NICE National Institute for Health and Care Excellence

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

1st Evaluation Committee Meeting
Highly Specialised Technology, 25th July 2019
Background and clinical effectiveness

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Chair: Peter Jackson
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Key issues for consideration

- Clinical effectiveness

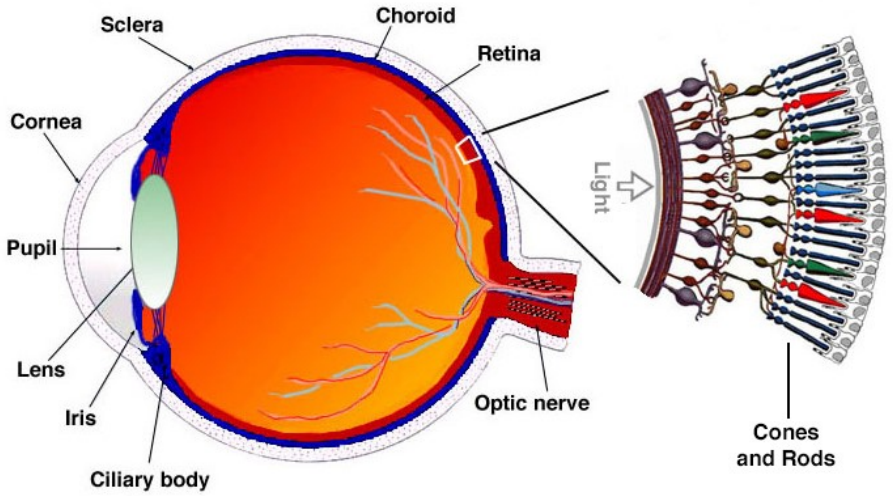
- **Study 301/302 recruited patients diagnosed with LCA and those with sufficient viable retinal cells:**
  - How would sufficient viable retinal cells be defined in clinical practice?
  - What population would be considered for treatment with VN?
  - Are there differences between UK incident and prevalent populations? Are the trial results more applicable to one than the other?
  - Is the evidence generalisable to clinical practice in the UK?

- **What is the committee's view on:**
  - The imbalances in baseline characteristics and visual performance measures in study 301/302?
  - 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, 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 and leads to cell apoptosis
  - Rhodopsin is found in rod cells which are responsible for vision at low light levels
- ***RPE65*-mediated IRD:** presents at a range of ages between infancy and adolescence
  - Includes some types of Retinitis pigmentosa (RP), and Leber's congenital amaurosis (LCA)
  - LCA and RP differentiated by clinical presentation and family history
  - LCA is less common, presenting earlier and having a more aggressive prognosis
  - It is estimated that there are 57–564 people with *RPE65*-mediated IRD in England; among them, about 86 will be eligible for the treatment



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

Clinical symptoms of *RPE65*-mediated IRD and current treatments

- **Diagnosis:** assessment of medical history, clinical symptoms, and analysis of family history prior to genetic screening
- **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). RPE65-mediated IRD can lead to complete blindness
- **Complications:** of IRD mainly include cataracts and cystoid macular oedema
- **Current treatments:** 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, adults receive supportive care from clinicians, employers and social services
  - Genetic counselling is provided to affected families

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

Overall quality of life (QoL)

- More than 50% said their sight loss had a severe or very severe impact on their overall QoL

Mental health

- 92% 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**: most 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"

"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*)

- Stress from managing the **financial impact of reducing work to care for children alongside additional expenses for adaptive aids and travel** to specialist appointments
- '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:

- 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

[redacted]

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 education was marked by frequent battles to ensure that my needs were recognised and 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"
>
> "my **mobility, particularly after dark**, was poor and I relied heavily on my peers"
>
> **"Perceived deterioration in my sight** made it impossible to keep up with the reading for my course"

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"

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… 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… [and] indirectly assist the mental wellbeing of some patients"

"It is my reducing **visual acuity and field of vision** which **has 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

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

- VN is the 1st treatment option → aiming to stabilise vision and prevent further visual loss
- VN offers hope for people living with RPE65-mediated IRD
- Surgery is one-time event, relatively quick and will only be given to a small number of patients (about 30-50 in the UK) so limited impact on service provision
- Surgeons already adept at the required surgery

Outcomes

- RCOphth: **the most important outcome is gain of navigation**, which will have a 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

Population

- Estimated prevalent population of 70-80 patients (mainly adults), incident population of 3-4 per year (paediatric)
- Potential increase in identification of patients as genetic testing is rolled out

Pathway of care

- Currently there are no specific genetic treatments available in England
- Management for affected patients is supportive and is a local authority responsibility
- Low visual aids are provided and supportive care is provided between clinical care, educational authorities, employers and social services
- Genetic counselling is provided via medical genetic services to affected families.
  - Access to genomic testing will improve with the national rollout of genomic testing

Commissioning

- NHS England directly commissions specialised ophthalmology services
- Potential for 2 service models for VN treatment:
  - short-term service to treat the prevalent population
  - long-term service to treat the incident population

Voretigene neparvovec

- Following surgery (for each eye) the patient may require access to the specialist provider and therefore accommodation near the specialist centre for an extended period

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

Marketing authorisation	Approved 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 (1.5×10^{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	

[redacted]

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

[redacted]

Measurement of study primary end point

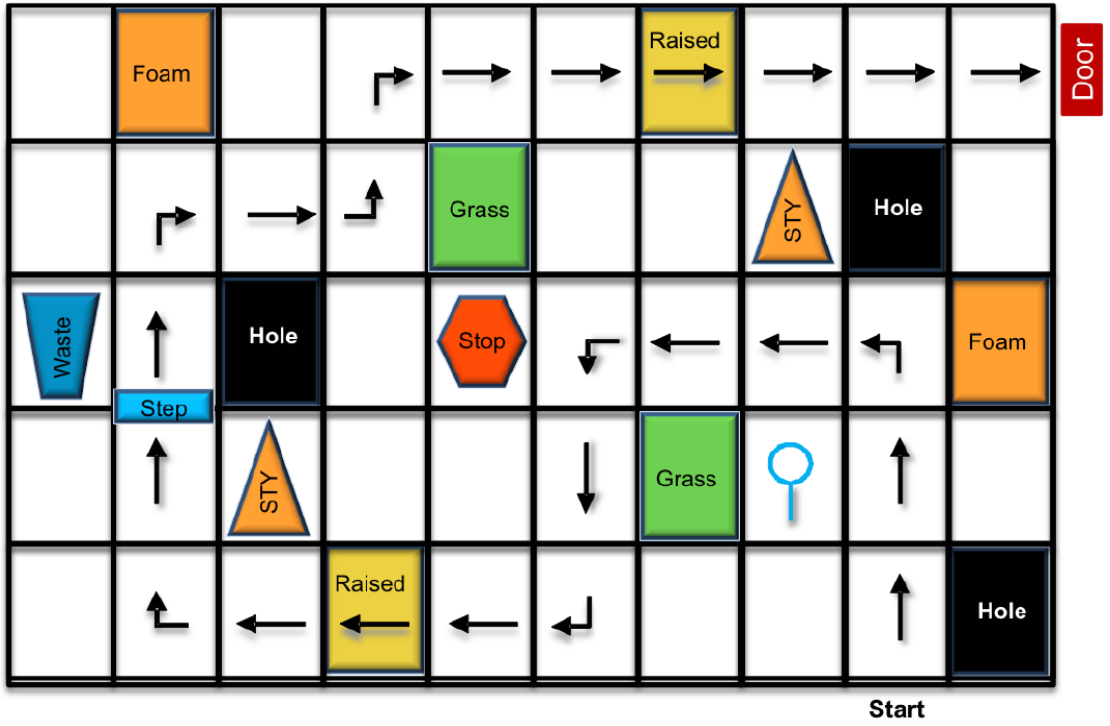
Multi-luminance mobility test (primary endpoint)

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'

[redacted]

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 [n=31] (age range: 4-44, >18 n=11 [35%]) Sufficient viable retinal cells	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

[redacted]

Company's main evidence of clinical effectiveness

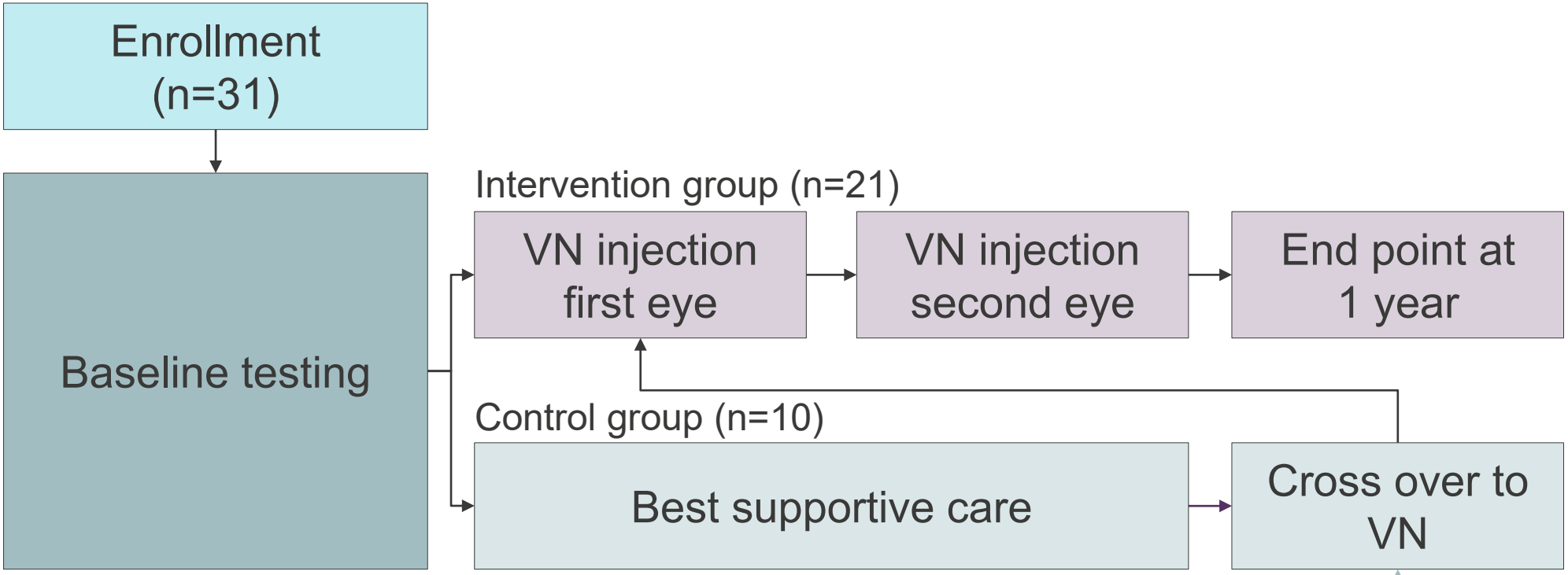
	Study 101/102	Study 301/302
Design	**Study 101:** phase 1, dose-escalating study, open-label **Study 102:** follow-on, safety study → re-administration of VN to other eye	**Study 301:** phase 3, randomised controlled trial, open-label **Study 302:** After 1-year control patients eligible to receive VN
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 (1 year):** 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

[redacted]

Committee: Is the evidence generalisable to clinical practice in the UK?

Study 301/302 trial - summary



Key inclusion criteria:

- 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)

Committee: How would sufficient viable retinal cells be defined in clinical practice?

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

Committee: What is the impact of the imbalances in baseline characteristics and baseline measures on treatment effect?

Baseline characteristics Study 101/102

Category	Study 101				Study 102
	Low Dose [redacted]	Middle Dose [redacted]	High Dose [redacted]	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]

[redacted]

Baseline characteristics for RPE65 NHx (natural history study)

Parameter/Category/Statistic		RPE65 NHx (n=70)
Clinical diagnosis, n (%) *n=78	Tapetal retinal dystrophy	4 (5.1)
	LCA	37 (47.4)
	Retinitis Pigmentosa	6 (7.7)
	Other	31 (39.7)
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%)

Measurement of study outcomes

	MLMT	Visual acuity	Visual field	FST testing	Contrast sensitivity
Definition	Measures ability to navigate a course accurately at specified light levels	Measures sharpness of vision, using ETDRS or HOTV test	Function of regions of the retina (area seen when looking forward)	Measures minimum brightness when light reliably seen	Measures ability to discern targets presented at varying levels of contrast
Interpretation	Lower scores = better performance	Lower scores = better acuity	Higher scores = greater visual field	Lower value = better sensitivity	Higher scores = better contrast sensitivity
Clinically meaningful change	Change ≥1 lux levels	Change in LogMAR ≥0.3	20% change from baseline score	Change of 10 dB or 1 log unit	Change of 0.3 log units

Abbreviations: BCVA, best corrected visual acuity; ETDRS; Early Treatment Diabetic Retinopathy Study; FST, full-field light sensitivity; MLMT, multi-luminance mobility test

Committee: What is committee's view on the clinically meaningful changes defined by the company for MLMT, VA, VF and FST?

ERG's comments on clinical evidence (I)

Population	• All patients had a diagnosis of LCA due to biallelic RPE65 mutations (with molecular diagnosis) → LCA may have a worse prognosis than other diagnoses • 301/302 inclusion criteria of sufficient retinal cells → how would this be determined in clinical practice
Quality of Evidence	• 101/102 under-powered to evaluate clinical efficacy • RCT 301/302: subject to high risk of bias due to small population size
Baseline characteristics study 101/102	• [redacted] • No clear relationship between outcomes and age; but greater retinal function at baseline → may mediate improved treatment effect, and may be correlated with age
Baseline characteristics study 301/302	• Limited baseline characteristics reported • Differences in baseline characteristics (including age) → but no clear bias • Baseline differences in visual performance: ○ [redacted] ○ [redacted] • Company unable to adjust outcome data for baseline visual performance due to sample size → uncertainty in the true treatment effect

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

ERG's comments on clinical evidence (II)

Intervention and comparator	• Limited detail for BSC • Assumed to include monitoring, psychological support, visual rehabilitation, and wearing sunglasses • Patients receiving VN would also receive BSC
Outcomes	**Primary endpoint:** • MLMT change scores capped at lowest light setting → may underestimate the 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, but considered unreliable due to inter-test variability • VA, VF and contrast sensitivity 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: BSC, best supportive care; HRQoL, health related quality of life; MLMT, multi-luminance mobility test; PRO, patient reported outcomes; VA, visual acuity; VF, visual field; VQF, Visual Function Questionnaire

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

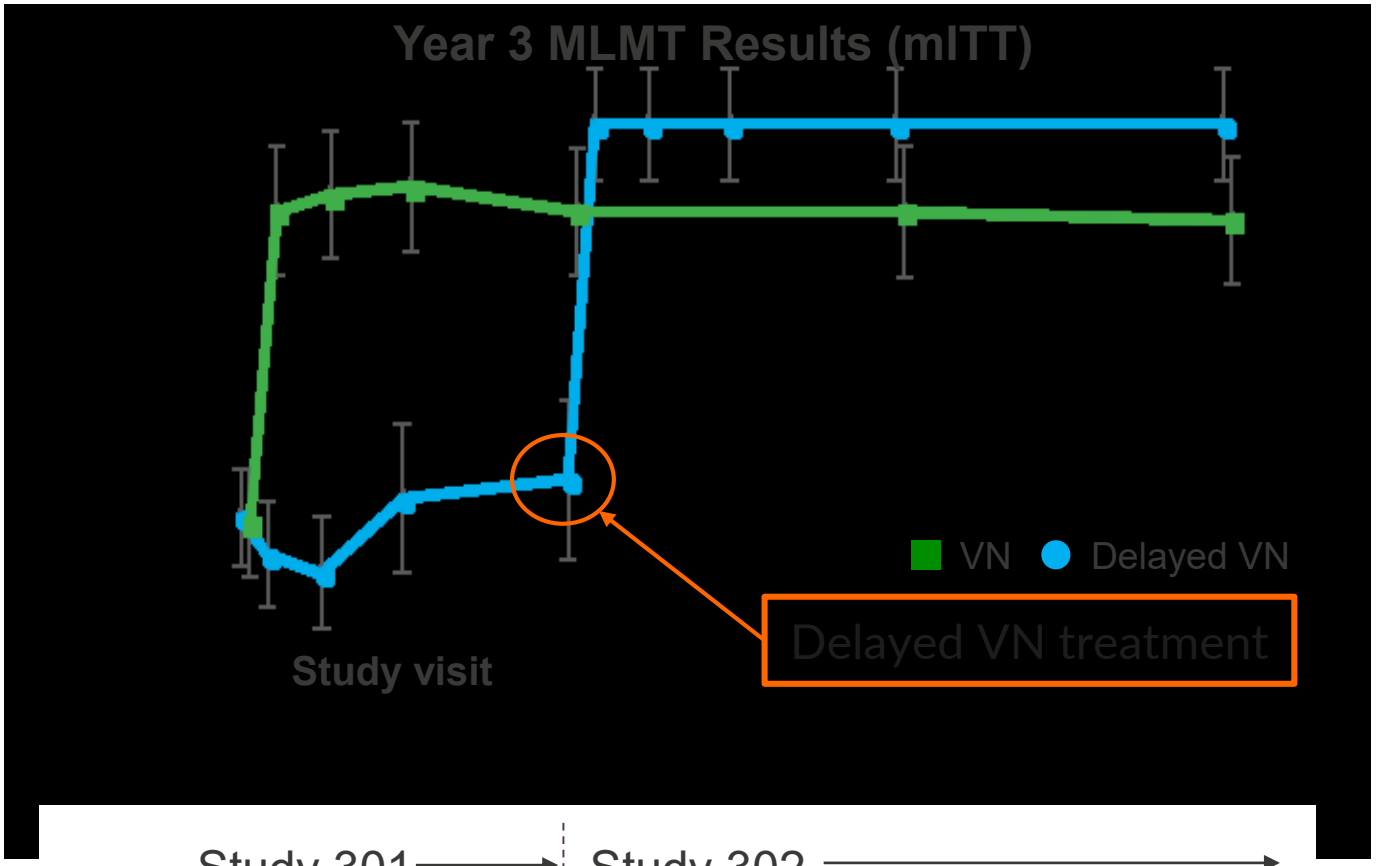
Study 301

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



Outcome		Original VN (n=20)	Delayed VN (n=9)
Mean change from baseline (SD)	Year 2	[redacted]	[redacted]
	Year 3	[redacted]	[redacted]
	Year 4	[redacted]	[redacted]
Clinically meaningful change: ≥1 light level			

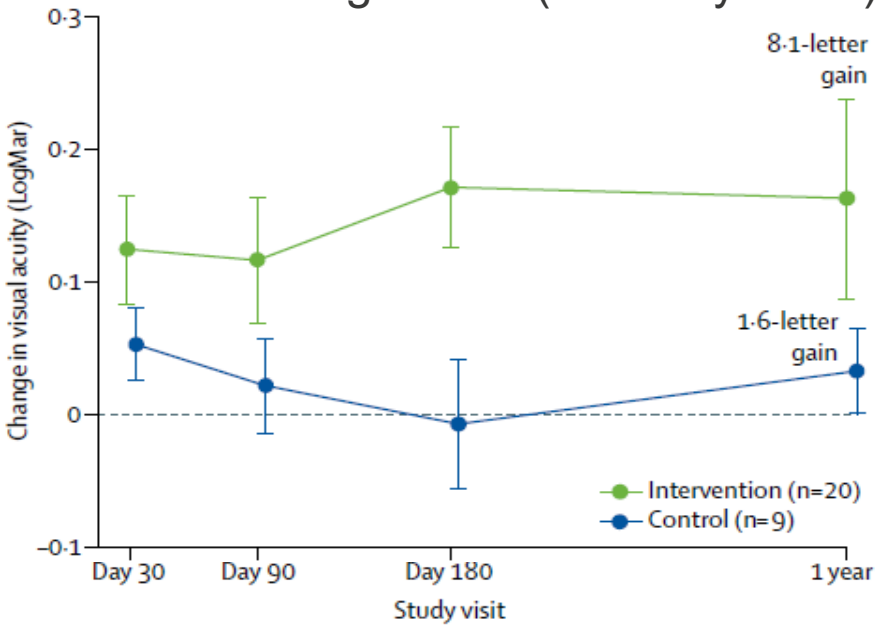
ERG:
MLMT outcome better suited to evaluating visual impairments in this population compared to other measures of visual performance
[redacted] → uncertainty in the true size of treatment effect

- **Year 3** – proportion who passed MLMT at 1 lux (lowest light level): **original VN:** 60% (12/20), **delayed VN** 89% (8/9)
- [redacted]

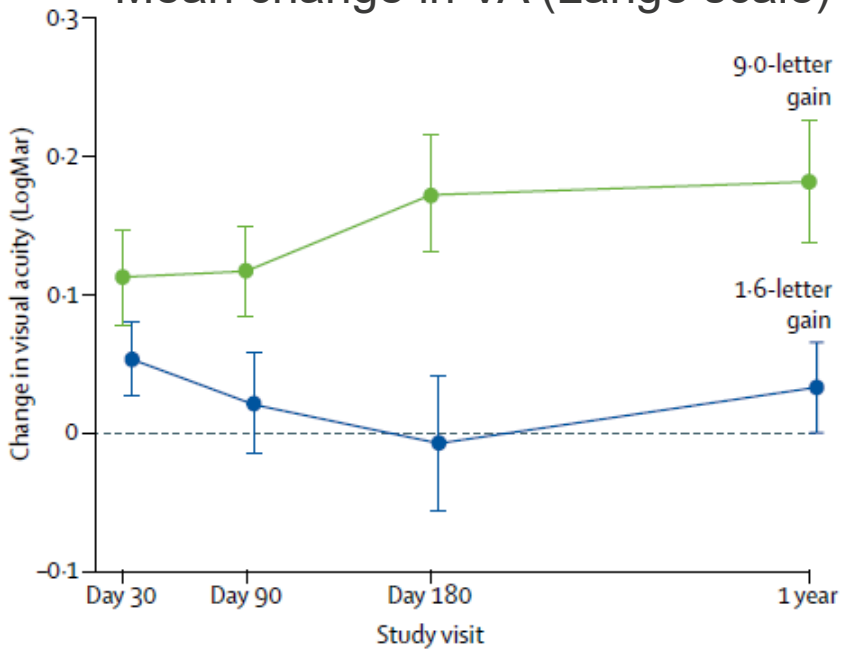
Clinical effectiveness: Visual acuity (VA)

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

- Improvement in VA between baseline at 1 year in VN arm vs. BSC (ITT)
- Mean difference 0.16 LogMAR (95%CI -0.41, 0.08; p=0.17)
- Not statistically significant
- Results comparable to mITT population

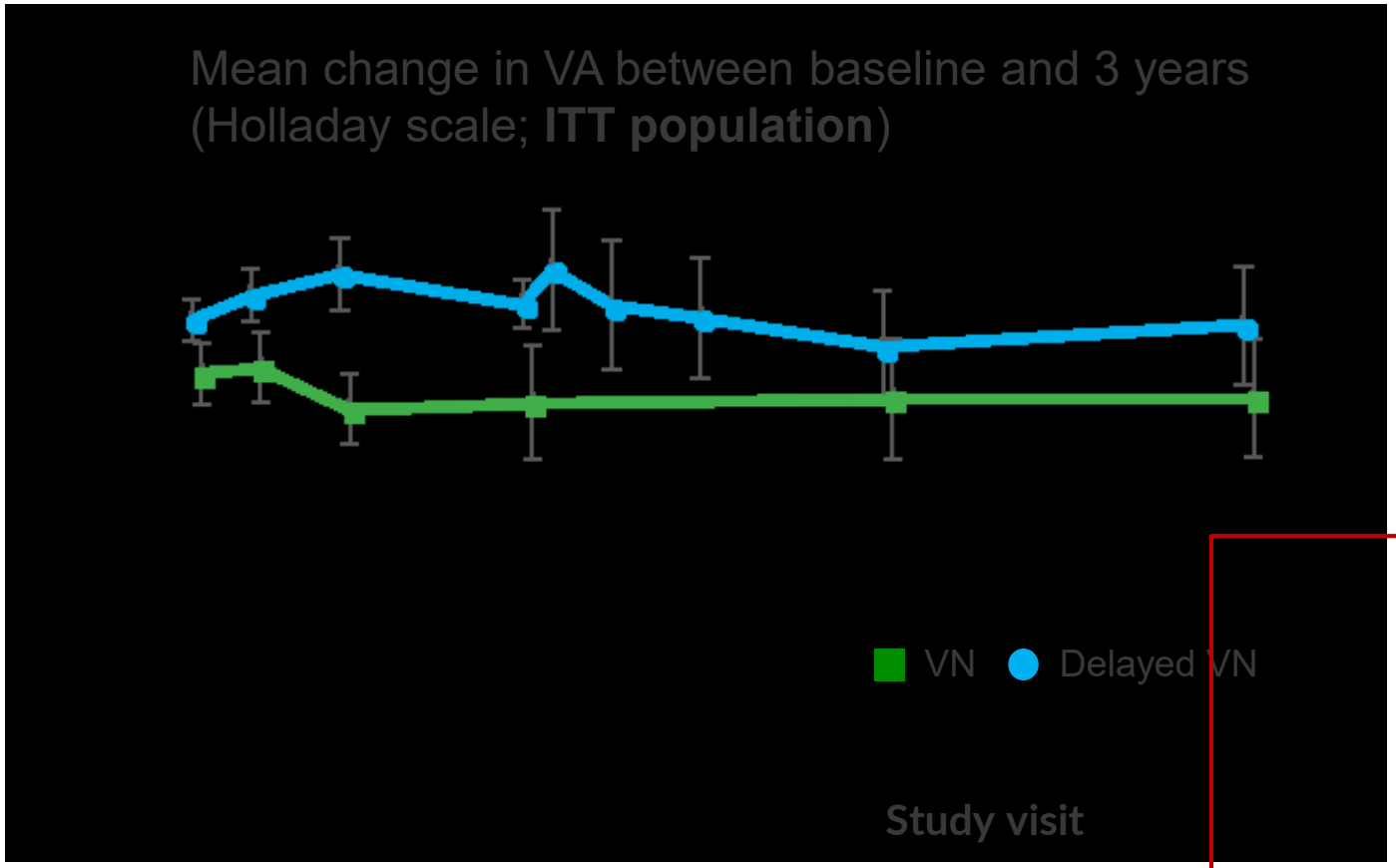
Lange scale

- Post-hoc analysis → reduced variability as a result of smaller off-chart changes
- Mean difference (ITT) -0.15 (95%CI -0.29, 0.00; p=0.047)
- Not clinically meaningful

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

Clinical effectiveness: visual acuity (VA)

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



ERG:

- Changes in VA not clinically meaningful
- [redacted]
- [redacted]
- [redacted]

Year of follow up [mITT population]		Original VN (n=20)	Delayed VN (n=9)
Mean change from baseline (SD) Holladay scale	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)

Outcome at 1 year		VN (n=21)	BSC (n=10)	Change	95% CI
Goldmann visual field III4e (º)	Mean change from baseline	302.1	-76.7	378.7	146-612 (p=0.006)
Humphrey VF macular threshold (dB)		7.9	0.0	7.9	3.5-12.2 (p=0.0005)

Clinical effectiveness: visual field (VF)

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

ERG:

- Clinically meaningful impact of VN on VF [redacted]
- Changes clinically significant in improving mobility and navigational vision
- [redacted]
- Uncertainty on VN's long-term effect on VF and VA

Improvement in VF seen after delayed VN treatment

Clinical effectiveness: Photosensitivity

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

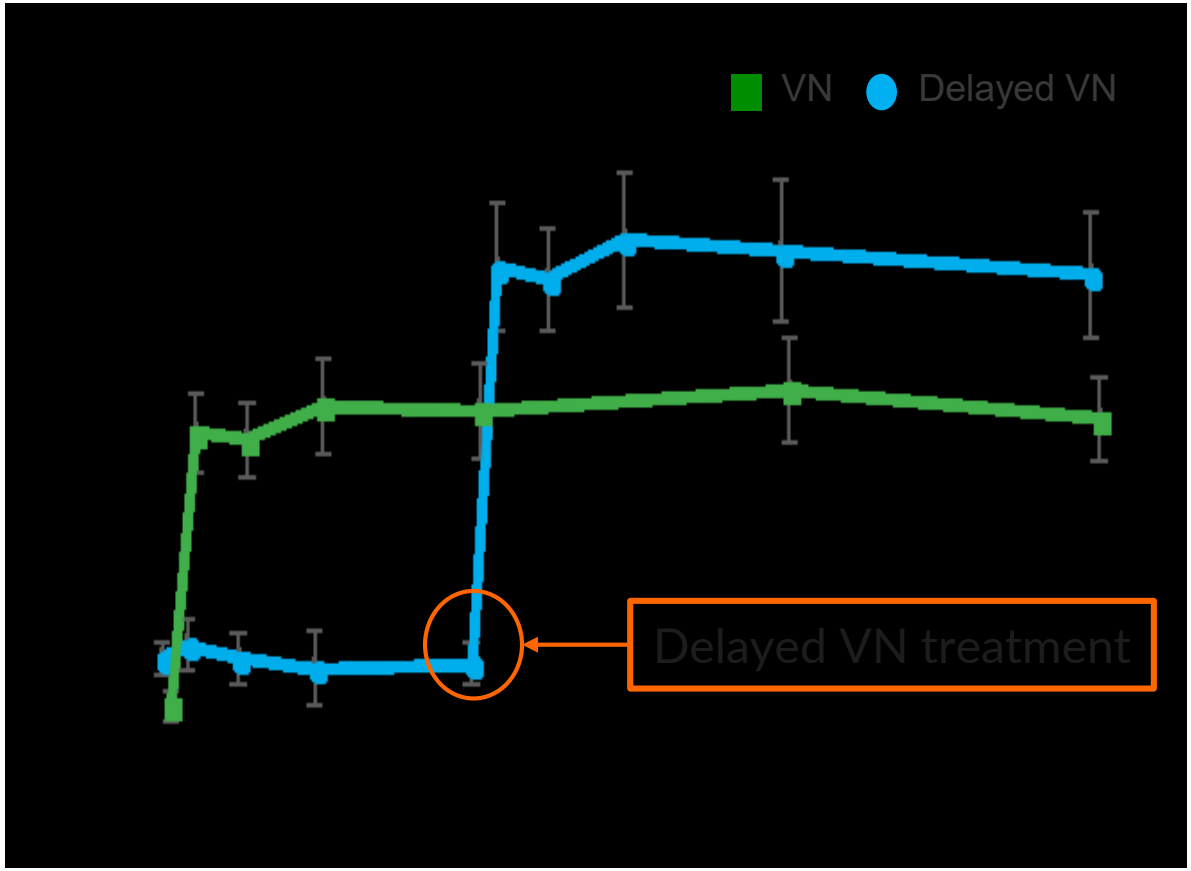
Study 301

- 2-log unit improvement in 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) - ITT population

Study 302

	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)

Improvement above the company's threshold for clinical significance (≥1 log unit)



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]

Clinical effectiveness: visual function questionnaire

- Study 301 used a customised visual function questionnaire (VFQ): higher scores = reduction in the difficulty of daily living activities
- [redacted]

- Difference in mean change from baseline to Year 1 between VN and BSC was statistically significant for patients [redacted] p=0.001) and parents [redacted] p=0.002)

Additional ERG comments on clinical effectiveness

HRQoL

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

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

Committee:
What is committee's view on the effect of VN in the short, and long term (biological plausibility)?
Do the clinical trials capture outcomes/benefits that are important to patients?

[redacted]

Adverse events

No deaths and no patients withdrew from any trials due to adverse events (AEs)

Treatment-emergent AEs (TEAEs):

Study 301: 13/20 (65%) experienced TEAEs in the VN arm, 1/9 (11.1%) in the BSC arm
Study 302: TEAEs similar between Original (13/20; 65%) and Delayed VN arms (6/9; 67%)
Study 101/102: [redacted]

Non-serious TEAEs experienced by ≥10% ppts	VN / original arm	
	n/N (%)	# Events
Study 301 (from baseline to 1 year)		
Cataract	3/20 (15.0%)	4
Elevated intraocular pressure	4/20 (20.0%)	5
Retinal tear	2/20 (10.0%)	2
Eye inflammation	2/20 (10.0%)	6

Serious adverse events (SAEs):

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

ERG: VN is associated with an acceptable safety profile
However, the administration is associated with a high risk of AEs

[redacted]

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NICE National Institute for Health and Care Excellence

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

1st Evaluation Committee Meeting
Highly Specialised Technology, 25th July 2019
Economic effectiveness

Lead team: Carrie Gardner, Shehla Mohammed and Linn Phipps
Company: Novartis
Chair: Peter Jackson
Evidence review group: PenTAG
NICE team: Lorna Dunning, Yelan Guo, Sheela Upadhyaya

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?

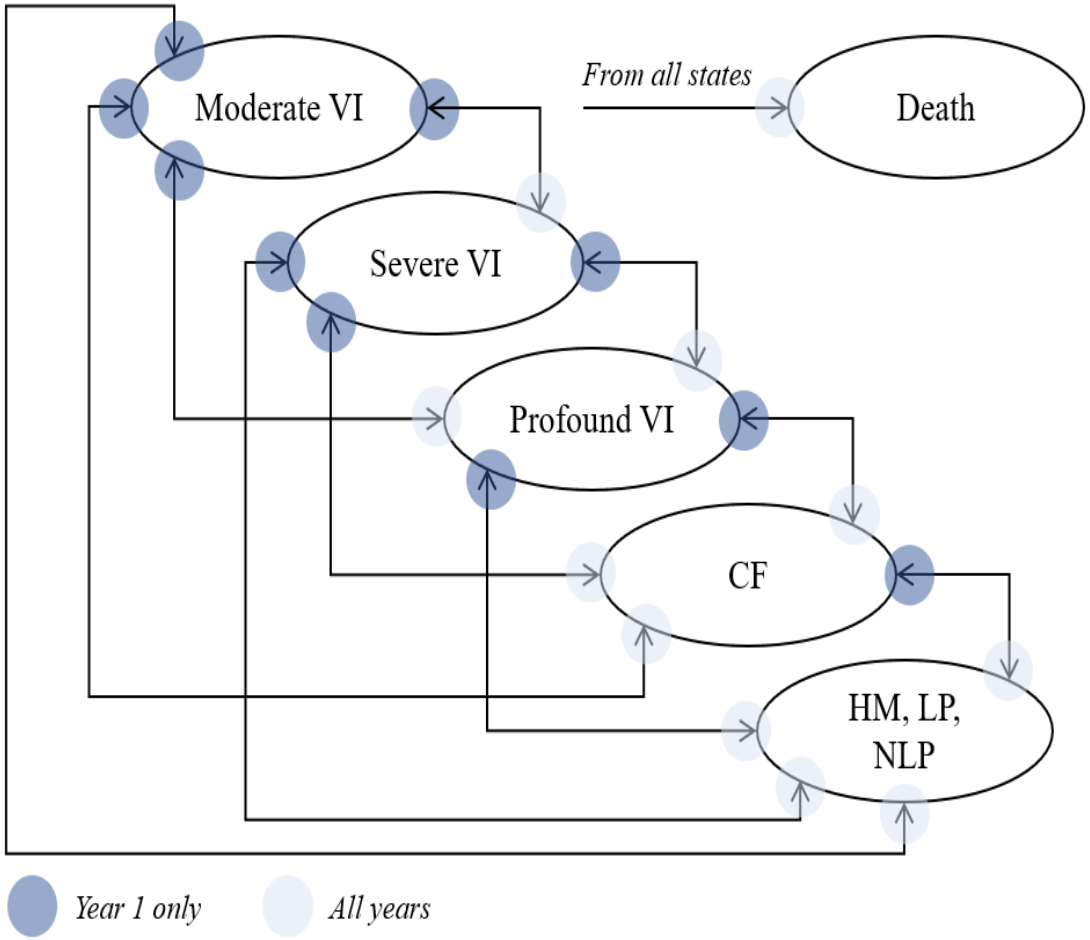
Key issues for consideration

- *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?

[redacted]

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)

Company's evidence sources and assumptions

Population	• 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 using MSM model • MSM models risk of moving between health states varying over time • VN arm: treatment effect persists for 40 years (transitions to death only) • 10-year waning period where efficacy of VN decreases from 100% to 25% (patients follow the natural history model projections) • BSC arm: data from natural history study (RPE65 NHx) fitted to MSM model
HRQoL	• Patients: utilities derived via an expert elicitation exercise (Lloyd et al 2019) • Carer: disutility (0.08) applied from *Wittenberg 2013* to HS2-5 for <18, half 18+
AEs	• Disutilities applied as one-off QALY loss at the time of VN from NICE NG82
Resource use & costs	• Administration of VN (including surgery and immunomodulatory regimes) • 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)

Abbreviations: AEs, adverse events; ITT, intention to treat; MSM, multi-state model; NG, NICE Guideline; ONS, Office of National Statistics; QALY, Quality adjusted life year; VA, visual acuity; VF, visual field

Population: baseline distribution

Baseline characteristics: (mean age 15.1 years, 42% male) from Study 301

Baseline health state distributions:

Company base-case: **Study 301**

Company scenario: **RPE65 NHx (*Chung 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

ERG base-case pooled ITT and NHx: Mean age 15.0 years, 41% male

ERG:

- 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) in Study 301 may impact treatment outcomes and adds to uncertainty of VN treatment effect
- ERG prefer to use a ***pooled average*** of health state occupancy from Study 301/302 and the RPE65 NHx study to increase sample size and generalizability

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

[redacted]

Transition in the model: initial phase

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

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
- [redacted]

Transitions in the model: long-term phase

Markov state transition model

Year 1

Initial phase

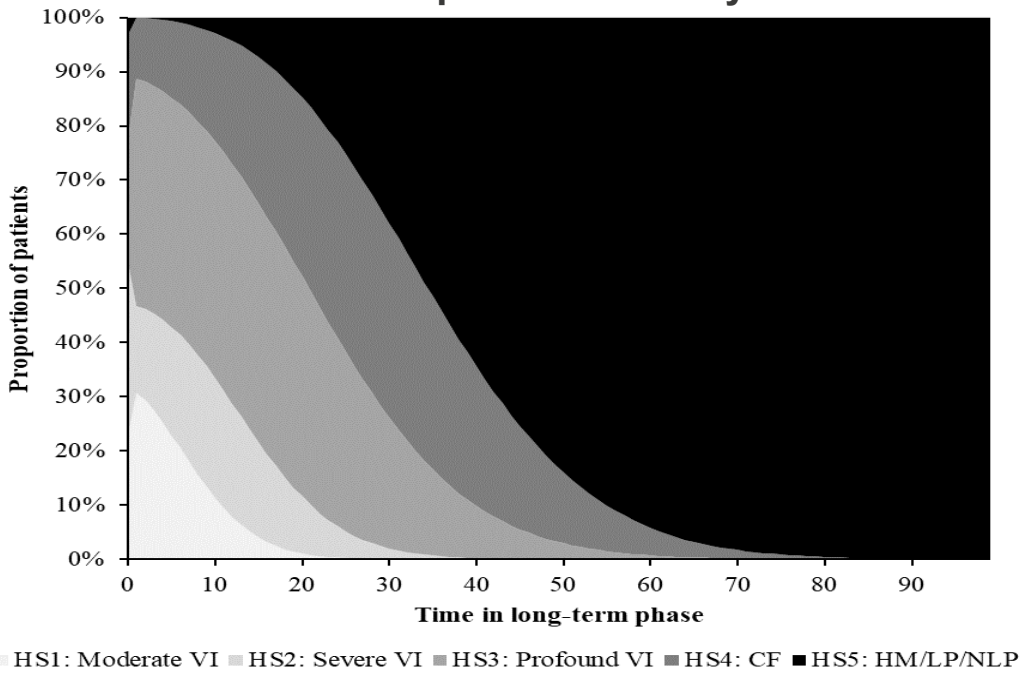
- **State transition model**
- Transitions based on **Study 301**

Year 2+

Long-term phase

- **Multi-state model (MSM)**
- Fitted to **RPE65 NHx** study (n=70)
- Transition rates converted to probabilities
- Progressive only → patients can't 'improve' health states
- Probability of movement to another health state based on time since model entry
- Weibull selected as base case on visual inspection and statistical fit
- Transitions to 'dead' not captured by MSM

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 and not all patients received licensed dose
- Limitations with RPE65 NHx study but use of the data is appropriate
- 2 patients omitted from RPE65 NHx study without explanation
- MSM is overly complex and may 'over fit' data

ERG's comments on the MSM

- MSM implemented correctly but longer-term projections remains a key limitation
- Cox-Snell residual plots do not provide clear evidence of the best fitting model
- Markov assumption (probability of movement to another health state) may not hold, but small sample size limits the ability to validate the assumption
- Extrapolations have not been validated and 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

[redacted]

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

[redacted]

Mortality

- Mortality data from general population life tables for England and Wales (ONS)
- Probability of death based on the mean baseline characteristics (age and sex) and a health state-specific mortality multiplier (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:

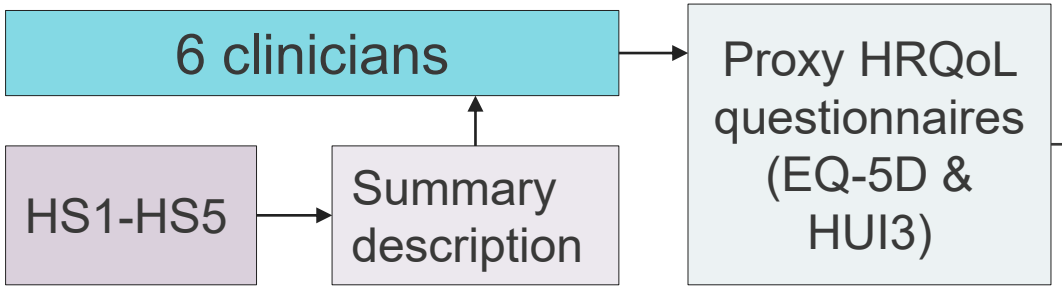
- Agree that mortality should be captured separately to the transitions between living health states
- Disagrees that the model health states are associated with an increased risk of death
  - No deaths occurred in any study included in the evidence base
  - *Christ et al* includes a population substantially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

Committee: Should additional mortality risks being included in the model?

[redacted]

HRQoL: company's utility values

- No HRQoL available
- Company performed an elicitation exercise with 6 clinicians:



- EQ-5D has poor validity in visual disorders
- HUI3 contains a vision component so preferred as company base case

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
- Lowest utility values for vision loss in previous NICE submissions between 0.26 and 0.548
- Previous definitions of blindness in NICE TAs would include several health states

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

Health state	Company base case (HUI3)	Rentz et al. 2014 (n=607)	Rentz et al. (UK only, n=152)	HS5 matched to penultimate worse health state (n=607)
HS1	0.52(0.16)	0.717	0.687	0.717
HS2	0.36 (0.11)	0.624	0.581	0.638
HS3	0.22 (0.10)	0.530	0.476	0.560
HS4	0.14 (0.09)	0.437	0.370	0.481
HS5	-0.04 (0.07)	0.343	0.264	0.402

ERG base-case

ERG:

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

Committee: Does the committee consider that the HRQoL of people living with RPE65 mediated IRD appropriately captured?

Adverse event disutilities

- Disutilities 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 disutilities 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 for discomfort or inconvenience associated with the administration procedure of VN

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

[redacted]

Carer disutility

- Kuhlthau et al 2010 → parents of children with activity limitations: 0.08 lower EQ-5D score than parents of children without activity limitations
- Applied as carer disutility in HS2-HS5 to children (<18 years)
- Disutility for carers of adults assumed to be 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 may have more than one caregiver → multiplied by 1.78 (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

[redacted]

Resources and costs – one-time 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 2 surgeries for children (65%) and adults (35%)

One-time event	Cost
VN acquisition (list price)	£613,410
Administration Surgery Immunomodulation	 £2,269.80 £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

[redacted]

ERG: costs associated with depression removed from ERG base case. 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 • 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, however:

- It remains unproven that benefits may extend beyond 30 years
- VN requires the NHS to commit significant, irrecoverable costs as a 'one-off' gene therapy

[redacted]

Cost effectiveness – results

Company base-case (list price)

	Total			Incremental			ICER
	Costs	LYGs	QALYs	Costs	LYGs	QALYs	
Deterministic company base-case							
BSC	£46,473	25.46	3.6	-	-	-	-
VN	£658,486	25.50	10.7	£612,013	0.04	7.1	£86,635

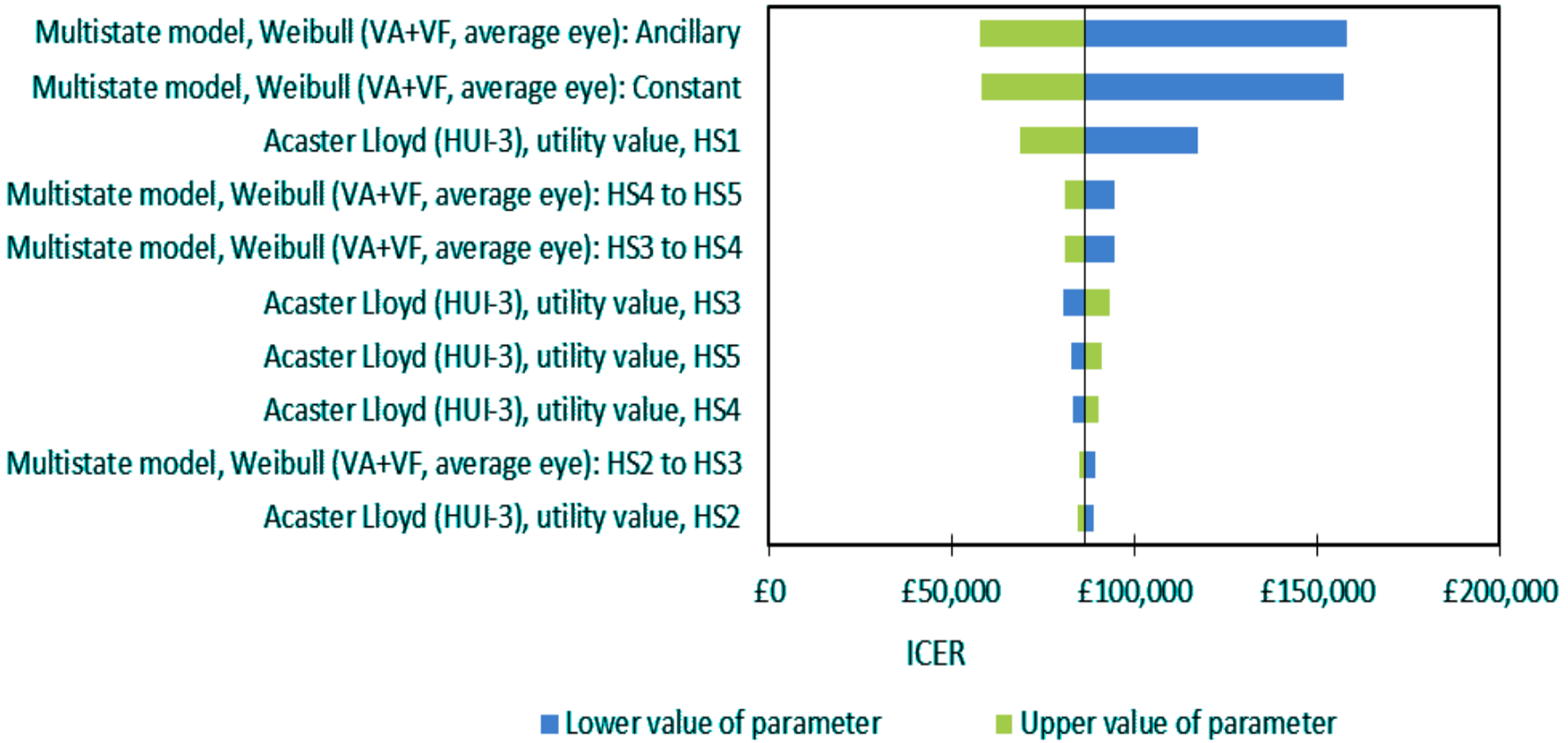
Abbreviations: LYG, life years gained, QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Probabilistic company updated base-case		Costs	QALYs	ICER
VN vs BSC	10,000 simulations	£612,018	6.8	£89,878

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

[redacted]

Company's uni-variate deterministic sensitivity analyses (list price)



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

The company varied each parameter value by ±15%.
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 (list

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	£612,013	7.06	£86,635	0%
1.5% discount rate for costs and outcomes	£605,187	12.32	£49,111	-43%
Health states 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	£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 w/no data: remain in same state	£612,013	6.95	£88,061	2%
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%
Waning period: 5 years	£612,501	7.02	£87,278	1%
Waning period: 20 years	£610,539	7.16	£85,270	-2%
Log-normal multistate model distribution	£611,576	6.61	£92,501	6%
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%
No healthcare resource use in HS1	£604,864	7.06	£85,623	-2%

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 • Applied for children and 50% of adults	• 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 exclude PAS discount for VN are given for list price
- Each change varied independently

Arm	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER	Δ ICER
Company's base case						
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 by 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

ERG's cost-effectiveness results (II)

- Analyses exclude PAS discount for VN are given for list price
- 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	£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 (list price)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Company base-case					
BSC	£46,473	3.6	-	-	-
VN	£658,486	10.7	£612,013	7.1	£86,635
ERG preferred base-case (all changes combined)					
BSC	£35,731	12.9			
VN	£654,079	16.9	£618,348	4.0	£155,750

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

[redacted]

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)

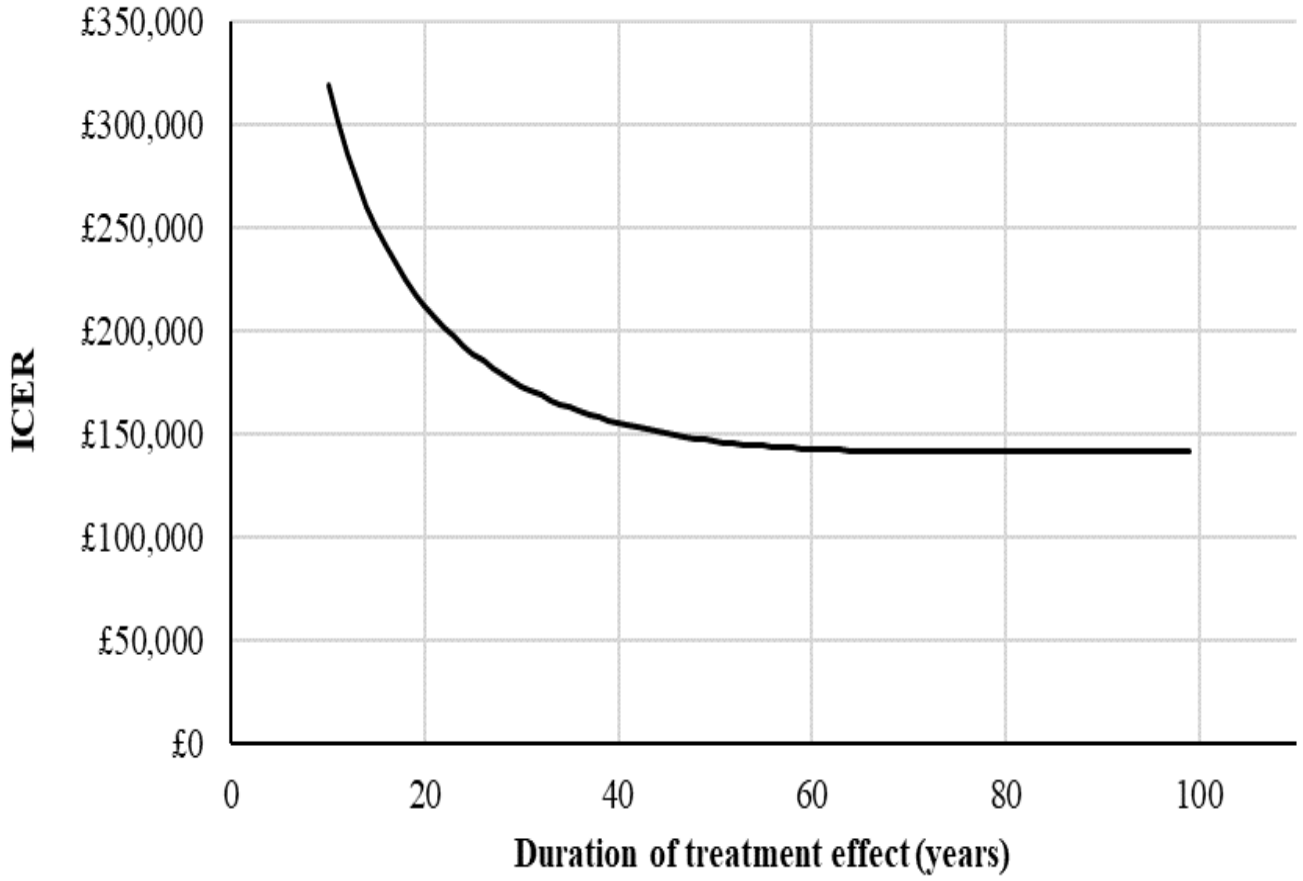
Baseline characteristics

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

[redacted]

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

Threshold analysis varying the duration of treatment effect (list price)



- 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

[redacted]

ERG's exploratory analyses (list price)

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 (10yrs)					
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
Use company-preferred 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. 2014)					
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. 2014)					
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

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

[redacted]

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 needed to fall below £100,000 per QALY

Incr. QALYs	Weight
11–29	1→3 (using equal incr.)
≥30	3

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 (list price)** (per QALY gained)
Company base case*	20.3	7.1	£86,635
ERG preferred base case*	12.1	4.0	£155,750

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

ERG most pessimistic scenario (assuming ICERs' treatment effect [10 years]): **4.4**

* Both company and ERG's base case assume 40 year treatment effect

Budget impact analysis (list price)

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)	£3,291,787	£15,889,011	£15,902,027	£15,915,026	£6,733,015

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

Committee: Taking into account RPE65-mediated IRD as a disability what, if any, further adjustments should be made to the processes, methods and committee's considerations?

- 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

[redacted]

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