Gene Therapy for Rare Eye Diseases

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UNIVERSITEIT GENT

European Reference Network
for rare or low prevalence complex diseases

Network Eye Diseases (ERN-EYE)

Bart P LEROY, MD, PhD

Financial Disclosures

4DMT: consultancy fees

AAVantgardeBio: consultancy fees

Akouos: consultancy fees

Alia Therapeutics: consultancy fees

Alnylam Pharmaceuticals: trial support

Atsena Therapeutics: consultancy fees & trial support

Bayer: consultancy fees

Belite Bio: trial support

Biogen: consultancy fees, trial support

Coave Therapeutics: consultancy fees

GenSight Biologics: consultancy fees, travel support, trial support

Gyroscope: DMC membership

IVERIC Bio: consultancy fees, travel support

Jansen Pharmaceuticals J&J: consultancy fees, trial support

MeiraGTx: trial support

Novartis: consultancy fees, travel support, trial support, research support

Opus Genetics: consultancy fees

Oxurion: consultancy fees

ProQR Therapeutics: consultancy fees, travel support, trial support

Ray Therapeutics: consultancy fees

REGENXBIO: consultancy fees

SalioGen: consultancy fees

Santen: consultancy fees

SparingVision: consultancy fees

Spark Therapeutics: consultancy fees, travel support

SpliceBio: consultancy fees

Stoke Therapeutics: consultancy fees

Transine Therapeutics: consultancy fees

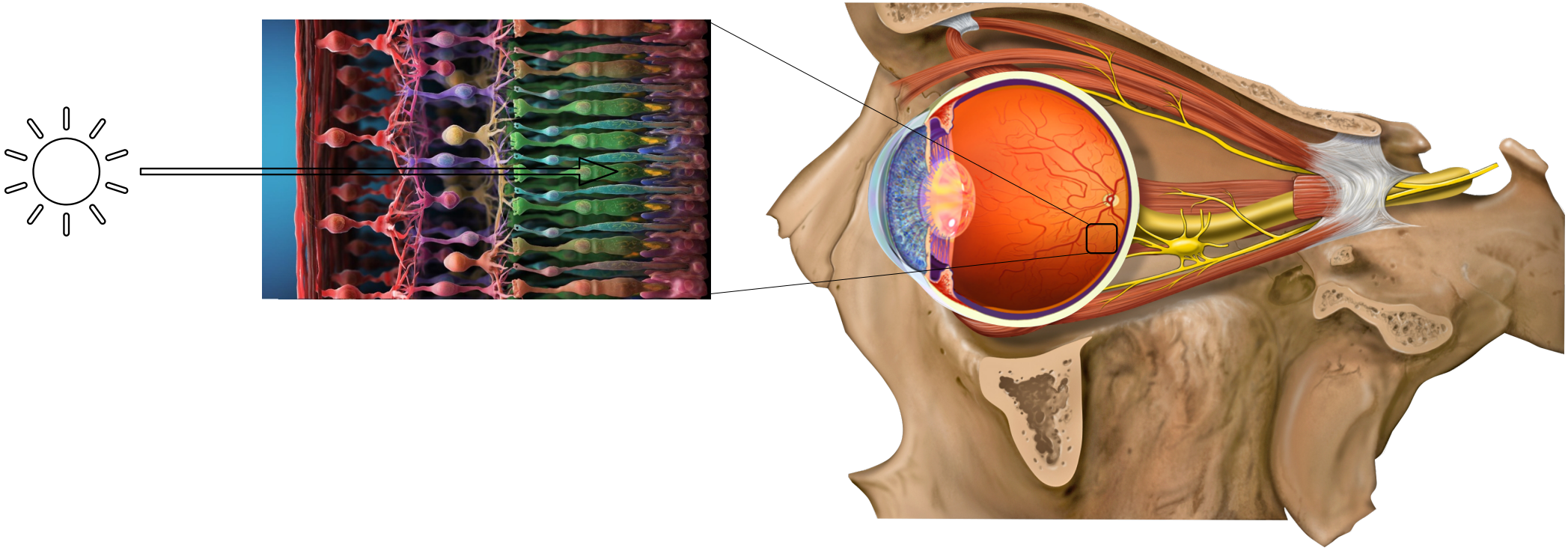
Vedere Bio I & II: consultancy fees

ViGeneron: consultancy fees, DMC member

The Human Eye, Retina & Retinal Disease

Rods, Cones & Retinal Pigment Epithelium (RPE)

Human Retina



Eye translates light into electricity

Introduction Retinal Cells & Circuitry

Adapted from ***The Neurology of Vision*** by JD Trobe

Ganglion cells

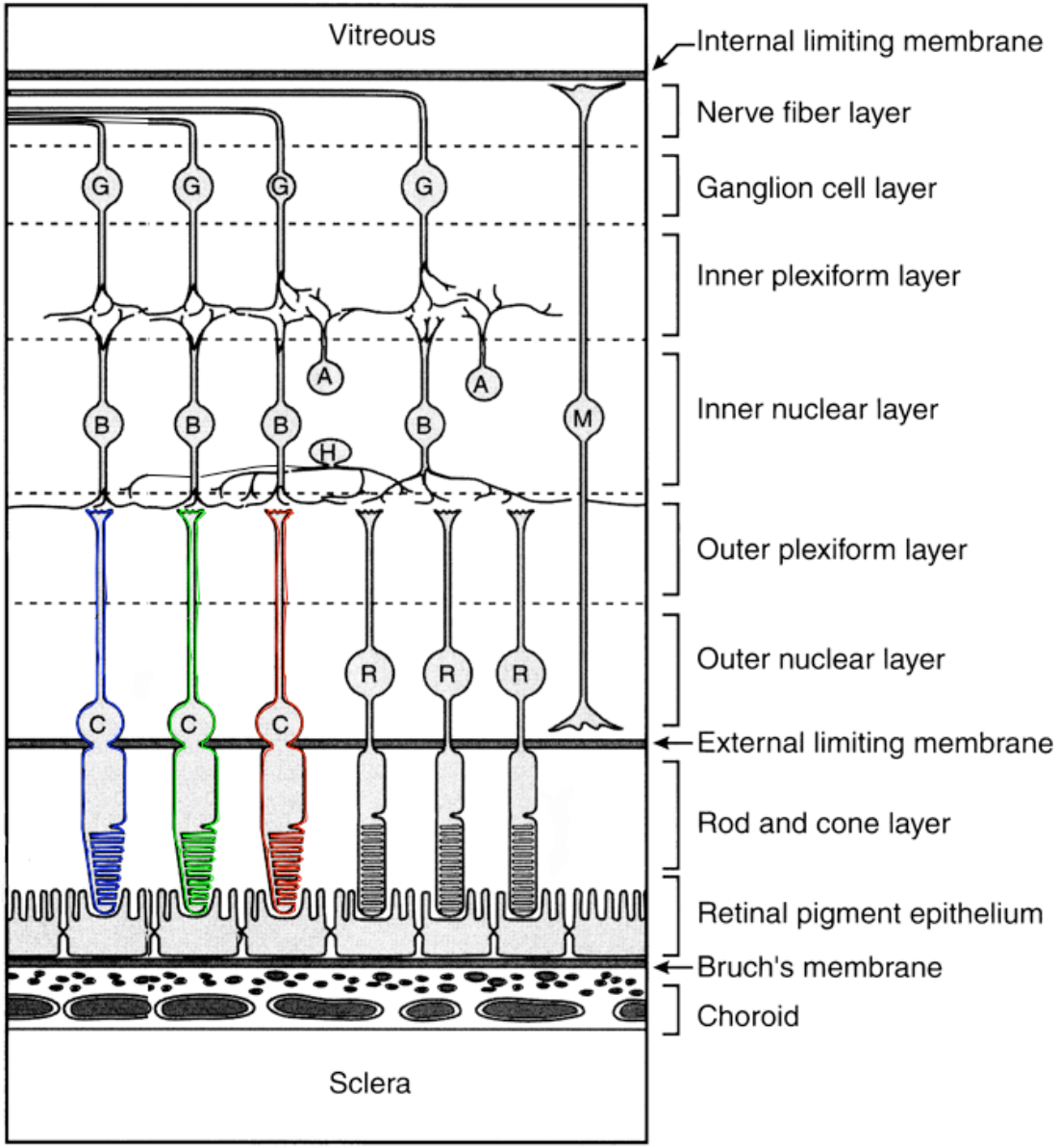
Amacrine cells

Bipolar cells

Horizontal cells

Photoreceptor cells (cones & rods)

Retinal pigment epithelium



Genes & Inherited Retinal Diseases (IRDs)

Leber Congenital Amaurosis (LCA) as a Model

Leber Congenital Amaurosis

Symptoms & Signs

No or little sensitivity for visual stimuli from birth

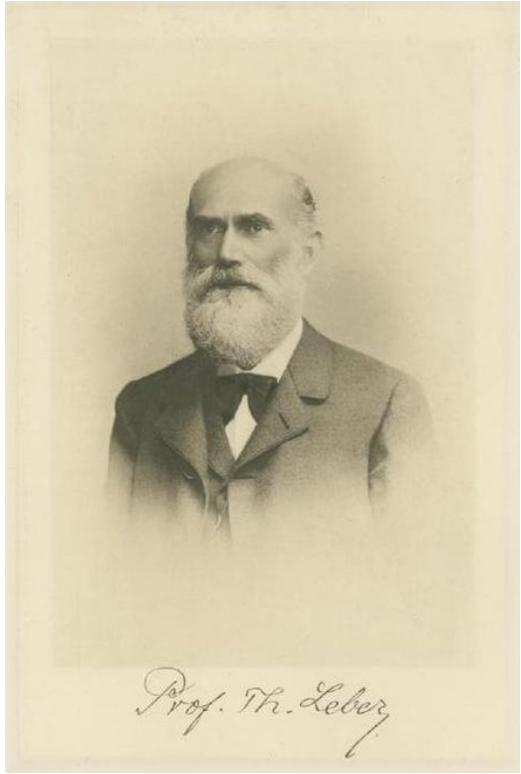
Variable aspect of retina

ERG abolished or profoundly abnormal

Autosomal recessive inheritance

Leber T: Uber retinitis pigmentosa und angeborene amaurose
Graefes Arch Klin Exp Ophthalmol, **15**, 13-20, 1869

LCA is responsible for 18% of legal blindness in children worldwide



Theodor Karl Gustav von Leber
19 Feb 1840 - 17 Apr 1917

Leber Congenital Amaurosis

Symptoms & Signs

No or little sensitivity for visual stimuli from birth

Variable aspect of retina

ERG abolished or profoundly abnormal

Autosomal recessive inheritance

Hyperopia

Sluggish pupillary responses

Oculodigital sign

Keratoconus

Occasional photophobia

LCA & EORD Genotypes

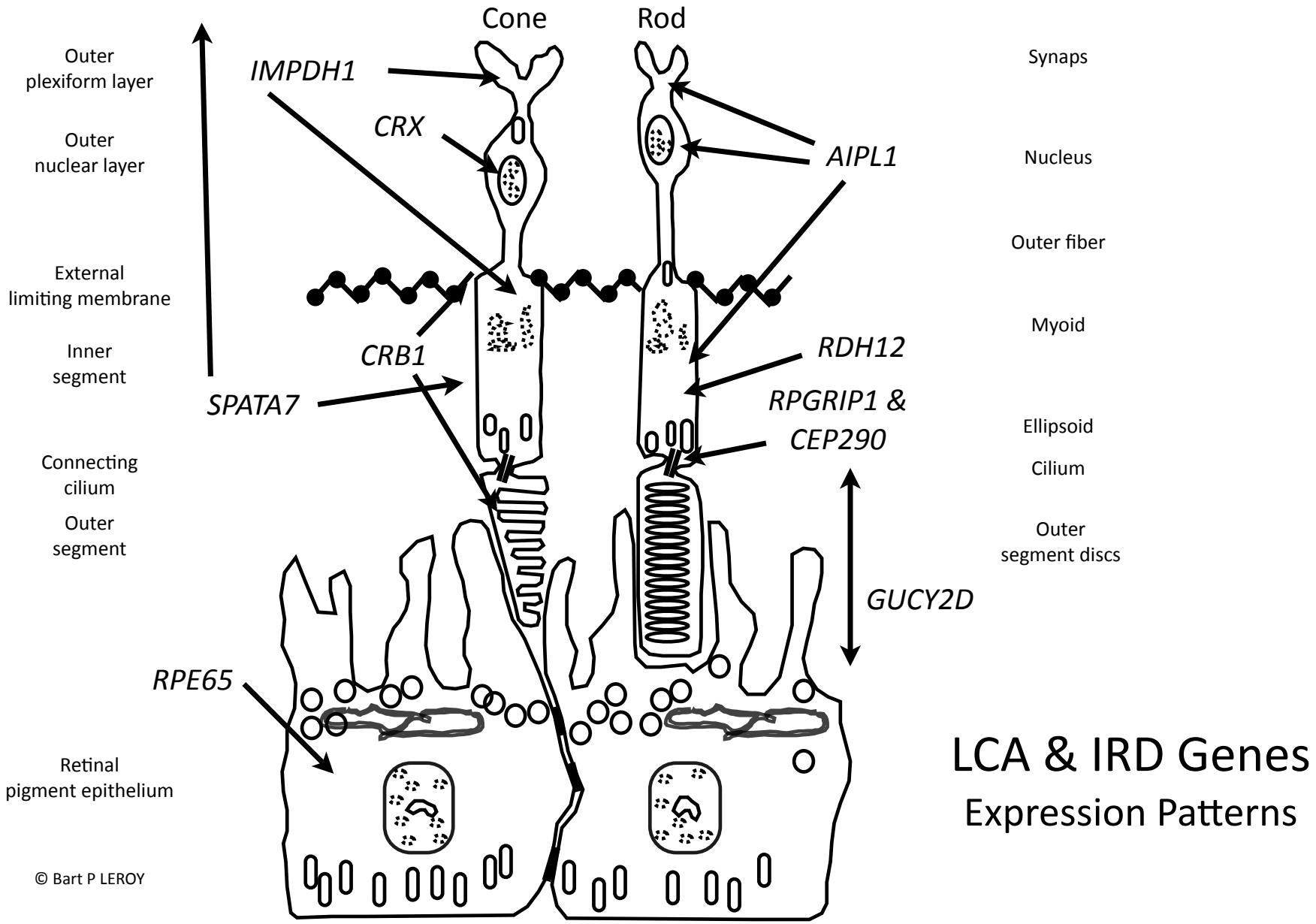
24 LCA genes:

GUCY2D on 17p13.1
RPE65 on 1p31
CRX on 19q13.3
AIPL1 on 17p13.1
CRB1 on 1q31-q32.1
RPGRIP1 on 14q11.2
MERTK on 2q14.1
RDH12 on 14q24.1
IMPDH1 on 7q31.3-32
TULP1 on 6p21
CEP290 on 12q21-q22
LCA5 on 6q11-q16
SPATA7 on 14q24
OTX2 on 14q21-22
IQCB1 on 3q21.1
PDE6G on 17q25
KCNJ13 on 2q37.1
RD3 on 1q32
NMNAT1 on 1p36
DTHD1 on 4p14
CAPB4 on Xp11.4
GDF6 on 8q22.1
IFT140 on 16p13.3
PRPH2 on 6p21.1

6 early-onset RP genes:

RDH12 on 14q23.3
LRAT on 4q31.2
MERTK on 2q14.1
TULP1 on 6p21.3
SPATA7 on 14q24
ADAMTS18 on 16q23.1

70% of patients

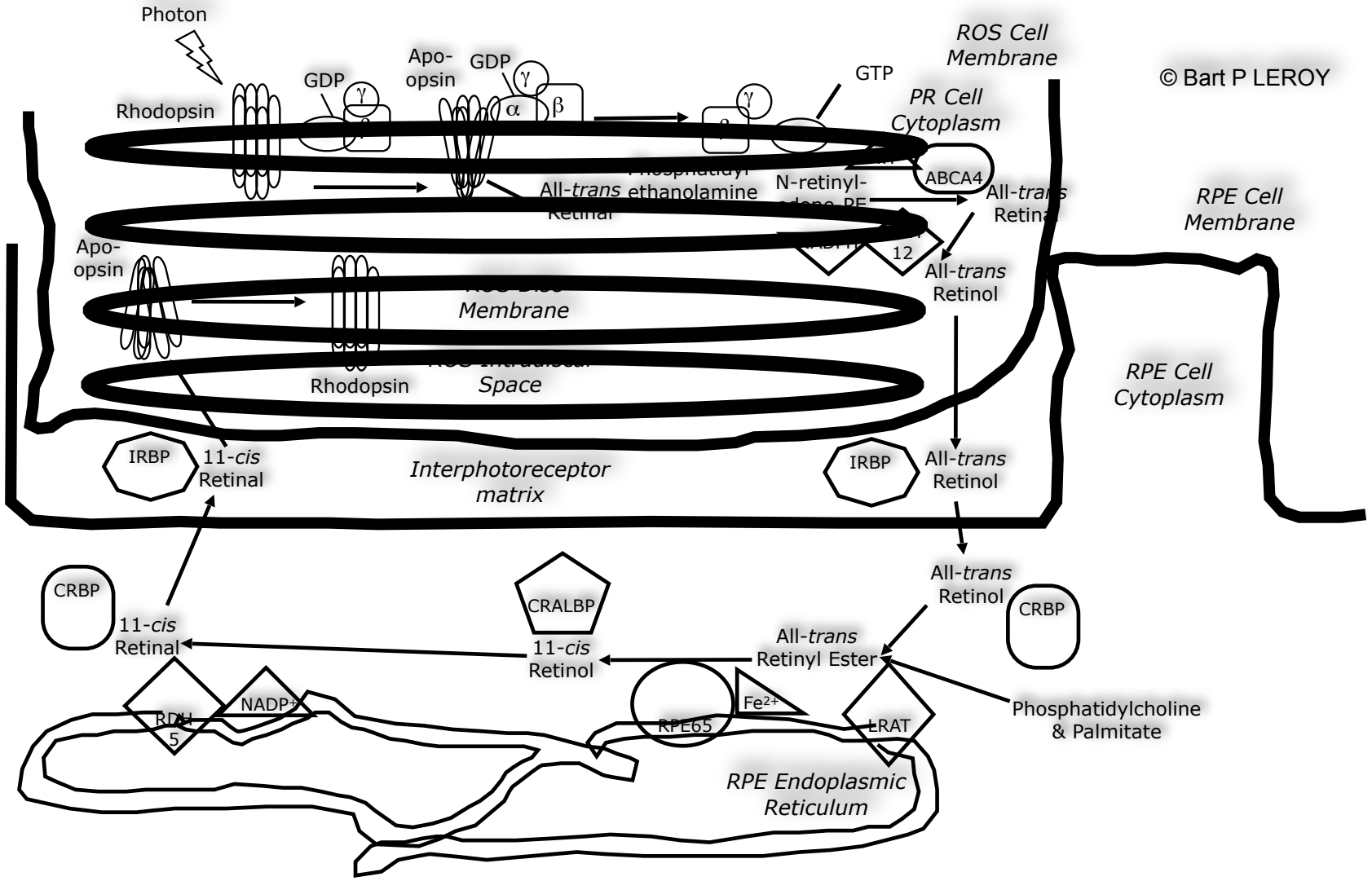


LCA & IRD Genes

Expression Patterns

Gene Augmentation Therapy with AAV2 *RPE65*-IRD (LCA2)

The Retinoid Cycle



RPE65-Related IRD
Timeline of Discoveries

Prof Christian HAMEL
1955-2017

Discovery of *RPE65* gene: Hamel CP, Jenkins NA, Gilbert DJ, Copeland NG, Redmond, TM: The gene for the retinal pigment epithelium-specific protein RPE65 is localized to human 1p31 and mouse 3, *Genomics*, 20, 509-512, 1994

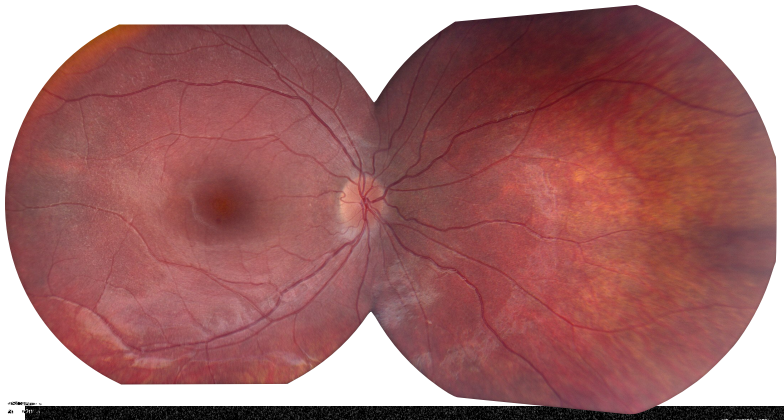
Mutations in *RPE65* cause retinal disease:

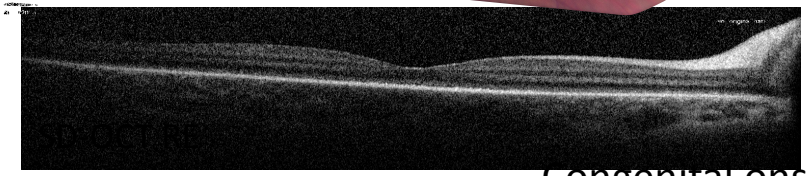
Marlhens F, Bareil C, Griffoin JM, Zrenner E, Amalric P, Eliaou C, Liu SY, Harris E, Redmond TM, Arnaud B, Claustres M, Hamel CP, *Nat Genet*, 17, 139-141, 1997

Gu SM, Thompson DA, Srikumari CR, Lorenz B, Finckh U, Nicoletti A, Murthy KR, Rathmann M, Kumaramanickavel G, Denton MJ, Gal A, *Nat Genet*, 17, 194-197, 1997

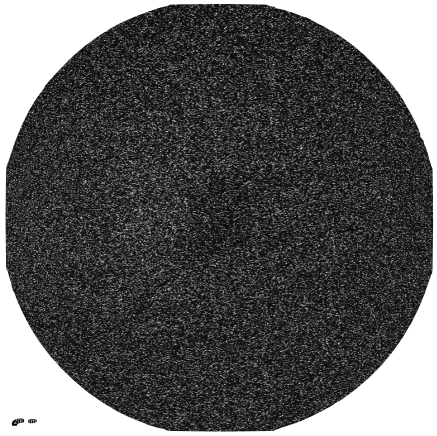
AR *RPE65*-related Retinal Dystrophy Phenotype

F, 4 4/12 yrs
EORD





Early Stage
Phenotype

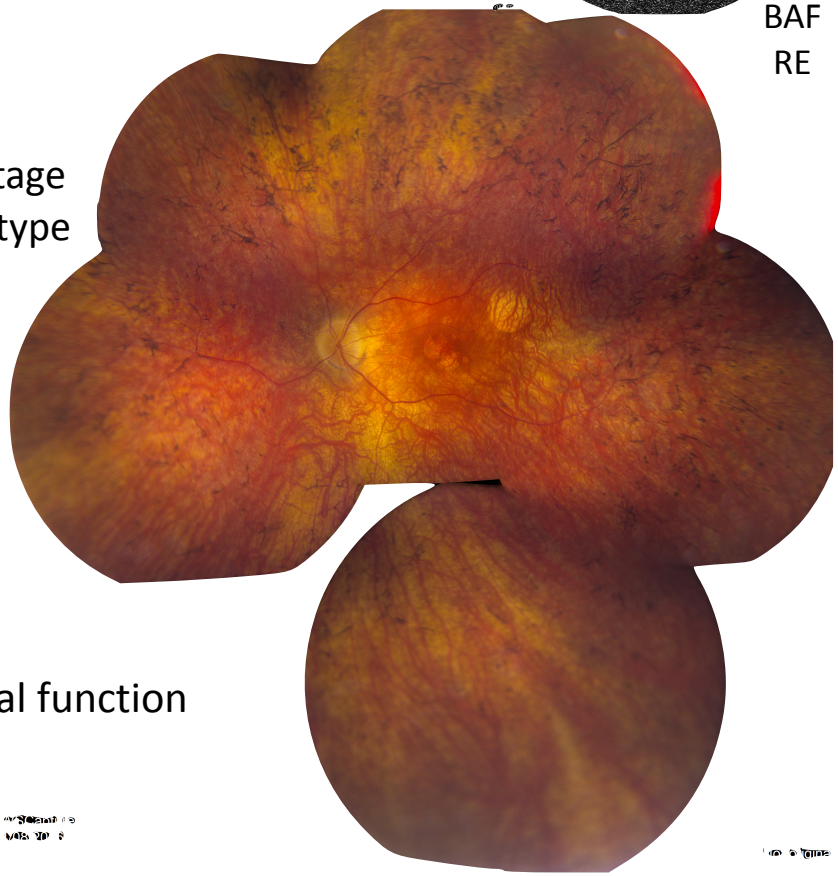


BAF RE

F, 29 yrs
EORD

BAF
RE

Late Stage
Phenotype



- Congenital onset of night blindness
- Nystagmus often
- Initially retina looks fairly normal
- Many different initial diagnoses
- Later phenotype identical to that of classic RP
- Vascular attenuation suggests early loss of retinal function
- Absence of blue light autofluorescence typical
- Sometimes picked up late w/ Dx of RP
- Progression towards complete blindness; early treatment paramount

RPE65-Related IRD
Unique

RPE65 expressed in RPE: retinal pigment epithelium-specific protein 65kDa

Disproportionately normal outer retinal structure given degree of visual loss

Window of opportunity to treat

AF Wright, Editorial, NEJM, 372, 1954-1955, 2015

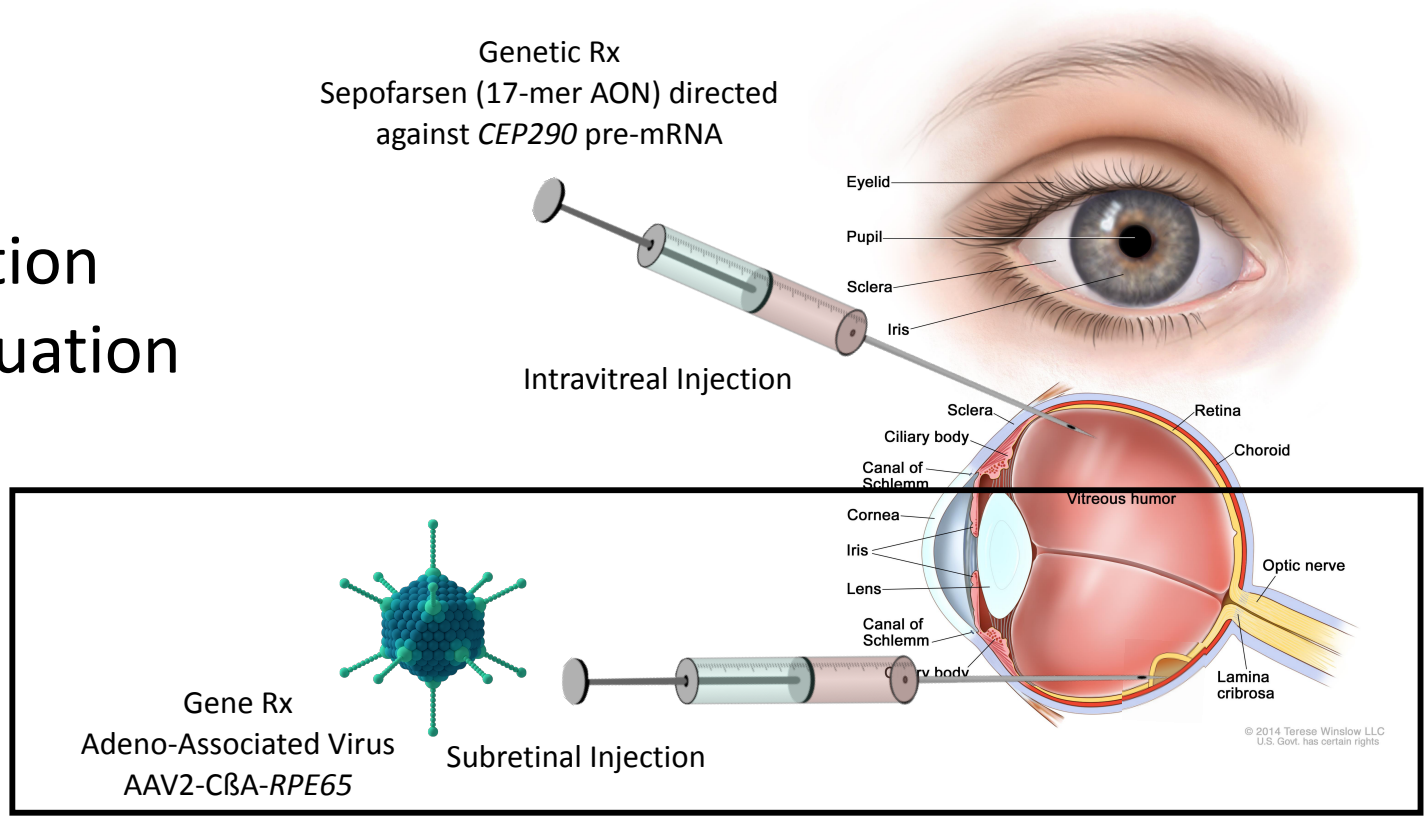
Gene Therapy for *RPE65*-IRD

From Animal Models to Approved Therapy in Humans

Gene & Genetic Rx for IRDs

Eye = Ideal Treatment Target

Accessible for injection
Allows real-life evaluation
Immune priviliged



Gene Rx w/ Voretigene Neparvovec

Development = Hacking Path through Jungle with Machete

On the “Path”
to Luxturna Approval

Courtesy of David Mann, Back to the Machete, Aug 3, 2012

Gene Therapy for *RPE65*-related LCA Effective in Briard Dogs

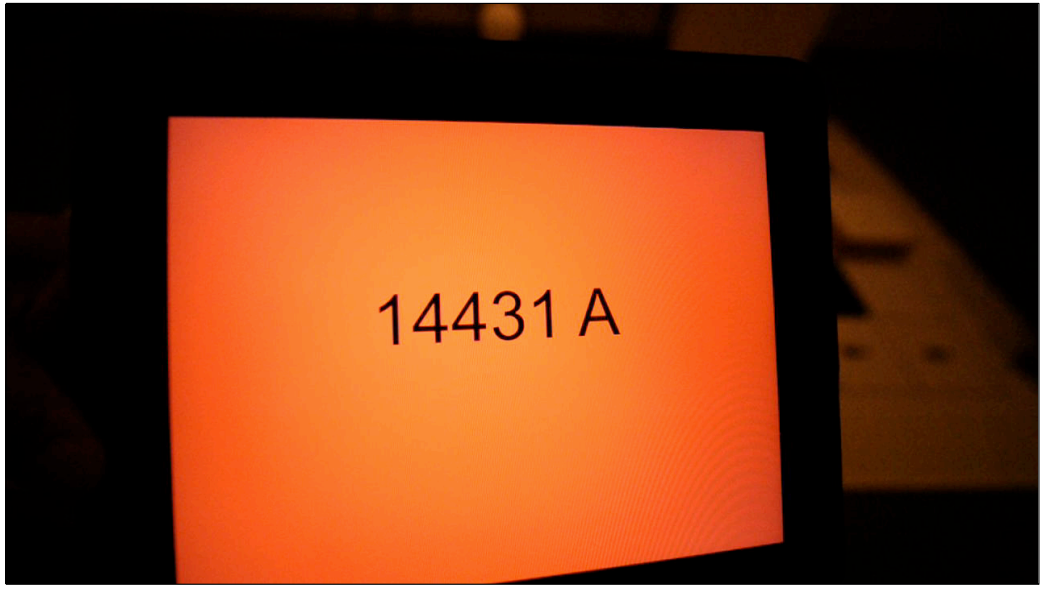
Courtesy of
Jean Bennett, MD, PhD

Briard dog treated w/ subretinal rAAV.*RPE65*

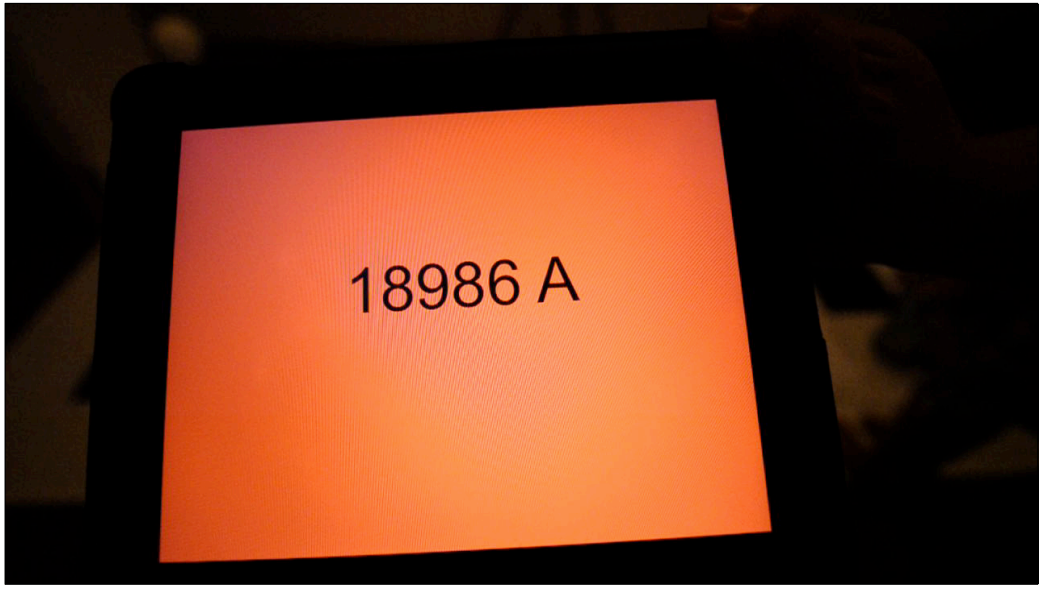
GM Acland *et al*, Nat Genet, 28, 92-95, 2001
GM Acland *et al*, Mol Ther, 16, 458-465, 2005

Gene Rx Phase 3: Results
Representative MLMT Videos (Bilateral Testing)

CH-41: baseline visit
at 4 lux (**Fail**)



CH-41: 1-year visit after voretigene
neparvovec administration at 4 lux (**Pass**)



S Russell, *et al.*: Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in subjects with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label phase 3 trial, Lancet, 2017

Gene Rx Phase 3
Conclusions

Improvements in MLMT, FST, & VF at year 1 in DI subjects consistent with those seen in OI cohort at 1 yr

Improvements observed in OI subjects generally maintained at 2 yrs

Gene augmentation by VN therapy improved functional vision & visual function in subjects with biallelic *RPE65*-mediated IRD as measured by improvements in:

- Ambulatory navigation
- Light sensitivity
- Visual field size

S Russell, *et al.*: Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in subjects with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label phase 3 trial, Lancet, 2017

FDA (2017) & EMA (2018) approval of AAV2-CBA-*RPE65* (aka Luxturna®) for treatment of adult & paediatric patients with vision loss due to IRD caused by biallelic mutations in *RPE65*, who have sufficient retinal cells

FDA NEWS RELEASE

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

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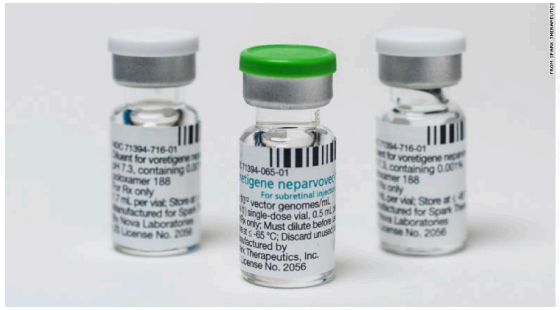
For Immediate Release: December 18, 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/823783/2018
EMEA/H/C/004451

Luxturna (*voretigene neparvovec*)
An overview of Luxturna and why it is authorised in the EU

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection



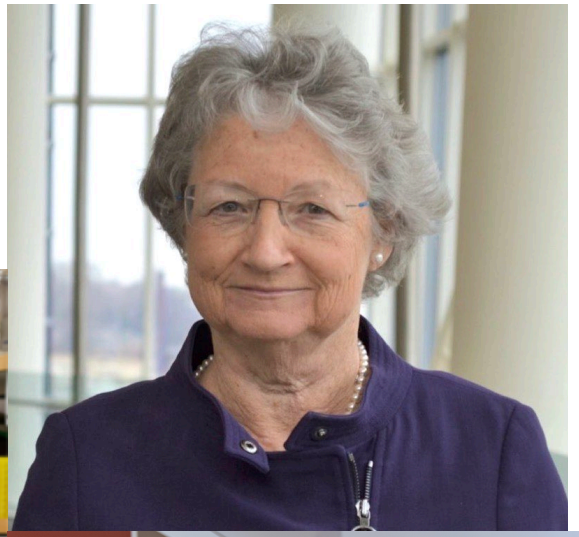
Spark™ THERAPEUTICS

NOVARTIS

Voretigene Neparvovec

Dr Jean BENNETT

Dr Jean BENNETT
Dr Albert M MAGUIRE



Dr Katherine HIGH

Dr Daniel CHUNG

Gene Rx with Voretigene Neparvovec (Luxturna®)
Patient Eligibility Criteria

EU Indication[1]:

"Voretigene neparvovec is an adeno-associated virus vector-based gene therapy indicated for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells."

Retinal cell viability in practice:

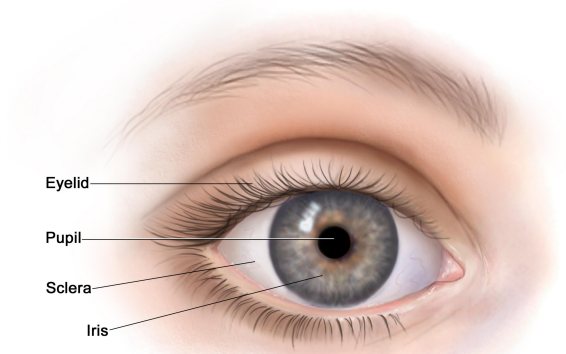
- presence of outer retinal cells on SD-OCT as determined by IRD specialist
- presence of at least Light Perception vision
- some additional measurement of visual function desirable e.g. FST

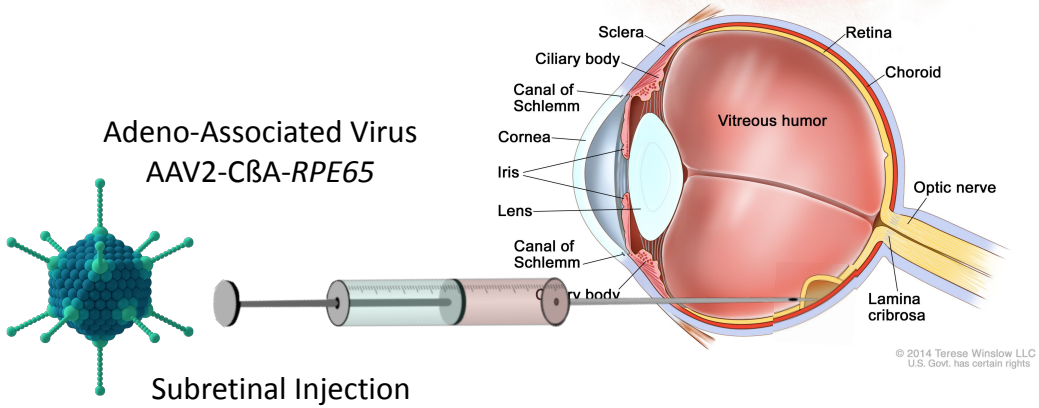
1. https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf

Gene Rx

Voretigene Neparvovec (Luxturna®)

- Subretinal injection
- 300µl w/ 1,5 x 10^{11} AAV2-CßA-*RPE65*
- Central retina (macula)





AM Maguire, KA High, A Auricchio, EA Pierce, F Testa, F Mingozzi, J Bennicelli, GS Ying, C Acerra, A Fulton, KA Marshall, S Banfi, D Chung, JIW Morgan, B Hauck, O Zelanaia, X Zhu, L Raffini, F Coppieters, E De Baere, KS Shindler, NJ Volpe, EM Surace, S Rossi, A Lyubarsky, TM Redmond, E Stone, J Sun, JF Wright, J Wellman McDonnell, BP Leroy, F Simonelli, J Bennett, Lancet, 374: 1597-1605, 2009

J Bennett, J Wellman, KA Marshall, S McCague, M Ashtari, J DiStefano-Pappas, OU Elci, DC Chung, J Sun, JF Wright, DR Cross, P Aravand, LL Cyckowski, JL Bennicelli, F Mingozzi, A Auricchio, EA Pierce, J Ruggiero, BP Leroy, F Simonelli, KA High, AM Maguire: 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, Lancet, 388, 661-72, 2016

S Russell, J Bennett, JA Wellman, DC Chung, ZF Yu, A Tillman, J Wittes, J Pappas, E Okan, S McCague, D Cross, KA Marshall, J Walshire, TL Kehoe, H Reichert, M Davis, L Raffini, MD; LA George, FP Hudson, L Dingfield, X Zhu, JA Haller, E Stone, EH Sohn, VB Mahajan, W Pfeifer, M Weckmann, CA Johnson, D Gewaily, A Drack, K Wachtel, F Simonelli, BP Leroy, JF Wright, KA High, AM Maguire, Lancet, 390, 849-860, 2017

AM Maguire, S Russell, J Wellman, D Chung, ZF Yu, A Tillman, J Wittes, J Pappas, O Elci, K Marshall, S McCague, H Reichert, M Davis, F Simonelli, BP Leroy, JF Wright, K High, J Bennett, Ophthalmology,126, 1273-1285, 2019

AM Maguire, J Bennett, EM Aleman, BP Leroy, TS Aleman, Mol Ther, 29, 442-463, 2021

AM Maguire, S Russell, DC Chung, ZF Yu, A Tillman, AV Drack, F Simonelli, BP Leroy, KZ Reape, KA High, J Bennett: Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 Years and 4 Years, Ophthalmology, 2021

What Have We Learned Since?

Real-World Data

What Have We Learned Since?
Real-World Data

Chorioretinal atrophy

Inflammation

Long-lasting effect of Rx

Chorioretinal Atrophy as a New AESI

Data from the Real-World Experience

Multicenter Study > Ophthalmol Retina. 2022 Jan;6(1):58-64. doi: 10.1016/j.oret.2021.03.016.
Epub 2021 Apr 8.

Perifoveal Chorioretinal Atrophy after Subretinal Voretigene Neparvovec-rzyl for RPE65-Mediated Leber Congenital Amaurosis

William S Gange [1], Robert A Sisk [2], Cagri G Besirli [3], Thomas C Lee [1], Margaret Havunjian [4], Hillary Schwartz [4], Mark Borchert [1], Jesse D Sengillo [5], Carlos Mendoza [5], Audina M Berrocal [5], Aaron Nagiel [6]

Affiliations + expand

PMID: 33838313 PMCID: PMC8497635 (available on 2023-01-01)
DOI: 10.1016/j.oret.2021.03.016

Abstract

Purpose: To report an anatomic change following subretinal injection of voretigene neparvovec-rzyl (VN) for RPE65-mediated Leber congenital amaurosis.

Design: Multicenter, retrospective chart review.

Participants: Patients who underwent subretinal VN injection at each of 4 participating institutions

Methods: Patients were identified as having perifoveal chorioretinal atrophy if (1) the areas of atrophy were not directly related to the touch-down site of the subretinal cannula; and (2) the area of atrophy progressively enlarged over time. Demographic data, visual acuity, refractive error, fundus photographs, OCT, visual fields, and full-field stimulus threshold (FST) were analyzed.

Main outcome measures: Outcome measures included change in visual acuity, FST, visual fields, and location of atrophy relative to subretinal bleb position.

Results: A total of 18 eyes of 10 patients who underwent subretinal injection of VN were identified as having developed perifoveal chorioretinal atrophy. Eight of 10 patients (80%) developed bilateral atrophy. The mean age was 11.6 years (range, 5-20 years), and 6 patients (60%) were male. Baseline mean logarithm of the minimum angle of resolution visual acuity and FST were 0.82 (standard deviation [SD], 0.51) and -1.3 log cd.s/m^2 (SD, 0.44), respectively. The mean spherical equivalent was -5.7 diopters (D) (range, -11.50 to +1.75 D). Atrophy was identifiable at an average of 4.7 months (SD, 4.3) after surgery and progressively enlarged in all cases up to a mean follow-up period of 11.3 months (range, 4-18 months). Atrophy developed within and outside the area of the subretinal bleb in 10 eyes (55.5%), exclusively within the area of the bleb in 7 eyes (38.9%), and exclusively outside the bleb in 1 eye (5.5%). There was no significant change in visual acuity ($P = 0.45$). There was a consistent improvement in FST with a mean improvement of -3.21 log cd.s/m^2 ($P < 0.0001$). Additionally, all 13 eyes with reliable Goldmann visual fields demonstrated improvement, but 3 eyes (23.1%) demonstrated paracentral scotomas related to the atrophy.

Conclusions: A subset of patients undergoing subretinal VN injection developed progressive perifoveal chorioretinal atrophy after surgery. Further study is necessary to determine what ocular, surgical delivery, and vector-related factors predispose to this complication.

Keywords: Chorioretinal atrophy; Complications; Gene therapy; Leber congenital amaurosis; Luxturna; Outcomes Research; Subretinal injection; Voretigene neparvovec-rzyl.

Chorioretinal Atrophy After Gene Rx for *RPE65*-LCA

Three Types

At injection sites

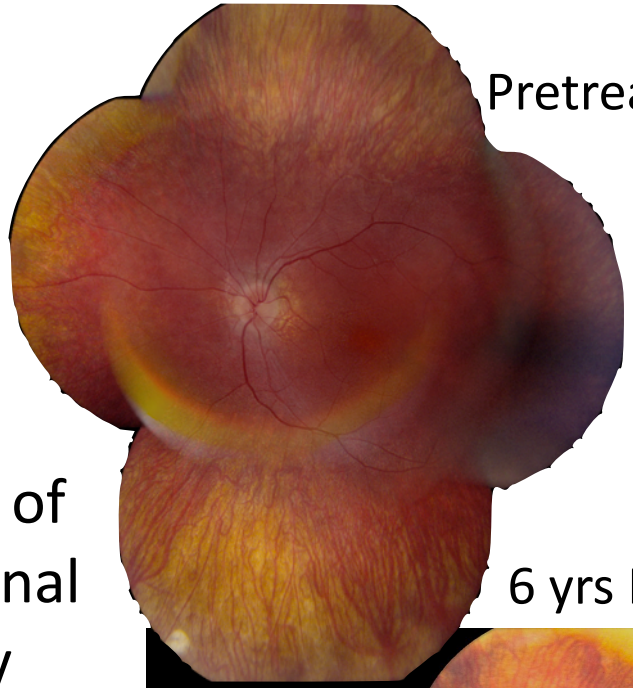
Within treatment area

Beyond treatment area

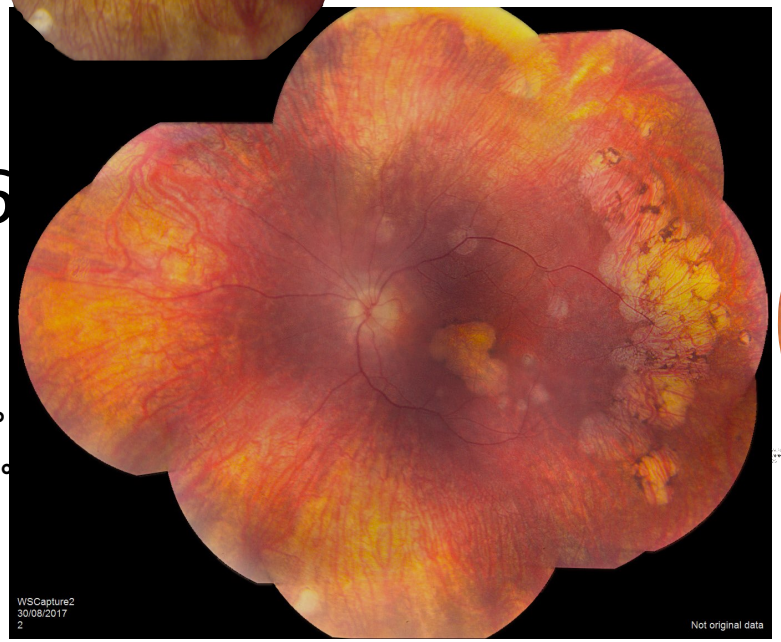
LE
Evolution of
Chorioretinal
Atrophy

Phase 1 CH-06

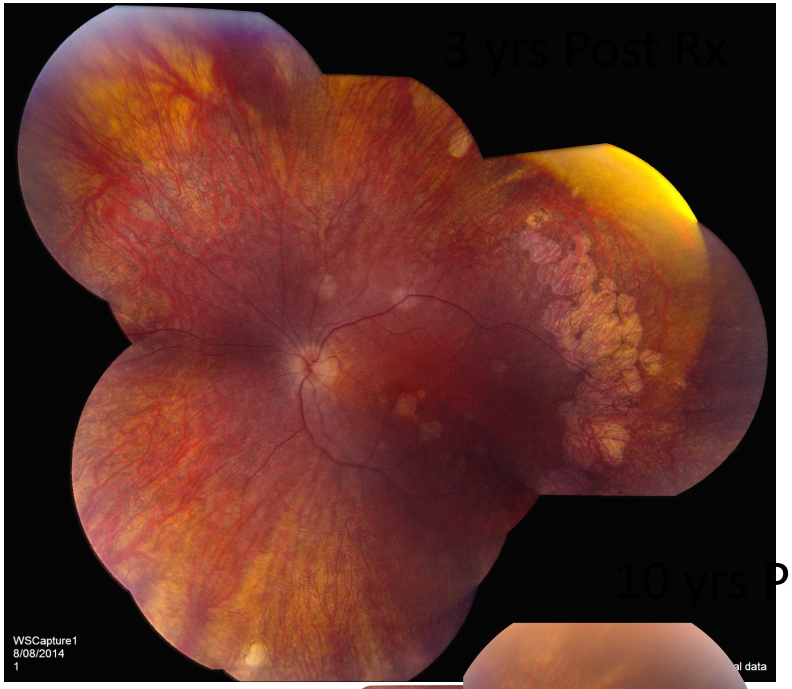
M, 9 yrs, LCA
HoZ c.1590delC in *RPE65*
BCVA
RE 3/60 w/ +4.5D(-1.0D)20°
LE 3/60 w/ +5.0D(-1.0D)170°



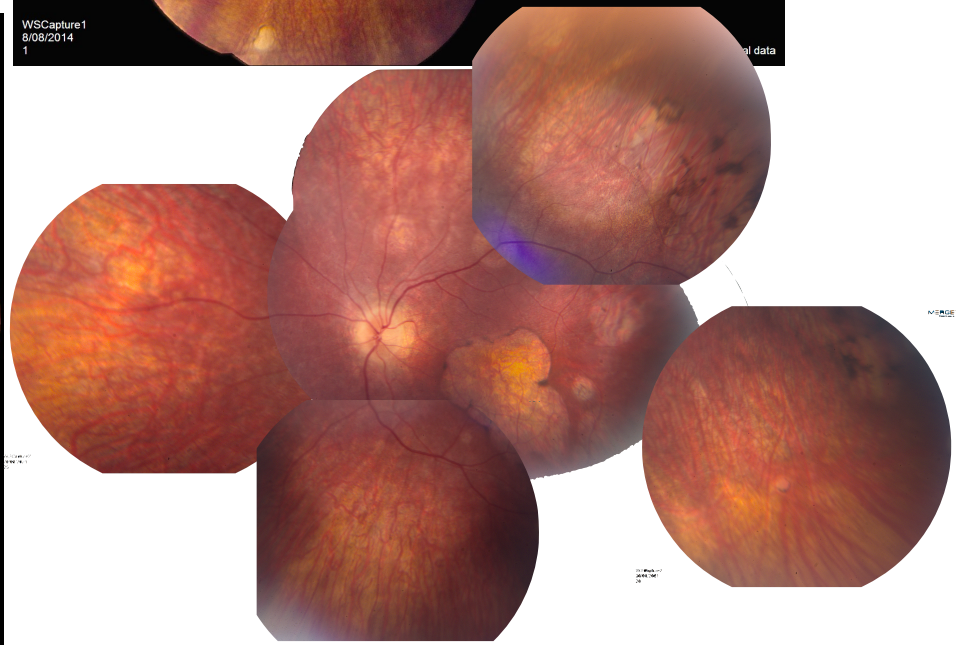
Pretreatment



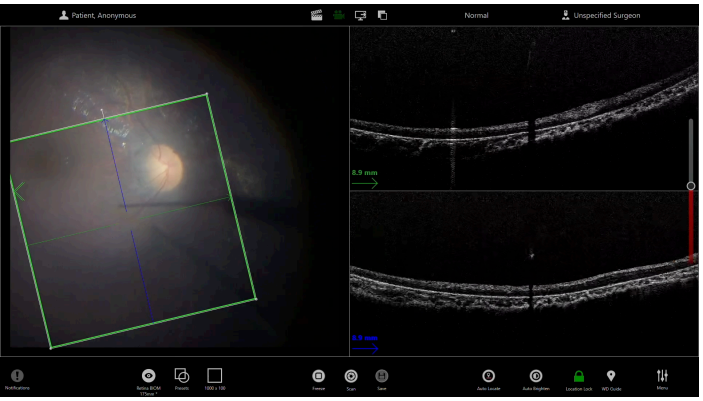
6 yrs Post Rx



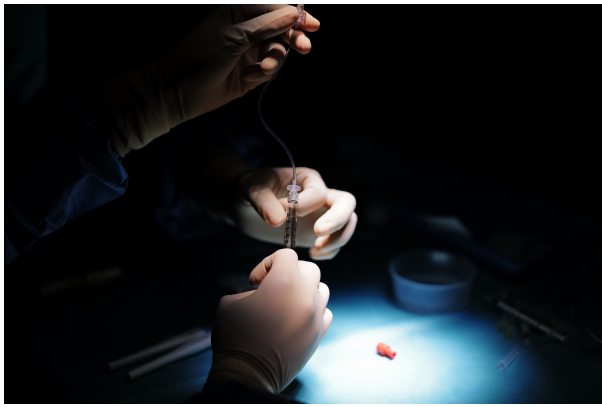
3 yrs Post Rx

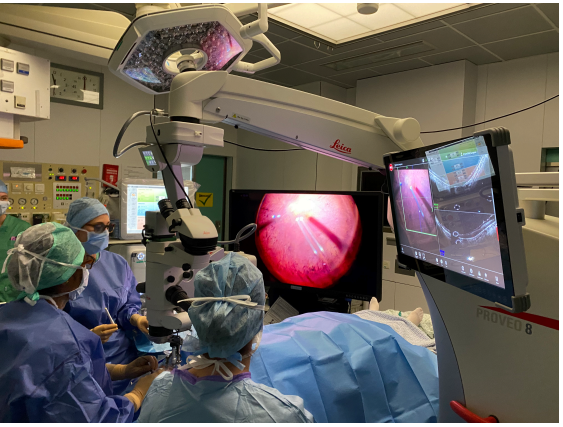


10 yrs Post Rx



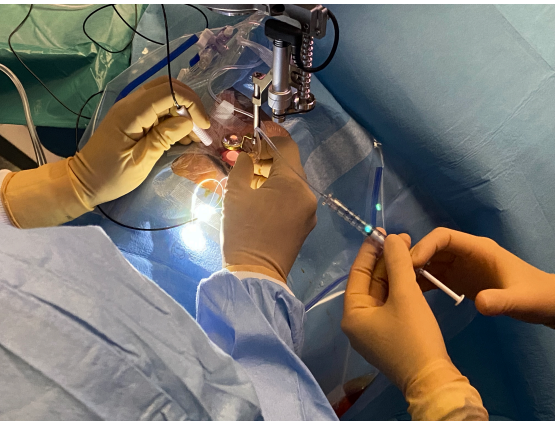
Ghent University Hospital
Dept of Ophthalmology & Ctr for Medical Genetics





National Referral Center for Ocular Genetics & Gene Therapy

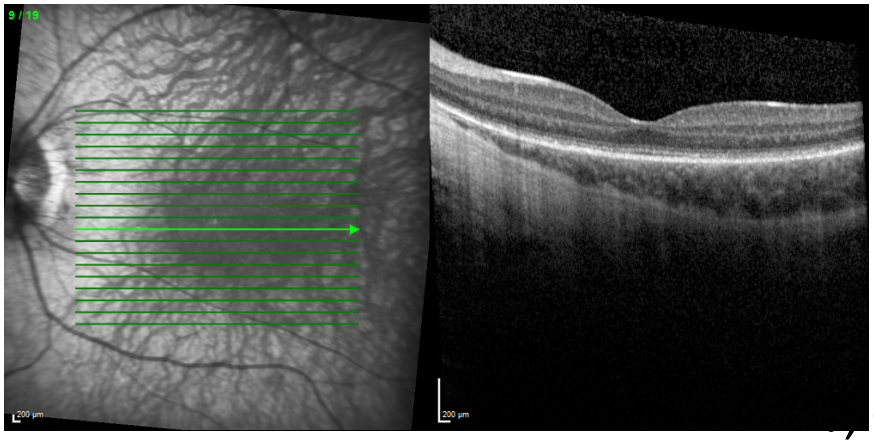
- Specific, multidisciplinary expertise built up over 25 years
- Embedded within international networks such as ERN-EYE & ERDC
- *RPE65*-related Inherited Retinal Dystrophy:
  - 36 eyes of 19 patients successfully treated with vitrectomy & subretinal injection of 300µl voretigene neparvovec
  - Efficacy results comparable to Phase 1-2 & Phase 3 studies
  - Data included into Phase 4 study (PERCEIVE) in EU
- Other gene therapies: >20 Belgian & international patients

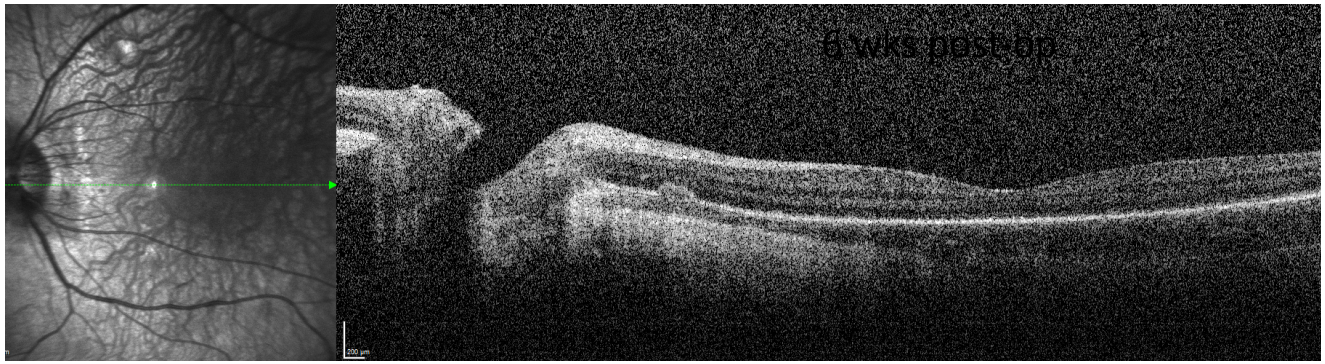


Dr Fanny NERINCKX
VR Surgeon

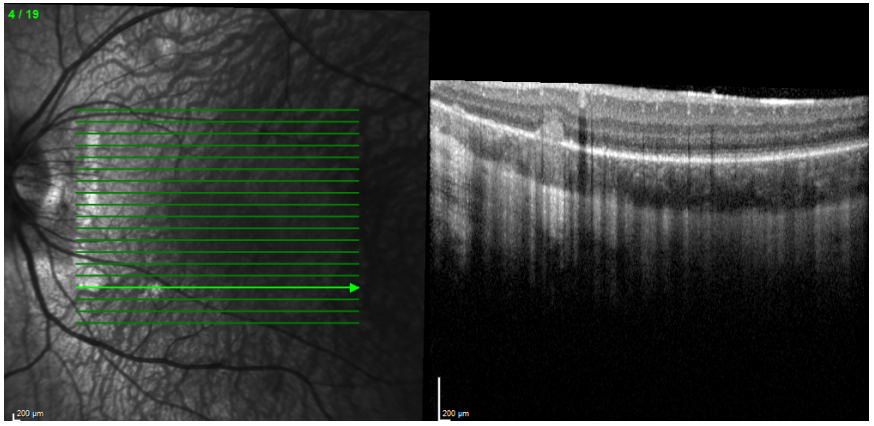
Chorioretinal Atrophy & Inflammation?

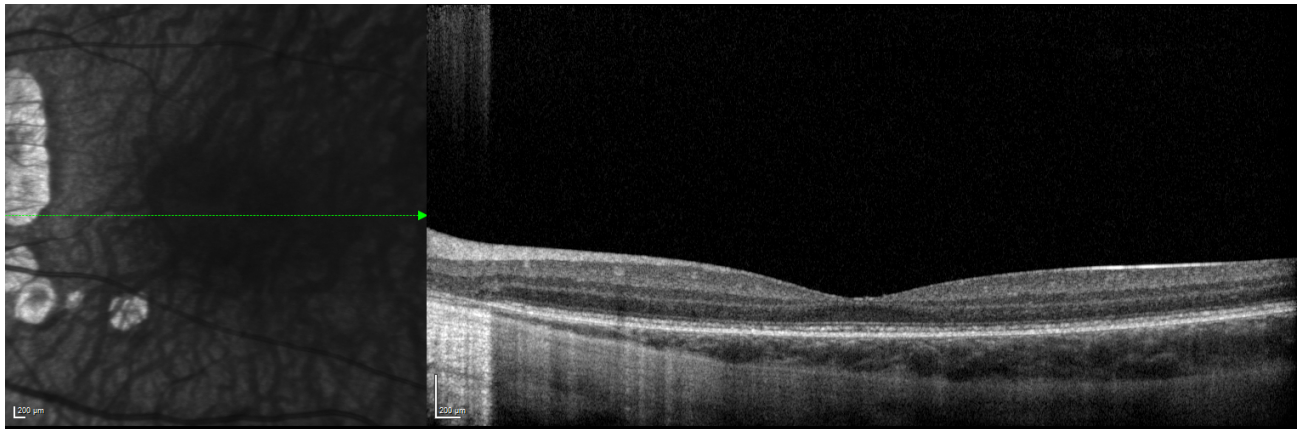
Belgian Patient





6 yrs, LE = second eye





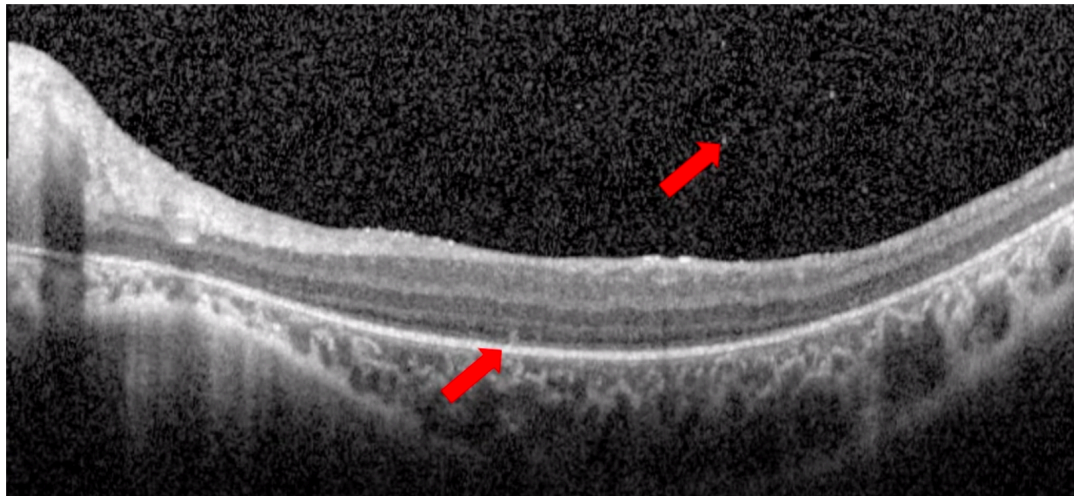
RPE65-related Retinal Dystrophy
Need for Tight Control of Inflammation

Tight control of retinal and vitreal inflammation required:

Bucher *et al.* Immune responses to retinal gene therapy using adeno-associated viral vectors - Implications for treatment success and safety, Progress in Retinal & Eye Research, https://doi.org/10.1016/j.pretereyes.2020.100915

Even if retinal and vitreal inflammation are mild: use high doses of local steroids

From Bucher *et al.*, PRER, 2020



What Have We Learned Since?
Real-World Data

Data from European PERCEIVE Study (Phase 4)

M. Dominik Fischer
mdominikfischer@gmail.com

4-Year interim results of the PERCEIVE Study: Long term real-world safety and effectiveness of voretigene neparvovec

M. Dominik Fischer,[1,2,3] Francesca Simonelli,[4] Isabelle Audo,[5] Bart P. Leroy,[6,7] Line Kessel,[8] Joao Pedro Marques,[9] Mirjana Bjelos,[10] James Bainbridge,[11] Rehna Khan,[12] Michelle Henley,[13] Rainer Maier,[13] Andreas Clemens,[13] and Frank G. Holz[14]

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Financial Disclosures:
M. Dominik Fischer: Reports consulting fees from Adelphi Values, Advent France Biotechnology, Adverum, Alder Therapeutics, Alphasights, Arctos Medical, Astellas, Atheneum, Axiom Healthcare Strategies, Bayer, Biogen, Cambridge Consultants, Coave Therapeutics, Decision Resources, Dialectica, DORC, F-Prime, Frontera Therapeutics, Janssen Research & Development, Mogrify, Navigant, Novartis, Regenxbio, Revvity, Roche, Sirion, Sofinnova Partners, Sparing Vision, STZ eyetrial, Tenpoint, THEA; **Francesca Simonelli:** Reports consulting fees from Acucela Inc, Kodiak, Bayer, Alia Therapeutics, Allergan, Biogen, Uvet, Iveric Bio, ProQR therapeutics, AIM group srl, 3P solution, MeiraGTx, K-link SH, Novartis, Janssen; **Isabelle Audo:** Consultant for Novartis and Janssen Pharmaceuticals; **Bart P. Leroy:** Receives consulting fees from 4DMT, AAVantgarde Bio, Akouos, Alia Therapeutics, Alnylam Pharmaceuticals, Atsena Therapeutics, Bayer, Belite Bio, Biogen, Coave Therapeutics, GenSight Therapeutics, Gyroscope, Iveric Bio, Janssen Pharmaceuticals J&J, MeiraGTx, Novartis, Opus Genetics, Oxurion, ProQR Therapeutics, Ray Therapeutics, Regenxbio, Santen, SpliceBio, Stoke Therapeutics, Transine Therapeutics, Vedere Bio I & II, ViGeneron; travel support from GenSight Therapeutics, Iveric Bio, Novartis, ProQR Therapeutics, Spark Therapeutics, Inc.; all financial gains are reinvested in IRD research at Ghent University Hospital; **Line Kessel:** No conflict of interest to declare; **Joao Pedro Marques:** Consultant for Bayer, Novartis, Roche, and Coave Therapeutics; **Mirjana Bjelos:** Receives consulting fees from Novartis; **James Bainbridge:** Consultant for Astellas, Axiom, Janssen Pharmaceuticals J&J, MeiraGTx, Novartis, Santen, Transine Therapeutics, Decision Resources; **Rehna Kahn:** Former employee of Novartis Pharmaceutical Corporation, Cambridge, U.S.A; **Michelle Henley, Rainer Maier and Andreas Clemens:** Employees of Novartis Pharma AG, Basel, Switzerland; **Frank G. Holz:** Research grants and consulting fees from Acucela, Allergan, Apellis, Bayer, Biogen, Bioeq/Formycon, Roche/Genentech, Geuder, Heidelberg Engineering, Iveric Bio, Pixium Vision, Novartis, Zeiss; consulting fees from Alexion, Alzheon, Annexon, Astellas, Boehringer-Ingelheim, Grayburg Vision, Janssen, LinBioscience, Stealth BioTherapeutics, Aerie, Oxurion, Oculis.

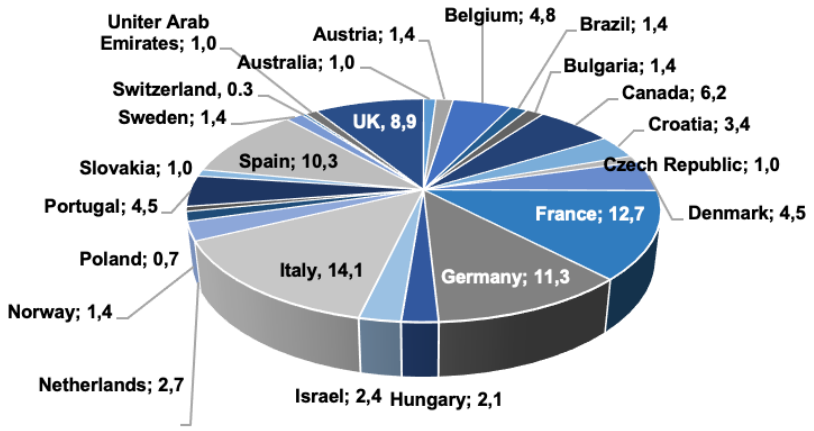
* Affiliation at the time of conduct of study.

EURETINA 2024 (September 19–22, Barcelona, Spain)

Patient disposition, demographics, and treatment characteristics

- A total of 291 patients were enrolled, of whom all patients received VN
- The mean age (SD)* of the patients was 23.7 (14.8), range (1–72) years. More than half of the patients were adults (58.4%) and males (52.2%)
- The mean (SD) length of follow-up was 1.87 (1.09) years (Maximum: 4.4 years)
- Patients were enrolled from 24 countries. The majority of them were from Italy (14.1%), France (12.7%), Germany (11.3%), Spain (10.3%), and the UK (8.9%)
- The recommended dose of 300 µL was administered in 462 eyes (87.7%); 51 eyes (9.7%) received a dose less than and 12 eyes (2.3%) received a dose more than 300 µL

Proportion of patients (%) from different countries (FAS, N=291)



- A total of 527 eyes (90.5%) had received VN at the time of data cut-off
- In majority of cases, single retinotomy sites (385 eyes; 73.1%) and single bleb (398 eyes; 75.5%) were created
- Deviations from the standard procedure were mainly the use of an automated injection system

FAS, full analysis set; N, total number of patients; SD, standard deviation; UK, United Kingdom; VN, voretigene neparvovec.
*Age is defined as age at time of study enrollment.
Data cut-off: Aug 31, 2023. FAS includes all enrolled individuals who received VN in at least 1 eye and provided informed consent; FAS is used to summarize all data.

Ocular AEs and AESIs

- Ocular AEs were reported in 186 patients (63.9%), affecting a total of 308 treated eyes (58.4%)
- Ocular AESIs occurred in 167 patients (57.4%), affecting a total of 274 treated eyes (52.0%)

Ocular AEs ≥2%

Preferred term	Patients, N=291 n (%)	Eyes, N=527 n (%)	No. of events for eyes
Number with ≥1 event	**186 (63.9)**	**308 (58.4)**	**554**
Retinal degeneration	77 (26.5)	126 (23.9)	132
IOP increased	49 (16.8)	72 (13.7)	78
Injection site atrophy	19 (6.5)	26 (4.9)	26
Foveal degeneration	18 (6.2)	25 (4.7)	25
Eye inflammation	17 (5.8)	22 (4.2)	26
Cataract	16 (5.5)	21 (4.0)	21
Lenticular opacities	16 (5.5)	31 (5.9)	31
Vitritis	13 (4.5)	22 (4.2)	22
Visual acuity reduced	10 (3.4)	12 (2.3)	14
Epiretinal membrane	9 (3.1)	10 (1.9)	10
Retinal tear	7 (2.4)	7 (1.3)	7
Metamorphopsia	6 (2.1)	7 (1.3)	7
Ocular hypertension	6 (2.1)	10 (1.9)	10
Retinal fovea disorder	6 (2.1)	8 (1.5)	8

Ocular AESIs ≥2%

Terms of interest	Patients, N=291 n (%)	Eyes, N=527 n (%)	No. of events for eyes
Number with ≥1 event	**167 (57.4)**	**274 (52.0)**	**436**
Chorioretinal atrophy[a]	86 (29.6)	144 (27.3)	162
IOP increased[b]	55 (18.9)	82 (15.6)	90
Intraocular inflammation and or infection related to procedure[c]	37 (12.7)	53 (10.1)	57
Cataract[d]	24 (8.2)	33 (6.3)	33
Foveal thinning[e]	20 (6.9)	28 (5.3)	29
Maculopathy[f]	15 (5.2)	18 (3.4)	19
Lack of efficacy[g]	10 (3.4)	14 (2.7)	14
Loss of foveal function[h]	9 (3.1)	12 (2.3)	12
Retinal tear[i]	8 (2.7)	8 (1.5)	9

[a]Includes PTs: Retinal degeneration 74 (25.4%), injection site atrophy 19 (6.5%), retinal depigmentation 2 (0.7%), retinal dystrophy 2 (0.7%), injection site discolouration 1 (0.3%), macular degeneration 1 (0.3%). [b]Includes IOP increased 49 (16.8%), ocular hypertension 6 (2.1%), glaucoma 1 (0.3%), intraocular pressure fluctuation 1 (0.3%). [c]Includes eye inflammation 17 (5.8%), vitritis 13 (4.5%), iridocyclitis 3 (1.0%), uveitis 2 (0.7%), papilloedema 1 (0.3%), post procedural infection 1(0.3%), retinal deposits 1(0.3%). [d]Includes PTs: Cataract 16 (5.5%), cataract subcapsular 5 (1.7%), lenticular opacities 2 (0.7%), ocular procedural complication 1(0.3%). [e]Includes PTs: Foveal degeneration 18 (6.2%), retinal degeneration 2 (0.7%), macular scar 1 (0.3%). [f]Includes PTs: Epiretinal membrane 9 (3.1%), cystoid macular oedema 2 (0.7%), maculopathy 1 (0.3%), retinal haemorrhage 1 (0.3%), retinal thickening 1 (0.3%), retinoschisis 1 (0.3%), visual acuity reduced 1 (0.3%). [g]Includes PTs: Drug ineffective 5 (1.7%), therapeutic product effect decreased 3 (1.0%), visual acuity reduced 1 (0.3%), visual impairment 1 (0.3%). [h]Includes PTs: Retinal fovea disorder 6 (2.1%), disruption of the photoreceptor inner segment-outer segment 1 (0.3%), retinal depigmentation 1 (0.3%), visual acuity reduced 1 (0.3%). [i]Includes PTs: Retinal tear 6 (2.1%), ocular procedural complication 2 (0.7%).
PTs are expressed as n (%); n=number of patients.

AE, adverse event; AESI, adverse events of special interest; IOP, intraocular pressure; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patient/eyes; n, number of patients/eyes; PT, preferred term.
Full analysis set. A patient/treated eye with multiple occurrences of an AE for PT is counted only once for each PT. All events including recurrences are counted in column for number of events. PTs are sorted by descending frequency in the "Patients" column. Ocular AEs in ≥2% patients are listed here by preferred terms. Ocular AESIs in ≥2% patients are listed here by terms of interest. MedDRA Version 26.0 was used for the reporting of AEs. AESIs were collected through a standardized safety questionnaire.

Chorioretinal atrophy, non-ocular, and serious AEs

Chorioretinal atrophy (CRA)

- CRA is an AESI that was reported based on investigator judgement
- There were 86 patients (29.6%) and 144 eyes (27.3%) with reported onset of CRA
- Females: n=50 (58.1%); Mean age:* 20.7 (range: 2–67) years
- Notably, 12 eyes had at least one event that involved the fovea, while 127 eyes (91.4%) had no such events
- Ninety-three eyes (67.9%) had at least one event that affected the macula and arcade
- Seventy-seven eyes (56.2%) had at least one event that affected the retina outside the posterior pole
- Ninety-eight eyes (74.8%) had at least one event at the injection site
- Seventy-three eyes (56.6%) had at least one event that affected inside the bleb area, and in 53 eyes (41.1%), at least one event that was outside the bleb area

CRA by preferred terms

Preferred terms	Patients, N=291 n (%)	Eyes, N=527 n (%)	No. of events for eyes
Chorioretinal atrophy	**86 (29.6)**	**144 (27.3)**	**162**
Retinal degeneration	74 (25.4)	122 (23.1)	128
Injection site atrophy	19 (6.5)	26 (4.9)	26
Retinal depigmentation	2 (0.7)	3 (0.6)	3
Retinal dystrophy	2 (0.7)	2 (0.4)	2
Injection site discolouration	1 (0.3)	2 (0.4)	2
Macular degeneration	1 (0.3)	1 (0.2)	1

Non-ocular AEs

- Non-ocular AEs occurred in 31 patients (10.7%); most frequent was headache (n=9 patients; 11 events)

Ocular and non-ocular SAEs

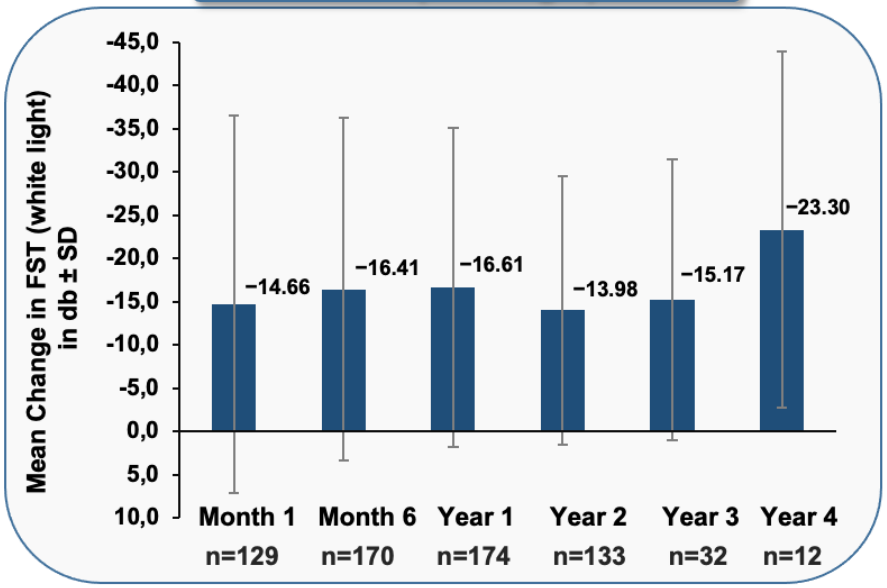
- Ocular SAEs were reported in 14 patients (4.8%), affecting 18 eyes (3.4%), including retinal fovea disorder (n=2; 3 eyes), retinal degeneration (n=2; 4 eyes), and reduced visual acuity (n=3; 4 eyes)
- One non-ocular serious AEs (psychotic disorder) occurred in 1 patient

AE, adverse event; AESI, adverse event of special interest; CRA, chorioretinal atrophy; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patient/eyes; n, number of patients/eyes; SAE, serious adverse event.
*Age is defined as age at time of study enrollment.
Full analysis set. All events including recurrences are counted in column for number of events; MedDRA Version 26.0 was used for the reporting of AEs; AESIs were collected through a standardized safety questionnaire.

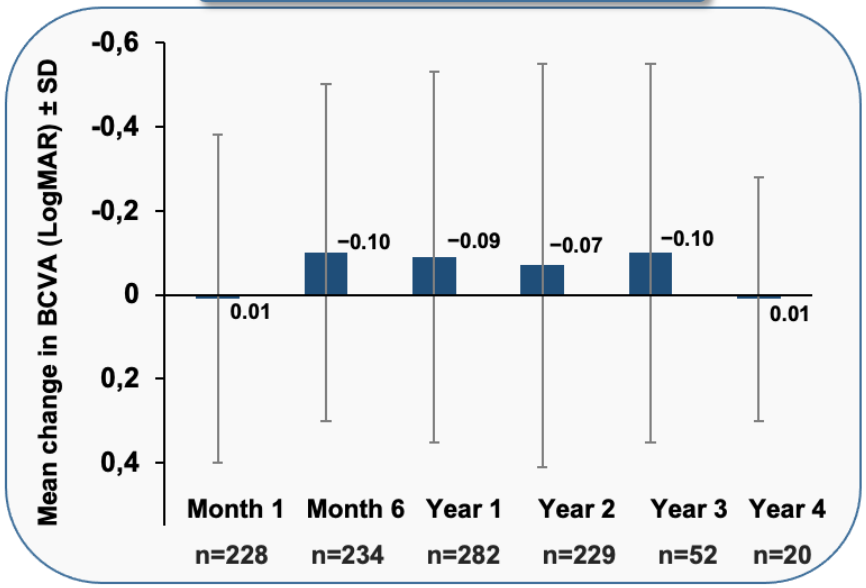
Visual function: FST (white light) and BCVA

- Mean FST at baseline was −7.20 db (348 eyes). An increase in mean white light sensitivity from baseline was observed as early as Month 1; the highest gain was at Year 4
- Sustained FST improvement was observed at Up to Year 4
- Mean BCVA at baseline was 1.15 LogMAR (504 eyes). No clinically meaningful change was observed in mean BCVA from baseline over time

FST (white light)



BCVA

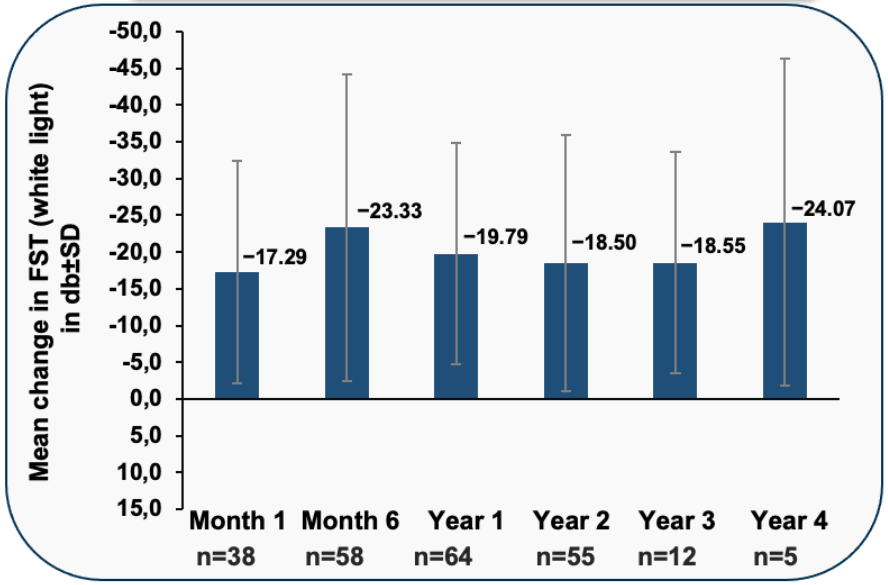


BCVA, best-corrected visual acuity; db, decibel; FST, full-field light sensitivity threshold; LogMAR, logarithm of the minimum angle of resolution; n, number of treated eyes with non-missing data at baseline and the post-baseline time point.
Full analysis set; error bars indicate SD.

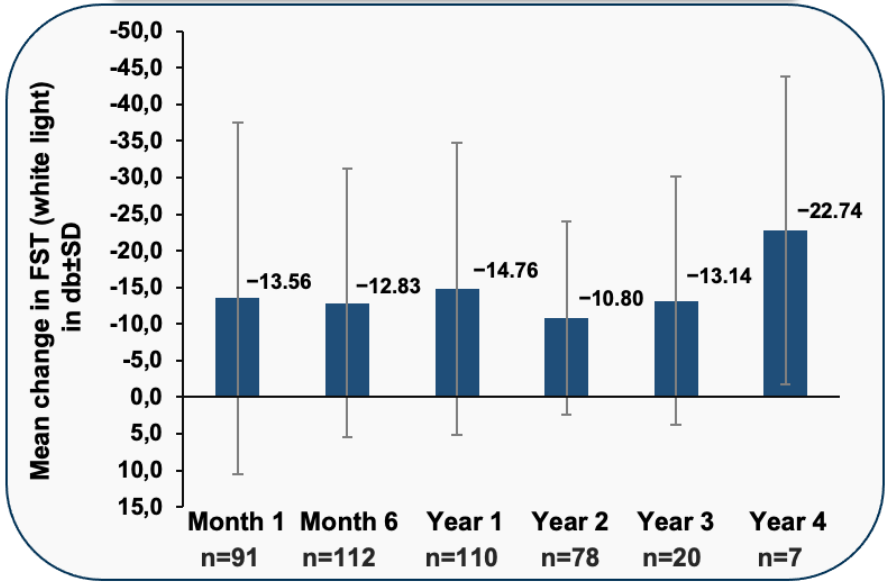
Visual function: FST (white light) by presence of CRA

- Mean FST at baseline was −6.77 db (103 eyes) and −7.38 db (245 eyes) for eyes with and without CRA, respectively
- Mean change of the sensitivity threshold from baseline was larger in treated eyes with CRA vs treated eyes without CRA, both indicating improvement

FST (white light) for eyes with CRA



FST (white light) for eyes without CRA



CRA, chorioretinal atrophy; db, decibel; FST, full-field light sensitivity threshold; LogMAR, logarithm of the minimum angle of resolution; n, number of treated eyes with non-missing data at baseline and the post-baseline time point; SD, standard deviation.
Full analysis set; error bars indicate SD.

Conclusions

- Based on the Year 4 interim analysis, the PERCEIVE study demonstrates the safety and effectiveness of VN, which are generally consistent with the known safety profile of VN
- A majority of patients showed sustained improvement in visual function over this 4-year observation period, including patients with reported events of AESI CRA
- As the study progresses, such AEs and the long-term safety profile of VN will be better characterized
- Furthermore, PERCEIVE will provide real-world evidence on the long-term durability of vision improvements observed with VN therapy

AE, adverse event; AESI, adverse event of special interest; CRA, chorioretinal atrophy; VN, voretigene neparvovec.

What Have We Learned Since?
Real-World Data

Data from US Phase 3 Study

Safety and Durability of Voretigene Neparvovec for Biallelic *RPE65*-Mediated Inherited Retinal Disease: Phase 3 Results at 8 and 9 Years

Stephen R. Russell[1], Jean Bennett[2,3], Bart P. Leroy[4], Jennifer Stark[1], Katherine A. High[5*], Virginia Haurigot[5], David L. Rousso[5], Juha-Matti Savola[5], and Albert M. Maguire[2,3]

[1]University of Iowa, Iowa City, IA; [2]Children's Hospital of Philadelphia, Philadelphia, PA; [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [4]Ghent University Hospital & Ghent University, Ghent, Belgium; [5]Spark Therapeutics, Inc., Philadelphia, PA

ASRS Annual Meeting, July 17-20, 2024 Stockholm, Sweden

Multi-Luminance Mobility Test® (MLMT®) for Functional Ambulatory Vision:
Phase 3, Primary Efficacy Endpoint

MLMT light levels with examples

1 lux
Moonless summer night or indoor night-light

4 lux
Cloudless summer night with half moon or outdoor parking lot at night

10 lux
60 minutes after sunset in a city setting or a bus stop at night

50 lux
Outdoor train station at night or inside of illuminated office stairwell

125 lux
30 minutes before sunrise or interior of a shopping mall, train, or bus at night

250 lux
Interior of an elevator, library, or office hallway

400 lux
Office environment or food court

MLMT course layout
(1 of 12 standardized configurations)

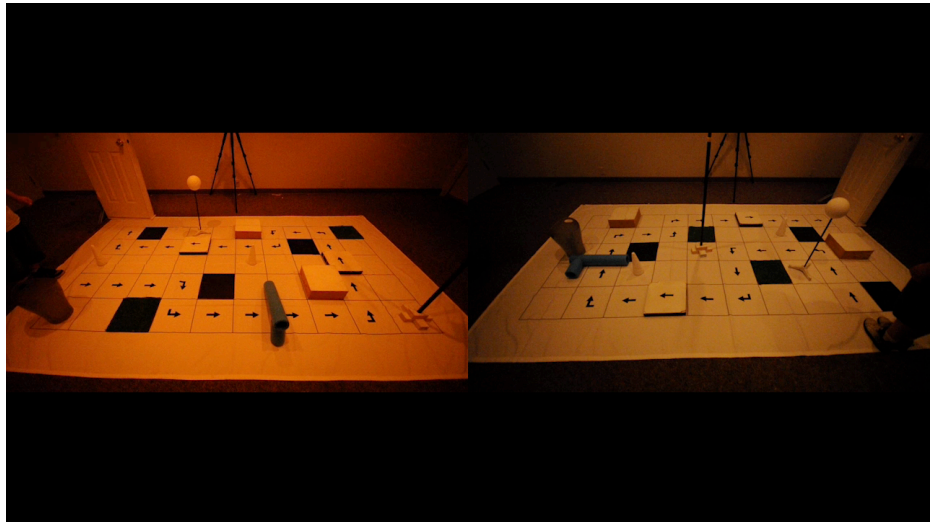
Images presented for illustrative purposes only. Light meter: National Institute of Standards and Technology-calibrated, Extech model #EA33 light meters used to provide examples and to set/verify specified light levels used for mobility testing.

Chung DC, et al. *Clin Exp Ophthalmol.* 2018;46:247-259.

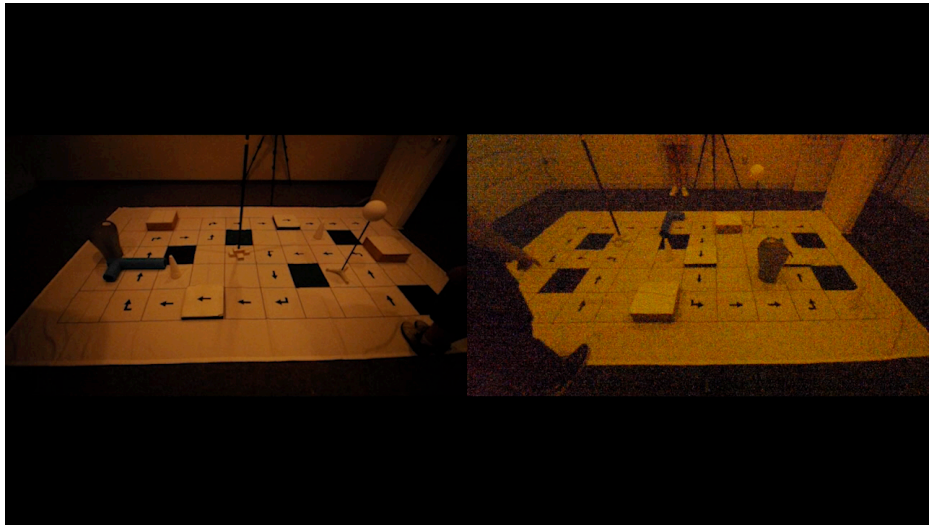
Trial Participant MLMT® Videos (Bilateral Testing)

Representative of clinical trial participant with a clinically meaningful score change of 2 from baseline

Baseline Visit 1 Lux **(FAIL)**	Year 1 Post-Treatment Visit 1 Lux **(PASS)**	Year 1 Post-Treatment Visit 1 Lux **(PASS)**	Year 9 Post-Treatment Visit 1 Lux **(PASS)**



The subject's Baseline passing light level was 10 Lux (Score 4) and Year 1 passing light level was 1 Lux (Score 6), representing a 2 Lux score change from Baseline at Year 1.



The same subject's passing light level was 1 Lux (Score 6) at Year 1 through Year 9, representing a 2 Lux score change from Baseline at Year 1 through Year 9. An error in the camera settings during the video recording of the test at 1 lux at Year 9 altered the video quality.

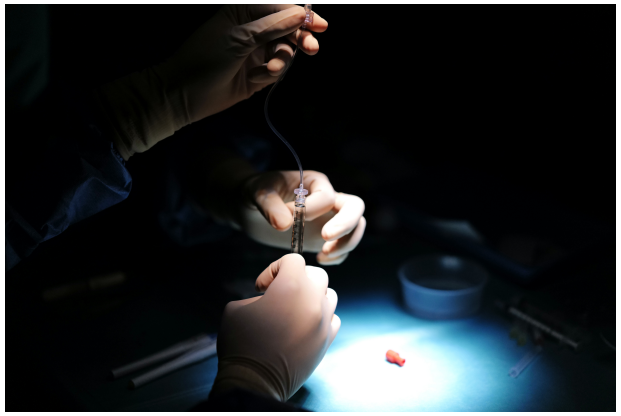
The camera adjusts the level and temperature of light that it captures. Because of this feature, there may be slight variations in hue when filming at low light levels (e.g., 1 lux). An error in this feature occurred at Year 9, resulting in reduced video quality. All videos shown were filmed at 1 lux.

Data on File. Study 301/302 MLMT Video Library. [2024] Spark Therapeutics, Inc. Philadelphia, PA.

Conclusions

- Persistent **improvements in ambulatory vision, light sensitivity,** and **visual field** are maintained for at least 5 years after VN administration in most OI and DI patients, and up to 8 and 9 years in OI and DI patients combined
- **Increased variability after 5 years** due in part to COVID-related missed visits limits interpretation beyond 5 years. However, mean changes in MLMT®, FST, and GVF remain above baseline
- Safety profile is generally consistent with vitrectomy and subretinal injection procedure:
  - No AEs of chorioretinal atrophy (CRA) were reported. However, clinical study reports from the entire clinical development program (Phase 1 through Phase 3) describe **findings similar to CRA in 5 subjects**, attributed to natural disease progression
  - One patient experienced an SAE of **acute myeloid leukemia (AML)** at year 7 resulting in death, assessed as unlikely related to VN or administration procedure
- Continued data collection up to the planned follow-up period of 15 years will facilitate further understanding of **long-term safety and efficacy** from one-time VN administration

Real-World Learnings from VN for *RPE65*-IRD



Conclusions

Voretigene Neparvovec (Luxturna®) works in AR *RPE65*-IRD

VN does not normalise visual function

Improvements continue after up to 9 yrs

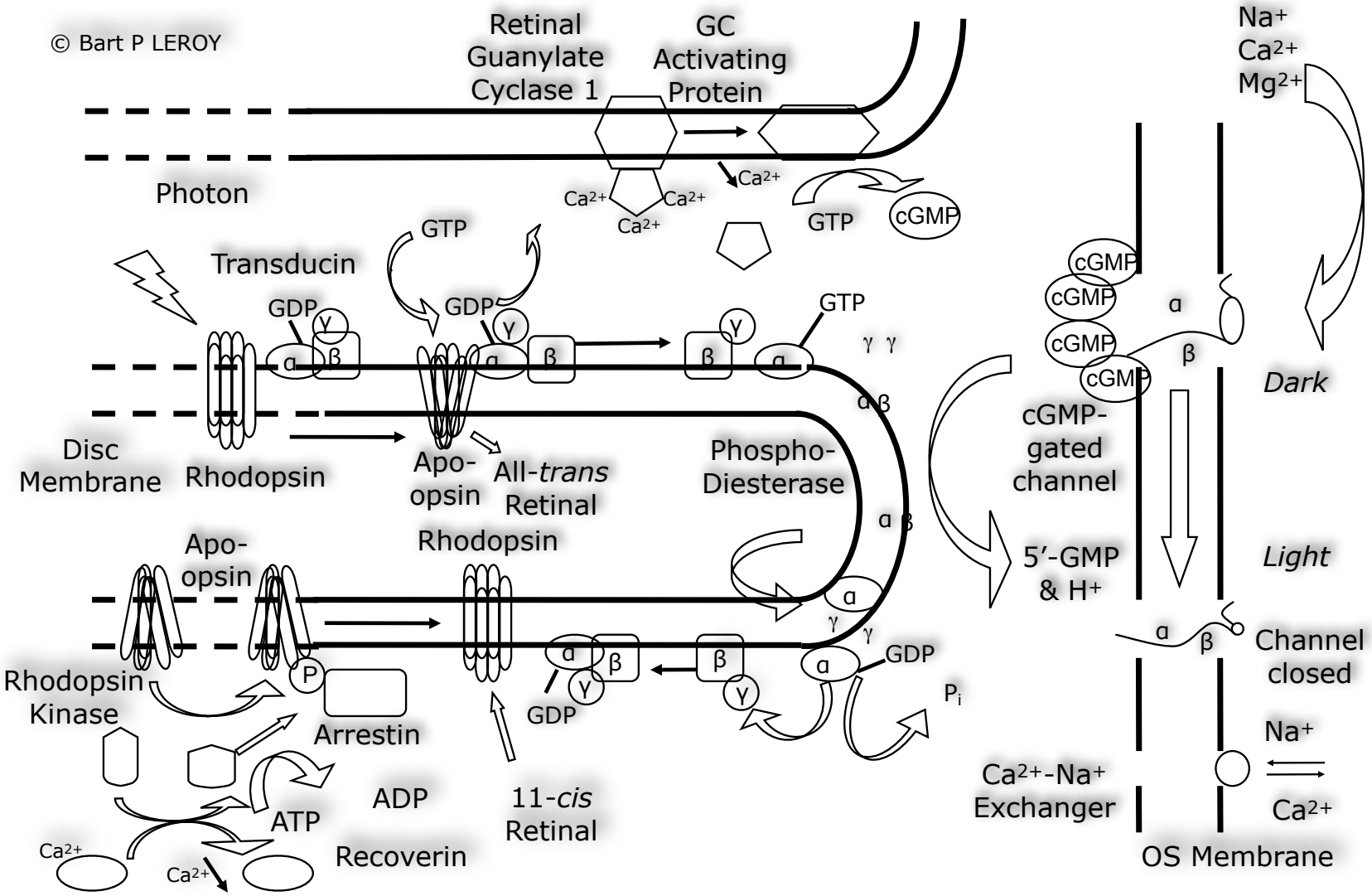
More beneficial when treated at younger age

Inflammation incompletely understood

Chorioretinal atrophy of 3 types requires further study

Gene Augmentation Therapy with AAV5 *GUCY2D*-LCA1

The Phototransduction Cascade



Gene Rx for *GUCY2D*-LCA

AAV5-hGRK1-*GUCY2D* (ATSN-101)

Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in *GUCY2D*: a phase 1/2, multicentre, open-label, unilateral dose escalation study

Paul Yang, Laura P Pardon, Allen C Ho, Andreas K Lauer, Dan Yoon, Shannon E Boye, Sanford L Boye, Alejandro J Roman, Vivian Wu, Alexandra V Garafalo, Alexander Sumaroka, Malgorzata Swider, Iryna Viarbitskaya, Tomas S Aleman, Mark E Pennesi, Christine N Kay, Kenji P Fujita, Artur V Cideciyan

P Yang *et al,*, Lancet, 404, 962-970, 2024

Gene Rx for *GUCY2D*-LCA
Methods

Phase 1/2, open-label, unilateral, dose escalation study

AAV5-hGRK1-*GUCY2D* (ATSN-101)

Subretinal injection

Recruitment from 2 sites (Penn & OHSU)

15 patients w/ clinical Dx of LCA1 w/ biallelic mutations in *GUCY2D*

Study eye 20/100 or worse (cohorts 1, 2, 3) or 20/80 or worse (cohorts 4, 5)

Dose escalation & dose expansion phases

P Yang *et al.*, Lancet, 404, 962-970, 2024

Gene Rx for *GUCY2D*-LCA

Methods

Dose escalation phase: n = 3 for 3 doses: 1.0 x 10^{10} vg/eye (low), 3.0 x 10^{10} (middle dose) & 1.0 x 10^{11} vg/eye (high)

Dose expansion phase: n = 3 (adult) & n = 3 (paediatric) at high dose

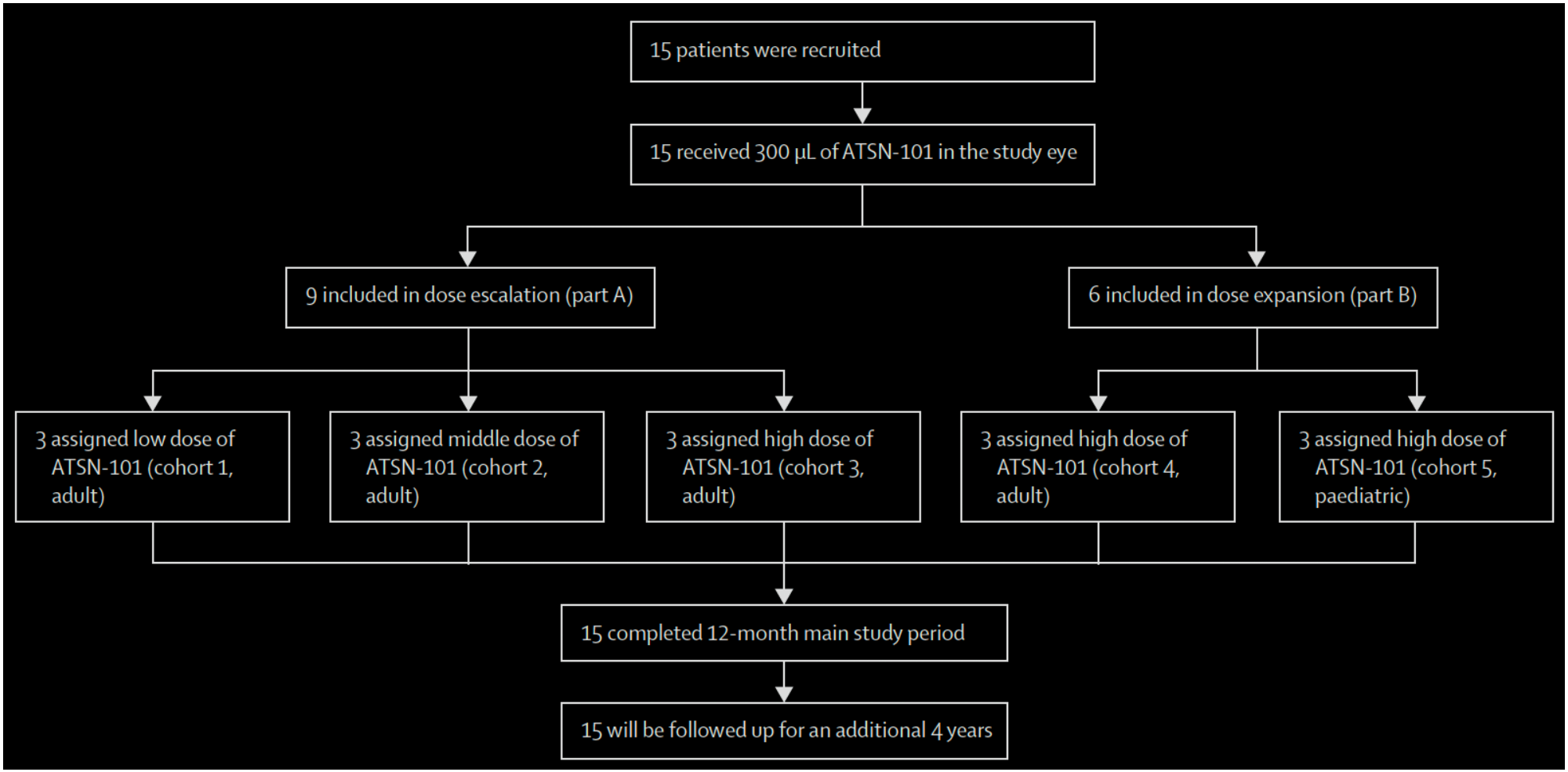
Primary outcome = TEAEs

Secondary outcomes: BCVA, FST & MLMT

P Yang *et al.*, Lancet, 404, 962-970, 2024

Gene Rx for *GUCY2D*-LCA

AAV5-hGRK1-*GUCY2D* (ATSN-101)



Gene Rx for *GUCY2D*-LCA
Results

68 TEAEs (56 surgery-related); no serious TEAEs

Only mild ocular inflammation

Patients who received high dose @ mth 12: mean change of FST 20,3 dB for treated, 1,1 dB for untreated eyes

Mild BCVA improvements (p=0,10)

3 of 6 high dose patients who did MLMT: highest score on MLMT

P Yang *et al.*, Lancet, 404, 962-970, 2024

Gene Augmentation Therapy with AAV8 *AIPL1*-LCA4

Gene Rx for *AIPL1*-LCA

rAAV8.*hRKp*.*AIPL1*

Gene therapy in children with *AIPL1*-associated severe retinal dystrophy: an open-label, first-in-human interventional study

Michel Michaelides, Yannik Laich*, Sui Chien Wong, Ngozi Oluonye, Serena Zaman, Neruban Kumaran, Angelos Kalitzeos, Harry Petrushkin, Michalis Georgiou, Vijay Tailor, Marc Pabst, Kim Staeubli, Roni O Maimon-Mor, Peter R Jones, Steven H Scholte, Anastasios Georgiadis, Jacqueline van der Spuy, Stuart Naylor, Alexandria Forbes, Tessa M Dekker, Eugene R Arulmuthu, Alexander J Smith, Robin R Ali, James W B Bainbridge*

M Michaelides *et al,* Lancet, 405, 648-657, 2025

Gene Rx for *AIPL1*-LCA4
Methods

Phase 1/2, open-label, unilateral, single dose study

rAAV8-hRKp-*AIPL1*

Subretinal injection

Recruitment from 1 site (MEH)

Specials Licence from Medicines & Health products Regulatory Authority (UK)

4 paediatric patients aged (1,0 - 2,8 yrs) w/ clinical Dx of LCA4 w/ biallelic mutations in *AIPL1*

LP vision in both eyes (equivalent to 2,7 LogMAR)

M Michaelides *et al,* Lancet, 405, 648-657, 2025

Gene Rx for *AIPL1*-LCA4
Methods

Outcomes =

- BCVA with novel touchscreen test
- Functional vision (observation of visual behaviour & ability to perform simple vision-guided tasks)
- VEPs
- Retinal structure (handheld OCT& widefield fundus images)

M Michaelides *et al,* Lancet, 405, 648-657, 2025

Gene Rx for *AIPL1*-LCA4
Results

At age 3,0 - 4,1 yrs old

BCVA improved to LogMAR 0,8 - 1,0 (decimal equivalent 0,10 - 0,16) in treated eyes

BCVA in untreated eyes became unmeasurable

In 2 children old enough to reliably perform objective test showed objective improvement of BCVA & VEP

In 3 children, structural lamination of outer retina in treated eye better preserved than in untreated eye

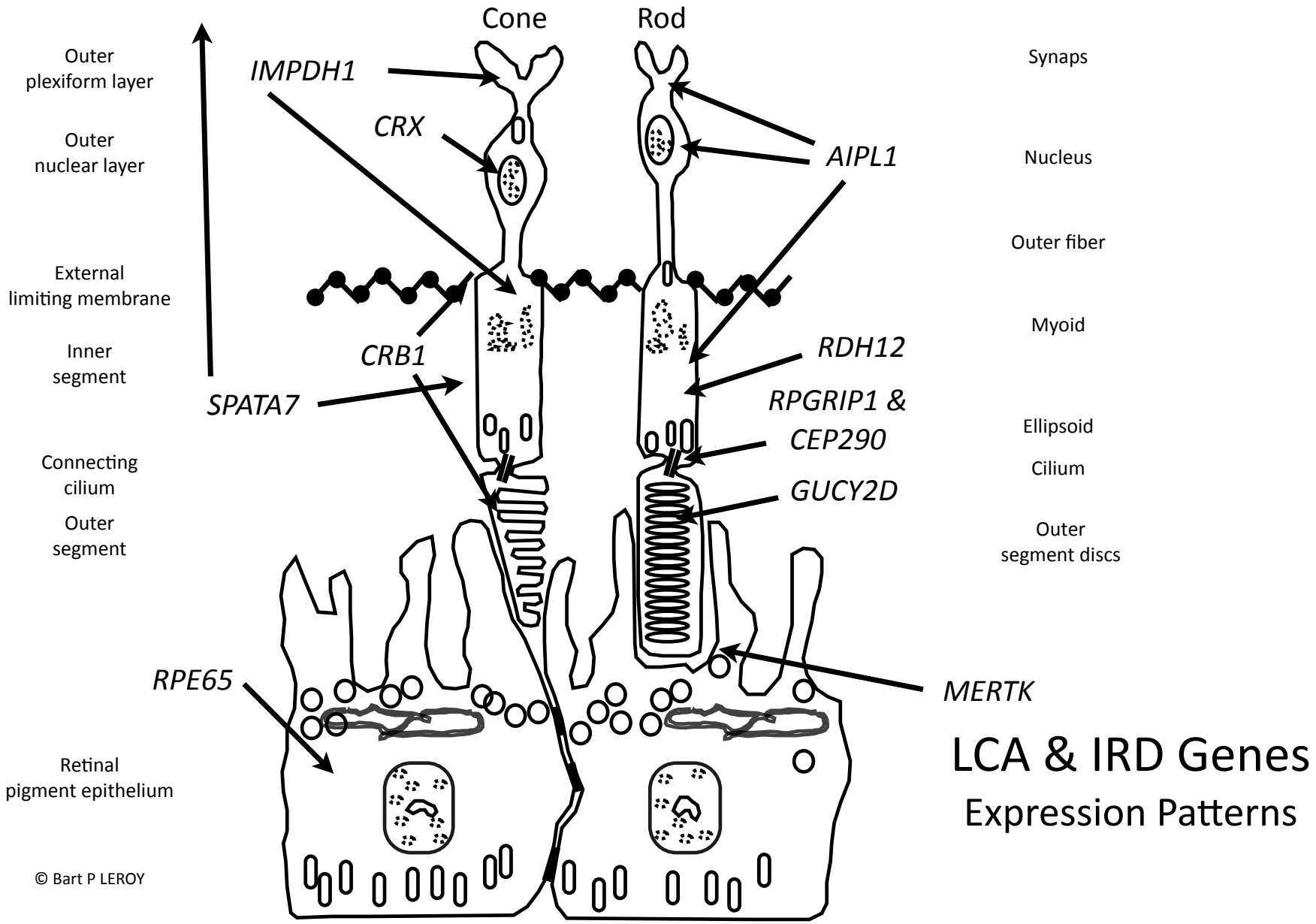
In all 4 patients, retinal thickness in treated better than in untreated eye

Treated eye in 1 patient developed CMO; no other safety concerns

M Michaelides *et al,* Lancet, 405, 648-657, 2025

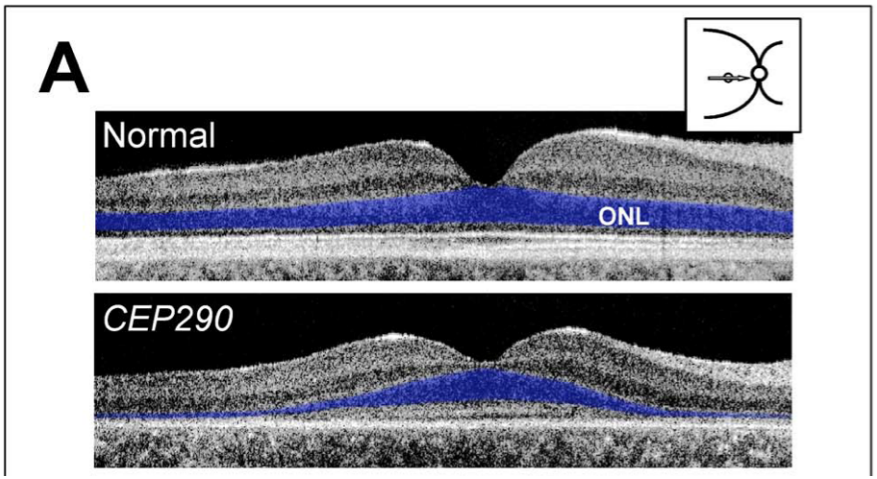
Approaches for Large Genes

Antisense OligoNucleotide (AON) Rx for *CEP290*-LCA10


Cone
Rod
Outer plexiform layer
Outer nuclear layer
External limiting membrane
Inner segment
Connecting cilium
Outer segment
Retinal pigment epithelium
Synaps
Nucleus
Outer fiber
Myoid
Ellipsoid
Cilium
Outer segment discs
IMPDH1
CRX
AIPL1
CRB1
RDH12
SPATA7
RPGRIP1 & CEP290
GUCY2D
RPE65
MERTK
LCA & IRD Genes
Expression Patterns
© Bart P LEROY

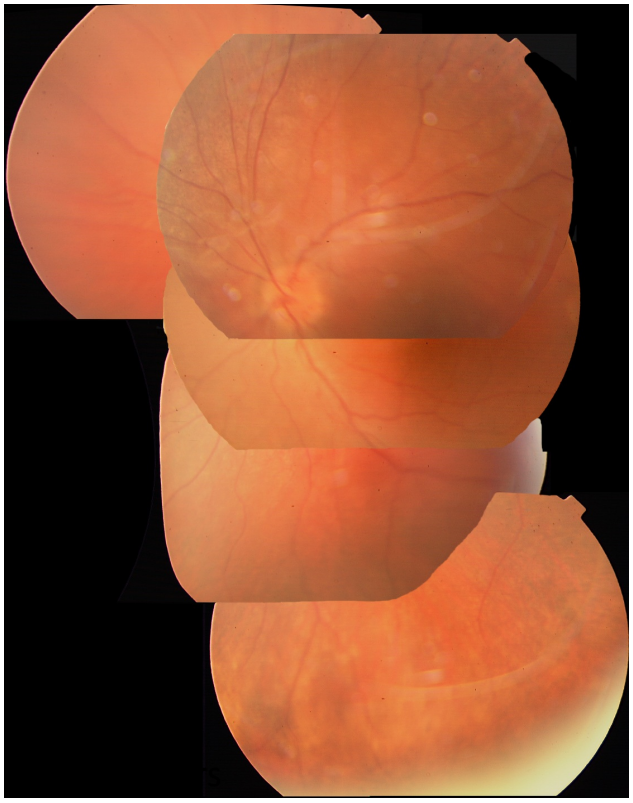
CEP290-LCA10

Severe Phenotype

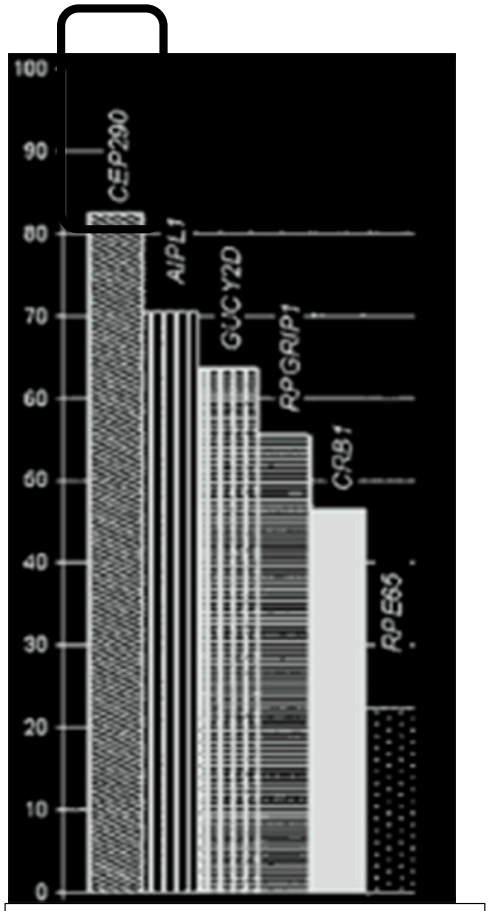


Retained central retinal photoreceptors & RPE disproportionate to low level of vision

Gene encompasses 54 exons w/ open reading frame of 7,440 bp) that exceeds typical cargo size (4.7 kb) of rAAV



Compound HeZ
p.Cys998X &
p.Glu1956GlyfsX9



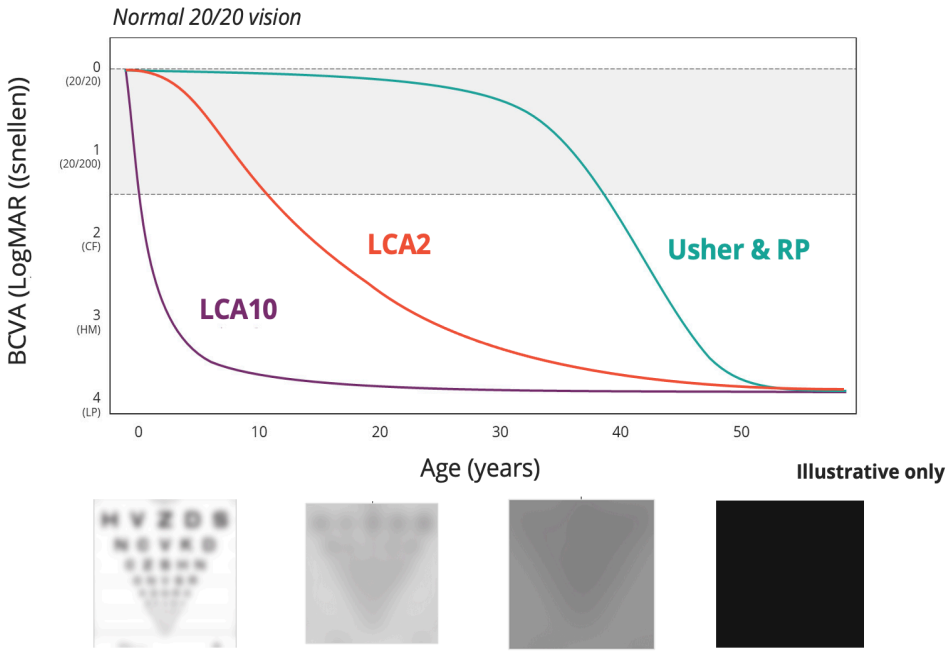
Modified from
Walia et al. *Ophthalmology* 2010

Percentage of patients w/ very severe vision loss w/ best-corrected visual acuities= CF, HM, LP & NLP

High unmet medical need in LCA10

- Autosomal recessive retinal disease leading to severe and early vision loss
- Caused by mutations in the *CEP290* gene
- c.2991+1655A>G variant accounts for approximately 2,000 patients in the Western world
- The vision loss associated with LCA10 impacts quality of life of individuals living with the disease

A severe and early onset vision loss in LCA10 vs. other IRDs

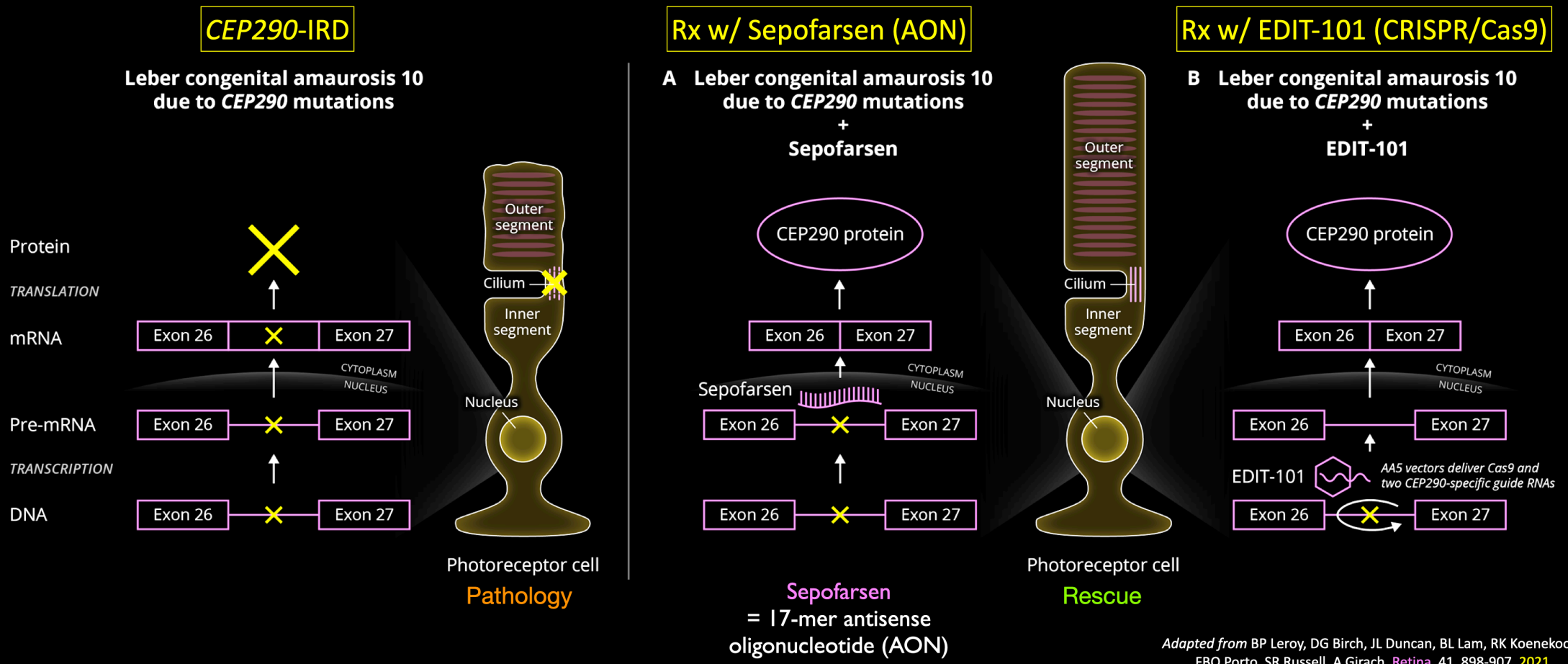


There are currently no approved therapies for LCA10

LCA, Leber congenital amaurosis; 1. Chacon-Camacho OF, Zenteno JC. *World J Clin Cases*. 2015;3(2):112–24; 2. Cideciyan AV, Jacobson SG. *Invest Ophthalmol Vis Sci.* 2019;60(5):1680–95; 3. Jacobson SG, et al. *Invest Ophthalmol Vis Sci*. 2017;58(5):2609–22; 4. Leroy BP, et al. *Retina* 2021;41(5):898-907.

CEP290-LCA10

Splice Correction for p.Cys998X *CEP290* mRNA



Adapted from BP Leroy, DG Birch, JL Duncan, BL Lam, RK Koenekoop, FBO Porto, SR Russell, A Girach, Retina, 41, 898-907, 2021

Genetic Rx

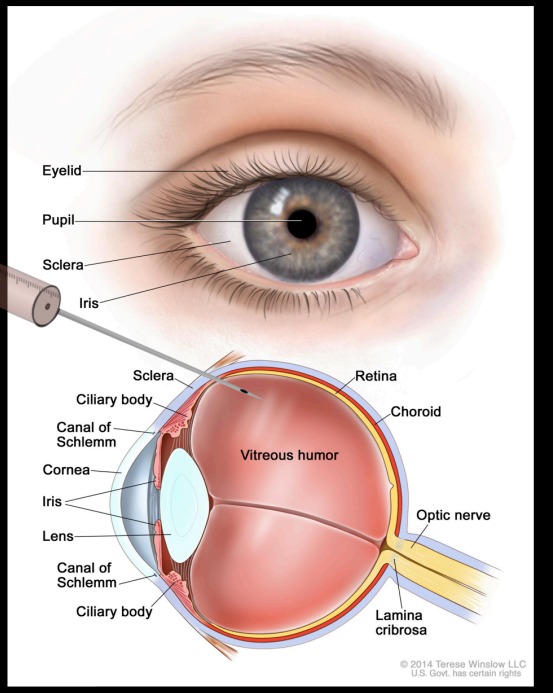
Sepofarsen (17-mer AON)

AV Cideciyan, SG Jacobson, A Drack, AC Ho, J Charng, AV Garafalo, AJ Roman, A Sumaroka, IC Han, MD Hochstedtler, W Pfeiffer, EH Sohn, M Taiel, MR Schwartz, P Biasutto, W de Wit, ME Cheetham, P Adamson, DM Rodman, G Platenburg, MD Tome, I Balikova, F Nerinckx, J De Zaeytijd, C Van Cauwenbergh, BP Leroy, SR Russell, Nat Med, 25, 225-228, 2019

BP Leroy, SR Russell, AV Drack, AV Cideciyan, SG Jacobson, AC Ho, C Van Cauwenbergh, J De Zaeytijd, AK Krishnan, W den Hollander, A Hollestein-Havelaar, MR Schwartz, A Girach: Safety and efficacy of sepofarsen in the second treated eye in the Phase 1b/2 extension trial in Leber congenital amaurosis due to mutations in the CEP290 gene (Insight Trial), EURETINA 2021 Virtual Meeting, 09-12/09/2021

Sepofarsen (17-mer AON) directed against *CEP290* pre-mRNA

Intravitreal Injection



- Intravitreal injection - broad distribution
- Sepofarsen is 17-mer antisense oligonucleotide (AON) 160 µg/80 µg in 50 µl
- Effect not permanent - thus reversible

PQ-110-003 (Sepofarsen) Phase 2/3 Illuminate Trial

A Story of a Suboptimal Comparison

First year results: Illuminate did not meet primary endpoint of Best-Corrected Visual Acuity (BCVA) at Month 12 compared to sham procedure control group

Traditional analysis approach of TE vs sham is difficult to show Tx effect due to high variability & small N

However, when adjusting TE & sham eyes by subtracting effects of their corresponding CE, a numeric treatment difference between sepofarsen & sham is observed

- Consistent w/ Phase 1b/2 study results
- Individual participants demonstrated improvement from baseline in multiple endpoints
- Responses also seen in year 2 when 2nd eye/sham was treated

Overall good safety profile: no intraocular inflammation, no systemic effects

EMA & FDA recommended setting up another phase 2/3 trial prior to submitting Marketing Authorization Application

ProQR Therapeutics Announces Transaction Completed for Théa to Acquire Sepofarsen and Ultevursen Ophthalmic Assets

Download PDF

Divestment of sepofarsen and ultevursen completed – Théa to continue development of sepofarsen and ultevursen for patients with LCA10 and Usher syndrome

Agreement provides ProQR with initial payment of €8M and up to €165M in earn-out payments, as well as potential double-digit royalties based on commercial sales in the US and EU

Transaction supports ProQR's strategic focus on its proprietary Axiomer® RNA editing technology platform and continued advancement of pipeline

LEIDEN, Netherlands & CAMBRIDGE, Mass., Dec. 08, 2023 (GLOBE NEWSWIRE) --
ProQR Therapeutics N.V. (Nasdaq: PRQR) (ProQR), a company dedicated to changing lives through transformative RNA therapies, today announced it has completed a transaction divesting late stage ophthalmic assets, sepofarsen and ultevursen, to Laboratoires Théa (Théa).

https://www.proqr.com/press-releases/proqr-therapeutics-announces-transaction-completed-for-thea-to-acquire-sepofarsen-and-ultevursen-ophthalmic-assets

08 Dec 2023

Sepul Bio, a Théa Pharma Company
Patient recruitment ongoing
Patients HeZ or HoZ for
frequent c.2991+1655A>G mutation in *CEP290*

Approaches for Large Genes

Dual Vector Technology for
ABCA4-IRD (Stargardt Disease)
&
MYO7A-IRD (Usher Syndrome Type 1B)

AAVANTGARDE is a clinical-stage next-generation gene therapy platform company

2 Platforms

- **Large gene delivery**

  Dual Hybrid AAV platform (validated in Akouos study)

  Intein mediated Protein trans-splicing

- **Broad IP and exclusive license**

2 Programs

- **Usher syndrome 1B**
  - AAVB-081 Luce study: First patient dosed in 2024; clinical PoC in 2025

  MYO7A

- **Stargardt disease**
  - AAVB-039 Stella natural history study & First-in-human studies in 2025; Clinical PoC in 2027
  - Strong PC package including NHP data

  ABCA4

Expansion opportunities

- **Pipeline expansion and BD opportunities**

  Additional IRDs (Ophthalmology)

  Pipeline ex-ophthalmology

Dual AAV hybrid platform

DNA splicing to generate a full-length protein

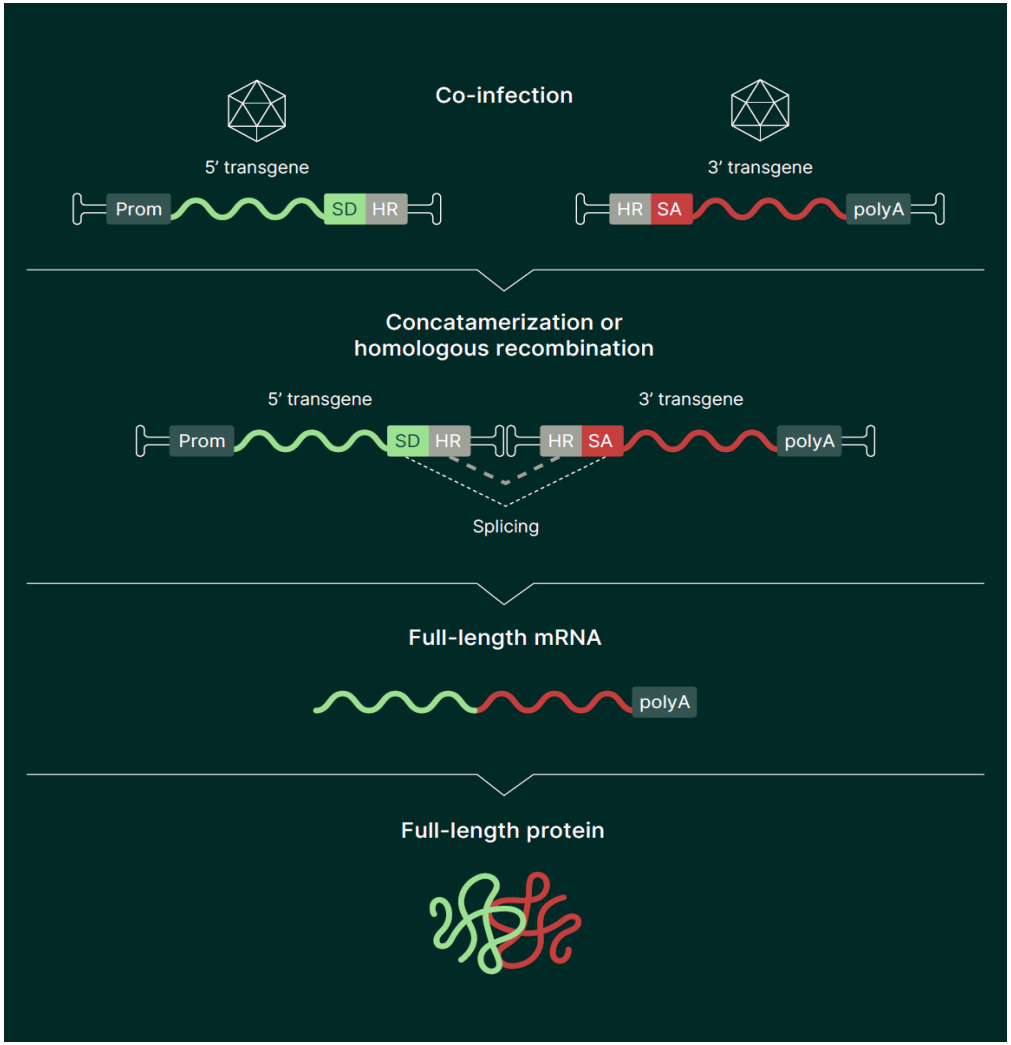
Uses **2 AAV vectors**, containing 5' or 3' halves of therapeutic gene

Works by **recombining DNA within cell**

Efficient recombination & versatile approach

Generates **therapeutically meaningful protein levels**

Usher 1B program



Intein-mediated platform

Protein trans-splicing to generate a full-length protein

Uses **2 AAV vectors** encoding each for one of the halves of target proteins flanked by **short split inteins**

Works by **protein trans-splicing** within the cell

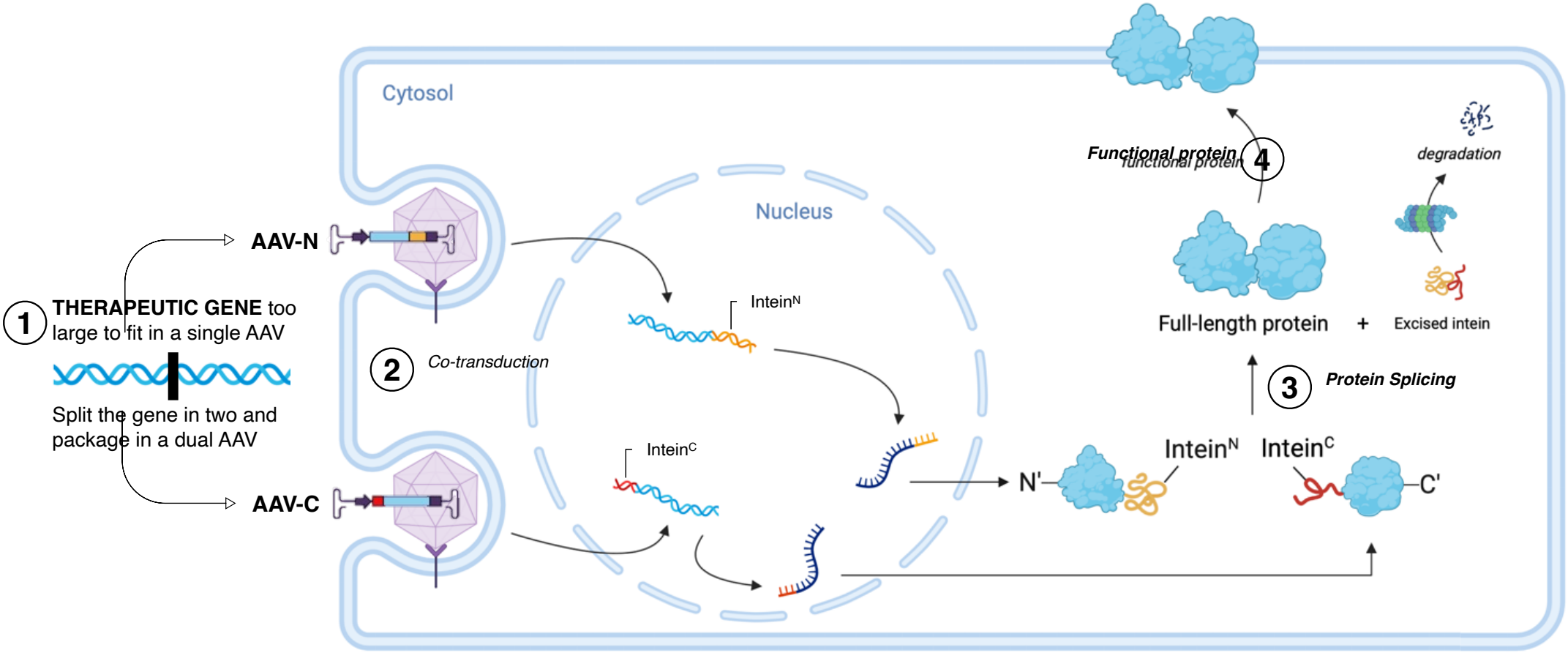
Demonstrated safety and very **efficient recombination** in different species (**mouse, pig and NHP**)

Delivers therapeutically meaningful protein levels

Stargardt program

SpliceBio Protein Splicing: a New Gene Therapy Modality

SpliceBio's Protein Splicing platform has demonstrated efficiencies of > 95%.



Generic Gene Therapy Approaches

Optogenetics

Genetic Therapy for IRDs

Conclusions

Rx for Genetic Retinal Disease

Need For Genotyping

Need for genotyping enormous:

Frequency of inherited retinal disease = 1/2500

World population = 8.200.350.300 (Jan 2025)

3.281.000 patients (Jan 2025)

Gene-specific Rx feasible for everyone?

Perspectives of Patients, IRD Experts, Industry & Regulatory Bodies

Background

Patients want decrease in speed of degeneration, stability or improvement

IRD experts desire to help IRD patients keep function for as long as possible

Industry prefers an efficient treatment w/ return on investment

Regulatory agents need to see real-World evidence of improvement in activities of daily living

Genetic Therapies for IRDs
Overall Conclusions

Very recent field (+/- 20 yrs)

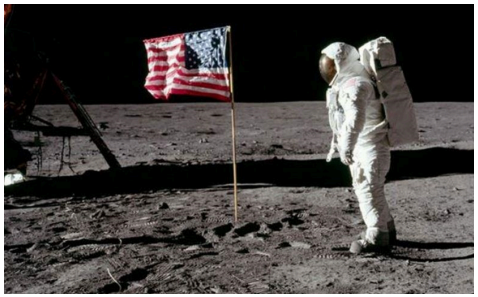
Gene Rx efforts are mushrooming (Luxturna® is 1st of many)

Genetic Rx requires intact target cells, works but is not perfect

A lot remains to be learned

A difficult path lies ahead, but future is bright

20 Jul 1969 NASA's Apollo 11
landed on the Moon
w/ Neil Armstrong, Buzz Aldrin &
Michael Collins aboard



Urgent need to improve patient identification through systematic genotyping

Better understanding of CRA & inflammation required

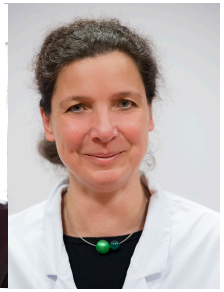
Ghent Ocular Genetics Team

Ophthalmic Genetics & Visual Function Team

Julie
DE ZAEYTIJD

Bart
LEROY

Joke
RUYS



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