James LP, Prosser LA. Spillover Effects on Caregivers' and Family Members' Utility: A Systematic Review of the Literature. PharmacoEconomics. 2019.
94. Al-Janabi H, Van Exel J, Brouwer W, Trotter C, Glennie L, Hannigan L, et al. Measuring Health Spillovers for Economic Evaluation: A Case Study in Meningitis. Health economics. 2016;25(12):1529-44.
95. Lloyd A, Nafees B, Gavriel S, Rousculp MD, Boye KS, Ahmad A. Health utility values associated with diabetic retinopathy. Diabetic Medicine. 2008;25(5):618-24.
96. National Health Service. Reference costs | NHS Improvement. Available from: https://improvement.nhs.uk/resources/reference-costs/.
97. National Institute for Health and Care Excellence. BNF: British National Formulary.
98. Personal Social Services Research Unit. Unit Costs of Health and Social Care | PSSRU. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/.
99. Ren S, Minton J, Whyte S, Latimer NR, Stevenson M. A New Approach for Sampling Ordered Parameters in Probabilistic Sensitivity Analysis. Pharmacoeconomics. 2018;36(3):341-7.
100. Hull S, Holder GE, Robson AG, Mukherjee R, Michaelides M, Webster AR, et al. Preserved visual function in retinal dystrophy due to hypomorphic RPE65 mutations. Br J Ophthalmol. 2016;100(11):1499-505.
101. Hull S, Mukherjee R, Holder GE, Moore AT, Webster AR. The clinical features of retinal disease due to a dominant mutation in RPE65. Mol Vis. 2016;22:626-35.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12noon** on **Thursday 9 May 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Note: Issues are divided into key issues and minor issues. For simplicity, issues are identified by page and line number (with numbering restarting on each new page).

Key issues

Issue 1 Description of LCA and RP as separate disorders

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15, lines 13–14 Page 31, line 20 Page 41, lines 11–15	Highlight the lack of reliability in assigning clinical diagnoses, and the recent movement in the field of IRD towards assigning molecular diagnoses rather than clinical diagnoses.	It is important to note that the indication is not limited to only RP and LCA. No formal classification system exists for assigning clinical labels. The use of terms in clinical diagnosis tends to reflect the regional or personal preferences of individual ophthalmologists. As such, ambiguities and significant overlap exists with other terms such as SECORD, early-onset RP, EOSRD, etc. which are also applied to patients with RPE65 mutations. Scientifically, the field is moving towards genetic based diagnosis. As the genetic defect determines the pathophysiology, clinical diagnosis becomes less relevant with respect to treatment targeting a specific gene or mutation. IRD due to biallelic RPE65 mutations constitutes a distinct medical entity with clinical characteristics driven by an underlying molecular defect (i.e., RPE65 deficiency) which can be treated with voretigene neparvovec.	The ERG recognise that there is poor reliability of clinical diagnosis for IRD, as this is noted in Section 2.1.5 of the ERG report. No change needed.
Page 41, lines 8–11 Page 55, lines 6–11 Page 61, lines 16–17	Highlight that genetic diagnosis was more important than clinical diagnosis in assessing trial eligibility.	As above, it is important to note that eligibility for voretigene neparvovec is driven by the genetic diagnosis, not clinical diagnosis. Genetic diagnosis (i.e., biallelic RPE65 mutations) was the primary driver for clinical trial enrolment, rather than clinical diagnosis. The CSR acknowledges that “Patients with mutations in the RPE65 gene have commonly been diagnosed as Leber congenital amaurosis type 2 (LCA2), but have also been	This is not a factual inaccuracy. It is acknowledged in the ERG report that trial inclusion for Study 101/102 and Study 301/302 specified patients with biallelic RPE65 mutations (e.g. p. 54 and 118). However, as also noted in the report (p. 55) an LCA

Page 117, lines 10–11		described clinically as early-onset retinal dystrophy (EORD), early onset severe retinal dystrophy (EOSRD), retinitis pigmentosa (RP), early onset RP, and other similar clinical diagnoses.”	diagnosis was specified in the trial objectives (CS p. 71, 84, 87), without clear explanation of whether patients with LCA were prioritised for inclusion over other types of genetic IRD. No breakdown of clinical diagnoses of patients in the trials were reported in the CS.

Issue 2 Description of visual acuity outcomes as “primary”

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, line 10	Delete “primary”.	Visual acuity (VA) was one of the secondary outcomes of the trial. Use of the word “primary” in this context may incorrectly imply that it was the primary endpoint. RPE65-mediated IRD is a rod-mediated retinal dystrophy, in which the peripheral retina is primarily affected. VA change is not the primary target of treatment and was a secondary outcome in the trials. Outcomes such as MLMT, VF and FST are important for assessing rod-mediated conditions, and emphasis on VA particularly as a ‘primary’ endpoint is incorrect. A comprehensive assessment of the disease rather than considering the individual measures of visual function in isolation is important.	This sentence reads as "Primary visual acuity (VA) outcomes", and refers to the company's primary method of measuring VA in Study 301/302; it does not describe VA as a primary outcome in the trial and the ERG disagree that this sentence could lead to confusion.

Issue 3 Order of trial endpoints in summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, paragraph 2	Reorder references to trial outcomes based on the clinical trial and relevance of outcomes in assessment of the disease.	The current phrasing and sentence order implies that VA was the primary outcome, and that MLMT was an exploratory outcome. In addition to being the primary outcome of the clinical trial, navigational mobility/functional vision is regarded as a key outcome for assessing the effect of treatment on the ability to perform daily activities. As stated in Section 8.1.3 of the ERG report: “A clinician from the Royal College of Ophthalmologists expressed a view that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Expert advisors to the ERG are in agreement with this view.” MLMT outcomes in the trial correlated particularly well with FST and VF outcomes, highlighting the importance of these outcomes in assessing the condition.	The ERG do not consider a change to be necessary here. Outcomes in this section are discussed in the same order as they are presented in the NICE scope, and in the order in which the outcomes are presented in Section 4.2.3 of the ERG report.

Issue 4 Inaccurate description of trial VA changes

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, line 12	Replace “All changes in VA” with “Mean changes in VA”. Add that some patients did experience clinically	Some trial patients did experience clinically meaningful improvements in VA. While mean changes in VA did not meet thresholds for clinical significance, [redacted]	The phrase "All changes in VA' follows from the previous sentence, referring to changes from baseline in Study 301/302. The ERG do not agree that this sentence is unclear or that it requires amendment.

	meaningful improvements.		

Issue 5 Misinterpretation of FST units in Phase 3 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, lines 19–20 Page 84, lines 11–14 Page 86, lines 10–19	Revise summary of results and conclusions to clarify that FST results did exceed clinical significance thresholds.	The report currently states that results were not clinically significant, because log units have been incorrectly compared against a dB threshold. In Study 301/302 light sensitivity was reported in log10(cd.s/m^2). The defined threshold for clinical significance is 10 dB (the units used in the Phase 1 trial) or 1 log unit (the units used in the Phase 3 trial). A change in light sensitivity of 2.11 log units greatly exceeds the threshold for clinical significance. This misinterpretation may have contributed to the conclusion of visual gains being “modest” (see issue 6).	Thank you for your comment. These sentences have been edited accordingly. The MID was mistakenly interpreted using 10 dB in these sentences; however, the ERG were aware that data for FST exceeded the MID, as discussed in Section 4.4 (p. 109, line 7). As such, this was considered in the ERG's interpretation of the findings as "modest".

Issue 6 Conclusion that improvements in vision were modest

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24, lines 2–3 Page 189, line 15	Revise wording where clinical outcomes from the trial are described as “modest”	Substantial clinically meaningful improvements in functional vision and visual function were observed with several trial endpoints, including the primary endpoint (MLMT) and VF, FST and VFQ. It is not factually accurate to conclude that these represent “modest” improvements. As stated in Issue 3, MLMT is considered a key outcome, and it correlated well with VF and FST outcomes. Improvements in MLMT, VF and FST were highly	We do not regard this as a factual error. The description of findings as modest does not relate strictly to statistical significance, nor does it relate strictly to clinical significance. The ERG also noted that MIDs for MLMT are still

		statistically significant and exceeded clinical significance thresholds. These improvements have been maintained through to the latest follow-up visits. Although VA results did not reach statistical significance, VA showed numerical improvement and the significance was driven by the selection of the off-scale conversion approach (Holladay vs Lange). Also, as discussed in Issues 2 and 4 above, some patients did experience clinically significant improvements in VA, which is not expected to capture the full benefit of treatment in this rod-mediated disease. The description of improvements as modest may also be partly due to the misinterpretation of units in the FST endpoint (see Issue 5 above).	developing and that evidence of what constitutes a clinically meaningful change for this outcome--which was the primary outcome of the company's trial evidence--is still unclear.

Issue 7 Description of MLMT endpoint as an additional outcome

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 87, line 9	Replace "Additional Outcomes" with "Primary outcome"	MLMT was the primary outcome of the trial, so describing it as an "additional outcome" is not accurate.	We agree that MLMT was measured as a primary outcome in the pivotal 301/302 RCT. However, we have listed it as an additional outcome in our report as it was an additional outcome measure to those stated in the NICE decision problem. In addition, it is made clear that MLMT is the primary outcome of Study 301/302 on page 87, line 9. No change needed.

Issue 8 Inaccurate reporting of VFQ results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 95, lines 3–5	Delete the statement: [redacted]	The origin of the quoted figure is unclear. Mean changes were [redacted], respectively, for patient- and parent-reported questionnaires (see Table 18 in ERG report). These changes fall below the threshold for clinical significance.	The ERG regret the confusion and have deleted the sentence accordingly.
Page 95, lines 9–12	Replace "[redacted]".	The origin of the quoted percentage increases is unclear. The increases from baseline to Year 1 were [redacted] (see Table 18 of ERG report).	The ERG regret the confusion and have deleted the sentence accordingly.

Issue 9 Use of phrase "numerical improvement" to describe statistically significant results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 109, line 6	Clarify that improvements in VF and FST were statistically and clinically significant	Use of term "numerical improvements" implies that results were not statistically significant.	The ERG has stated in the report that the numerical improvements exceeded MIDs for VF and FST. No change required.

Issue 10 Description of proxy elicitation exercise (Acaster Lloyd study) as inaccurate/inappropriate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21, lines 20–21 Page 22, lines 18–19 Page 114, "Source of preference data…" row of table, third column Page 138–Page 141 ("ERG	Remove conclusion 'the ERG does not consider these utility values to constitute an appropriate basis for decision making'.	The Acaster Lloyd study is closer to the NICE reference case than the approach proposed by the ERG and is less subject to bias: • Both approaches map the vignette descriptions of model health states to HRQoL questionnaires • However, in the Acaster Lloyd study, this mapping is performed by six retina specialists with additional expertise in IRDs, while the ERG approach is mapped by members of the ERG • The Acaster Lloyd study includes the EQ-5D (reference case) and another generic preference-based measure, while the ERG approach uses a condition-specific measure	This is not a factual inaccuracy. The ERG does not consider the values provided by the company to be robust as they are far from the NICE reference case, and thus do not constitute an appropriate basis for decision making. No change needed.

comment" section)		• In the Acaster Lloyd study, the full range of questionnaire responses were available, whereas the ERG approach was limited to the eight health states described in Rentz et al • In the Acaster Lloyd study, the questionnaires were completed for each health state, whereas the ERG approach used linear interpolation between the best and worst states • The ERG assume that HS5 was equivalent to the worst health state in the Rentz et al. study (555555). However, this does not reflect the severity in the HM/LP/NLP state; it describes activities as extremely difficult but not impossible, and does not describe mental health problems other than worry. Additionally, the ERG analysis appears to use overall values in the base-case, rather than UK values, which is not consistent with the NICE reference case. Although methodological uncertainties with each approach may be highlighted and discussed, we consider it inappropriate for the ERG to state that 'the ERG does not consider these utility values to constitute an appropriate basis for decision making'. This is particularly important in the context of a HST framework, where there is precedent for use of clinicians as proxies for patients in previous HST evaluations, and committees using these values as the basis of decision-making.	
Page 138, line 11	Remove "These include the use of proxies (clinicians in this case) for patient values, which have been seen in multiple instances to be a poor surrogate of patient values"	This description is not correct. The clinicians did not provide patient values – they provided a proxy assessment of HRQL by rating each state in terms of the descriptive system of the EQ-5D and HUI. Standard value sets were then then applied to these questionnaire responses.	The ERG does not agree that the explanation provided by the company warrants removal of this statement. The company agrees that the clinicians provided a proxy assessment of health-related quality of life (HRQL), and so the ERG's point regarding the poor surrogacy of proxies stands. The use of standard value sets is not

			disputed by the ERG. No change needed.
Page 138, lines 12–13	Remove “and the questions being asked over the telephone by researchers, as opposed to completed by the clinicians without interaction”	We are not aware of why capturing data in an interview is a source of bias, and it is very common practice for PRO data to be captured through interviews in clinical trials. The clinicians were not led in any way in their responses.	This is not a factual inaccuracy. Clinicians were interviewed by a human, instead of using an automated system (such as an Interactive voice response [IVRS] system), and so the approach taken to eliciting opinion is subject to a degree of bias.
Page 138, lines 13–14	Remove the statement “the health state descriptions are vivid in their descriptions of limitations”	This statement implies that the descriptions of limitations are exaggerated. The language in the descriptions came from families affected, and from clinicians and rehab specialists who work with these patients. It was also reviewed and approved by them for accuracy. The descriptions were purposefully meant to be as descriptive as possible to provide as much information as possible and are considered accurate in this context.	The ERG provided a comparison to the Rentz study to illustrate the difference in detail used for health state descriptions. The ERG does not raise particular issue with the language used, or the specific content. Rather, the ERG notes that the descriptions provided contain substantially more information about the limitations such that the descriptions may be considered vivid in nature (in other words, the descriptions provide a strong, clear image of the health state in the readers mind). This is not a factual inaccuracy.
Page 138, lines 14–16	Remove statement “this will introduce a ‘framing’ effect wherein	The is not correct because descriptions are presented in the context of vision loss, but also describe usual activities and ability to work, ability to live independently, social activities, participation in sports and physical activity and psychological impact. There are also examples in the states of things	The ERG does not consider this a factual inaccuracy. The framing effect may be noted in several instances where a positive aspect of the health state is immediately

	clinicians are unlikely to take into account the broad range of activities patients can perform that are unrelated to vision loss”	people can do despite vision loss; e.g. “running, swimming or gym work is possible”.	caveated with a negative - for example: "The person does not need to use visual aids or a cane, but may rely on a flashlight." and "The person can see the TV, but may not always recognise characters on the TV until they hear them speak". The ERG notes their use of the phrase "will" may be unjust, and so has revised the report to say that this "may" introduce a framing effect, however overall the statement is not considered to be factually inaccurate.
Page 138, lines 30–32	Revise wording in the statement “the absolute values given by clinicians not appearing to match with the patient experience described by the ERG’s clinical advisors, and secondly, the negative value for HS5.”	It is not correct to state that the clinicians assigned utility values. The clinicians completed questionnaires rather than valuing health states. It should also be noted that the negative utility value was only associated with the HUI and not the EQ-5D.	This justification provided by the company is factually inaccurate - the company are correct that the clinicians did not provide the utility values, however the clinicians served as proxies for completing the questionnaires. Negative value only applies for HUI3 analysis. The wording in the report has been revised to state "the absolute values derived via the proxy elicitation exercise..." and "the negative value for HS5 (HUI3 analysis)"
Page 138, line 32–page 139, line 1	Revise wording in the statement “the ERG’s	People with deteriorating vision commonly suffer from poor mental health. This common co-morbidity is also detailed elsewhere in the ERG report.	ERG's clinical advisers were primarily referring to physical health problems within the context

	clinical advisors stated that patients had restrictions imposed by their vision, but in general did not have other health problems”		of the discussion, as mental health problems were discussed separately. The ERG report does not reflect the nature of this discussion and so has been re-worded to clarify that, unlike many other vision disorders, in general patients did not have other physical health problems.
Page 139, lines 1–2	Remove the statement “As the patients had always experienced vision problems, they did not experience a sense of ‘loss’ from otherwise average vision”	This assessment of the natural history of the disease is incorrect. RPE65-mediated IRD is a progressive disease, with vision declining over time – it is not stable, as implied by this statement. Patients constantly need to adapt to deteriorating vision, so do experience a sense of loss. The patient testimonial on page 188 discusses the “stress of the constant adaptation”.	Not a factual inaccuracy. RPE65-mediated IRD is associated with vision loss over a lifetime. The ERG does not claim patients experience no change in vision over time. Rather, the ERG has stated that a sense of ‘loss’ from otherwise average vision does not describe the patient experience for those with RPE65-mediated IRD
Page 140, lines 11–14	Add that fundamental limitation of the Czoski-Murray study is that the data are not collected from people with vision loss, but instead from people with normal vision who are	Not including this limitation is an important omission.	The ERG report accurately highlights that details of the limitations of the Czoski-Murray et al. study are not described in the company submission (CS). As limitations in the Czoski-Murray study identified by the ERG resulted in the ERG considering utility scores from the Brown et al. study only, the ERG does not feel a change is necessary here.

	temporarily blind because they have are wearing distorting contact lenses		

Issue 11 Description of multi-state model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21, lines 10–12 Page 22, lines 27–29 Page 24, line 18 Page 131, line 13–page 133, line 16	Revision statement about MSM being "unnecessarily complex" Revision of wording about extrapolations conflicting with statements on long-term natural history outcomes to note that long-term outcomes are unknown, but the model is likely conservative	Describing the company model as *unnecessarily complex* is not justified. The current wording in the ERG report introduces open-ended uncertainty whereas we consider the model predictions are likely to be conservative. Although the method to convert from transition intensities to transition probabilities is somewhat complex, the multi-state model itself is relatively simple (i.e. all transitions are contained within a single statistical model). Alternative approaches proposed by the ERG are either a partitioned survival model (PSM) or a state-transition model. State-transition model: • The multistate model implemented is, by definition, a type of state-transition model. As such, it is unclear how the proposed approach would differ, or be implemented. • One such implementation might include, for example, non-parametric estimation of Markov transition probabilities (creating a 'transition probability matrix') representing the probability of moving state between time *t* and *t+1*. This approach was not adopted because:	The statement regarding the unnecessary complexity of the company's MSM approach is entirely justified within the ERG's report. It is stated within section 5.2.6 that "The company's base-case analysis (a Weibull MSM) requires the estimation of 11 parameters. Consequently, the Weibull MSM was fitted based on an average of 3.2 transitions (events) per parameter (n=35 transitions for 11 parameters), or 6.2 patients per parameter (n=68 patients for 11 parameters). It is the ERG's opinion that the specification of such a model is overly complex and likely "over fits" the available data from the RPE65 NHx study." The company is correct to highlight the issues that may have been present were an alternative model

		o To incorporate time trends would require estimation of multiple matrices, leading to an increase in the number of model parameters required to be estimated. ▪ The alternative would be to assume constant transition probabilities, an assumption which we do not believe to have face validity o As patients are not observed for common follow-up durations, dealing with patients who are censored between t and t+1 would be extremely challenging and may lead to a loss of information. PSM: • A PSM would be extremely challenging, if not impossible, to implement in this setting on the basis that not all patients start the model in the mildest state • Depending on the exact implementation envisaged, PSM could require even more parameters to be estimated from limited data than is required for the multi-state model. o For example, if multiple survival models are required to be estimated each with multiple parameters • PSMs are subject to limitations, as outlined in Technical Support Document 19, as issued by the NICE Decision Support Unit On this basis, any complexity associated with the implementation of the multi-state survival model is considered necessary to ensure the limited available data is used as efficiently as possible. Model predictions are expected to be conservative on the basis that the decline in the BSC arm is likely underestimated, as noted by the ERG. This results in higher QALYs in the BSC arm, and so a higher ICER for VN.	structure developed. However, this is not an exhaustive list of alternative structures, and the suggestion by the ERG of using either a (simpler) state-transition model or PSM was provided to illustrate other options that are available. The ERG considers it important to distinguish between model structures and statistical methods used to inform model approaches - the MSM approach is a statistical model used to inform health state occupancy. The company is correct that this is a single statistical model to inform all model transitions, however the MSM was fitted while acknowledging some transitions were unobserved. A simpler model structure which assumed no skipping of intermediate health states (e.g. via a simple state-transition model) may have been appropriate - it is the ERG's understanding that while progression of the disease may occur quickly, patients would not truly "skip" intermediate health states (rather, this is an artefact of data collection). The company's other suggested revision (regarding long-term extrapolation) is not based on a factual inaccuracy.

Issue 12 Summary of adverse events does not reflect report conclusions

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19, lines 16–21	Add that the evidence indicates a good safety profile.	The ERG concludes on page 24 that “evidence indicates a good safety profile“ but this is not reflected in the summary on page 19.	While it was acknowledged in the ERG report that there is a generally good safety profile associated with this intervention, the ERG considered it appropriate that the summary also highlighted the more serious risks associated with subretinal administration of VN and concomitant oral corticosteroid use. A sentence has been added to the summary to note the overall safety profile of VN

Minor issues

Issue 13 Name of company

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15, line 29	Replace “Spark Therapeutics, Inc.” with “Novartis Pharmaceuticals (UK)”	Novartis has development, registration and commercialisation rights to Luxturna in markets outside the US	Thank you, this has been edited in the ERG report.

Issue 14 Marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
Page 16, lines 13–14 Page 36, lines 5–7	Update marketing authorisation wording, which is “for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have	This is the correct wording of the marketing authorisation	Thank you, the wording in the ERG report has been fully aligned with the marketing authorisation.

	sufficient viable retinal cells.”		
Page 36, lines 23–26	Add clarification that the presence of sufficient viable retinal cells is a marketing authorisation requirement	The current wording implies that the presence of sufficient viable retinal cells is desirable rather than essential. Patients with insufficient viable retinal cells would be ineligible for treatment.	Thank you, the wording in the ERG report has been fully aligned with the marketing authorisation.

Issue 15 Rationale for population restriction

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16, line 18 Page 21, lines 5–6 Page 120, lines 6–7	Add that the restriction in the population is in line with the marketing authorisation, which is the remit of the evaluation	The current wording does not fully explain the rationale for restricting the patient population to those with sufficient viable retinal cells	Thank you, the wording in the ERG report has been amended to note the marketing authorisation for VN.

Issue 16 Reference to lux units instead of light levels

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, line 25 Page 65, lines 23–24 Page 69, all three columns in the "Definition" row Page 90, row 15	Replace references to "lux" or "lux units" or "lux levels" with "light levels"	The current wording is inaccurate. The primary endpoint was measured using light levels. Lux is a unit of brightness (which ranged from >400 to 1 across the seven light levels tested).	Thank you, the wording in the ERG report has been amended as suggested.

Issue 17 Frequent adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17, line 34	Delete [redacted]	[redacted] This sentence is referring to medium term (i.e. four year) adverse events, so it should be removed from this sentence.	Thank you, the wording in the ERG report has been amended as suggested.
Page 17, line 34–page 18, line 1	Replace [redacted]	The adverse events currently listed are the most frequent overall TEAEs, rather than the most frequent related to the administration procedure	Thank you, the wording in the ERG report has been amended as suggested.

	[redacted]		
Page 18, lines 2–3	Replace [redacted]	The adverse events currently listed are the most frequent overall TEAEs, rather than the most frequent related to the administration procedure.	Thank you, the wording in the ERG report has been amended as suggested.

Issue 18 Treatment locations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18, lines 8–9 Page 53, line 4	Change wording to “the majority of patients (23/31) were from the US and all were treated in the US”.	All patients were treated in the US. 23/31 were from the US and 8/31 were from other countries.	Thank you for your comment, these sentences have been edited to clarify that treatment was delivered in the US

Issue 19 PRO terminology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19, line 2	Replace “PRO data for the carers of patients” with “HRQoL data for the carers of patients”	Carers in Study 301/302 completed a PRO on behalf of young patients, and this is reported in the submission (Figure 19), but we believe this statement is referring to HRQoL of carers, which is not strictly a “patient-reported” outcome.	This is not a factual error. No patient-reported outcomes (PRO) data, HRQoL or otherwise, was reported for carers in the CS. A PRO completed by carers on behalf of, and about, patients is not PRO data for carer outcomes, which we consider to be an important omission. No change needed.

Issue 20 Mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 136, lines 11–12	Add acknowledgement that a mortality effect is not implausible with severe visual impairment and blindness	Although the Christ study was not conducted in individuals with RPE65-mediated IRD, the directional effect is expected to hold in these individuals; it is considered highly implausible that individuals who have lost their vision entirely or who have severe visual impairment have no increased risk of mortality. The removal of any mortality effect is therefore expected to be conservative.	While the ERG appreciate that there may be a heightened risk of mortality amongst patients with severe visual impairment and blindness, no evidence was presented in the CS for this. No change needed.

Issue 21 Assumption relating to ICER of a model constructed around MLMT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23, lines 4–5	Add that the most plausible result is that the ICER would be lower if the model were constructed around the MLMT outcome	The wording in the ERG report introduces an open-ended uncertainty whereas it seems very likely that the ICER would be better, as clinicians agree that the MLMT is the best tool to capture the full benefit of voretigene neparvovec treatment. The model constructed around visual acuity and visual field outcomes is likely to be conservative, as these endpoints do not capture all aspects of the condition. As stated in Section 8.1.3 of the ERG report: “A clinician from the Royal College of Ophthalmologists expressed a view that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Expert advisors to the ERG are in agreement with this view.”	The ERG report states "it remains uncertain what the cost-effectiveness of voretigene neparvovec would be were the model constructed around the MLMT outcome." This is factually accurate. The ERG disagrees with the company's assertion that this statement introduces "an open-ended uncertainty" - while it is expected that a model constructed around the outcome of MLMT would further demonstrate the benefit of VN, the impact on the ICER remains unknown (i.e. outcomes for BSC may also increase, and so the incremental QALY gain may potentially be lower).

Issue 22 Epidemiology sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Inaccurate summary of method used to derive	Replace “international studies” with “studies from the UK, and if	In Section 6.2 of the company submission (“Number of patients in England”) and in the budget impact model only sources from the UK (or if not available, Western Europe and North America) were used. This explains for example the discrepancy in % of LCA that is RPE65 mediated (6.4% median taking into account all studies; 3.4% from a UK study).	The ERG believe that this comment from the company refers to page 28 of the ERG report (lines 4-6). The ERG do not believe that a change is necessary here, as the information

epidemiology evidence Page 27, lines 4–6	none were available, North America and Western Europe". Change conclusion as appropriate.		presented in the ERG report is accurate.

Issue 23 Inaccurate summary of company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15, line 28 Page 26, line 9	Replace "86 patients" with "78 patients"	As stated on page 42 of the company submission, "a small number of these patients are expected to be ineligible for treatment with VN due to participation in the MeiraGTx trial. 15 patients have enrolled in the MeiraGTx trial across sites in the UK and the US [93]; assuming an even distribution between UK and US sites, 7-8 UK patients are expected to be ineligible for treatment with VN, giving a total eligible population of 78 patients."	The ERG acknowledge that while the figure 86 is based on numbers provided in the CS (see Table 1, p. 27), not all patients will be eligible for treatment. Clarification has been provided in the ERG report.
Page 30, lines 15–16	Delete "however this was not reported in the CS".	Nystagmus is discussed several times in the submission, including on Page 39 in Section 6.1.3 ("Symptoms").	The ERG agrees and has deleted this sentence from the ERG report.
Page 32, lines 12–13	Remove the first sentence of this paragraph or modify it to allow readers to refer	The clinical pathway of care including details of diagnosis is provided in Section 8.2 of the company submission.	The ERG agrees with the Company's proposed revision. This detail has been clarified in the ERG report.

	to information about diagnosis that was provided in the company submission.		
Page 39, “Outcomes” row of table, last column	Delete “contrast sensitivity and”	The table currently states that data for contrast sensitivity were not presented in the company submission. Contrast sensitivity results from the Phase 3 trial are presented in Section 9.6.1.1.7 of the company submission.	While the CS contained a figure depicting data for Study 301, no accompanying data were reported, and no data were reported for the other included trials. Accurate reporting of data is important for interpretation and comparison of outcome data; the reporting of figures alone is insufficient, since the interpretation of figures is inaccurate and susceptible to bias. No change needed.
Page 78, line 5 Page 80, line 15	Delete sentence claiming that “VF data beyond year 1 were not provided in the CS” (page 78) and delete “again” from start of line 15 on page 80.	VF data up to three years are reported in Figure 15, p 108 of the submission. In clarification a graph showing four years of data was provided.	While the CS contained a figure depicting VF after 1 year, no data for timepoints following 1 year were reported. Accurate reporting of data is important for interpretation and comparison of outcome data; the reporting of figures alone is insufficient, since the interpretation of figures is inaccurate and susceptible to bias. The information reporting in the CS is accurate and no change has been made.
Page 86, lines 13–15	Delete sentence claiming that “FST data	FST data up to three years for Study 301/302 were provided in the company submission, and this is presented in the ERG report (Figure 15)	While the CS contained a figure depicting FST after 1 year, no data for timepoints following 1 year were

	beyond year 1 were not provided in the CS"	Data from 7.5 years of Phase 1 follow-up show that improvements in FST have been maintained. These are presented in Figure 21 of the company submission.	reported. Accurate reporting of data is important for interpretation and comparison of outcome data; the reporting of figures alone is insufficient, since the interpretation of figures is inaccurate and susceptible to bias. The information reporting in the CS is accurate and no change has been made.
Page 95, lines 15–16	Delete sentence claiming that "there is an absence of evidence beyond 1 year for VFQ results"	Three-year data are provided on the previous page of the ERG report (page 94)	The ERG has clarified that this absence of evidence relates to the information presented in the CS
Page 97, line 23	Delete sentence claiming that "SAE data for patients receiving VN and BSC during Study 301 was not reported in the CS"	Section 9.7.2.1.5 in the company submission describes the SAEs reported by patients in Study 301	This is not a factual error. This sentence is highlighting that the CS does not report separate data comparing SAEs between intervention and the control group (best supportive care) in Study 301, and that consequently data was identified from the trial CSR.
Page 99, lines 8–9	Replace "It was not reported whether the TEAE was considered to be related to the administration of	The company submission does provide this information. Page 127 of the company submission states "One SAE was reported, which was considered unlikely to be related to the study drug, but that resulted from treatment given for a previous TEAE (intraocular inflammation endophthalmitis), which was considered to be related to the administration procedure."	The sentence has been amended as suggested; this has been clarified in the ERG comment (p.103)

	VN" with "which was related to the administration of VN".		
Page 140, line 11	Delete "which are not stated" and replace with "which are detailed in Butt et al, 2015".	This amendment will add clarity by signposting the reader to the discussion of limitations	This comment is duplicated in Issue 10 above; no change needed.
Page 143, lines 11–12	Delete the sentence "This study was not identified in the company's systematic literature review, as the review was targeted specifically at RPE65 mediated vision loss."	This is not true. As stated on page 140 of the company submission, "A systematic review was conducted to identify studies from the published literature reporting health state utility values (HSUVs) associated with patients with visual impairment, including blindness". The Rentz study was captured in this review but was excluded by the reviewers because it does not present utility values in individuals with vision loss, but instead develops a standardised value set for any combination of questionnaire responses.	Thank you for noting this. This sentence has been deleted in the ERG report as suggested.

Issue 24 Interpretation of Snellen visual acuity scores

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 55, lines 23–26	Replace “more severe” with “less severe” and replace “although as baseline VA was not reported in the CS for Study 101/102, it was not possible for the ERG to determine if the change in inclusion criteria resulted in worse VA at baseline in Study 301/302” with “and consequently VA at baseline was better in Study 301/302”.	The opposite is true. VA of 20/160 represents poorer vision than VA of 20/60. Therefore, criteria for Study 301 were restricted to include those with less severe deficits in VA. As detailed in the response to clarification question A20, this led to patients having better baseline vision in Study 301/302 [redacted]	Thank you for your comment, this Section of the ERG report has been edited as suggested.

Issue 25 Lack of supporting evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63, lines 6–8	Please provide justification for assumption that BSC interventions may have led to a different effect size in the clinical trial	We are not aware of any evidence that use of visual aids would have altered the effect size. As mentioned on page 62 of the ERG report, “the ERG considered the intervention could be described as VN plus BSC”. Use of visual aids such as glasses was permitted in patients in both arms of the trial, so would not be expected to bias either arm.	This is not a factual error. Current BSC interventions aim to optimise remaining vision, including the use of low vision aids, specialised computer software and mobility training [Smith, et al. 2015; Thompson et al. 2015], and thus aim to improve visual function. The type and proportion of BSC interventions used by patients in the included trials was not described in the CS, and therefore it's not clear which interventions were used.

Issue 26 MLMT terminology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 69, first column in the “Definition” row	Replace “MLMT” with “mobility testing”	The term “MLMT” refers to the standardised version of the mobility test that was developed for the Phase 3 study. Mobility testing was performed in the Phase 1 studies but there were differences in methodology.	Thank you, this sentence has been amended as suggested in the ERG report.

Issue 27 Incorrect labelling of graph

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 84, Figure 15	Reword title to indicate that the graph shows three years of data	The graph shows three years of data, but the title says “one year”	Thank you, this sentence in the ERG report has been amended as suggested.

Issue 28 Inaccurate description of trial VFQ results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 91, line 17	Replace “mean difference” (page 91) and “mean (SD) change from baseline” (page 94) with “mean difference in change from baseline”	Clarification required that these numbers represent the mean difference in change from baseline between the arms, not the mean difference in scores between arms	Thank you, this sentence in the ERG report has been amended as suggested.

Issue 29 Discussion of Bainbridge study

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 134, lines 21–23	Clarify that a number of differences exist between VN and the gene therapy described in the cited reference, including differences in the vector, storage techniques, and the number of photoreceptors transduced. The Bainbridge et al study found that improvements in vision peaked between 6 to 12 months after treatment, but clinical trial follow-up with VN demonstrates that improvements	There were important differences between the Bainbridge study and the VN clinical trials programme, which should be highlighted here to avoid generalisation of the results of one gene therapy trial.	This is not a factual inaccuracy. The ERG was mindful that the Bainbridge study concerns a different gene therapy within its report. No change needed.

	in vision have been maintained through to 7.5 years post-treatment, with no evidence of decline in efficacy to date.		

Issue 30 Misinterpretation of health state costs and carer disutility

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 170, bottom row and final column of Table 57 Page 144, lines 25 to 28 Page 155, lines 10 to 13	Clarify that the application of the same health state costs and carer disutility across all health states is effectively the same as removing these components of the model entirely.	The implications of the ERG assumptions are not currently clear.	While the impact on the ICER is the same, the ERG considered it appropriate to note that these costs do contribute to the overall costs of managing the condition, even though they do not impact the final ICER. No change needed.

Issue 31 Descriptions of the disease not consistent with patient experience

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 155, lines 13–16	Include depression costs in model	The justification for removal of depression costs from the model contradicts statements from the patient group summary in the ERG report. In the Fight for Sight submission summary in the ERG report, lines 25–28 of page 188 state “The patient community spoken to by the Fight for Sight charity reported a feeling of extreme anxiety and worry when they started to notice changes within their vision, which the charity state can lead to depression and other mental health issues. This link between the condition and poorer mental health was cited by the patient expert and endorsed by expert advisors to the ERG. The patient expert stated that uncertainty about his future sight is a contributing factor in bouts of depression he has experienced in the past 5 years”	The ERG does not dispute the impact of the condition on a patient's mental health. However, the justification provided by the company for the inclusion of these depression costs was deemed inappropriate. This is not a factual inaccuracy. No change needed
Page 139, lines 4–5	Reword this sentence	The statement that patients with extremely poor vision experience “high levels of enjoyment” undermines the severity of the disease, and is not consistent with the patient experience presented by the Patient Organisation, and in other sections of the ERG report.	This is not a factual inaccuracy. The ERG disagrees that this statement undermines the severity of the disease - the report makes repeated reference to the severity of vision loss. However, it was noted by the ERG's clinical advisers that some patients experience fulfilling lives even within the "worst" health states included within the company's model. No change needed.

Issue 32 Description of dominant allele not relevant to the scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 185, line 25	Delete sentence referring to dominant allele or add clarification that these patients would not be eligible for treatment with VN and do not fall within the scope of this appraisal	The marketing authorisation and this submission is for patients with biallelic RPE65-mediated IRD (caused by recessive mutations), so patients with a dominant RPE65 mutation do not fall within the scope	Thank you, this has been clarified in the ERG report.

Issue 33 Missing/incorrect words

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39, "Population" row of table, last column Page 113, "Defining the decision problem" row of table, second column	Replace "The population is broader" with "The population is narrower"	The current wording is incorrect	Thank you, this has been edited in the ERG report.
Missing word Page 99, line 6	Add "high" before "intraocular pressure"	The current wording is unclear	Thank you, this has been edited in the ERG report.
Page 129, line 12	Replace "observed" with "reported"	The natural history study was a non-interventional retrospective chart review so data on deaths were not recorded	Thank you, this has been edited in the ERG report.

Issue 34 Typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60, line 6	Replace "lose" with "low"	Spelling error	Thank you, the spelling error has been corrected in the ERG report.

Page 186, line 10	Replace “VA” in “the clinician stated that impact of VA” with “VN”	Current wording could lead to confusion given that VA means “visual acuity” in this context	Thank you, this has been edited in the ERG report.
Page 32, line 3	Replace “RPE54” with “RPE65” and replace “undiagnosed” with “underdiagnosed”	Current wording is inaccurate	Thank you, this has been edited in the ERG report.
Page 180, line 19–21	Replace “lower” with “higher” in the sentence “As such, the total QALYs accrued in the analysis with baseline characteristics based on Study 301/302 is lower than the analysis based on the RPE65 NHx study”	Current wording is inaccurate	This is not a factual inaccuracy. The ERG suspects that the company are referring to the incremental QALY gain which is larger in the Study 301/302 scenario versus the RPE65 NHx study. However, this statement in the ERG report is concerned with the total QALYs gained. No change needed.

Issue 35 Labelling errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Incorrect name of questionnaire Page 64, line 31	Replace “VFQ” with “NEI VFQ-25”		Thank you, this has been edited in the ERG report.
Wrong study names are used Page 99, lines 18-22	This section should read “The proportion of administration-related AEs were not reported separately for patients in Study 302; i.e. the first year after treatment for patients in the Original VN arm of Study 301. These AEs are incorporated into follow-up data for Study 301. The company provides a summary table of administration procedure-related TEAEs reported by patients in Study 301/302 from baseline to final follow-up (Table 22).”	The wrong trials are referenced resulting in a lack of clarity	Thank you, this has been edited in the ERG report.

Issue 36 Unclear phrasing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Unclear sentence Page 65, lines 16–17	Rephrase sentence that currently says “MIDs for these outcomes are derived in considered of inter-test variability.”	The sentence is unclear	Thank you, this has been edited in the ERG report.
Unclear sentence Page 43, lines 11–13	Rephrase sentence that currently says “The measurement of VA, VF and contrast sensitivity to be clinically relevant in the population in this assessment, and is consistent with the evaluation of visual impairment across other populations.”	The sentence is unclear	Thank you, this has been clarified in the ERG report.
Unclear use of word “optional” Page 53, line 12	Replace “each with an optional phase to extend treatment to the contralateral eye” with “with a phase to extend treatment to the contralateral eye in the Phase 1 study, and a phase to extend	We feel that use of the word “optional” introduces unnecessary ambiguity, as all clinical trials are optional, and patients can withdraw at any time	The ERG considers that the wording used in the report is accurate and not misleading or ambiguous. No change needed.

	treatment to patients in the control arm in the Phase 3 study".		
Page 17, line 16 – ambiguous sentence	After "these changes" add "from baseline".	The current wording does not make clear whether the change from baseline or the decline are being described as clinically meaningful. Use of the word "despite" suggests that the latter is true, but this should be clarified.	Thank you, this has been clarified in the ERG report.

Issue 37 Incorrect costs and ICERs reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 20, line 26	Replace incorrect incremental costs (£612,013) with [redacted] and replace incorrect ICER (£86,635) with [redacted]	These key model outputs have been misreported	The ERG has mistakenly reported the list price incremental costs and ICER instead of the associated values including the proposed PAS discount. The figures have been revised in the ERG's report.
Page 178, bottom two rows of Table 63	Replace with correct results for this scenario: • BSC costs: £35,773 • BSC QALYs: 13.1 • VN costs: [redacted]	The results presented for this scenario do not match the ERG model	The ERG agrees with the company's suggested revision. The table has been updated per the figures supplied by the company using the ERG's model.

	• VN QALYs: 17.0 • Incremental costs: [redacted] • Incremental QALYs: 3.9 • ICER: [redacted]		

Issue 38 Clarifications for completeness

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 37, line 5	Revise wording to: ”A single dose will be administered to each eye within a close interval at least six days apart”	The SmPC does not place an upper limit on the duration of treatment between eyes – the Phase 3 trial includes a stipulation of a maximum of 18 days.	There is no factual error in the ERG report. No change needed.
Page 62, lines 12–13	Revise wording to: ”These were not permitted during the trials”	Retinal prostheses were not permitted during the clinical trials	This information was not provided in the CS. No change needed.
Page 85, lines 7–10	Revise wording to: “The graph shows mean FST in dB units over 7.5 years of follow-up. At all time points post-baseline, mean FST is greater	The graph shows mean FST over time (not change from baseline) and the unit on the y-axis are dB	This information was not provided in the CS. No change needed.

	than 10 dB below the baseline value, indicating a clinically significant improvement in light sensitivity."		
Page 99, line 13 Page 109, lines 11–12	Revise wording to: "The CS reports three non-serious adverse reactions of retinal deposits in three of 41 (7%) patients that were considered to be related to VN. All three of these events were a transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site, 1-6 days after injection and resolved without sequelae"	These adverse events occurred after the publication data cut-offs of the CSRs, but were described in the submission as they were reported in the SmPC.	The CS repeatedly states that no TEAEs were associated with VN (p. 122, 126, 127) and the ERG consider this new information to be a significant omission. Following this further clarification from the company, we have adjusted the report to reflect this new information. This has required edits to multiple sections of the report where the ERG noted the apparent absence of TEAEs related to VN.

Erratum to:

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Please note that a list of replacement pages with summary of and rationale for corrections is provided below.

Section, page (line) reference (vs original report and issues identified in the company fact check	Summary rationale
Summary, pages 15-21	Page 15 (line 29): Removed "Spark Therapeutics Inc." as this was noted by the company to be incorrect Page 15 (line 28): Clarified that a minority of patients would not be eligible for treatment due to participation in other clinical trials. Page 16 (lines 13-15, & 20-21): Updated wording to align with the marketing authorisation and to highlight that the decision problem was in line with the marketing authorisation. Page 17 (lines 18 & 20): Clarification of wording in respect of the effect of VN on contrast sensitivity; i.e. "change from baseline" and correction to state that the differences at 1 year were "above" the company's defined threshold for clinical significance. Page 17 (line 26): Replaced references to "lux" or "lux units" or "lux levels" with "light levels" as the wording use was inaccurate. Page 18 (lines 2-6): Text was adjusted to correct the adverse events associated with the administration of VN and the tmiepoint at which these were assessed. Page 18 (line 12): Text was adjusted to clarify that all patients were treated in the US Page 19 (line 19): The text was amended to mention the overall good safety profile of VN. Page 20 (lines 30-31): Costs were replaced to include the PAS discount Page 21 (lines 7-8): Text was aligned with the marketing authorisation
Section 2, p.26 (lines 9-10)	Clarified that a minority of patients would not be eligible for treatment due to participation in other clinical trials.

Section, page (line) reference (vs original report and issues identified in the company fact check	Summary rationale
Section 2, p.30 (lines 15-16)	Deleted "however this was not reported in the CS". Nystagmus is discussed several times in the CS.
Section 2, p.32 (lines 12-13)	Sentence "Standard practice for the diagnosis of *RPE65*-mediated IRD was not reported in the company submission." was deleted, and the following sentence was added: "The clinical pathway of care including details of diagnosis is provided in Section 8.2 of the CS."
Section 2, p.36 (lines 6-8)	Added that the restriction in the population is in line with the marketing authorisation, which is the remit of the evaluation.
Section 3, p.39 (Population row)	Clarified that the population included in the submission is narrower than that specified in the NICE scope.
Section 3, p.43 (11-12)	The sentence was unclear and has been amended to provide clarification.
Section 4, p.54 (line 4) and p.55 (lines 24-28)	This sentence has been amended to clarify that all patients in the trial were treated in the US (p.54). In addition, text was amended to clarify that baseline VA was higher in patients treated in Study 301/302 than Study 101/102.
Section4, p.60 (line 6)	Corrected typographical error: "lose" to "low"
Section 4, p.64 (line 31) to	Added ***NEI*** VFQ. The full name of the questionnaire was needed to avoid confusion with the VFQ used in the trial.
Section , p.65 (line17 & line 24)	Corrected typographical error for clarity: "considered" to "consideration" Replaced references to "lux" or "lux units" or "lux levels" with "light
Section 4, p.69	Changed from ***MLMT*** to ***Mobility testing.*** Replaced references to "lux" or "lux units" or "lux levels" with "light levels" as the wording use was inaccurate.
Section 4, p.84 (lines 11-14)	Corrected to: "These changes were ***above*** the company's defined threshold for clinical significance (≥***1*** log unit)." Corrected figure caption (Figure 15): Study 302 Full-Field Light Sensitivity Threshold at ***3*** year***s***
Section 4, p.86 (lines 10-19)	Revised summary of results and conclusions to clarify that FST results did exceed clinical significance thresholds.
Section 4, p.90 (row 15)	Replaced references to "lux" or "lux units" or "lux levels" with "light levels" as the wording use was inaccurate.
Section 4, p.91 (line 17)	Replaced "mean difference" (page 91) and "mean (SD) change from baseline" (page 94) with "mean difference in change from baseline". Clarification was required that these numbers represent the mean difference in change from baseline between the arms, not the mean difference in scores between arms.

Section, page (line) reference (vs original report and issues identified in the company fact check	Summary rationale
Section 4, p.95 (lines 3-5)	Deleted the statement: "patients in the BSC arm could be considered to have experienced a clinically meaningful increase in VN scores in the 1st year of the trial (mean change 0.8 on both patient- and parent-reported scales)." The sentence was not accurate.
Section 4, page 95 (lines 9-12)	Corrected "[redacted]".
Section 4, p.99 (lines 8-9)	Replaced "It was not reported whether the TEAE was considered to be related to the administration of VN" with "which was related to the administration of VN" with "One SAE was reported, which was considered unlikely to be related to the study drug, but that resulted from treatment given for a previous TEAE (intraocular inflammation endophthalmitis), which was considered to be related to the administration procedure." This was also clarified in the ERG comment (p.103)
Section 4, p.103	See response to Section 4 (p99 (lines 8-9)) for context of change and rationale
Section 4, p.109 (line 13)	The CS repeatedly states that no TEAEs were associated with VN (p. 122, 126, 127) and the ERG consider this new information to be a significant omission. Following this further clarification from the company, the report has been adjusted to reflect this new information. This has required edits to multiple sections of the report where the ERG noted the apparent absence of TEAEs related to VN.
Section 5, p.113	Replaced "The population is broader" with "The population is narrower". The original wording was not correct.
Section 5, p.120 (line 7)	Added that the restriction in the population is in line with the marketing authorisation, which is the remit of the evaluation.
Section 5, p.129 (line 12)	Replaced "observed" with "reported". "The natural history study was a non-interventional retrospective chart review so data on deaths were not recorded."
Section 5, p.138 (lines 14-16)	The ERG notes their use of the phrase "will" may be unjust, and so has revised the report to say that this "may" introduce a framing effect, however overall the statement is not considered to be factually inaccurate.
Section 5, page 138-139 (line 32 page 138 to line 1 page 139)	Revised the wording in the statement "the ERG's clinical advisors stated that patients had restrictions imposed by their vision, but in general did not have other health problems" to contextualise the discussion.
Section 5 page 138 (lines 30-32)	The wording in the report has been revised to state "the absolute values derived via the proxy elicitation exercise..." and "the negative value for HS5 (HUI3 analysis)"

Section, page (line) reference (vs original report and issues identified in the company fact check	Summary rationale
Section 5, p.143 (lines 11–12)	The following sentence was deleted: "This study was not identified in the company's systematic literature review, as the review was targeted specifically at *RPE65* mediated vision loss." The Rentz study was captured in the company's systematic review but was excluded.
Section 5, p.178 (bottom two rows of Table 63)	The results presented for *Baseline characteristics derived from RPE65 NHx* were updated per the ERG model.
Section 8, p.185 (line 25)	"…patients with ***hypomorphic alleles giving a later less severe recessive phenotype who may have a different prognosis from the typical patient***.[100] ~~a dominant allele giving rise to a very different phenotype that may have a different prognosis from the typical patient.[101] Similarly, tThere~~ There are ***also*** a subgroup of patients ***with a dominant allele giving rise to a very different phenotype that may have a different prognosis from the typical patient,[101] although these patients are not eligible for VN under its current marketing authorisation***. ~~hypomorphic alleles giving a later less severe recessive phenotype who may have a different prognosis from the typical patient.[100]~~
Section, p. 186 (line 12)	The clinician stated that impact of V~~A~~***N*** on delivery

Summary p. 15-21

1. SUMMARY

1.1 Background

Inherited retinal dystrophies (IRD) are a heterogeneous group of rare diseases caused by germline mutations in more than 260 genes, including the *RPE65* gene. The key outcome of *RPE65*-mediated IRD is inexorable and progressive loss of vision, culminating in near or total blindness, though the rate of deterioration varies considerably between patients. The pathophysiology underlying progressive loss of vision relates to the inability to complete the visual cycle because of deficiencies in the *RPE65* enzyme. Deficiencies in this enzyme arrest the molecular pathways that culminate in transmission of signals to the brain. In addition, the accumulation of toxic precursors in the visual cycle leads to apoptosis, or cell death, in photoreceptor cells. IRD is often diagnosed in infancy and adolescence. Night blindness is a common first symptom, but in infants, the 'oculo-digital sign', or eye poking, is a common presentation, though its association with *RPE65*-mediated IRDs is unclear. *RPE65*-mediated IRD is an autosomal recessive-transmitted disorder, including two related disorders; retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA).

The impact of the condition begins in early life, with impacts on child social development arising from poor visual function. Adults may face decreased employment opportunities arising from challenges in accessing education. IRD also impacts carers and household members through increased caring burden, and is associated with an increased risk of depression among patients and their family members. The ERG noted that while evidence presented for these impacts drew from IRD generally, there was no evidence specific to *RPE65*-mediated IRD.

Diagnosis of *RPE65*-mediated IRD includes medical history and genetic testing. The company estimated that only 50% of people with the disease are currently diagnosed. Care for this condition is at present primarily supportive, and few national or expert guidelines exist. For children, visual aids and magnifiers are recommended, as well as supportive resources in school settings (e.g. specially qualified teachers).

While the ERG noted that the evidence related to incidence and prevalence of the condition is scant and thus any estimate is highly uncertain, the company estimated that the prevalence of IRD mediated by the *RPE65* gene would lead to a population of 86 patients in the UK although a minority of these patients would not be eligible for treatment due to participation in other clinical trials.

Voretigene neparvovec (VN; Luxturna®; Novartis Pharmaceuticals (UK).) is an adeno-associated virus (AAV) gene therapy treatment which introduces a healthy copy of the defective *RPE65* gene into the retinal cells of patients with *RPE65*-mediated IRD. VN is administered as two subretinal injections (no fewer than six days apart) once per lifetime. Prior to administration (approximately 3 day before), patients are required to receive an immunomodulatory regimen (such as prednisone), which is expected to be continued for a further 18 and 30 days, depending on the timing of the second administration (i.e. the other eye). The introduction of *RPE65* enables patients to produce functional *RPE65* protein. The subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells. This enables patients to produce functional *RPE65*, resulting in improved functional vision (improved ability to perform vision-related daily activities) and visual function (improved performance of the eyes at the organ level). In order to derive benefit from VN treatment, the company states that patients must have confirmed biallelic (pertaining to both paternal and maternal alleles) *RPE65* mutations and have sufficient viable retinal cells into which healthy copies of the *RPE65* gene can be introduced.

VN is not currently used in the UK for any patient population. The European Medicines Agency (EMA) awarded VN marketing authorisation on 22 November 2018. VN is expected to be used in line with the marketing authorisation for the treatment of adult and paediatric patients with vision loss due to IRD caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

1.2 Critique of the decision problem submitted by the company

The decision problem included in the company submission broadly adhered to the final NICE scope. The ERG noted that the company restricted the population of patients from those with *RPE65*-mediated IRD to include only those who additionally possessed sufficient viable retinal cells. The ERG regarded that this was clinically justified and was in line with the marketing authorisation for VN. The intervention as specified matched the NICE scope, but the ERG noted that comparators, broadly classes as best supportive care, were not defined in the company submission.

Outcomes presented by the company included the multi-luminance mobility test (MLMT), which was not in the scope but described by the company as a clinically relevant test of functional vision. The MLMT was the primary endpoint of the company's pivotal phase 3 trial. While most other scoped outcomes were reported in the CS, the ERG noted that health-related quality of life data were not collected as part of the phase 3 trial, nor were data reported relating to need for cataract surgery.

Finally, the company used an economic perspective in their evaluation in line with the NICE scope.

1.3 Summary of clinical effectiveness evidence submitted by the company

The company presented a systematic review that included evidence from two trials. The pivotal trial for the submission is Study 301/302; an open-label, multi-centre, phase 3 RCT involving 31 patients (Study 301), followed by an optional phase after one year where 9/10 (90%) patients from the control arm received VN (Study 302). Patients were recruited from multiple countries worldwide, and travelled to sites in the US for treatment administration and follow-up. Study 301/302 is ongoing: data up to and including a four-year follow-up was available for some, though not all, outcomes in this submission. Study 101/102 is an open-label, phase 1, single-arm trial. Study 101 employed a dose-ranging design; with patients receiving either a 'low', 'medium', or 'high' dose of VN in a single (worse, non-preferred) eye. Patients travelled to sites in the US for treatment administration, following which 7/12 (58.3%) were followed up in the US, and 5/12 (41.7%) were followed up in Italy. After a minimum of 1 year, patients from Study 101 were invited to receive VN in the contralateral eye: 11/12 (91.7%) patients from Study 101 were eligible for entry into Study 102. All patients in Study 102 received a 'high' dose of VN in their contralateral (better, preferred) eye.

Primary visual acuity (VA) outcomes in Study 301/302 did not demonstrate a significant difference in changes from baseline to 1 year between VN and BSC (0.16 LogMAR, 95% CI [-0.41, 0.08]; p=0.17). All changes in VA were under the company's definition of a clinically meaningful change (≥0.3 LogMAR). Study 101/102 had similar findings. In contrast, VF improved in VN patients as compared to BSC patients at 1 year in Study 301/302. Improvements in VF were demonstrated by 30 days in the VN arm, and these remained relatively stable until 1 year (assessed by Goldmann III4e, MD 378.7; 95% CI [145.5, 612.0]; post-hoc p = 0.0059). Despite numerical evidence of decline after the 2 year timepoint, clinical advice received by the ERG suggested changes from baseline were clinically meaningful. In Study 301/302, [redacted], but differences at 1 year in photosensitivity were significant and above the company's defined threshold for clinical significance (full-field light sensitivity MD -2.11 log units; 95% CI [-3.91, -1.04]; p=0.0004), which were sustained at 3 years following administration (2 years in the delayed treatment arm). The company also presented evidence for the MLMT, which suggested sharp and sustained improvement after administration in both the VN and BSC (delayed VN) arms through 3 years after administration (2 years in the delayed arm); at 1 year before the BSC arm patients received VN, the mean difference in light units was 2.0 (95% CI [1.14, 2.85]). Finally, patient-reported outcomes including a modified Visual Function Questionnaire (VFQ) were reported for Study 301/302. [redacted] No health-related quality of life nor cataract surgery data were reported.

With regard to common adverse events attributed by the company to administration procedure, in the short term (one year), [redacted]

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG regarded that the quality of methods used to locate the evidence was reasonable, though the use of unconventional search methods meant that there was a small, albeit unlikely, chance that studies may have been missed.

The pivotal phase 3 trial submitted, Study 301/302, generally matched the decision problem. Though all patients in this study were treated in the US, the ERG considered that the setting would generalise to UK practice. Of note is that inclusion and exclusion criteria for Study 301/302 were narrower than included in the NICE scope, given the study's requirement for sufficient viable retinal cells. The ERG considered that this was a clinically relevant consideration. However, the ERG noted that this additional criterion means it likely that there will be some patients included in the population specified in the NICE scope who will be excluded for treatment with VN because they have no viable retina to treat.

The small sample size in Study 301/302 (n=29; following the exclusion of 2 patients following randomisation) introduced uncertainty in the estimation of treatment effect. [redacted] While age differences were noted between the randomised groups at baseline, clinical advice suggested that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population. Retinal function at baseline was suggested to be a potentially stronger mediator of treatment response, which may be partially correlated with age. However, none of the differences at baseline were considered by the ERG to demonstrate a clear bias in any direction, although it was noted that only a small number of characteristics were reported at baseline.

The ERG regarded that outcome assessment was generally appropriate and clinically relevant in this population, and that statistical methods used to analyse outcome data were acceptable. However,

measurement of VA, VF and contrast sensitivity is widely considered to be unreliable, and some imprecision in their measurement should be expected. In addition, the ceiling effect inherent to the MLMT measure may underestimate the treatment effect reported for continuous data. The removal of HRQoL data from the VFQ suggested to the ERG that the VFQ was not an appropriate measure of HRQoL. No HRQoL data, or PRO data for the carers of patients with IRD, was reported in the CS, which the ERG considered to be an important omission. Finally, while the ERG noted that multiple years of follow-up were presented for multiple outcomes, the inconsistency of follow-up duration across outcomes and the small sample size present uncertainties in estimating duration of effect.

The quality of the submitted evidence was acceptable, though the ERG noted Study 301/302 may be at high risk of bias. The ERG agreed substantially with the company's risk of bias assessment for Study 301/302. Study 301/302 did not include blinding of patients and providers given that the use of sham injections was considered unethical. However, quality of methods used for randomisation and the evaluation of the primary endpoint, MLMT, by a blinded rater were strengths of the trial. The ERG did note, however, that the company did not report co-interventions in sufficient detail. The company did not provide quality assessment for Study 101/102, which the ERG undertook. The ERG concluded that the small sample size of the study was a key limitation. Ambiguities in the trial inclusion criteria relating to LCA vs RP meant that the ERG could not draw a conclusion about the applicability of the evidence base across diagnoses.

Overall the evidence indicates a good safety profile. More serious risks associated with subretinal administration of VN and concomitant oral corticosteroid use include endophthalmitis, permanent decline in visual acuity, increased intraocular pressure, retinal abnormalities (e.g., retinal tears or breaks), and cataract development and/or progression. The ERG highlight that these might have long term consequences, especially if they were left untreated. With concomitant use of oral corticosteroid (prednisone) at the time of subretinal injection of VN, the ERG agree that the immune response to AAV capsid and *RPE65* appears mild.

Due to the small patient population included in the trials and indeed the small population with the condition, the representativeness of patients with respect to the UK population of patients with inherited retinal dystrophies is difficult to assess. The ERG regarded that no important groups, by age, ethnicity or sex, were unduly excluded from the relevant trials. The small evidence base presented in the submission is reflective of the rare nature of this condition, but does limit the generalisability of the evidence base beyond the included trials. As there is poor understanding of the characteristics that may impact on disease prognosis and treatment efficacy, it is not possible for the ERG to determine whether the populations of the included trials is consistent with the UK population.

1.5 Summary of value for money evidence submitted by the company

The company submission comprised of a *de novo* cost-effectiveness model constructed to assess the cost-effectiveness of voretigene neparvovec versus best supportive care. The model adopted a Markovian state-transition cohort structure, and comprises of five "alive" health states plus a sixthabsorbing health state representing death. The cost-effectiveness model was constructed in line with the anticipated use of voretigene neparvovec in clinical practice. A lifetime horizon was modelled, and annual discount rates of 3.5% for costs and outcomes were used in the company base case.

The cohort model structure was developed primarily to capture the impact of voretigene neparvovec treatment on health-related quality of life outcomes. Five "alive" health states (based on differing degrees of vision impairment) were used such that different utility values could be assigned to these states. The use of these health states was considered necessary in order to reflect clinically-meaningful differences in health-related quality of life following treatment with VN, and as patients experience progression as part of the natural history of the condition.

Patient transitions from baseline to 1 year were informed by the pivotal Study 301/302, whereas long-term transitions were informed by a combination of clinical expert opinion regarding the long-term effect of voretigene neparvovec and a multistate model fitted to natural history data from the *RPE65* NHx study. Outcomes within the model were based on a combination of visual acuity (VA, clarity of vision) and visual field (VF, range of vision), though the primary endpoint of Study 301/302 was the improvement in the multi-luminance mobility test (MLMT).

Health-state utility values were derived through interviews held with clinicians to complete proxy generic health related quality of life questionnaires for each of the health states in the economic model, based on summary descriptions and their experience with patients. Costs were based on published sources, and were inflated where necessary to reflect the 2018 cost year. The included cost categories considered treatment acquisition, surgery, monitoring, medical resource use, resolution of adverse events, and eligibility testing. Medical resource use utilisation was informed through a combination of assumptions made by the company and input from clinical experts. The company also presented additional analyses to ascertain the impact of treatment beyond costs borne by the NHS and PSS.

In the company's base case analysis, voretigene neparvovec was associated with an incremental cost of [redacted] and a QALY gain of 7.06, leading to an incremental cost-effectiveness ratio of [redacted] (including the proposed simple PAS discount for voretigene neparvovec). The company also presented a range of one-way deterministic and multi-way probabilistic sensitivity analyses, which

illustrated that the key drivers of cost-effectiveness for voretigene neparvovec are the expected long-term outcomes and the quantification of patient health-related quality of life.

1.6 Summary of the ERG's critique of the value for money evidence submitted

The company's submission has been generally developed in accordance with the requirements stipulated within the NICE reference case, and is broadly aligned with the final scope issues by NICE. The company deviated slightly from the final scope to exclude patients without sufficient retinal cells from the economic analysis, which the ERG agreed was appropriate and aligned with the marketing authorisation for voretigene neparvovec and its anticipated use in clinical practice. While the ERG is generally satisfied that the company's model provides a sufficient basis for decision making, the ERG is concerned with a number of assumptions and settings incorporated within the company's submission which have the capacity to lead to substantially different cost-effectiveness estimates.

The cost-effectiveness model structure makes use of a multistate modelling component which the ERG considered to have been unnecessary to inform the estimation of cost-effectiveness within the context of a rare disease. Furthermore, the company's assumed duration of treatment effect for voretigene neparvovec is not considered by the ERG to be robustly supported by the available data from Studies 101/102 and 301/302. The ERG feels that the combined effect of these two features of the company's modelling approach means that the estimation of the long-term effect of voretigene neparvovec is highly uncertain.

Outside of the quantification of longer-term outcomes for patients with *RPE65*-mediated IRD, the estimation of utility values is an incredibly important aspect of the cost-effectiveness model which has the potential to greatly influence cost-effectiveness estimates. A number of methodological issues were identified with the values produced as part of the elicitation exercise, and so the ERG does not consider these utility values to constitute an appropriate basis for decision making.

The ERG also identified a number of other assumptions made in the model that were not clearly supported by the evidence presented. The company assumed vision impairment was associated with increased mortality, though this was based on the findings of a study conducted in elderly patients without *RPE65*-mediated IRD. Medical resource utilisation estimates were also primarily taken from a non-*RPE65*-mediated IRD population, and adjusted based on a number of assumptions relating to relative use between patients with differing extents of vision impairment, and across age groups.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

The company identified what is likely the only other published cost-effectiveness analysis of voretigene neparvovec, conducted by the Institute for Clinical and Economic Review in the United States. The ERG noted some limitations in the company's systematic review that led to the

Section 2, p.26

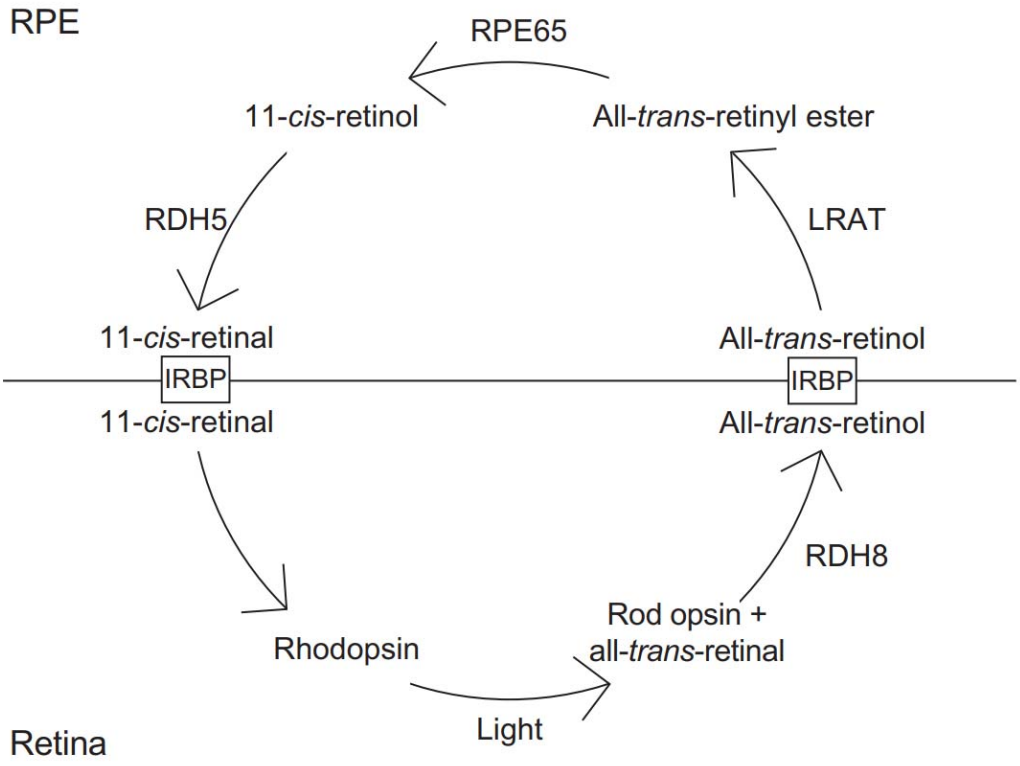
range of values documented in the literature. However, the methods used to arrive at the median values, were unclear.

The CS estimated the prevalence of RPE65-mediated IRD in England to be between 57-564 patients. No references were cited for this data, and the ERG could not find evidence to support these numbers. The incidence of RP was estimated in the CS to be between 0.6 – 1.6 per 100,000 people per year. This evidence was derived from Danish, South Korean and American populations.[7-9] No data was found for the incidence of LCA. The incidence data reported in the CS is consistent with evidence identified by the ERG.

The company estimates that the target patient population for VN in the UK is 86 patients, although it is anticipated that a minority of patients would not be eligible for treatment due to participation in other clinical trials. Their calculations, alongside comments from the ERG, are reported in Table 1.

Section 2, p. 30

Figure 2: The biochemistry of the visual cycle



Source: CS (page 38); original source Wright 2015[21]

Abbreviations: IRBP, interphotoreceptor retinoid-binding protein; LRAT, lecithin retinol acyltransferase; RDH5, retinol dehydrogenase 5; RDH8, retinol dehydrogenase 8; RPE, retinal pigment epithelium; *RPE65*, retinal pigment epithelium 65kDa protein.

2.1.4 Clinical features

The CS reports that individuals with *RPE65*-mediated disease can present at a range of ages between infancy and adolescence. The submission states that nyctalopia (night-blindness) is the first symptom of this disease. The ERG agreed that nyctalopia is typically considered the first symptoms of *RPE65*-mediated IRD,[22] however notes that not all affected patients experience this symptom.[19] The CS reports that infants frequently present with the 'oculo-digital sign' or eye poking. This symptom is a common feature of LCA;[23] however, based on the literature it is unclear how frequently this symptom presents in those with *RPE65*-mediated IRD. Evidence suggests that involuntary eye movement, termed nystagmus, is often observed within this population.[3,19,24]

The CS describes the degenerative nature of the condition and reports that both VF and VA deteriorate over time, accompanied by a loss of retinal sensitivity. It is also stated that there is no Section 2, p. 32

deletion/duplication analyses and/ or other non-sequence based analyses, and is therefore able to detect several of the different types of variants implicated in *RPE65*-mediated IRD.[23]

The CS reports that RPE65 IRD is currently under-diagnosed, with only 50% of people with the disease expected to be diagnosed (CS, p. 42). The company suggest this may be due to the lack of available treatment options undermining the needs for a diagnosis (CS, p.15).

The company note that differentiation of LCA and RP IRD is unreliable, with a minority of patients having received both diagnoses. LCA and RP are typically differentiated by clinical presentation and family history, with LCA presenting earlier and having a more aggressive prognosis (CS, p.36). Clinical experts to the ERG advised that LCA is typically diagnosed shortly after birth, while RP is typically diagnosed in late childhood or early adulthood.

ERG comment:

As discussed in Section 2.1.1, it's unclear whether a 50% diagnosis rate is representative of current practice in the UK; however, the ERG agreed with the company that it is likely that diagnosis rates will increase following the availability of a suitable treatment. The ERG also recognised that diagnosis of the subtypes of LCA and RP IRD may be unreliable. The clinical pathway of care including details of diagnosis is provided in Section 8.2 of the company submission.

2.1.6 Prognosis

The CS discussed the degenerative nature of the disease, which eventually culminates in complete/ near-total blindness.[22] Furthermore, the CS states that there is no evidence of spontaneous sustained improvements in either VA or VF.

The rate at which vision deteriorates in patients with this disease varies considerably, this is briefly acknowledged in the CS. The ERG found evidence which suggests that in some patients vision deteriorates rapidly, while some individuals retain some vision into the second and third decades of life, and others maintain central vision until the end of life.[25-27] Conversely, a cohort study of 70 individuals diagnosed with biallelic *RPE65*-mediated IRD reported that more than half of the cohort were blind by age 18, defined as VA<20/200.[3] This study reported that VA was impaired but stable up until age 15, rapid deterioration was reported between the ages of 15-20, followed by more accelerated deterioration after the age of 20.[3] Overall, this evidence suggests that the prognosis for individuals with *RPE65*-mediated IRD is heterogenous.

Section 2, p. 36

before), patients are required to receive an immunomodulatory regimen (such as prednisone), which is expected to be continued for a further 18 and 30 days, depending on the timing of the second administration (i.e. the other eye).

The European Medicines Agency (EMA) awarded VN marketing authorisation on 22 November 2018.[45] VN is expected to be used in line with the marketing authorisation for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells. Orphan status was maintained at the time of marketing authorisation:[46] the two previous orphan designations for the "treatment of LCA" and "treatment of RP" were merged to "treatment of IRDs".

The introduction of *RPE65* enables patients to produce functional *RPE65* protein. The subretinal injection of VN introduces a healthy copy of the defective *RPE65* gene into retinal cells.[44] This enables patients to produce functional *RPE65*, resulting in improved functional vision (improved ability to perform vision-related daily activities) and visual function (improved performance of the eyes at the organ level). In order to derive benefit from VN treatment, the company states that patients must have confirmed biallelic (pertaining to both paternal and maternal alleles) *RPE65* mutations and have sufficient viable retinal cells into which healthy copies of the *RPE65* gene can be introduced.

ERG comment:

The CS provides a relatively short description of VN. *RPE65* was noted by the clinical experts as crucial in the visual (retinoid) cycle, and is located in the retinal pigment epithelial cells (discussed further in Section 2.1). Successful introduction of a healthy copy of the *RPE65* gene is expected to lead to long-term improvements in visual function (and consequently, functional vision), though it was noted by the ERG's clinical experts that there is currently no evidence to suggest that introduction may stop degeneration entirely or cause regeneration. The ERG's clinical experts also noted the importance of having sufficient retinal cells in order to benefit from VN – some patients with *RPE65*-mediated IRD may have irreversible retinal deterioration and therefore would be highly unlikely to be able to benefit from treatment.

2.4 Current usage in the NHS

Voretigene neparvovec (VN) is not currently used in the UK for any patient population. VN is the first gene therapy to be approved for a retinal disease.

In the CS, the company proposed that treatment is offered to patients with confirmed biallelic *RPE65* mutations with sufficient viable retinal cells (Figure 3). Genetic testing will therefore be required to determine eligibility for treatment. In the clinical trials of VN, patients were deemed to have sufficient

Section 3, p. 39

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Introduction

The objective of this section is to critique to what extent the CS adheres to the final NICE scope. The scope aimed to evaluate the benefits and costs of VN within its marketing authorisation for treating inherited retinal dystrophies caused by *RPE65* gene mutation. The critique will consider the intervention, population, comparators, outcomes, nature of the condition, impact of the new technology and the cost to the NHS and Personal Social Services (PSS) addressed in the CS.

3.2 Adherence to the decision problem

Table 2 presents a summary of the decision problem as set out in the NICE and some comments from the ERG considering the CS.

Table 2: Adherence of the CS to the decision problem

	Final Scope	**Deviation of CS from final scope**
Population	People with inherited retinal dystrophies caused by *RPE65* mutations	The population is narrower than specified in the scope, but is in line with the licensed indication; i.e. Adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells
Intervention	Voretigene neparvovec	The intervention is in line with scope
Comparator(s)	Best supportive care	The comparator is in line with scope
Outcomes	• Best corrected visual acuity (both eyes) • Visual field • Contrast sensitivity • Photosensitivity • Need for cataract surgery • Adverse effects of treatment • Health-related quality of life (for patients and carers)	The outcomes assessed are broadly in line with the scope. Of note, the multi-luminance mobility test (MLMT) is also considered as an outcome measure in the CS. This outcome is the primary measure considered in the pivotal clinical trial. The ERG also noted that data for contrast sensitivity and the need of cataract surgery were not reported in the CS; and no health-related quality of life data was presented. No data for the impact of treatment on carers was presented.

	Final Scope	Deviation of CS from final scope
Subgroups to be considered	None specified	Not applicable
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of	The nature of the condition is broadly in line with scope. However, the ERG noted the

Section 3, p. 43

ERG Comment:

In summary, given the population for which evidence has been submitted, the ERG and its clinical advisors agreed with the company that BSC is the most relevant comparator in the setting of IRDs caused by *RPE65* gene mutations.

3.6 Outcomes

The company state that no treatments are currently available for *RPE65*-mediated IRD, and therefore no precedents exist for endpoints to assess the therapeutic benefits of products for this unique group of diseases. The measurement of visual acuity (VA), VF and contrast sensitivity are generally well accepted as the best visual predictors of mobility performance. For people with low vision, orientation and mobility are more affected by spatial contrast sensitivity and VF than by VA, although these parameters vary widely. The measurement of VA, VF and contrast sensitivity is clinically relevant in the population for this assessment, and is consistent with the evaluation of visual impairment across other populations. However, these endpoints are challenging to measure in the population considered in this assessment because baseline visual function is poor, and they do not capture characteristic features of the condition; e.g., night blindness, reduced light sensitivity, and nystagmus. These measures are also difficult to use in paediatric populations.

In context of these condition-specific features the company designed and validated the multi-luminance mobility test (MLMT).[47] The MLMT measures changes in functional vision, as assessed by the ability of a subject to navigate a course accurately at a reasonable pace at different levels of environmental illumination. Change in MLMT from baseline to one year was the primary endpoint of the company's pivotal Phase 3 clinical trial (Study 301/302). Although the ERG noted that these data are not used in the economic model.

The ERG noted that no data was reported for the need of cataract surgery following treatment. Safety data indicate that patients receiving VN are at a higher risk of cataracts, and the proportion of patients who would require cataract surgery was estimated in the company's economic model, although the basis for this estimation is unknown.

Finally, no health-related quality of life (HRQoL) was reported in the CS. Rather, the company present the impact of treatment with VN on visual function using a patient-reported outcome (PRO). However, this evidence does not capture the possible impact of treatment on the broader HRQoL of

patients. Further, no evidence was presented on the impact of treatment on the carers of patients with *RPE65* IRD.

Section 4, p. 54-55

impact on the sight of patients with biallelic *RPE65* IRD. This can evidently not be demonstrated from the current treatment follow-up; however the ERG judged that a four year follow-up is acceptable for determining whether VN may result in some clinical benefit for patients.

Treatment was administered at centres in the US, however feedback from clinical experts for the ERG was that the settings of the evidence base can be generalised to UK practice.

4.2.2.2 Population

The key inclusion and exclusion criteria reported in the CS for both studies are summarised below in Table 9.

The ERG noted that the population characteristics used in the included trials for the technology of interest (VN) and best supportive care (BSC) were consistent with licensing authorisation; i.e. adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations who have sufficient viable retinal cells. The ERG noted that the population characteristics included in all three studies were narrower than those specified in the NICE scope for this appraisal; however, the ERG judged the change to be appropriate. Expert advisors to the ERG suggested that the requirement for patients to have a sufficient number of viable retinal cells is necessary to facilitate the treatment mechanism of VN. The ERG noted that patients are excluded from the included trials if they have a retina less than 100 microns (equivalent to more than half of a normal retina's thickness). Expert advisors to the ERG acknowledged that while 100 microns seems to be an arbitrary number (and apparently being used as a proxy for the health of the photoreceptors), if VN is injected into a retina with thickness of less than 100 microns, it seems reasonable to assume that there would be fewer viable retinal cells and hence improvements would be less likely. Given the localised action of gene therapy, and the need for safe administration of VN to sufficient retinal cells to ensure there are grounds for improvement, the ERG agreed that it seems reasonable to limit the trial population to people with retina thickness of more than 100 microns at the site of injection. However, the ERG noted that this additional criterion would mean it likely that some patients included in the population specified in the NICE scope would be excluded for treatment with VN because they have no viable retina to treat. In practice, it's unclear whether this threshold of retinal thickness would be strictly used: the company state (CS, p.54) that they expect OCT tests in practice to be more qualitative, and to be supplemented by tests of VA and VF. Clinical advisors to the ERG suggested that this may result in a similar population identified for treatment, as patients who demonstrate visual function using VA and/or VF tests may be assumed to have sufficient retinal cells to experience some treatment benefit.

The ERG also noted that population inclusion criteria for Studies 101/102 and 301/302, as described in the CS and trial CSRs, specify the inclusion of patients with a specific subtype of *RPE65* related IRD, Leber's congenital amaurosis (LCA). However a footnote to the inclusion criteria (CS Table 9, p. 71-74; CS Table 11, p. 84-87) adds that patients were eligible if they had a "molecular diagnosis (or confirmation of diagnosis) of biallelic *RPE65* mutations… regardless of clinical diagnosis". This presumably permits the inclusion of patients with RP IRD. However if this is the case, the ERG are unclear why trial inclusion criteria primarily specify patients with LCA only, and whether this means that patients with LCA were favoured in recruitment strategies for the trials, or constituted a higher proportion of patients in the trial samples. The CS did not provide a breakdown of the proportion of patients diagnosed with LCA vs. RP IRD, and the ERG were unable to find this information in the respective CSRs. While the ERG acknowledge some overlap in the diagnostic criteria for RP and LCA, typically patients with LCA are rarer and exhibit a more aggressive prognosis.[65] Clinical advisors to the ERG were unaware of evidence that would prevent generalising evidence from patients with LCA to those with RP, and suggested that the treatment effect is likely to be unaffected by diagnosis. However, the ERG noted that absolute data (such as the speed of visual deterioration) may not be comparable between LCA and RP patients. Nevertheless, as it is not clear from the CS whether trial samples involved a greater proportion of LCA patients, it is not possible to draw a conclusion about whether this could affect the applicability of the evidence base.

Patient populations and eligibility criteria were broadly similar between the Phase 1 and Phase 3 trials, although three changes in inclusion criteria for Study 301/302 are notable. Firstly, trial inclusion criteria for Study 301/302 was extended to include younger children between the ages of 3 and 7 years. Age is thought to influence the potential treatment effect of VN, due to the potential benefits of administering VN prior to further retinal degeneration. Criteria for Study 301 were further restricted to include those with less severe deficits in VA (from VA of 20/160 in Study 101/102 to 20/60 in Study 301/302). Baseline VA was not reported in the CS for Study 101/102, although at clarification the company provided mean baseline VA for Study 101 (no variability data was provided), which suggested that baseline VA was better for patients in Study 301/302. Clinical experts to the ERG advised that both age and baseline VA may have an impact on treatment outcome, and therefore differences may be expected in the treatment outcome between Study 101/102 and Study 301/302; although the direction and magnitude of any difference is not yet understood. Ultimately as Study 101/102 is under-powered to evaluate clinical effectiveness of VN and is non-comparative in design, emphasis on clinical efficacy outcomes should be given to data from Study 301/302.

Changes in eligibility criteria were included for patients in Study 102 following their participation in Study 101; these were intended to ensure that patients had VA equal to or greater than light perception

Section 4, p. 60

Study 101/102

Population characteristics for patients in Study 101/102, as reported in the CS, are summarised in Table 12.

As expected for the low sample size within each dosing arm,

[redacted]. There is an absence of evidence for the role of gender in treatment prognosis for this patient group, however as noted above, clinical advisors to the ERG advised that age at baseline may impact on the likely treatment effect, with treatment at a younger age being potentially more beneficial. Baseline visual performance was not reported in the CS, although consistent with procedures for favouring the worst, non-preferred eye for injection in Study 101,

[redacted] (Study 101 CSR, p. 59).

Table 12: Study 101/102 Patient Demographics (all patients)

[redacted]		[redacted]				
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7 (58%)	6 (55%)
	[redacted]	[redacted]	[redacted]	[redacted]	5 (42%)	5 (46%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11 (92%)	10 (91%)
	[redacted]	[redacted]	[redacted]	[redacted]	1 (8%)	1 (9%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20.8 (11.2)	22.8 (10.26)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR, Appendix 6, Table 1

ERG Comment:

There are several differences in population characteristics between the VN and BSC arms in Study 301. Given the small size of the trial, the ERG considered a number of differences between arms to be inevitable and to not necessarily represent a violation in randomisation. None of the differences at

baseline were considered by the ERG to demonstrate a clear bias in any direction, although it was noted that only a small number of characteristics were reported at baseline.

Section 4, p. 64-65

The ITT population (all patients randomised) was stated to be prioritised for clinical outcomes, while the mITT/safety population (excluding 2 patients who dropped out of the study prior to knowing treatment allocation) is reported for AE data and for some outcomes, which was judged by the ERG to be appropriate.

Several limitations in outcome assessment were noted as important. Firstly, while randomisation was stratified by age (</≥ 10 years), it was not feasible for the company to adjust outcome data for baseline characteristics, due to the small sample size of both trials. It is unclear how this limitation may impact on the treatment outcome; based on the limited data provided and the evidence known about prognostic markers in this population, there is no consistent pattern in either amplifying or reducing the potential treatment effect.

Secondly, as noted in the CS, scoring for the MLMT exhibits a ceiling effect inherent to the design of the task. As the test does not allow for testing at light levels lower than 1 lux (equivalent to a moonless summer night or an indoor night light; CS p. 78), change scores will be capped at this light setting. The ERG agreed with the company's assertion that this may underestimate the mean change in patient scores on the test, which may result in an underestimation of the treatment effect. This will be applicable to continuous data only (mean final/change scores), but will not impact on the proportion of patients who achieved a change greater than 1 light level, which is also reported in the CS, as all patients were at least 1 light level away from the ceiling at baseline.

Thirdly, while VA and VF are the only two outcome measures that have been used successfully to approve new drugs for retinal application, there are known limitations with the reliability of their measurement. Natural variability in VA between assessments means that obtaining a representative estimate may require multiple tests. In Study 301/302, VA was assessed as the average BCVA of each eye (rather than bilaterally). The company state that this may underestimate the clinically useful vision that is achieved with both eyes open (CS, p. 136). Further, many patients with IRD have such poor vision or fixation that VF testing cannot be performed reliably; while VF testing is clinically relevant as a loss of visual field is a key and early symptom of the condition, this very feature can lead to indeterminate test results (CS, p. 82), and is likely only possible in children over 7 or 8 years of age. Further, it should be noted that available measures of contrast sensitivity rely on knowledge of the alphabet, and are therefore not suitable for use in children unable to recognise letters.

Fourthly, the ERG do not consider the VFQ to be an appropriate replacement for a measure of HRQoL. The NEI VFQ, which has been used extensively to evaluate vision-related functioning in patients with age-related macular degeneration, and demonstrates good reliability and construct

validity,[66] was modified for use in Study 301/302. The CS does not report details about the way in which the measure was modified, however a report of the psychometric properties of the measure provided by the company describes the modifications as 'substantial' (p.10).[67] These modifications are stated to have been made to better assess functional vision in patients with *RPE65* IRD, and clinical advisors to the ERG advised that the modifications were appropriate. Psychometric data for the tool also indicates that it demonstrates good reliability and validity. However, the ERG noted that in this process items related to HRQoL were removed from the tool, and therefore this outcome is considered by the ERG to be appropriate for evaluating visual function in this patient population, but cannot be used to evaluate HRQoL.

Finally, it should be noted that the objective of Study 101/102 was to evaluate the safety of VN, and while clinical efficacy endpoints were evaluated (including VA, VF, FST, contrast sensitivity, and mobility assessment), the study was not powered to evaluate change in these outcomes.

ERG Comment:

The measurement of VA, VF, and contrast sensitivity was clinically relevant in this patient population, and is consistent with evaluation of visual impairment across other populations. However, their measurement is widely considered to be unreliable, due to inter-test variability in this population requiring greater improvements from baseline to demonstrate a treatment benefit. MIDs for these outcomes are derived in consideration of inter-test variability.

The ERG agreed that the ceiling effect inherent to the MLMT measure may underestimate the treatment effect reported for continuous data. The ERG considered this to be an important outcome for evaluating the impact of visual impairment on functioning; however a clinical advisor to the ERG suggested that the current scoring (change in the light level under which patients could complete the course) may be less sensitive to assessing functional vision than a change in the time it takes patients to complete. The ERG also considered there to be uncertainty in the validity of the company's threshold for a clinically meaningful change (1 light level).

The modified VFQ should be considered an appropriate measure of functional vision in these patients, and has acceptable psychometric properties. However, items related to HRQoL from the original tool were removed, and the ERG did not consider this measure to measure HRQoL following treatment with VN. No HRQoL data, or PRO data to evaluate the burden of *RPE65*-mediated IRD for carers, was reported in the CS, which the ERG considered to be an important omission.

Section 4, p. 69

Endpoint		**Study 101**	**Study 102**	Study 301/302
	Statistical methods	Change in full-field light sensitivity before and after injection FST data were not available for all patients/timepoints as the equipment was not available at the start of the trial (CS, p. 116). Missing values were treated as missing without any imputation	Change in FST following injection to the contralateral eye evaluated using pre-injection, follow-on baseline evaluations as a control.	Change in white light FST averaged over both eyes at year 1 relative to baseline
	Analysis population	PP	ITT	ITT and mITT
Mobility testing	**Definition**	Subject's ability to navigate a short obstacle course with both eyes open (except for some cases where either the injected eye or the uninjected eye was occluded) and varying light levels. Lower scores = better performance Change ≥1 light levels indicates a clinically meaningful improvement	Subject's ability to navigate a short obstacle course with both eyes open and varying light levels. Lower scores = better performance Change ≥1 light levels indicates a clinically meaningful improvement	Subject's ability to navigate a short obstacle course with both eyes open. Lower scores = better performance Change ≥1 light levels indicates a clinically meaningful improvement
	Time-points outcome reported	N/A	Baseline, d60, d90, yr1, yr2, yr3 and yr4	Baseline, d30, d90, d180, yr1, yr2, yr3 and yr4
	Statistical methods	ITT population Monocular assessment: evaluated in first treated eye.	ITT population. Monocular and bilateral assessment. Change in MLMT following injection to the contralateral eye evaluated using	ITT [primary] and mITT [secondary] Monocular and bilateral assessment. Change in bilateral mobility test performance relative to baseline.

			pre-injection, follow-on baseline evaluations as a control	Bilateral performance on the MT as measured by a change score.

Section, p. 84

No data were reported in the CS with regards to contrast sensitivity for patients in Study 101/102.

ERG comment:

[redacted]

4.2.3.1.4 Photosensitivity

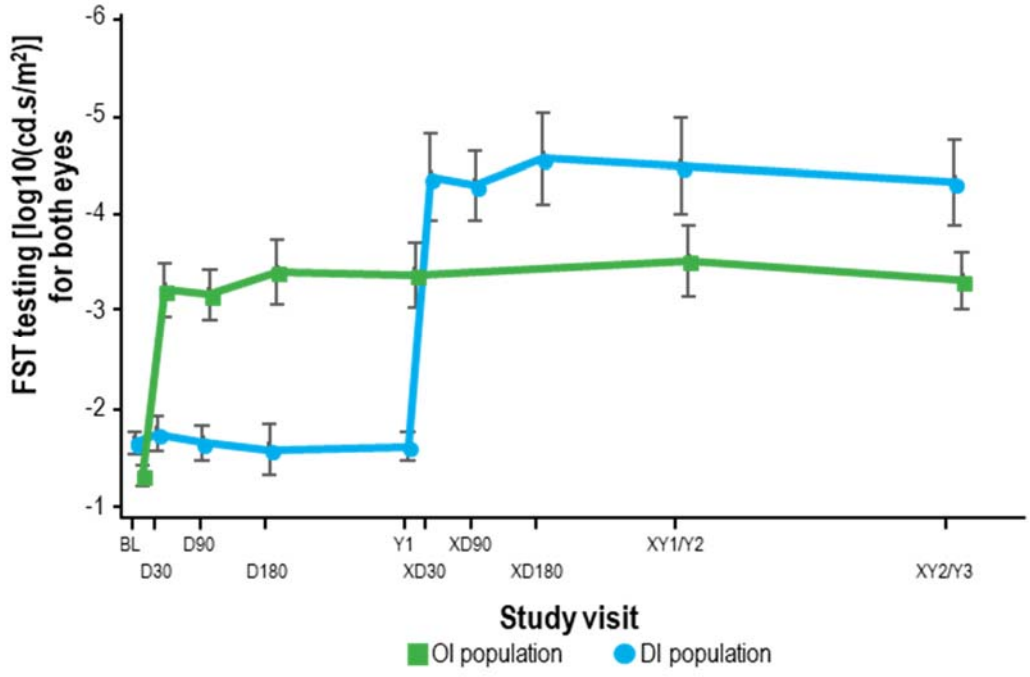
Details of the measurement of photosensitivity in the included trials is summarised in Section 4.2.2.4.

Study 301/302

A statistically significant difference in full-field light sensitivity (FST) threshold was reported at 1 year (MD -2.11 log units; 95%CI -3.91, -1.04; p=0.0004; ITT population). Patients in the VN arm exhibited a mean improvement in FST of -2.08 (SE 0.29), while no change was exhibited by patients receiving BSC (mean change 0.04; SE 0.44).

At 3-year follow- up, the effect of VN on FST was maintained in the original intervention arm (mean change -2.04; SD 1.43; N=19), as well as in those who crossed over from the BSC arm (mean change -2.69; SD 4.41; N=9; see Figure 15). These changes were above the company's defined threshold for clinical significance (≥1 log unit).

Figure 15: Study 302 Full-Field Light Sensitivity Threshold at 3 years



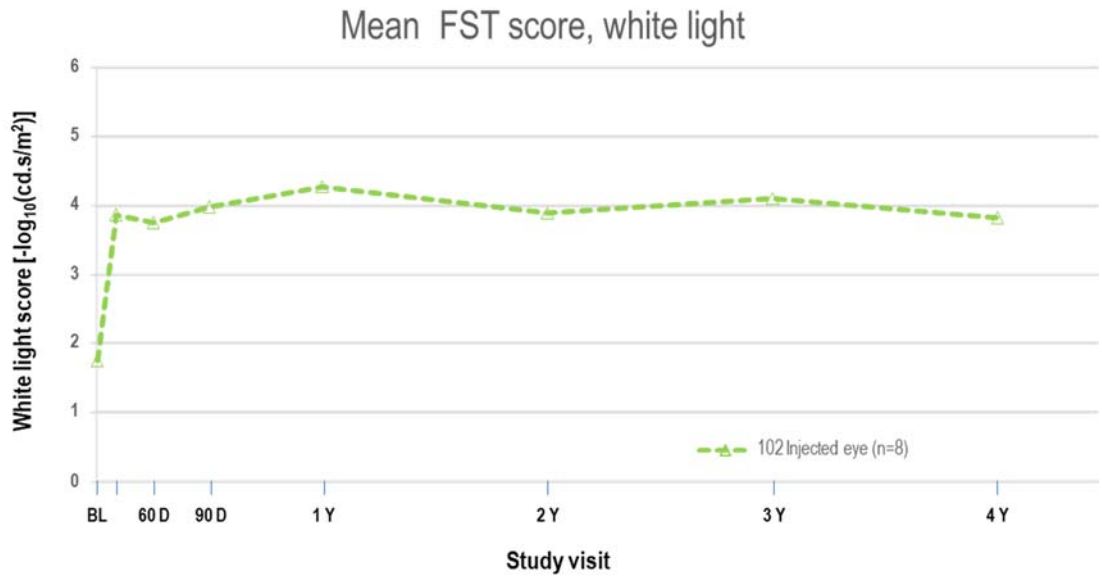
Abbreviations: DI, delayed intervention; OI, original intervention

Error bars represent standard errors

Section 4, p. 86

Eyes in Study 102 were better functioning at baseline, and all received a high dose of VN. The company provide a graph (Figure 17), which appears to show an improvement in FST from baseline, which is then maintained at four years (N=8).

Figure 17: Study 102 FST Mean Score for Eyes injected at 4 years



Abbreviations: FST, full-field light sensitivity threshold

Source: Maguire 2017[49]

ERG Comment:

The evidence from Study 301 suggests that VN has a small, statistically significant effect on FST at 1 year, which was above the company's threshold for a clinically meaningful difference (3.90 dB; Roman et al, 2005).[72] While the effect was seen consistently across follow-up, wide error bars around the effect were noted. No further data for FST is reported for study 301/302, and therefore it is not possible for the ERG to determine if the effect was maintained, or altered, after 1 year.

Evidence from Study 101 indicates a possible numerical improvement in FST following VN, which was shown consistently across follow-up, but again below the threshold for a clinically meaningful difference. A large effect on FST was reported in Study 102, however only 8 patients were included, and no variation data was reported.

Section 4, p. 90-91

[redacted]

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

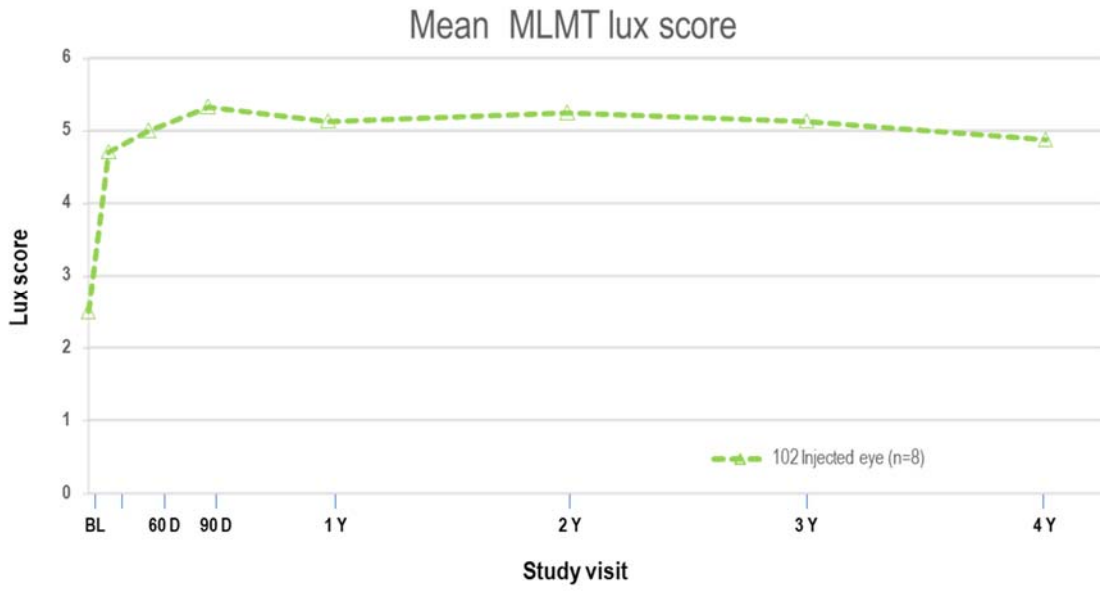
Source: Trial CSR,[59] p. 27

At clarification, the ERG requested if the company had found a difference in treatment effect between children (<18 years) and adult (≥18 years) patients. [redacted]

Study 101/102

In Study 102, 8/11 (72.7%) patients were evaluated using a mobility test (which subsequently became the MLMT). The CS reports that all 8 patients demonstrated a clinically significant improvement of ≥1 light level with their second (better, preferred) eye, and 5/8 (63%) patients passed the MLMT at the lowest level (1 lux). This data is presented in Figure 20 below. This figure demonstrates a sharp improvement in mean MLMT following administration of VN, which is maintained until follow-up at 4 years. Mean change in MLMT score was 2.6 (SD 0.56) at 1 year follow-up, and 2.4 (SD 0.46). These 8 patients were all stated to meet inclusion criteria for Study 301/302.

Figure 20: Study 102 MLMT Mean Score at 4 years



Abbreviations: MLMT, multi-luminance mobility test

Source: Maguire 2017[49]

ERG Comment:

The evidence from Study 301/302 indicates that treatment with VN was associated with a statistically significant improvement in MLMT, which is clinically significant according to the company's chosen clinically meaningful threshold (change ≥1 light level). Based on this threshold, all patients who received VN in the included trials exhibited a clinically meaningful change in MLMT score. This improvement was also shown to be maintained until follow-up at 4 years (3 years in delayed arm).

4.2.3.2 Patient-Reported Outcomes/Health-Related Quality of Life

Details of the measurement of visual function in the included trials is summarised in Section 4.2.2.4.

Study 301/302

Mean scores for the modified Visual Function Questionnaire (VFQ) at 1 year are presented in [redacted]

Section 4, p.95

It is interesting that – according to the distribution method of deriving MIDs[67] – [redacted] Clinical advisors to the ERG advised that patients are likely to adapt to their surroundings over time, which may explain a proportion of the change in HRQoL in both arms. [redacted] .However [redacted]

As with several of the other outcomes included here, evidence for the impact of VN on VFQ scores is based on one small RCT only, with no follow-up data. [redacted]

Finally, the ERG noted that the absence of HRQoL data in the trial adds an additional uncertainty to the economic evaluation. This is explored in depth in Section 5.2.7 below.

4.2.3.3 Safety data

The CS reports that no deaths were reported in any of the included trials. Safety data was reported as treatment-emergent AEs (TEAEs; Section 4.2.3.3.1); serious AEs (SAEs; Section 4.2.3.3.2); drug-related AEs (Section 4.2.3.3.3) and administration-related AEs (Section 4.2.3.3.4).

Details of the measurement of adverse events in the included trials is available here.

4.2.3.3.1 Treatment-emergent adverse events

The company did not report their definition of TEAE in the CS; however the ERG assumed that a general definition of TEAE was used, i.e. any AE occurring following administration of treatment, irrespective of the frequency or whether this was deemed to be related to the study drug. A breakdown of TEAEs according to whether these were deemed to be SAEs, drug- or administration-related is provided in Sections 4.2.3.3.2 and 4.2.3.3.4.

Section 4, p. 99

[redacted] was recorded in Study 101, [redacted]

Study 102

[redacted]

4.2.3.3.3 Drug-related adverse events

The CS reports that [redacted]

4.2.3.3.4 Administration procedure-related adverse events

Study 301/302

The proportion of administration-related AEs were not reported separately for patients in Study 302; i.e. the first year after treatment for patients in the Original VN arm of Study 301. These AEs are incorporated into follow-up data for Study 102.

The company provides a summary table of administration procedure-related TEAEs reported by patients in Study 301/302 from baseline to final follow-up ([redacted]). In total, [redacted] patients receiving VN exhibited a total of [redacted] that were considered by the company to be related to the administration procedure: [redacted] patients in the Original arm and [redacted] in the Delayed arm. In total, [redacted] patients experienced an eye disorder related to administration:

[redacted]

[redacted] although the company's criteria for determining this was not reported.

Section 4, p. 103

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: CS Table 23, p. 126

ERG Comment:

Overall, the evidence indicates that VN is associated with an acceptable safety profile. No deaths were recorded during the trials, and no serious AEs were thought to be related to VN itself. The company reported that 7.3% of patients experienced a non-serious, transient AE related to VN, which did not require treatment. The administration of VN, however, is associated [redacted]

4.2.4 Meta-analysis

Only 1 comparative study (Study 301/302)[61] has been conducted to evaluate the relative effectiveness of VN to treat IRD. As such, no meta-analysis of clinical effectiveness was provided, or expected.

4.2.5 Quality assessment of the included evidence

The company conducted quality assessment of Study 301/302; quality assessment judgements reported by the company are reported in Table 25, alongside ERG comments. No quality assessment was reported for Study 101/102, but was conducted by the ERG (Table 26).

Table 25: Study 301/302 Quality Appraisal

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
Was randomisation carried out appropriately?	Yes	A randomisation list was generated under the direction of the independent party biostatistician using a	Yes	The ERG agree that there is a low risk of selection bias associated with the randomisation procedure.

Study question	Company response (yes/no/not clear/ N/A)	Company description of how the question is addressed in the study	ERG response (yes/no/not clear/N/A)	ERG comments
		permuted block design, stratified by age (<10 years and ≥ 10 years) and baseline mobility testing passing level.		Randomisation was determined by order of enrolment, verification of study eligibility, and the participants' randomisation stratum.

Section 4, p.109

unreliable due to natural variations in visual function between tests. Nevertheless, there is some uncertainty over the validity of MIDs for both the MLMT and the modified-VFQ; both are new outcomes with limited validation. Furthermore, as no HRQoL data was reported, it is not possible for the ERG to conclude on whether improvements in visual function translate to broader improvements in patients' HRQoL.

The ERG noted that numerical improvements in visual function were exhibited by patients receiving VN; including VF, VA, FST, and [redacted]. These improvements exceeded MIDs for VF and FST. While improvements in VA and [redacted], these were nevertheless demonstrated consistently across follow-up timepoints, suggesting a potential minor effect of VN on these outcomes, beyond the natural variation that would be expected in these outcomes.

The evidence suggests that VN demonstrates an acceptable safety profile. No SAEs were considered to be due to VN, and no deaths were recorded in the included trials. The administration of VN is associated with [redacted]; [redacted]. However, as per the current license for VN, these risks would be limited to a single administration.

4.4.1 Key areas of uncertainty

The ERG noted that a small sample of patients available at later follow-up for Study 301 exhibit [redacted]; however the potential of VN for longer-term gains in visual performance and function remains unclear until longer follow-up data is available.

The small evidence base presented in the submission is reflective of the rare nature of this condition, but does limit the generalisability of the evidence base beyond the included trials. As there is poor understanding of the characteristics that may impact on disease prognosis and treatment efficacy, it is not possible for the ERG to determine whether the populations of the included trials are consistent with the UK population.

[redacted]

Section 5, p.113

The CS does not contain a clear summary of the findings of the review (including how the ICER study may have helped inform the cost-effectiveness model submitted to inform this appraisal). In clarification, the company provided the table of excluded studies for this systematic review. This is clearly presented with most studies being excluded on publication type, population or outcome. The company also provided the tables of excluded studies for the resources and health utilities reviews (almost all were excluded on outcome).

While not necessarily a summary of the findings of the review, the CS provides a comparison of outcomes between the company model and the study identified by the literature review, as well as where assumptions and/or analytical methods differed. Discussion of the identified cost-effectiveness study is presented in Section 11.2 of the CS (p. 158-159).

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 28: NICE reference case checklist

Element of health technology assessment	Comments with reference to the scope	Issues arising	Section providing details
Defining the decision problem	The company's description of the decision problem builds on the scope definition. The population is narrower than specified in the scope, but is in line with the licensed indication.	None.	**3.2 & 5.2.3**
Comparator(s)	The comparator described in the CS is BSC, which is in accordance with the final scope.	A formal definition for BSC is not provided. VN in the cost-effectiveness analysis might be equivalent to VN+BSC.	**5.2.4**
Perspective on outcomes	The list of the outcomes in the CS includes all those listed in the final scope, as well as MLMT, the primary measure in the pivotal clinical trial. Some of these, including MLMT, are not used in the economic evaluation due to a lack of related cost and utility data. Health states in the economic evaluation are defined by VA and VF.	It is written in section 9.4.1.1.1 of the CS that VA and VF do not capture all of the features of the condition, and hence some direct health effects may not be accounted for in the economic evaluation.	**3.6 & 5.2.2**
Perspective on costs	The company consider costs from the perspective of the NHS and PSS.	None.	**5.2.5**
Type of economic evaluation	A cost-utility analysis with outcomes reported as ICERs in cost per QALY gained.	None.	**5.2.2**

Element of health technology assessment	Comments with reference to the scope	Issues arising	Section providing details
Time horizon	A lifetime horizon has been adopted, which means that patients have been followed until maximum age of 100 years.	None.	**5.2.5**

Section 5, p.120

ERG Comment:

The ERG was generally satisfied that the cost-effectiveness model reflects the patient population specified within the final NICE scope, which is aligned with the 301/302 study and the European Marketing Authorisation. The ERG acknowledged that studies of rare diseases are often fraught with issues relating to sample sizes, generalisability and non-standard clinical study design. The decision to deviate from the scope in regards to the population of patients with insufficient retinal cells is consistent with the marketing authorisation for VN, and is aligned with the expected use of VN in clinical practice.

Clinical expert opinion sought by the ERG confirmed that it was appropriate for the two conditions (RP and LCA) to be grouped for the purpose of assessing the clinical- and cost-effectiveness of VN. However, it should be noted that only patients with LCA were enrolled within the clinical studies of VN, and therefore there is no clinical evidence pertaining to the use of VN in an RP-specific population.

Within the company's cost-effectiveness model, the distribution of patients at baseline by health state is based upon the pooled estimate across both treatment arms of Study 301/302. Due to the small sample size, the proportions of patients within each treatment arm differ to the pooled estimate (as shown in Table 31). Furthermore, the natural history study (*RPE65* NHx) comprises of a less severe population (87% of patients reside within HS1 or HS2 at baseline, versus approximately 55% of the ITT population within Study 301/302 [based on Table 31 and Table 32]).

The ERG noted that a total of n=70 patients were considered "eligible" in the *RPE65* NHx study. However, in Table 32 the total number of patients sums to 68. Further to this, within Section 12.1.8.3.3 of the CS, it is stated that *"67 patients were included in the analysis"*. The ERG requested clarity from the company regarding the baseline characteristics of patients in the *RPE65* NHx study, and were referred to the original study report which unfortunately does not provide information regarding health state allocation, or specific reasons why some patients may have been excluded.

For the purpose of the ERG report, a total of n=68 patients are assumed to be relevant to the analysis (based on the outputted log file from the statistical analysis discussed in Section 5.2.6).

The differences in characteristics between treatment arms extends to the average age of the cohort. The mean age for patients treated with VN is 14.8 years, versus 15.9 years for patients receiving BSC.

Clinical advice provided to the ERG suggested that treatment may be given at any age, and that there is no clear relationship between outcomes and age within an *RPE65*-mediated IRD population.

Within NICE HST7 (strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency, a different gene therapy),[79] it was stated that *"age is a factor that may*

Section 5, p.129

> *"A multistate survival model allows for the risk of moving between health states to vary over time, as may be expected in clinical practice. Multiple alternative survival distributions can be tested to determine the most plausible extrapolation of observed data, including the assumption of constant risk (i.e. the exponential distribution). In addition, by parameterising the risks of moving between health states, this approach allows for parameters determining the long-term health state distribution to be tested in univariate and probabilistic sensitivity analysis."* (CS, Section 12.1.8.3.2, page 185)

In line with clinical expert opinion, the company specified the MSM as *"progressive only"*, such that the only permitted transitions were those to "poorer" health states (i.e. it was not possible for patients to experience an improvement in health state beyond Year 1). The company also highlighted that the implementation of a progressive only MSM is less complex to implement within the cost-effectiveness model (versus an unrestricted MSM). Transitions to the "dead" health state were not captured by the MSM, as no death events were reported within the *RPE65* NHx study.

A parametric multistate (five state) Markov MSM was fitted by the company. Within the context of the MSM approach, the Markov assumption implies that the probability of movement to another state is independent of the time spent in the current state, instead the probability of movement to another state is dependent on the time since model entry. The ERG noted that it is important to flag that the Markov assumption within the context of an MSM differs to the traditional definition used to describe a Markov cost-effectiveness model wherein transitions may be considered Markovian (memoryless) if they are independent of time, such as in the case of an exponential distribution.

The company fitted the MSM using the Stata software package *MULTISTATE*.[82] The company successfully fitted a total of 5 MSMs, based on the following statistical distributions: exponential, Weibull, Gompertz, log-logistic, and log-normal. A generalised gamma MSM was also attempted, though the company noted that this model did not converge. The MSM fits were specified assuming proportionality between baseline hazard functions and the transition intensities within the same distributional model.

The statistical fits of the models were compared using Akaike and Bayesian information criteria (AIC and BIC, respectively), in addition to an analysis of Cox-Snell residual plots. The ERG requested further information regarding the Cox-Snell residual plots provided within the CS at clarification stage. The company provided some data used to inform the Cox-Snell residual plots, but did not provide as explanation as to what exactly they were intended to illustrate.

The Weibull MSM was selected to inform the company's base case, and was selected according to both statistical fit (lowest AIC and BIC) and "*visual inspection*". To illustrate the base-case projections of the MSM component of the model, a plot is presented in Figure 25 which shows

Section 5, p.138-139

ERG Comment:

The lack of patient-reported values for patients treated with VN is a key limitation of the evidence base provided by the company, and introduces considerable uncertainty to the economic evaluation. This uncertainty relates to both the ERG's assessment of the clinical-effectiveness of VN, as the impact of treatment on patient HRQoL is unclear due to the lack of a validated patient-reported outcome measure, and in terms of the economic evaluation, as it is unclear which utility values are the most appropriate for use.

The proxy elicitation exercise that was conducted by the company suffers from severe methodological and face validity issues, as well as being subject to a number of biases. These include the use of proxies (clinicians in this case) for patient values, which have been seen in multiple instances to be a poor surrogate of patient values, and the questions being asked over the telephone by researchers, as opposed to completed by the clinicians without interaction. Methodologically, the ERG is concerned that as clinicians will be focused primarily on vision-related issues faced by patients (the health state descriptions are vivid in their descriptions of limitations), and that this may introduce a 'framing' effect wherein clinicians are unlikely to take into account the broad range of activities patients can perform that are unrelated to vision loss. The use of only 6 respondents (not taken from the general public), also limits the generalisability of the results and is not aligned with the NICE reference case.

At clarification stage, the ERG asked the company to confirm which order questions were asked in, as this may also influence the responses provided. The company provided a further report detailing the design of the elicitation exercise, but unfortunately this did not explicitly state the order the questions were asked. However, given the order of the report, it appears that clinicians were asked to first complete the questionnaires for the 'best' health state, and then subsequently the questionnaires for deteriorating health states. This ordering is likely to have impacted results by 'capping' the utilities of each state by the previous one. Were the order of the health states reversed and HS5 (hand motion, light perception, no light perception) valued first, the results may have been substantially different. A clear example of the effect of ordering can be seen in the Czoski-Murray et al (2009) study referenced by the company.[86] In the study members of the public were given vision altering contact lenses to simulate different levels of vision impairment - their valuation of the states however varied depending on the order in which they received the contact lenses (Table 2 of the paper).

The lack of face validity is due to two related issues: firstly, the absolute values derived via the proxy elicitation exercise not appearing to match with the patient experience described by the ERG's clinical advisors, and secondly, the negative value for HS5 (HUI3 analysis). When asked to describe the

HRQoL of patients, the ERG's clinical advisors stated that unlike many other vision disorders, patients had restrictions imposed by their vision, but in general did not have other physical health problems. As the patients had always experienced vision problems, they did not experience a sense of 'loss' from otherwise average vision, and continued to perform their usual activities, modifying these over time – for instance taking up disability sport (possibly to high levels). Even with extremely poor vision, patients were described as leading meaningful lives with high levels of enjoyment. The description given of patient's lives did not correspond to the utility values provided by the company. When asked specifically about the value for HS5 (for which a negative value is indicative of a health state *"worse than death"*), this was not recognised by clinicians for patients in this indication, and did not appear to be representative of the patient population residing in this health state.

To investigate the apparent lack of face validity, the ERG reviewed all previous NICE submissions involving vision loss to gain a broader understanding of the utility values used to inform previous appraisals. While there have been no specific submissions in *RPE65*-mediated IRD, nearly all appraisals incorporated health states based on vision loss. The results of this review are reported in Table 37.

Table 37: Summary of range of utility values in previous NICE TAs

Number	Category	Lowest and highest utilities
TA155	Macular degeneration	0.40 and 0.89
TA229	Macular oedema and retinal vein occlusion	0.548 and 0.750
TA274	Macular oedema and retinal vein occlusion	0.353 and 0.869
TA283	Macular oedema and retinal vein occlusion	0.314 and 0.869
TA294	Macular degeneration	0.31 and 0.920
TA297	Eye conditions: general and other	0.314 and 0.8280
TA298	Refractive errors including astigmatism, myopia and presbyopia	0.353 and 0.991
TA301	Macular oedema and retinal vein occlusion	0.245 and 0.920
TA305	Macular oedema and retinal vein occlusion	0.469 and 0.828
TA346	Macular oedema and retinal vein occlusion	0.26 and 0.86
TA349	Macular oedema and retinal vein occlusion	Not reported
TA369	Eye conditions: general and other	Not relevant
TA409	Macular oedema and retinal vein occlusion	0.29 and 0.83
TA460	Eye conditions: general and other	0.353 and 0.869
TA467	Corneal conditions	Not relevant
TA486	Refractive errors including astigmatism, myopia and presbyopia	Not reported
TA532	Corneal conditions	Not relevant

Abbreviations**:** TA, Technology Appraisal.

Section 5, p.143

presented in Rentz et al. (433354). The resulting values used in the ERG's analysis are presented in Table 40.

Table 40: ERG analysis utility values

Health state	Values based on value from Rentz et al.	Values based on value from Rentz et al. (UK only)	Values using health state 433354 for Health State 5
HS1 (Moderate VI)	0.717	0.687	0.717
HS2 (Severe VI)	*0.624*	*0.581*	*0.638*
HS3 (Profound VI)	*0.530*	*0.476*	*0.560*
HS4 (CF)	*0.437*	*0.370*	*0.481*
HS5 (HM, LP, NLP)	0.343	0.264	0.402

Abbreviations**:** CF, counting fingers; HM, hand motion; LP, light perception; NLP, no light perception; SD, standard deviation; VI, visual impairment.
Note**:** Interpolated values shown in *italics*.

The values produced in the analysis based on the study by Rentz *et al*.[89] are clearly imperfect, however a strength of the study is that the descriptions (shown above for 333322) are described via the functional impact of vision problems, as opposed to being linked to VA alone as in many other conditions. Importantly however when valued by 600 members of the general public, the results indicated a poor but plausible utility for blindness (0.343 for all patients, 0.2644 for UK patients), as opposed to a 'worse than death' health state.

5.2.7.2 Adverse event disutilities

The company submission includes disutilities for three adverse events; cataract (-0.14 for 1 month), eye inflammation (-0.30 for 3.6 months), and increased intraocular pressure (-0.10 for 1 month). Both cataract and eye inflammation were referenced to previous macular degeneration submissions, with a reference to the literature for increased intraocular pressure.

ERG Comment:

The company's approach to accounting for the impact of adverse events on HRQoL appears broadly acceptable, though the disutility for eye inflammation appears to be particularly large, especially when patients already have relatively low health-state utilities (versus the general population). Nevertheless, the ERG maintains this assumption in the preferred base case, given the lack of an alternative value that may instead be used.

Section 5, p.178

Table 63: Summary of the ERG's exploratory and sensitivity analyses (including PAS)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£35,731	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£35,731	12.9			
VN	[redacted]	15.0	[redacted]	2.1	[redacted]
Remove all healthcare resource use costs					
BSC	£0	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
Use company-preferred healthcare resource use costs					
BSC	£48,254	12.9			
VN	[redacted]	16.9	[redacted]	4.0	[redacted]
UK utility values (based on Rentz et al.)					
BSC	£35,731	11.4			
VN	[redacted]	15.9	[redacted]	4.5	[redacted]
Alternative (higher) utility values (based on Rentz et al.)					
BSC	£35,731	13.8			
VN	[redacted]	17.1	[redacted]	3.3	[redacted]
Baseline characteristics derived from Study 301/302					
BSC	£35,667	12.4			
VN	[redacted]	16.5	[redacted]	4.1	[redacted]
Baseline characteristics derived from RPE65 NHx					
BSC	£35,773	13.1			
VN	[redacted]	17.0	[redacted]	3.9	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Section 8, p.185-186

8.1.2 Current management of RP

NHS England reported that because there are no specific genetic treatments available in England, current management for affected patients is supportive and involves ensuring good liaison between clinical and educational care together with low vision aids as appropriate for children. For affected adults, treatment is also supportive between clinical care, employers and social services. Low visual aids are provided for adults. Genetic counselling is provided via medical genetic services to affected families.

8.1.3 VN

NHS England stated that treatment with VN would provide the first treatment option for patients with the aim of stabilising vision and preventing further visual loss. The impact would be to improve mobility and independence for those patients very poor vision. In addition if treatment with VN is given earlier in the course of the disease, NHS England stated there is the potential to preserve central vision. A clinician from the Royal College of Ophthalmologists expressed a view that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Expert advisors to the ERG are in agreement with this view. A clinician from the Royal College of Ophthalmologists expressed the view that side-effects were unlikely to be a barrier to adoption of the treatment, again a view endorsed by clinical advisors to the ERG. Both the clinician from Royal College of Ophthalmologists and clinical advisors to the ERG consider that adverse reactions caused by a short course of steroids administered post-operatively (e.g. red eye, transient blurred vision, etc.) would be no more than expected or from a similar eye operation.

8.1.3.1 Subgroups

A clinician from the Royal College of Ophthalmologists stated that while all patients with RP and some retained retinal structure might benefit from treatment with VN to some extent irrespective of age, there are a subgroup of patients with hypomorphic alleles giving a later less severe recessive phenotype who may have a different prognosis from the typical patient.[100] There are also a subgroup of patients with a dominant allele giving rise to a very different phenotype that may have a different prognosis from the typical patient,[101] although these patients are not eligible for VN under its current marketing authorisation.

8.1.4 Changes to service delivery and resources required if VN is recommended

NHS England stated that because genetic networks are in place across England, patients with known molecular diagnoses who could benefit from treatment can be identified. A clinician from the Royal College of Ophthalmologists reported that diagnosis and monitoring uses technology that is standard in specialist clinics (imaging, psychophysics, and electrophysiology).

NHS England currently directly commissions specialised ophthalmology services including the treatment of ocular genetic disorders. NHS England state that these are best managed by specialist networks which provide multidisciplinary services including diagnosis, testing, counselling and imaging as well as treatment. NHS England anticipate that the treatment with VN can be implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services. This view is endorsed by a clinician from the Royal College of Ophthalmologists who reported that the surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units. The clinician stated that impact of VN on delivery will be limited as the number of patients affected is small and the treatment is relatively quick; i.e. it is a single treatment given to each eye in an operation that takes about one hour.

8.1.5 Conclusion

There are no specific treatments currently available in England for this small patient group and current management for affected patients is supportive. Treatment with VN would provide the first treatment option for patients with this condition with the aim of stabilising vision and preventing further visual loss and with the potential to preserve central vision if given early.

Clinical experts, both from the Royal College of Ophthalmologists and advisors to the ERG, agree that the most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients. Furthermore, all the clinical experts agree that side-effects are unlikely to be a barrier to adoption of the treatment and that adverse reactions caused by a short course of steroids administered post-operatively (e.g. red eye, transient blurred vision, etc.) would be no more than expected or from a similar eye operation.

NHS England anticipate that the treatment with VN can be implemented using the current clinical services available for ophthalmic medical genetic services and vitreoretinal services. This view is endorsed by a clinician from the Royal College of Ophthalmologists who reported that the surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

8.2 Patient support group and patient submissions

Submissions were received from the Fight for Sight charity and a patient expert with the condition nominated by the Fight for Sight charity. The patient expert's statement was in keeping with the

Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054]

Addendum #1

Summary of Stakeholder Testimonials

31/05/2019

1 Introduction

This addendum was produced following the submission of additional stakeholder testimonials, following completion of the ERG report. These testimonials include: patient and carer viewpoints elicited in a survey for those affected by any gene-mediated IRD, conducted by Retina UK; the views of patients, carers and healthcare professionals speaking at a meeting of the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee in October 2017; video evidence provided by the company showing a patient navigating the MLMT outcome measure pre- and post-treatment; and a short video produced by the company that includes the views of a patient and his carer. This addendum is provided to supplement the evidence summarised in Section 8 of the ERG report.

2 Summary of Stakeholder Testimonials

2.1 Patient and carer views elicited in Retina UK submission

While the study survey described in Retina UK's submission is large (916 responders), the ERG note that the survey was targeted generally to patients and carers affected by inherited sight loss caused by mutations in any gene i.e. which included but was not restricted to the patient population considered in the company submission for treatment by VN. In this survey, 73.51% of respondents had a diagnosis of retinitis pigmentosa while 1.05% had a diagnosis of Leber's congenital amaurosis (LCA). The ERG also note that no details are given regarding methods employed in conducting this survey or data extraction and analysis, and so it is not possible for the ERG to assess or comment on the quality of the survey or the reliability of the survey findings presented in the submission. Despite these limitations, the ERG note that many of the points presented in the submission by Retina UK are in agreement with many of the points described in the ERG's summary of patient support group submissions as presented in section 8.2 of the ERG report (and highlighted in bold below). These points of agreement are as follows:

Anxiety and worry on noticing changes to vision, leading to depression and mental health issues. Retina UK stated that 92% of respondents with vision loss conditions reported that vision loss impacted on mental health, with almost three quarters reporting that they had experienced anxiety, 62% had experienced stress, 41% had experienced depression and 33% had experienced loneliness.

People living with the condition stated the condition deprives them of opportunities in education, the labour market e.g. getting a job and/or job security. The Retina UK survey results indicate that over three quarters of respondents with vision loss conditions felt that their career / job was affected, with this being significant or extreme in 46%, while over half of respondents indicated that their condition had impacted their education.

Substantial effect on parents, carers and loved ones of people living with the condition. Retina UK agree with other stakeholder submissions that parents caring for affected children often fear for their child's future and many experience guilt due to the inherited nature of the condition. An additional point made by Retina UK is that there can be stress from managing the financial impact of reducing or giving up work to care for their child alongside additional expenses such as adaptive aids and travel to specialist appointments.

Retina UK, along with other patient stakeholders in the ERG's main report, suggested there is **unmet need for people living with RPE65-mediated IRD as there are currently no treatments for people with this condition available on the NHS**. Retina UK state in their submission that there is currently no treatment that slows or stops the progression of sight loss and cite how a 2013 James Lind Priority Setting Partnership on inherited retinal dystrophies identified the highest priority research question as: Can a treatment to slow down progression or reverse sight loss in inherited retinal diseases be developed?

In Section 8.2 of the ERG report, the patient expert expressed the view that there would be considerable benefit in stabilizing or reversing the visual deterioration of school age or younger

children, even if the effect was limited in time. Retina UK similarly noted that effective treatment for those experiencing childhood onset sight loss could provide lifetime benefit in terms of education, employment and quality of life.

Retina UK state that the progressive nature of sight loss conditions leads to a continual series of losses, with associated grief, and that **the need to continually adapt to increasing disability is stressful.** This is in alignment with the patient expert view summarised in the ERG report.

In Section 8.2 of the ERG report, the patient expert expressed the view that **reducing the effects of night blindness could improve mobility and give patients confidence, improve their safety and prevent isolation, while improved visual acuity would help patients access written material, to recognise faces and interact naturally with colleagues and stakeholders.** Retina UK confirm that sight loss affected mobility in 90% of responders with visual loss conditions and 95% of respondents said that their condition impacted on their leisure time and hobbies. The majority of respondents with visual loss conditions said that their sight loss condition affected their social life, day-to-day routines, relationships and family life, and the likelihood of falls or accidents.

The ERG note two points of disagreement between Retina UK and the points described in the ERG's summary of clinician expert submissions as presented in the ERG report (Section 8.1). These points of disagreement are summarised below:

Because genetic networks are in place across England, patients with known molecular diagnoses who could benefit from treatment can be identified. In their statement, Retina UK state that while treatment with VN is only suitable to those with a specific genotype (and therefore not appropriate for the majority of the inherited sight loss community), access to genetic testing to confirm genotype is not consistent across the country, so that those in areas where testing is not readily available will be unable to benefit from the treatment.

Side effects are unlikely to be a barrier to adoption of the treatment. In their submission, Retina UK state that patients and carers are aware of possible side effects including retinal damage and vision loss and that some patients may prefer not to risk their remaining vision early in the disease course.

2.2 Patient and clinician testimonials presented at the FDA's 67th meeting of the cellular, tissue, and gene therapies advisory committee

The ERG note that many of the points presented by patients and clinician experts at the 67th meeting of the cellular, tissue, and gene therapies advisory committee are in agreement with many of the points in the ERG's summary of patient support group submissions as presented in the ERG report (Section 8.2). These points of agreement are summarised below:

- Substantial effect on parents, carers and loved ones of people living with the condition.
- Successful treatment has the potential to have a huge influence at a critical stage of childhood development and learning.
- The need to continually adapt to increasing disability is highly stressful.
- Reducing the effects of night blindness could improve mobility and give patients confidence, improve their safety and prevent isolation, while improved visual acuity

would help patients access written material, to recognise faces and interact naturally with colleagues and stakeholders.

In addition, the ERG note that many of the points presented by clinician experts in the FDA's 67th meeting of the cellular, tissue, and gene therapies advisory committee are in agreement with points reported in the ERG's summary of clinician expert submissions as presented in the ERG report (Section 8.1) These points are summarised below:

- The most important outcome in the assessment of VN is gain of navigation, which will likely have a significant effect on the independence of affected patients.
- Side effects are unlikely to be a barrier to adoption of the treatment.
- Surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

Two additional issues were raised in the provided comments.

Eligibility for treatment with VN. A clinical expert and a service user advocate both noted that an upper age limit for treatment was inadvisable.

Durability of treatment effect. A clinical expert noted that in his view, treatment response to VN is durable over several years, citing anecdotal evidence of one patient nine years post-treatment.

2.3 Video and power point materials submitted by the company

The company provide MLMT (a novel measure of functional vision ability to conduct visually dependent activities of daily living independently) assessment videos showing evidence of successful navigation of the MLMT maze following treatment with VN at 1 year and 3 years at 1 lux (equivalent to a moonless summer night or indoor night-light), alongside a patient testimonial.

2.4 Summary

There is recognition in all submissions of an unmet need for people living with RPE65 as there are currently no treatments for people with this condition available on the NHS. There is agreement between all the received submissions that vision loss impacts on mental health, manifesting in symptoms such as stress, anxiety, depression and loneliness, and impacts on education and career / job prospects. Submissions agreed that successful treatment can support a critical stage of childhood development and learning and could provide lifetime benefit in terms of education, employment and quality of life. All submissions agreed that there is substantial impact on parents / carers / loved ones, ranging from emotional distress from raising a child with vision loss to stress arising from associated financial burden e.g. having to give up job to care for a child. There is a recognition in all the submissions that the need to continually adapt to increasing disability is stressful. All submissions agreed that reducing the effects of night blindness could improve mobility and that vision loss significantly impacted on relationships and social life.

There is agreement between clinician experts from all submissions regarding the suitability of MLMT assessment as an outcome measure for evaluating the effectiveness of VN. Clinician experts also share a view that surgery is standard i.e. not significantly different to present clinical vitrectomies and is within the capabilities of specialist units.

There are two points of disagreement between submissions. The first relates to the provision of genetic networks. In the ERG report (Section 8.1), NHS England assert that genetic networks are in place across England and that patients with known molecular diagnoses who could benefit from treatment can be identified. However, Retina UK disagree. They state in their submission that their survey indicates that access to genetic testing to confirm genotype is not consistent across the country, so that those in areas where testing is not readily available will be unable to benefit from the treatment. A second point of disagreement is that while clinician experts agree that side effects are unlikely to be a barrier to adoption of the treatment, Retinal UK states that some patients may prefer not to risk their remaining vision early in the disease course.

Voretigene neparvovec for treating inherited retinal dystrophies caused by *RPE65* gene mutations [ID1054]

Addendum #1

Annual discounting (0% costs and outcomes): Impact on the ICER of additional analyses undertaken by the ERG

16 July 2019

1 INTRODUCTION

Following a request from the NICE technical team, this addendum provides the results of the ERG's additional analyses within the company's model excluding annual discounting (i.e. 0% for costs and outcomes).

1.1 Corrections to the company's and ERG's preferred base case analysis

For details regarding the corrections made to the company's model refer to Section 6.1 of the ERG report and for details regarding the ERG's preferred base case refer to Section 6.2 of the ERG report.

The impact of these changes on the ICER excluding annual discounting (for costs and outcomes), is presented in the following tables:

- Table 1 (including the PAS discount for VN, with each change varied independently)
- Table 2 (including the PAS discount for VN, with all changes varied in combination)
- Table 3 (excluding the PAS discount for VN, with each change varied independently)
- Table 4 (excluding the PAS discount for VN, with all changes varied in combination)

Table 1: Summary of the ERG's preferred base case (independent, including PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	-
Error corrections						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
Cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
Change application of medical resource use (remove depression, equal across health states)						
BSC	£243,622	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
Remove mortality multipliers						
BSC	£304,021	4.2				
VN	[redacted]	24.8	[redacted]	20.6	[redacted]	[redacted]
Amend application of carer disutilities						
BSC	£282,365	6.7				
VN	[redacted]	25.6	[redacted]	19.0	[redacted]	[redacted]
Pooled baseline health state occupancy						
BSC	£282,421	5.5				
VN	[redacted]	26.4	[redacted]	20.8	[redacted]	[redacted]
Use of crossover transition probabilities						
BSC	£282,365	4.3				
VN	[redacted]	23.6	[redacted]	19.3	[redacted]	[redacted]
Removal of waning period and residual treatment effect						
BSC	£282,365	4.3				
VN	[redacted]	23.5	[redacted]	19.2	[redacted]	[redacted]
Alternative utility values						
BSC	£282,365	25.6				
VN	[redacted]	40.0	[redacted]	14.4	[redacted]	[redacted]
ERG's preferred base case (all changes combined)						
BSC	£264,414	29.3				
VN	[redacted]	41.4	[redacted]	12.1	[redacted]	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 2: Summary of the ERG's preferred base case (cumulative, including PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
As above + error corrections						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
As above + cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£282,365	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
As above + change application of medical resource use (remove depression, equal across health states)						
BSC	£243,622	4.3				
VN	[redacted]	24.6	[redacted]	20.3	[redacted]	[redacted]
As above + remove mortality multipliers						
BSC	£263,812	4.2				
VN	[redacted]	24.8	[redacted]	20.6	[redacted]	[redacted]
As above + amend application of carer disutilities						
BSC	£263,812	6.6				
VN	[redacted]	25.9	[redacted]	19.3	[redacted]	[redacted]
As above + pooled baseline health state occupancy						
BSC	£264,414	7.8				
VN	[redacted]	27.4	[redacted]	19.7	[redacted]	[redacted]
As above + use of crossover transition probabilities						
BSC	£264,414	7.8				
VN	[redacted]	26.4	[redacted]	18.7	[redacted]	[redacted]
As above + removal of waning period and residual treatment effect						
BSC	£264,414	7.8				
VN	[redacted]	25.4	[redacted]	17.6	[redacted]	[redacted]
As above + alternative utility values						
BSC	£264,414	29.3				
VN	[redacted]	41.4	[redacted]	12.1	[redacted]	[redacted]
ERG's preferred base case (all changes combined)						
BSC	£264,414	29.3				
VN	[redacted]	41.4	[redacted]	12.1	[redacted]	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 3: Summary of the ERG's preferred base case (independent, excluding PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£282,365	4.3				
VN	£876,144	24.6	£593,779	20.3	£29,233	-
Error corrections						
BSC	£282,365	4.3				
VN	£875,636	24.6	£593,270	20.3	£29,208	-£25
Cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£282,365	4.3				
VN	£876,162	24.6	£593,797	20.3	£29,234	+£1
Change application of medical resource use (remove depression, equal across health states)						
BSC	£243,622	4.3				
VN	£864,792	24.6	£621,169	20.3	£30,581	+£1,348
Remove mortality multipliers						
BSC	£304,021	4.2				
VN	£895,000	24.8	£590,979	20.6	£28,650	-£583
Amend application of carer disutilities						
BSC	£282,365	6.7				
VN	£876,144	25.6	£593,779	19.0	£31,286	+£2,053
Pooled baseline health state occupancy						
BSC	£282,421	5.5				
VN	£872,586	26.4	£590,165	20.8	£28,314	-£919
Use of crossover transition probabilities						
BSC	£282,365	4.3				
VN	£879,970	23.6	£597,605	19.3	£31,013	+£1,781
Removal of waning period and residual treatment effect						
BSC	£282,365	4.3				
VN	£885,223	23.5	£602,857	19.2	£31,376	+£2,143
Alternative utility values						
BSC	£282,365	25.6				
VN	£876,144	40.0	£593,779	14.4	£41,333	+£12,100
ERG's preferred base case (all changes combined)						
BSC	£264,414	29.3				
VN	£882,765	41.4	£618,351	12.1	£51,235	+£22,003

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 4: Summary of the ERG's preferred base case (cumulative, excluding PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case (following clarification response)						
BSC	£282,365	4.3				
VN	£876,144	24.6	£593,779	20.3	£29,233	-
As above + error corrections						
BSC	£282,365	4.3				
VN	£875,636	24.6	£593,270	20.3	£29,208	-£25
As above + cost of resolving adverse events least outpatient ophthalmologist consultation						
BSC	£282,365	4.3				
VN	£875,655	24.6	£593,290	20.3	£29,209	-£24
As above + change application of medical resource use (remove depression, equal across health states)						
BSC	£243,622	4.3				
VN	£864,303	24.6	£620,681	20.3	£30,557	+£1,324
As above + remove mortality multipliers						
BSC	£263,812	4.2				
VN	£882,163	24.8	£618,351	20.6	£29,977	+£744
As above + amend application of carer disutilities						
BSC	£263,812	6.6				
VN	£882,163	25.9	£618,351	19.3	£32,070	+£2,837
As above + pooled baseline health state occupancy						
BSC	£264,414	7.8				
VN	£882,765	27.4	£618,351	19.7	£31,427	+£2,194
As above + use of crossover transition probabilities						
BSC	£264,414	7.8				
VN	£882,765	26.4	£618,351	18.7	£33,108	+£3,875
As above + removal of waning period and residual treatment effect						
BSC	£264,414	7.8				
VN	£882,765	25.4	£618,351	17.6	£35,135	+£5,902
As above + alternative utility values						
BSC	£264,414	29.3				
VN	£882,765	41.4	£618,351	12.1	£51,235	+£22,003
ERG's preferred base case (all changes combined)						
BSC	£264,414	29.3				
VN	£882,765	41.4	£618,351	12.1	£51,235	+£22,003

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

The ERG's preferred base-case leads to an ICER of [redacted] (including the PAS discount for VN) and £51,235 (excluding the PAS discount for VN). The change associated with the largest individual impact on the ICER was the use of different health state utility values,

which caused the ICER to increase by approximately [redacted] (with PAS) and £12,100 (without PAS).

1.2 Additional analyses undertaken by the ERG

For details regarding the additional analyses performed by the ERG refer to Section 6.2 of the ERG report.

The impact of each analysis on the ICER excluding annual discounting (0% for costs and outcomes), is presented in the following tables and figures:

- Scenario #1
  - [redacted] (threshold analysis, including the PAS discount for VN)
  - [redacted] (threshold analysis, excluding the PAS discount for VN)
- Scenarios #2-8
  - Table 5 (individual analyses, including the PAS discount for VN)
  - Table 6 (individual analyses, excluding the PAS discount for VN)

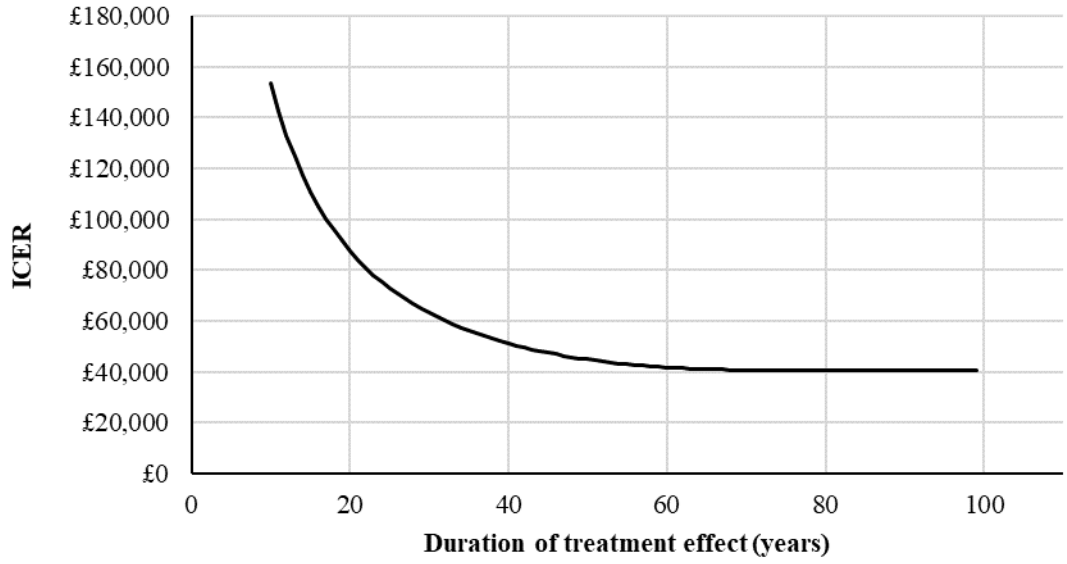
These additional analyses were performed in conjunction with the ERG's preferred base-case settings and assumptions, described in Section 6.2 of the ERG report.

[redacted]

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio.

Figure 2: Threshold analysis conducted by ERG (excluding PAS): 0% annual discount rates (costs and outcomes)



Abbreviations: ICER, incremental cost-effectiveness ratio.

For the threshold analysis, the duration of treatment effect would need to be at least [redacted] years (with PAS, [redacted]1) or 18 years (without PAS, Figure 2) in order for the ICER to be less than £100,000 per QALY gained.

Table 5: Summary of the ERG's exploratory and sensitivity analyses (including PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£264,414	29.3			
VN	[redacted]	41.4	[redacted]	12.1	[redacted]
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£264,414	29.3			
VN	[redacted]	33.8	[redacted]	4.4	[redacted]
Remove all healthcare resource use costs					
BSC	£0	29.3			
VN	[redacted]	41.4	[redacted]	12.1	[redacted]
Use company-preferred healthcare resource use costs					
BSC	£304,044	29.3			
VN	[redacted]	41.4	[redacted]	12.1	[redacted]
UK utility values (based on Rentz et al.)					
10BSC	£264,414	25.0			
VN	[redacted]	38.7	[redacted]	13.6	[redacted]
Alternative (higher): utility values (based on Rentz et al.)					
BSC	£264,414	32.1			
VN	[redacted]	42.3	[redacted]	10.2	[redacted]
Baseline characteristics derived from Study 301/302					
BSC	£263,812	28.5			
VN	[redacted]	40.5	[redacted]	12.0	[redacted]
Baseline characteristics derived from RPE65 NHx					
BSC	£264,921	29.6			
VN	[redacted]	41.7	[redacted]	12.1	[redacted]

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

Table 6: Summary of the ERG's exploratory and sensitivity analyses (excluding PAS): 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (all changes combined)					
BSC	£264,414	29.3			
VN	£882,765	41.4	£618,351	12.1	£51,235
Duration of treatment effect per Institute for Clinical and Economic Review analysis					
BSC	£264,414	29.3			
VN	£882,765	33.8	£618,351	4.4	£139,437
Remove all healthcare resource use costs					
BSC	£0	29.3			
VN	£618,351	41.4	£618,351	12.1	£51,235
Apply original healthcare resource use costs					
BSC	£304,044	29.3			
VN	£905,300	41.4	£601,256	12.1	£49,819
UK utility values (based on Rentz et al.)					
BSC	£264,414	25.0			
VN	£882,765	38.7	£618,351	13.6	£45,322
Alternative (higher) utility values (based on Rentz et al.)					
BSC	£264,414	32.1			
VN	£882,765	42.3	£618,351	10.2	£60,890
Baseline characteristics derived from Study 301/302					
BSC	£263,812	28.5			
VN	£882,163	40.5	£618,351	12.0	£51,629
Baseline characteristics derived from RPE65 NHx					
BSC	£264,921	29.6			
VN	£883,272	41.7	£618,351	12.1	£51,055

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; VN, voretigene neparvovec.

The ERG also conducted an assessment of the ICER were a governmental perspective to be adopted. The findings of this analysis are presented in Table 7. If a governmental perspective is considered, the ICER decreases slightly from [redacted] to [redacted] (with a PAS discount).

A summary of the ERG's base-case cost-effectiveness results for UK NHS PSS and UK government perspective are provided in Table 7.

Table 7: Summary of ERG's base-case cost-effectiveness results: 0% annual discount rates (costs and outcomes)

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER
ERG's preferred base case (NHS and PSS perspective, including PAS discount)					
BSC	£264,414	29.3			
VN	[redacted]	41.4	[redacted]	12.1	[redacted]
ERG's preferred base case (NHS and PSS perspective, excluding PAS discount)					
BSC	£264,414	29.3			
VN	£882,765	41.4	£618,351	12.1	£51,235
ERG's preferred base case (UK government perspective, including PAS discount)					
BSC	£402,037	29.3			
VN	[redacted]	41.4	[redacted]	12.1	[redacted]
ERG's preferred base case (UK government perspective, excluding PAS discount)					
BSC	£402,037	29.3			
VN	£990,837	41.4	£588,800	12.1	£48,787

Abbreviations**:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year; VN, voretigene neparvovec.