COST-EFFECTIVENESS ANALYSIS OF VORETIGENE NEPARVOVEC VERSUS BEST SUPPORTIVE CARE IN PATIENTS WITH RPE65-MEDIATED INHERITED RETINAL DYSTROPHY: A FRENCH HEALTHCARE SYSTEM PERSPECTIVE

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ISPOR 2019 - Copenhagen

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Submitted abstract

OBJECTIVES: An economic model was developed to evaluate the cost-effectiveness of voretigene neparvovec (VN) compared to best supportive care (BSC) in individuals with RPE65-mediated inherited retinal dystrophy (IRD), from a French healthcare system perspective. Methods were based on HAS guidelines and international good research practices for modelling.

METHODS: A Markov model was used and included six health states (HS) based on AMA visual deficiencies classification: Moderate Visual Impairment (VI), Severe VI, Profound VI, vision limited to "counting fingers", vision limited to "hand motion" to "no light perception" and death. A lifetime horizon was used. Transition probabilities were calculated based on the results from the VN phase III trial and a natural history study. The economic endpoints used in the model were blindness-free years (BFY) and quality-adjusted life years (QALYs). Utility data from a vignette study were used. Resource utilization and costs included: disease-related costs (diagnosis, mutation testing, paramedical care and follow-up), drug costs (acquisition, administration and adverse events), costs of medical transport and accommodation and death.

RESULTS: Patients treated with VN stayed longer in better HS while patients in the BSC arm progressed more quickly to worse HS. The treatment with VN results in a gain of 11.7 BFY and 4.5 QALY versus BSC. The ICER for VN versus BSC was €51, 552 per BFY and €132, 607 per QALY. Deterministic and probabilistic sensitivity analyses generally showed consistency with base case findings. When additional scenarios were explored, ICERs were most sensitive to variations in the multi-state model parameters and duration of treatment effect.

CONCLUSIONS: VN is the first gene therapy approved in RPE65-mediated IRD and represents a clinically significant advancement in the management of this disease. VN was associated with an important gain of QALYs versus BSC and can be considered a cost-effective therapy in this orphan disease.

Objectives

An economic model was developed to evaluate the cost-effectiveness of voretigene neparvovec (VN) compared to best supportive care (BSC) in individuals with RPE65-mediated inherited retinal dystrophy (IRD), from a French healthcare system perspective.

Clinical context

RPE65-mediated IRD is an ultra-rare disease leading to vision loss and blindness before the age of 40

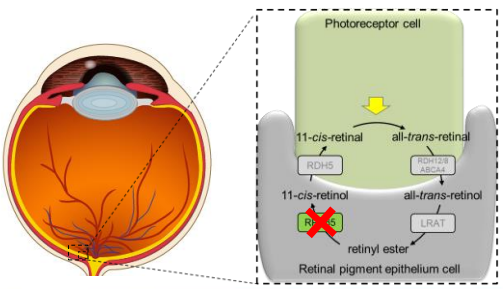
Photo-receptors	Impairment in biallelic RPE65-mediated IRD[1-3]
Rods	• Decreased light sensitivity • Diminished visual field • Nyctalopia • Nystagmus • Poor adaptation to suboptimal light situations
Cones	• Inability to resolve finer central detail

Functional vision impairment
Symptoms increasingly limit an affected individual's ability to independently navigate the environment, especially under suboptimal light

1. Thompson et al. Invest Ophthalmol Vis Sci. 2000;41:4293-4299.
2. Weleber et al. Invest Ophthalmol Vis Sci. 2011;52:292-302.
3. Lorenz et al. Invest Ophthalmol Vis Sci. 2000;41:2735-2742.

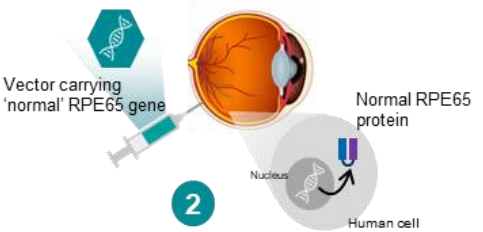
VN is the 1st gene therapy in ophthalmology

- The *RPE65* gene encodes a protein, RPE65[1-2]
  - critical component in the visual cycle
  - necessary for vitamin A metabolism in photoreceptor cells
- Mutations in the *RPE65* gene lead to vision loss and degeneration of photoreceptors[2,3]



First approved gene therapy treatment for an inherited retinal disease

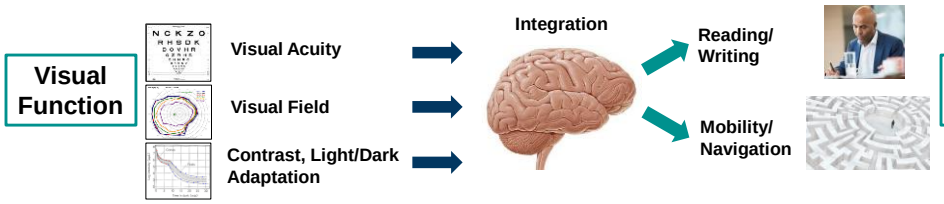
1. Subretinal injection with VN containing correct RPE65 gene

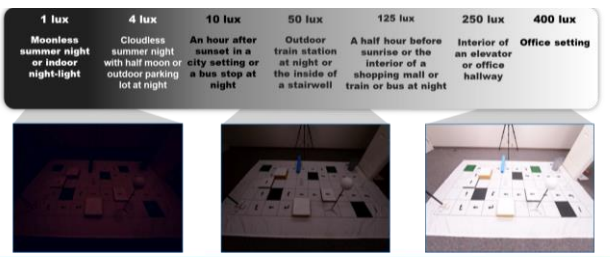


2. Retina expresses normal RPE65 protein to replace defect one

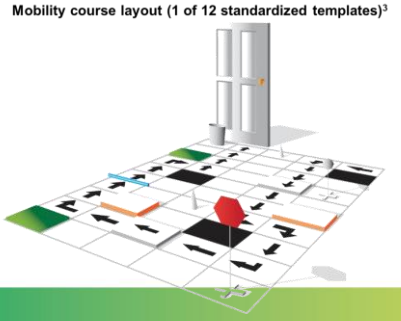
1. Gu et al. Nat Genet. 1997;17:194-197.
2. Weleber et al. Invest Ophthalmol Vis Sci. 2011;52:292-302.
3. Palczewski et al. Invest Ophthalmol Vis Sci. 2014;55:6651-6672.

New test needed to measure the impact on functional vision: Multi-Luminance Mobility Test

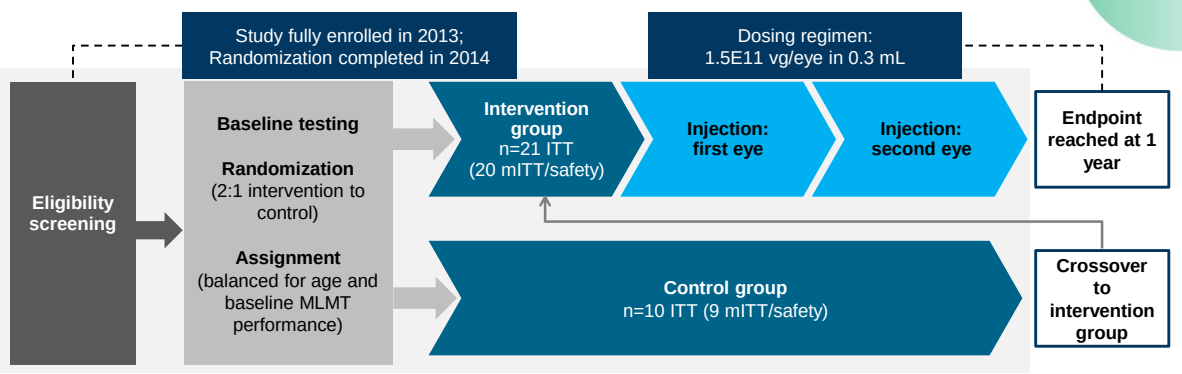




Mobility course layout (1 of 12 standardized templates)[3]



Phase III trial design



Key inclusion criteria:
- ≥3 years of age
- Confirmed *RPE65* mutations
- Sufficient viable retinal cells (can be confirmed by OCT)

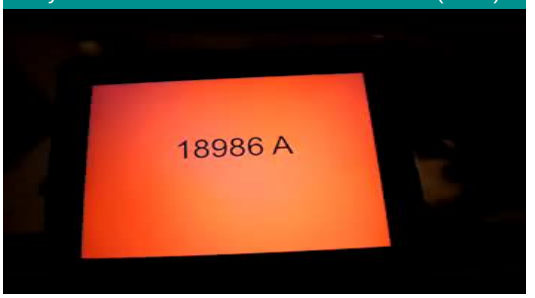
Endpoints:
- Primary: MLMT performance (bilateral)
- Secondary: FST testing, MLMT (assigned first eye), visual acuity and visual field

Russell 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. Lancet. 2017 Aug 26;390(10097):849-860

Phase III results : 90% of patients showed improved functional vision at Year 1

Pre-treatment
Baseline visit at 4 lux (**Fail**)

Post-treatment
1-year visit after VN administration at 4 lux (**Pass**)



Multi-Luminance Mobility (MLMT) tests of phase III trial participant (bilateral testing)*

- The camera used automatically adjusts the level and temperature of light that it captures.
- Because of this feature, there may be slight variations in hue when filming at low light levels (e.g. 1 lux).
- Both videos were filmed in low-light environments. 4 lux is equivalent to a cloudless summer night with half moon or outdoor parking lot at night.
- Light meter: National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing.

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*Representative of clinical trial participant with clinically meaningful score change (2 or greater) from baseline.
Note: This participant's baseline passing level was 50 lux and 1 year passing level was 1 lux.

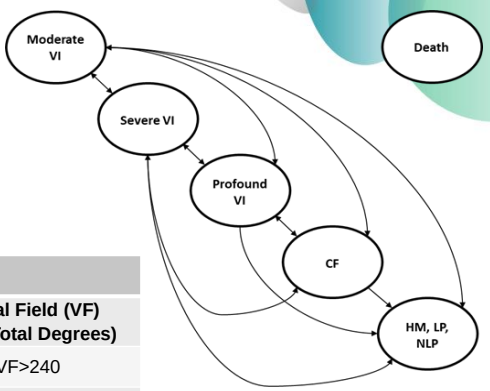
Cost effectiveness model

Methods
Model specifications

	Model specifications
Population	• Patients with RPE65-mediated IRD with sufficient viable retinal cells (mean age = 15 y.o)
Intervention	• Sequential, bilateral, subretinal administration of VN
Comparators	• Best supportive care
Outcomes	• Cost per QALY • Cost per blindness-free year (BFY)
Perspective	• Healthcare system perspective
Time horizon	• Lifetime (until patients are 100 y.o)
Cycle length	• 1 year
Discounting	• 4% until 30 years and 2% thereafter

Methods
Model structure

- A Markov model was used
- Modelled health states were based on the AMA visual deficiencies classification[1]



Health state	Worst of:		
	Visual Acuity (VA) (logMAR)		**Visual Field (VF) (Sum Total Degrees)**
Moderate VI	VA<1	Or	VF>240
Severe VI	VA≥1 and VA<1,4	Or	VF≤240 and VF>144
Profound VI	VA≥1,4 and VA<1,8	Or	VF≤144 and VF>48
Vision limited to "counting fingers"	VA≥1,8 and VA<3	Or	VF≤48
Vision limited to "hand motion" to "no light perception"	VA>3		

1. AMA Guides to the Evaluation of Permanent Impairment, 6th Edition
AMA: American Medical Association ; VI: visual impairment; CF: count fingers ; HM : Hand motion ; LP : light perception; NLP: no light perception

Methods
Model time periods

	Voretigene neparvovec	Best supportive care
Initial phase (year 1)	Transition probabilities (TP) based on phase III trial results[1] Surgery-related adverse events	TP based on phase III trial results[1] No adverse events
Stabilization phase	Sustained treatment effect for 20 years - Phase I trial[2] : 7 years follow-up - Phase III trial[1] : 4 years follow-up - Clinicians inputs	No stabilization phase
Long-term phase	TP based on natural history study[3] data calculated with a multistate model INSEE French mortality data[4]	

1. Russell et al. Lancet. 2017;390:849-860
2. Bennett et al. Lancet. 2016;388:661-672
3. Chung et al. Am J Ophthalmol. 2019; 199:58-70
4. https://www.insee.fr/fr/statistiques/2851503?sommaire=2851587

TP: transition probabilities ; INSEE : Institut national de la statistique et des études économiques

Methods
Utility data

- No utility data were available from VN phase III trial
- Alternative sources of data :
  - Systematic literature review
    - Brown et al. 2003[1] : study conducted on patients with diabetic retinopathy and macular degeneration, mean age = 68 years, only VA assessed, used in other CE models
  - A specific study was conducted: Lloyd et al. 2019[2]
    - Vignettes developed with RPE65-IRD patients, parents and clinicians for each model health states
    - EQ-5D and HUI-3 questionnaires filled by clinicians

	Brown	Lloyd (EQ-5D)	Lloyd (HUI-3)
Moderate VI	0.74	0.71	0.52
Severe VI	0.60	0.62	0.36
Profound VI	0.54	0.52	0.22
CF	0.52	0.35	0.14
HM/LP/NLP	0.31	0.15	-0.04

1. Brown et al. Health Care Economic Analyses and Value-Based Medicine. Surv Ophthalmol. 2003;48(2):204-23.
2. Lloyd A et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. Br J Ophthalmol. 18 janv 2019

VA: visual acuity ; VI: visual impairment; CF: count fingers ; HM : Hand motion ; LP : light perception; NLP: no light perception

Methods
Resource use and costs data

- Resource utilization and costs associated with each health state were identified and included :
  - Drug costs
    - VN cost, based on the early access program (ATU) cost (set by Novartis, reimbursed through a specific fund, not definitive)
    - Administration : retinal surgery DRG cost (PMSI 2018[1])
    - Adverse event-related costs (PMSI 2018[1])
  - Disease-related costs
    - Diagnosis and mutation testing
    - Consultations with ophthalmologist, paramedical team (orthoptist, psychologist,..)
    - Ocular exams : electroretinography, OCT,...
  - Transportation costs
    - added to each hospitalisation costs (Cour des Comptes, 2012[2])
  - Accommodation costs
  - Mortality costs
    - Cost of palliative care (PMSI 2018[1])

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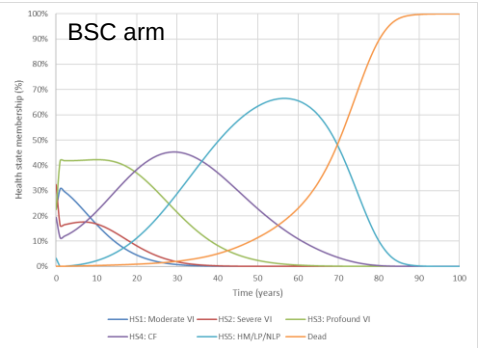
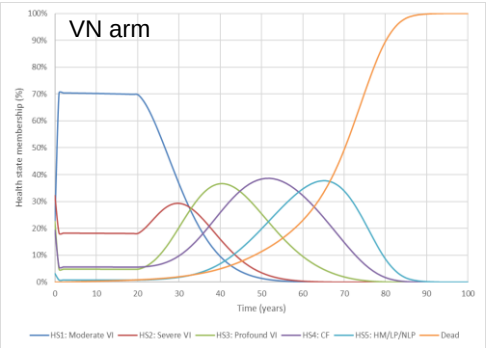
1. PMSI aggregated data available at: https://www.scansante.fr/
2. Cour des comptes. Rapport 2012 sur l'application des lois de financement de la sécurité sociale.

OTC: Optical Coherence tomography ; PMSI: Programme de Médicalisation des Systèmes d'Information

Results
Patient distribution within health states and ICER results





	QALYs	ΔQALY	BFY	ΔBFY	Costs	ΔCost	ICER
BSC	4.7	-	4.9	-	€ 350,556	-	-
VN	9.2	+4.5	16.5	+11.7	€ 951,517	€ 600,961	**€132,607 / QALY** **€51,552 / BFY**

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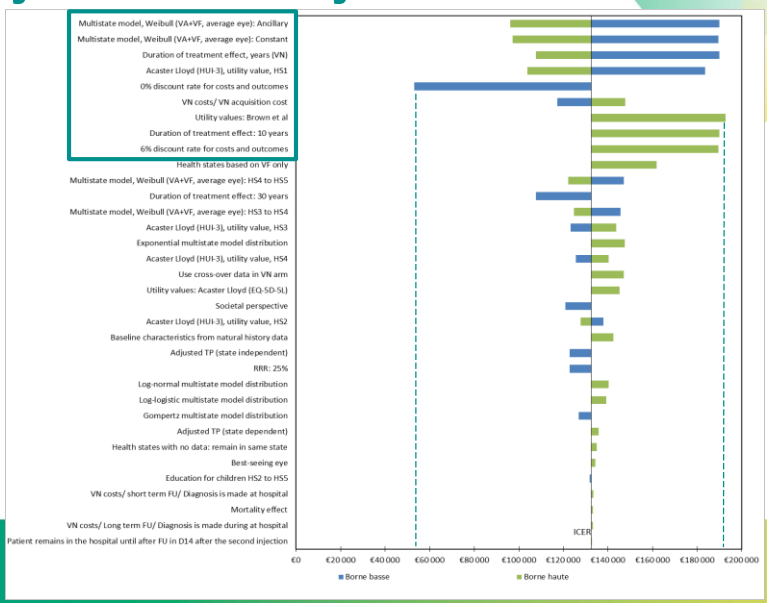
BFY: blindness-free year

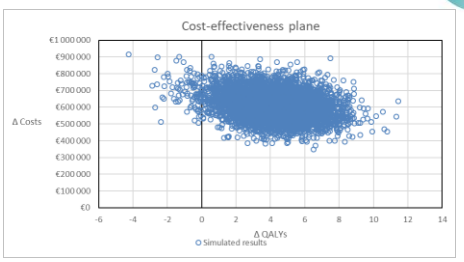
Results
Deterministic sensitivity analysis & scenario analysis

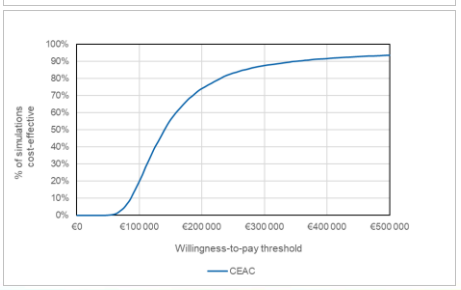
- In the DSA, parameters with the strongest influence on the ICER were:
  - Variations in the multistate model
  - Duration of treatment effect
  - Utility value for HS1
  - Discounting rates
  - VN cost
- When additional scenarios were explored, ICERs were most sensitive to variations in duration of treatment effect and utility values



Results
Probabilistic sensitivity analysis

- PSA showed consistency with base case findings
- After 5,000 Monte Carlo simulations, the resulting average ICER was €143,018/QALY
- At thresholds of €100,000, €150,000 and €200,000/QALY, there were 22%, 56% and 75% probabilities of VN cost-effectiveness, respectively





Conclusions

- VN is the first gene therapy approved in RPE65-mediated IRD and represents a clinically significant advancement in the management of this disease

- VN was associated with a substantial gain of QALYs (+4.5) and BFYs (+11.7) versus BSC and can be considered a cost-effective therapy in this orphan disease

Thank you