QR-421a: *An antisense oligonucleotide for the treatment of RP due to USH2A exon 13 mutations*

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Forward looking statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including but not limited to, statements regarding our strategy, future operations, future preclinical and clinical trial plans and related timing of trials and results, research and development, future financial position, future revenues, projected costs, prospects, therapeutic potential of our product candidates, plans and objectives of management, are forward-looking statements. The words “aim,” “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Forward-looking statements represent our management’s beliefs and assumptions only as of the date of this presentation. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those that may be described in greater detail in the annual report filed on Form 20-F for the year ended December 31, 2018 that we have filed with the U.S. Securities and Exchange Commission (the “SEC”) and any subsequent filings we have made with the SEC. We have included important factors in the cautionary statements included in that annual report, particularly in the Risk Factors section, and subsequent filings with the SEC that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

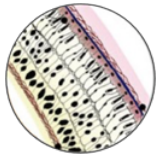
Eye is ideal for RNA (antisense oligonucleotide—ASO) therapeutics

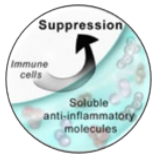
Small Compartment

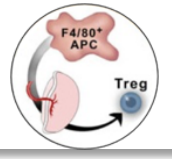
0.22 Fluid ounces

Relative Immuno-privileged Site

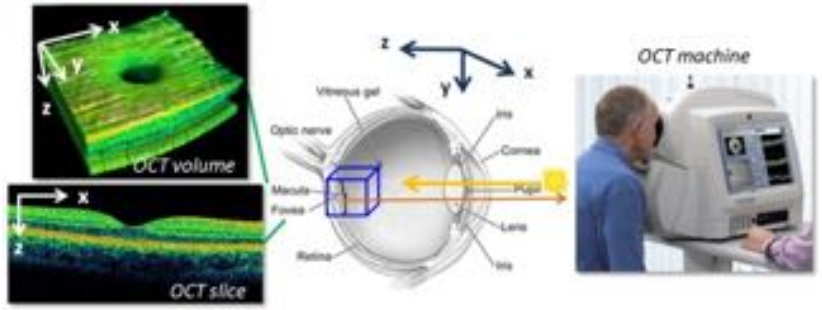
- Blood-retina barrier, tight cell junctions
- Local immunomodulatory factors present
- Scarcity of antigen presenting cells







Visible & Accessible



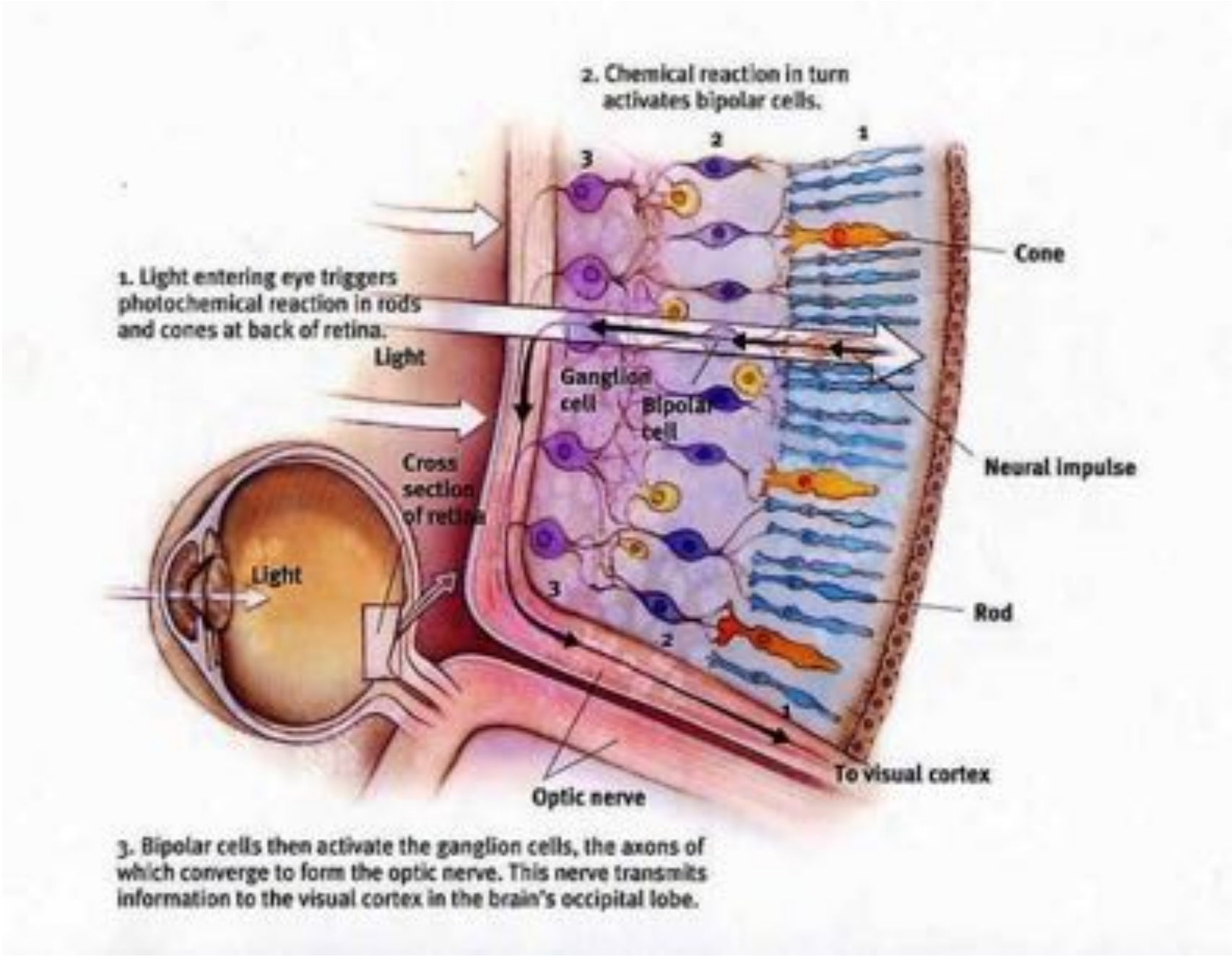
Facilitated by imaging systems, e.g. OCT machines

Target Rich

300 Known genetic causes of blindness

220 Mapped to specific gene

How we see:



Human retina. Courtesy Rowland Hall

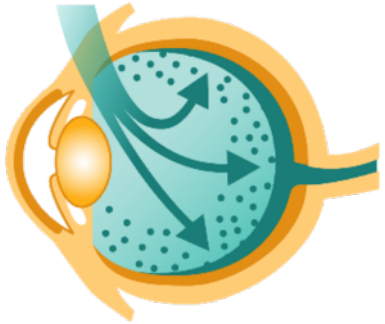
Inherited Retinal Disease(IRD) management: coming of age

- **Improved genetic diagnosis**
- **New treatment options**
  - Gene therapies
    - Luxturna for LCA2
    - Experimental therapies for other IRDs
      - Eg choroideremia, RP
  - RNA therapies
    - Macugen for Wet AMD
    - Vitravene for CMV Retinitis
    - Experimental therapies for other IRDs
      - Eg ASO for LCA10, Usher syndrome

How do antisense oligonucleotide(ASO) drugs compare with gene therapy?

RNA Antisense Oligonucleotide Therapy	Gene Therapy/Editing
Specific	Specific (replaces or edits)
Requires re-dosing	Potential one and done dosing
Naked, no vectors needed	Editing material is contained within viral vectors
Under local anesthesia	Usually requires general anesthesia
Reversible	Irreversible
Intravitreal Injection	Sub-retinal surgery with vitrectomy
Can be used in earlier disease, since central/peripheral retinal exposure	Usually suitable for end-stage disease only, since applied to sub-macular area

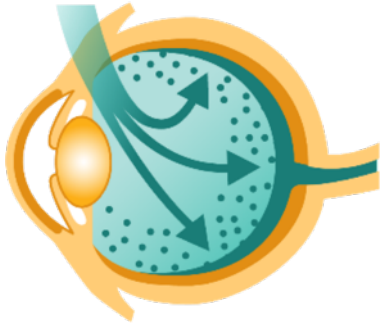
The Opportunity in Inherited Retinal Diseases



RNA Therapeutics characteristics, irrespective of the target

- Intravitreal administration is routine procedure
- Acceptable safety profile
- Broad distribution throughout the entire retina
- Long half life allowing for infrequent dosing

The Opportunity in Inherited Retinal Diseases



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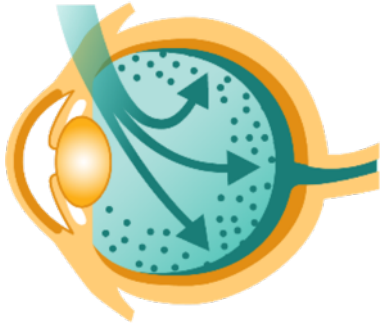

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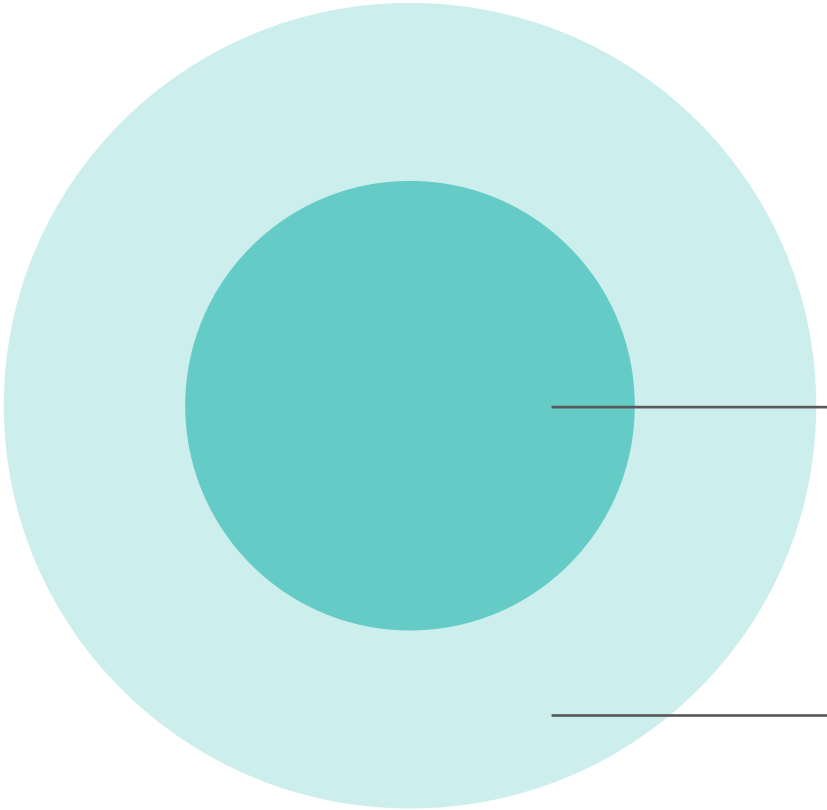

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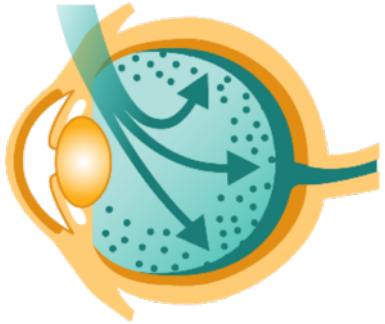

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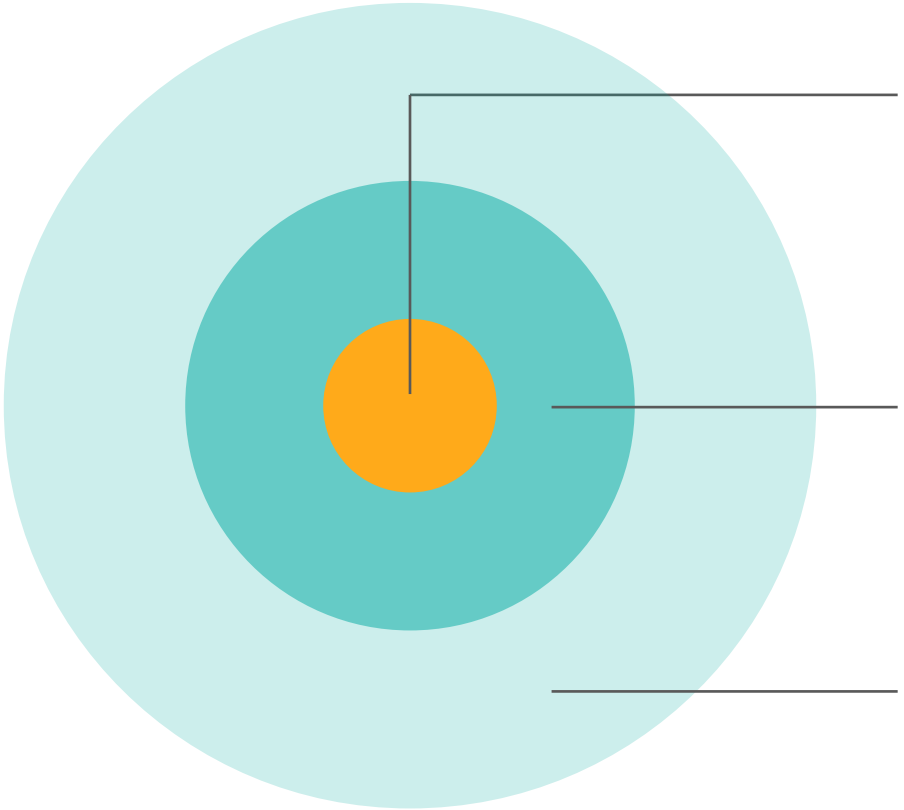


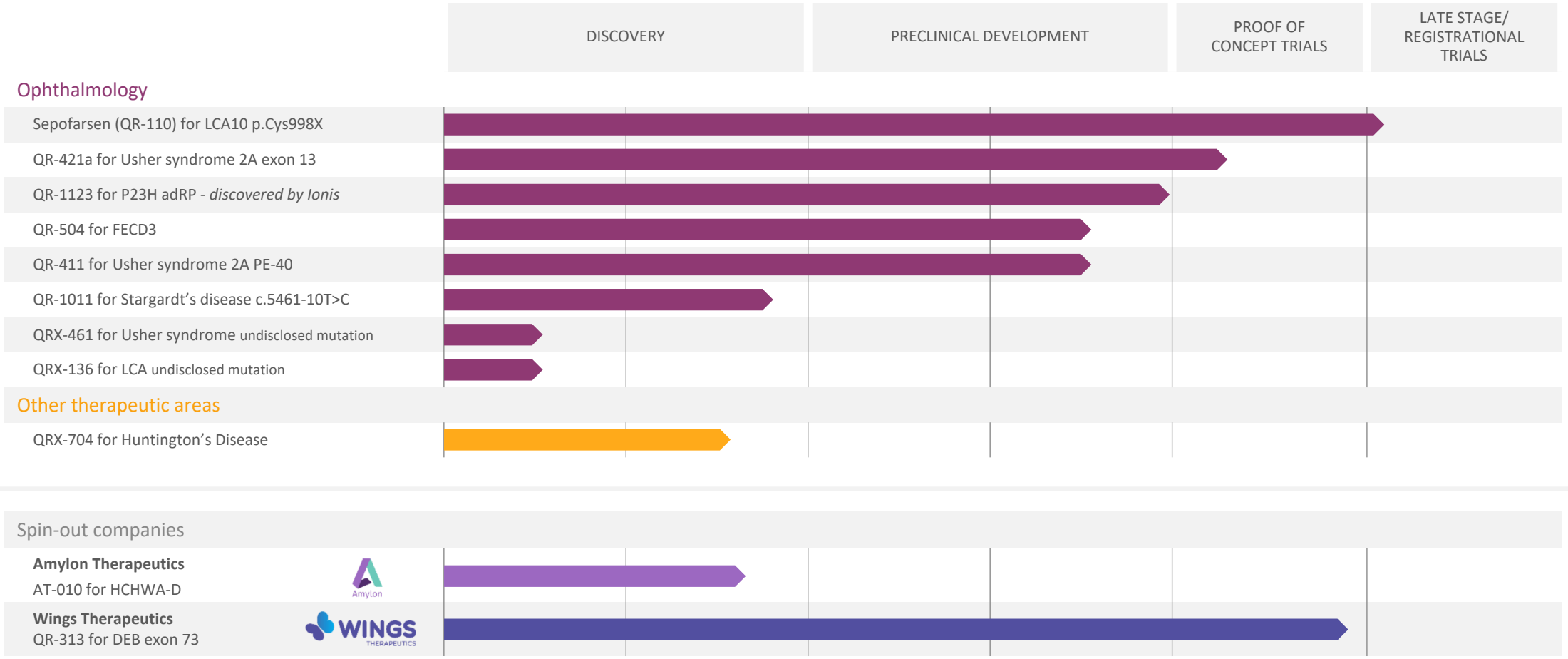
The opportunity:

>100 tangible targets remain after further filtering for disease state and population size

ProQR projects its technology can address about **25% of the mutations** at a molecular level

>300 genes causing Inherited Retinal Diseases, described with **>50 pathogenic mutations** per gene, leading to **>15,000 targets**.

ProQR development pipeline



Sepofarsen (QR-110) for Leber's Congenital Amaurosis Type 10 (LCA10)

LCA10

Lose sight in first years of life

No therapy available

p.Cys998X(CEP 290) mutation affects **~2,000** patients in the Western world

Sepofarsen

Goal: Restore vision/ prevent vision loss in patients with LCA10

Locally administered in the eye. Routine intravitreal procedure

Anticipated infrequent dosing of 2 times a year

- √ Established modality in eye
- √ Strong preclinical proof of concept in human retina in preclinical models
- √ Orphan drug designation
- √ Fast track designation
- √ Phase 1/2 interim analysis showed rapid and sustained efficacy and favorable safety
- • Pivotal Phase 2/3 ILLUMINATE trial initiated in April 2019; data expected around YE 2020

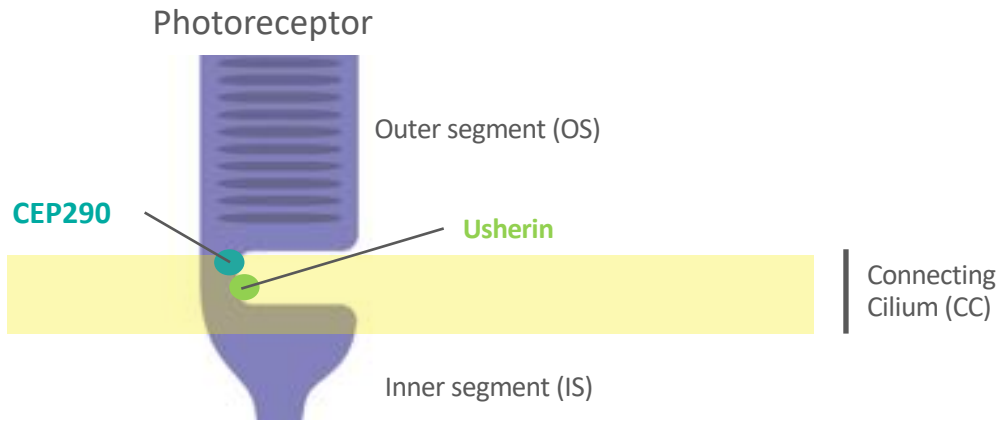
LCA 10 Phase 1/2: Top Line Efficacy Results

	Direction of improvement	Responder threshold	Change from baseline at Month 3 Mean (SEM)	
			Treated	Untreated
Visual Acuity (ETDRS/BRVT) – LogMAR (n=8)	↓= improved	≥ -0.3	-0.67 (0.32)	0.02 (0.05)
Mobility Course – level (n=7)	↑ = improved	≥2	2.57 (1.19)	1.36 (1.04)
Full field stimulus red (FST red) - cd/m2 (n=7)	↓= improved		-0.74 (0.35)	-0.23 (0.18)
Full field stimulus blue (FST blue) - cd/m2 (n=7)	↓= improved		-0.91 (0.38)	-0.02 (0.11)
Nystagmus tracking (OCI) - Log_{10}mm (n=7)	↓= improved		-0.14 (0.08)	-0.04 (0.06)

Concordant improvement in all key outcome measures

Similarities between LCA10 and Ush2a

- CEP290 and Usherin are co-localized in the connecting cilium of photoreceptors
- Sepofarsen and QR-421a have similar concentration-response curves in retinal organoids
- QR-421a has additional preclinical translational PoC in animal model

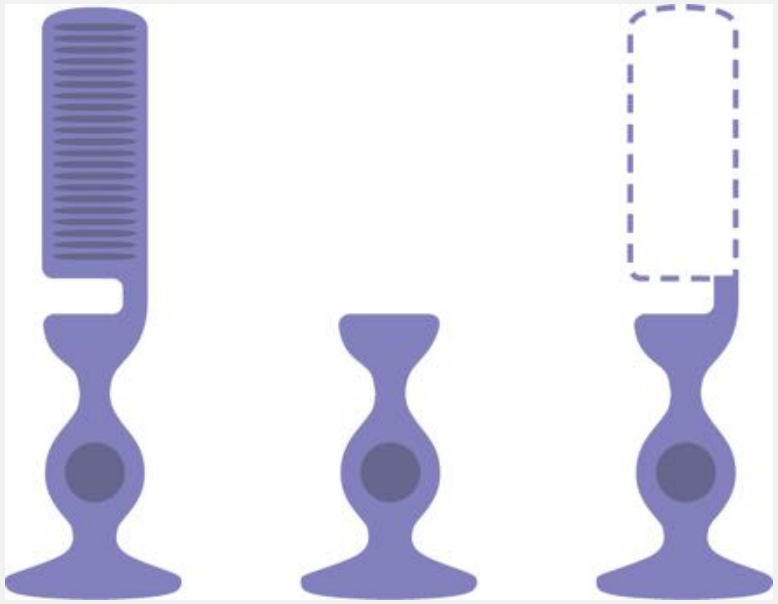


Candidate	Cellular MoA	Target cell	Active in retinal organoid/optic cup	Active in animals	Active in humans
sepofarsen	Restore cilium and OS	Photoreceptor Cones	Yes ≤1µM	Unknown	Yes
QR-421a	Restore cilium and OS	Photoreceptor Rods	Yes ≤1µM	Yes	TBD

Treatment rationale is similar in Ush2a and LCA10

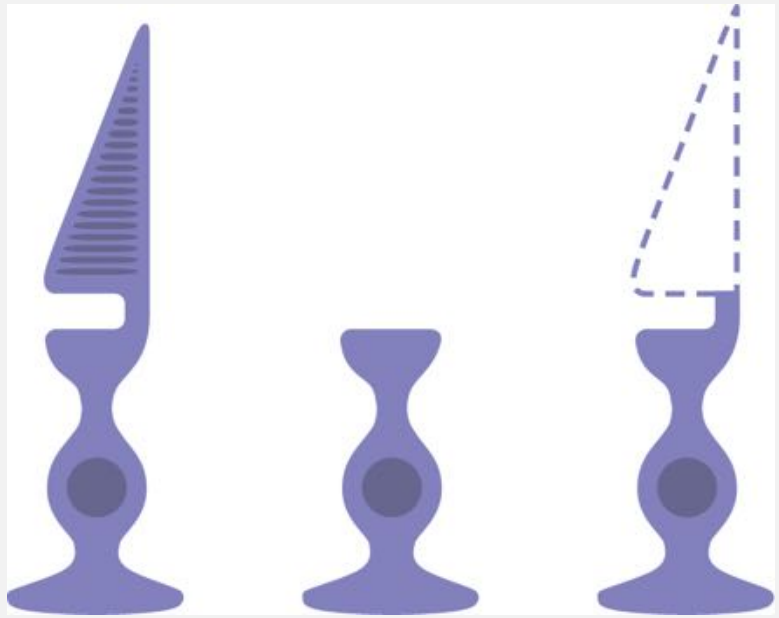
QR-421a primarily targets rod restoration

Ush2a



Normal | Ush2a | Ush2a + **QR-421a**

LCA10



Normal | LCA10 | LCA10 + **sepofarsen**

Usher Syndrome clinical disease progression

Hearing impairment

Loss of visual field (rod degeneration)

Complete blindness (rods and cones degenerated)

AGE* (YEARS) 0 10 20 30 40 50 60

*High within patient variability in onset and progression of disease

Night blindness (start rod degeneration)

Loss of central vision (cone degeneration)

QR-421a for Usher syndrome

Investigative treatment for vision loss in Usher and non-syndromic RP

Usher

Develop hearing and vision loss in childhood and are completely blind by mid adulthood

USH2A exon 13 mutations affect **~16,000** patients in Western world

Partnership

Awarded $7.5M financial support from FFB to conduct trial

Unmet need

For ***USH2A* exon 13** no therapy available

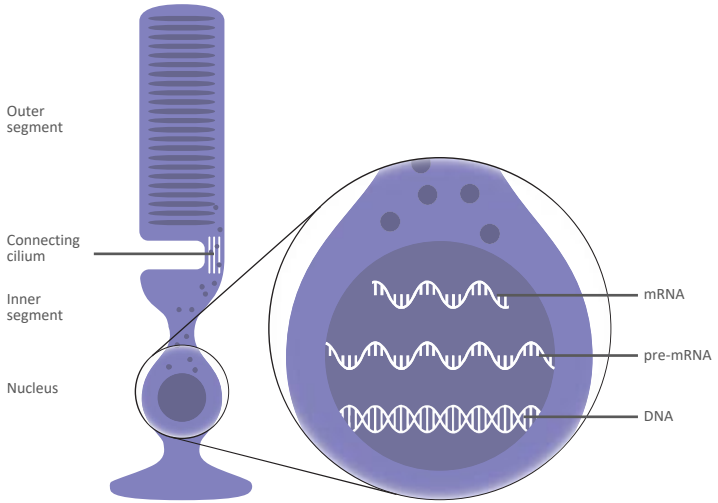
- √ Strong preclinical proof of concept in patient retinal model
- √ Orphan drug designation
- √ Fast track designation
- √ First patient dosed

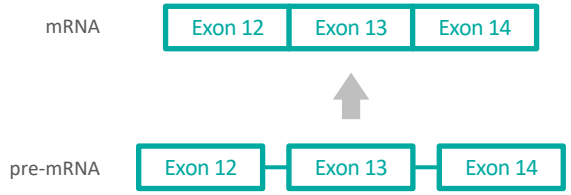
STELLAR Phase 1/2 trial

- 3 month Interim analysis on first and second cohort expected Q1 2020, including top line safety and efficacy data

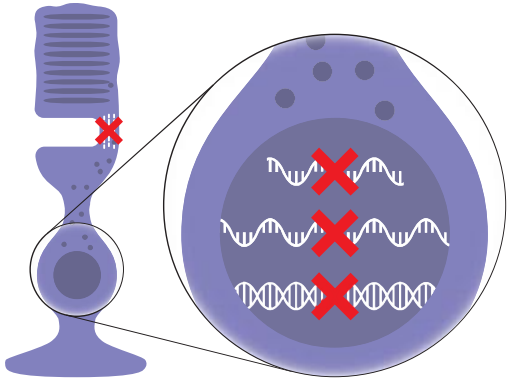
QR-421a for RP in Usher syndrome

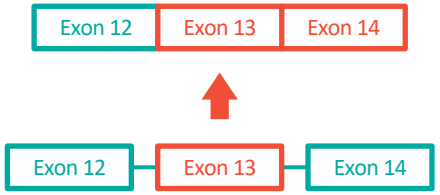
Skipping of exon 13 in USH2A mRNA



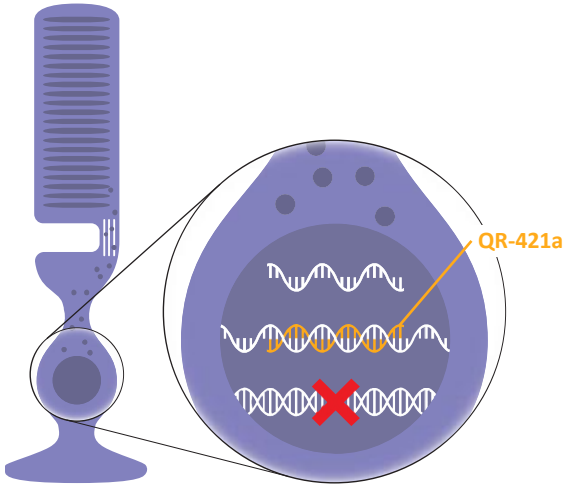


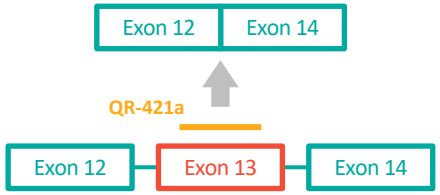
In wild type cells usherin enables protein transport through the connecting cilium





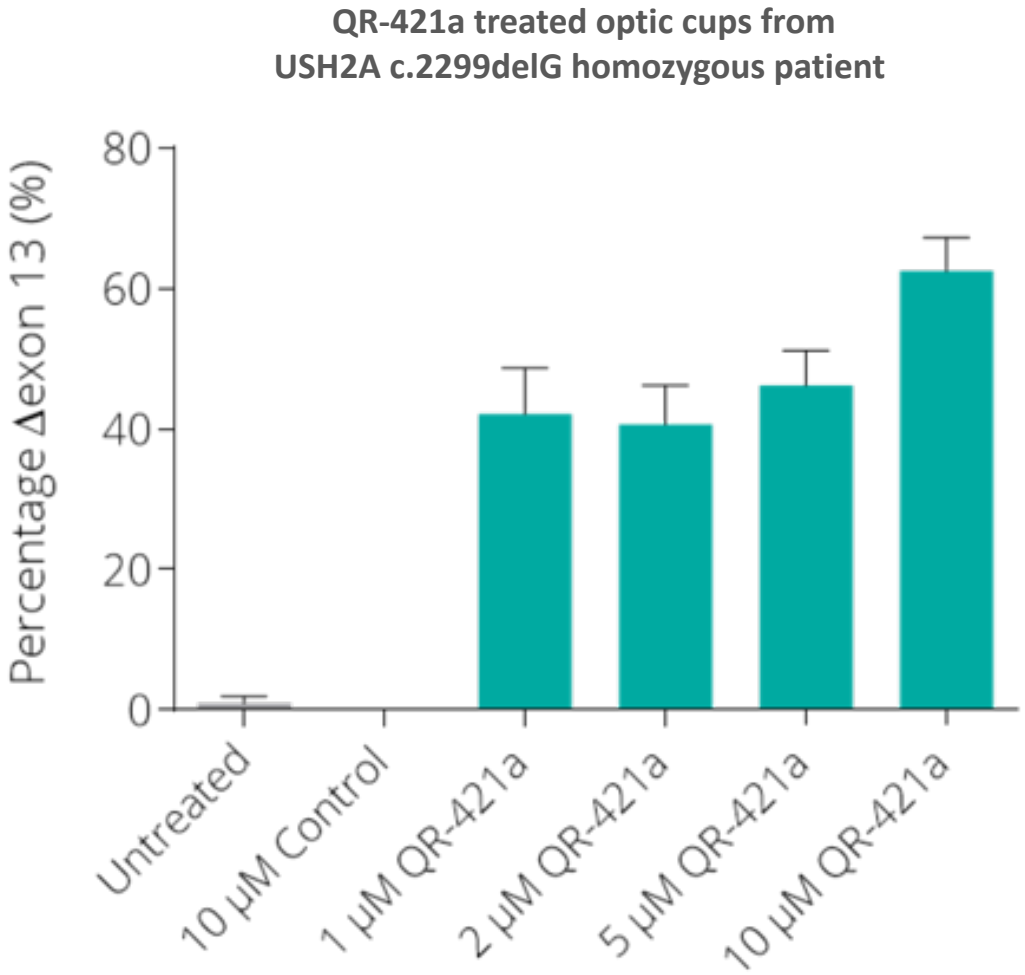
In cells with the USH2A mutation usherin is not active, hampering protein transport over the cilium





Exclusion of the exon harboring the mutation leads to restoration of functionality of usherin

QR-421a mediated USH2A exon 13 skip in optic cups



With QR-421a treatment there may be sufficient "normal" mRNA expression, which can lead to restoration of usherin protein

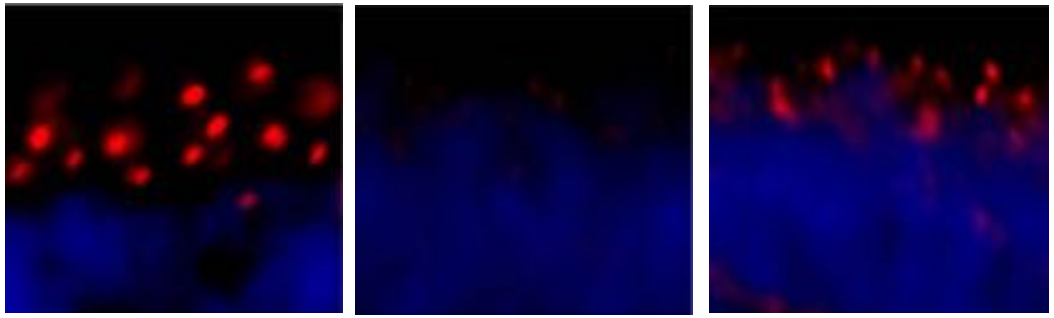
Restoration of usherin protein and ERG amplitude in exon 13 mutant zebrafish

Usherin protein (in red) in zebrafish retina

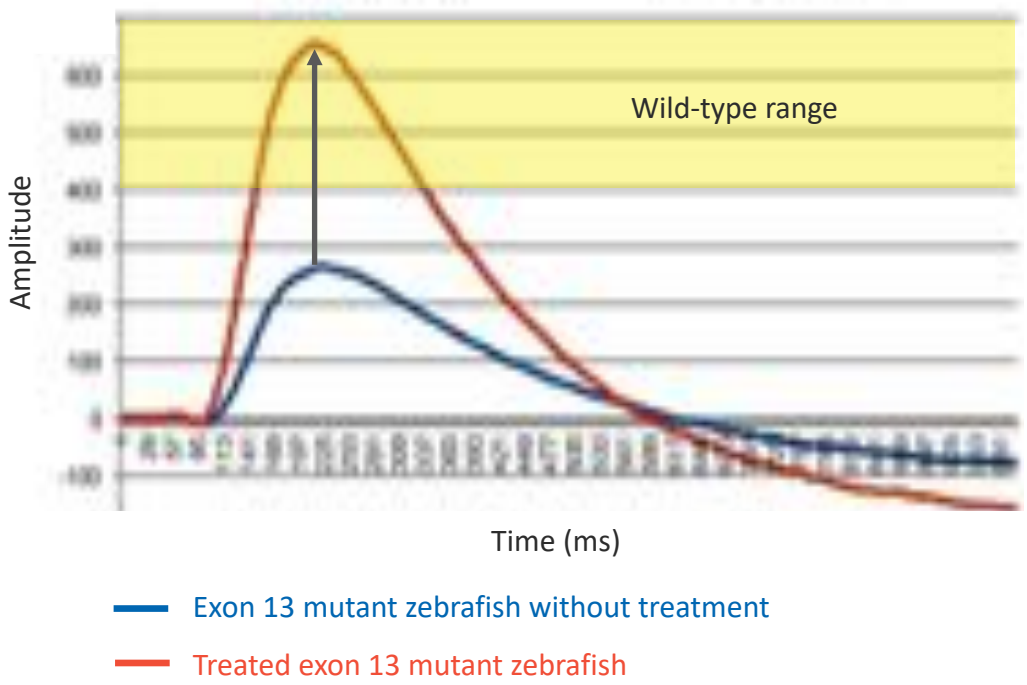
With usherin protein

Without usherin protein

Treated with oligo



ERG with light stimulus in zebrafish

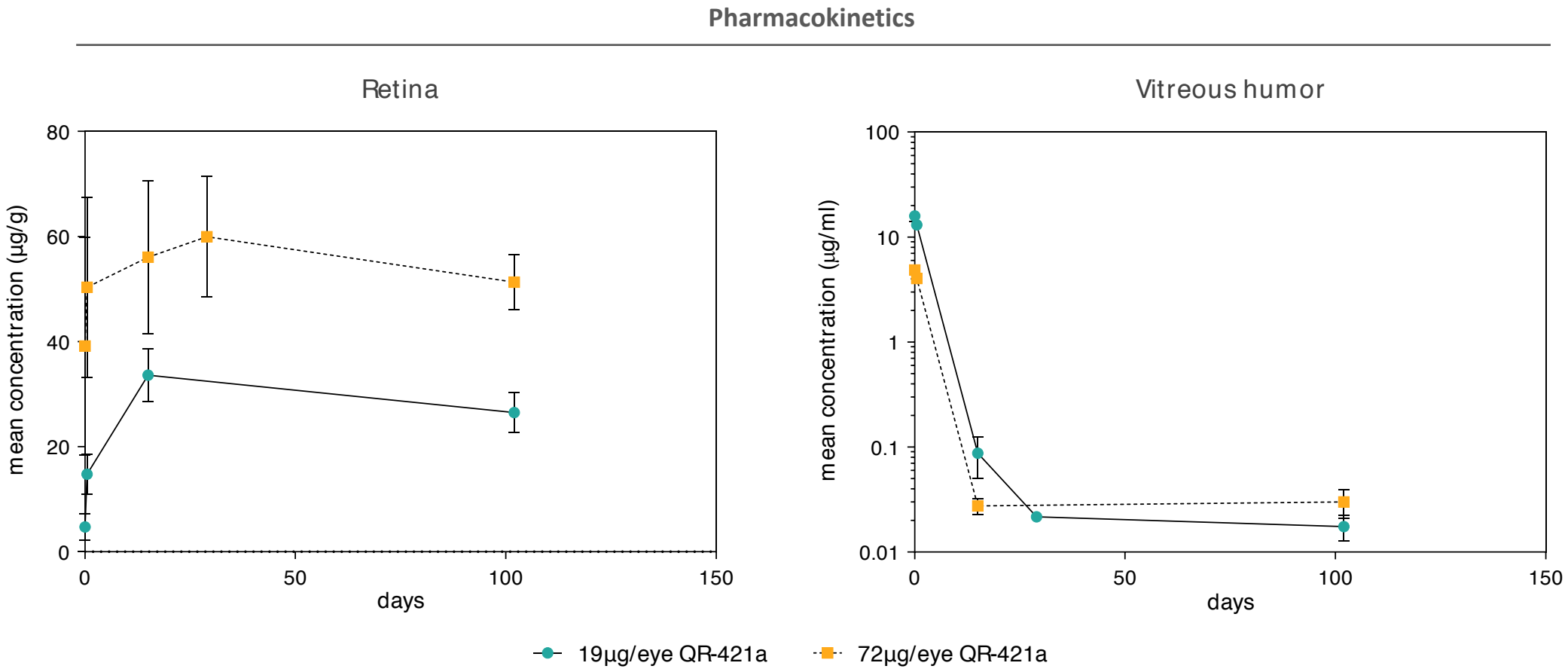


With QR-421a treatment, retina appearance and function improved

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

Pharmacokinetics in non human primates

Rapid clearance from vitreous with prolonged retention and activity in retina

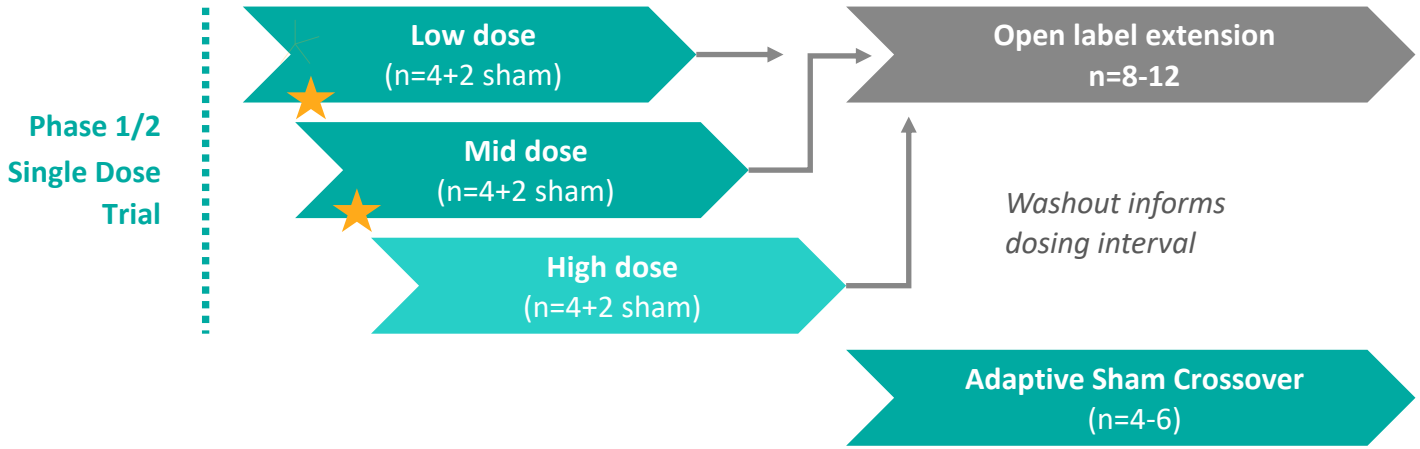


QR-421a treatment can be treated 2x/yr

QR-421a Phase 1/2 STELLAR trial in Usher 2a patients

STELLAR Phase 1/2 trial

- Single dose, double-masked, randomized, sham controlled, first-in-human trial
- Goals include safety, efficacy and dose exploration
- 24m study
- ~18-30 adult patients with moderate to severe eye disease
- Key inclusion criteria: visual field of ≥10°, visual acuity of 20/32 or worse
- Single intravitreal injection in one eye, or sham treatment (randomized 2:1 active:control per cohort)
- Key trial endpoints: visual acuity, visual field (DAC perimetry (Medmont), automated perimetry (Octopus), microperimetry (MAIA) and OCT
- First patient dosed in March 2019, early interim analysis data expected in end of Q12020



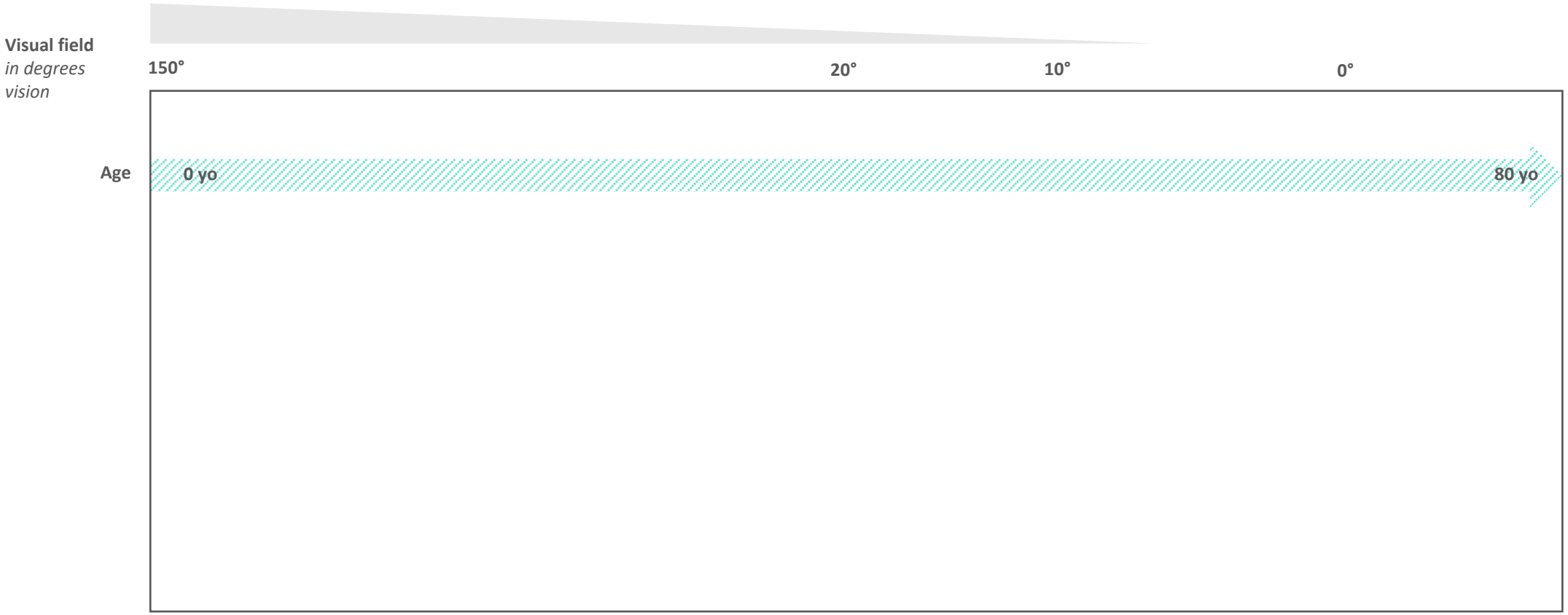
STELLAR

★ Meeting of independent DSMC

The study population and endpoints

Ranges are illustrative, not exact

The study population and endpoints



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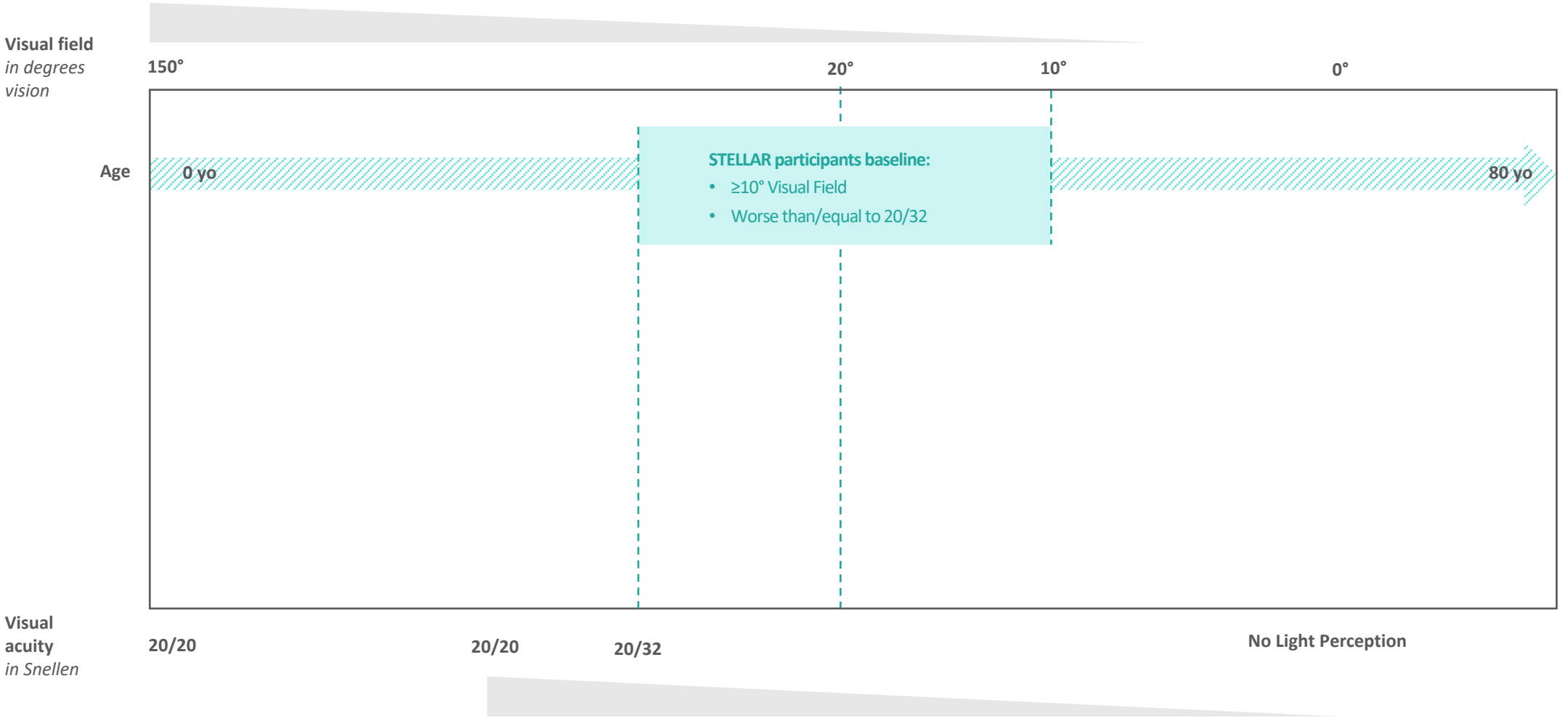

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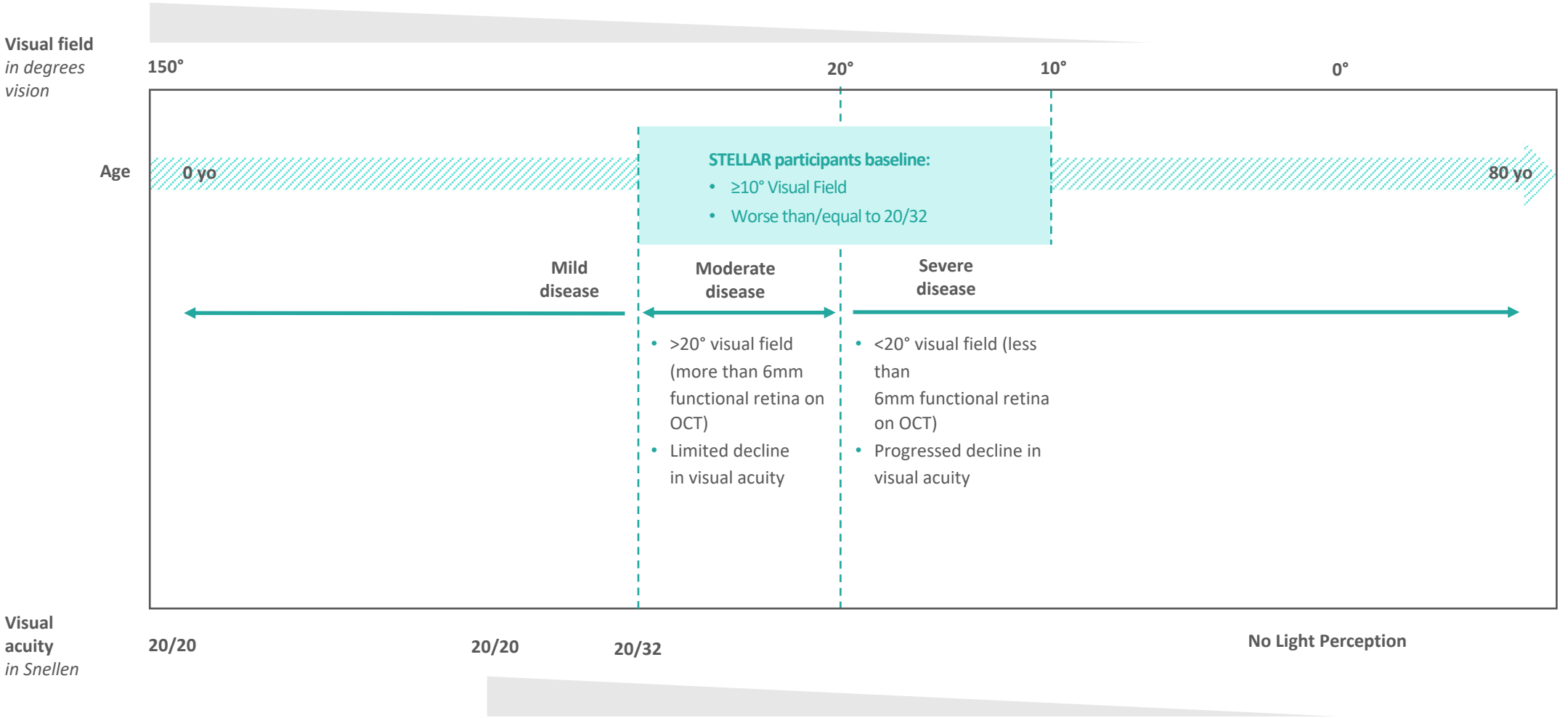

Ranges are illustrative, not exact

Some endpoints used in STELLAR (Ph 1/2 Trial)

*Patients with moderate disease**

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

*Patients with severe disease**

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- OCT(EZ)
- Patient Reported Outcomes

* Defined according to trial criteria

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Full Field Stimulus Test (FST)

All study subjects

- Test of most sensitive part of the retina
  - White light for total retina
  - Blue light for rods (mostly peripheral)
  - Red light for cones (mostly central macula)

Goal

Directional improvement in treatment group

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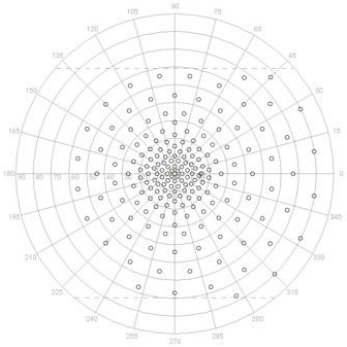
Visual Field (VF)

For moderate patients

- **Static visual field (Octopus)**
  - Measure of visual field in peripheral vision
  - Gold standard in measuring VF
  - Measures visual field with white light only
- **Dark Adapted Chromatic Perimetry (Medmont)**
  - Measure of visual field in peripheral vision
  - Patients are dark adapted prior to measurement
  - Measures visual field at different wavelengths (colors)

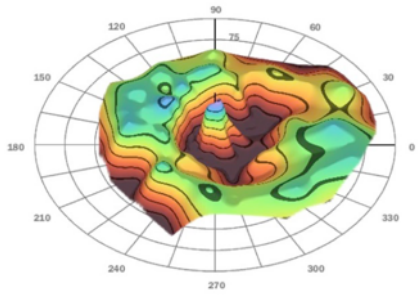
Goals

Improvement above the noise of the assay and/or improvement in hill of vision analysis



Perimetry data

Medmont device for DAC perimetry



Hill of Vision visual

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- Visual Acuity
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* Defined according to trial criteria

Visual Field (VF)

For severe patients

- Micro perimetry (Maia)
  - Measures visual field in the macula (0-20° visual field)
  - Measures visual field with white light

Goals

Improvement above the noise of the assay and/or improvement in hill of vision analysis

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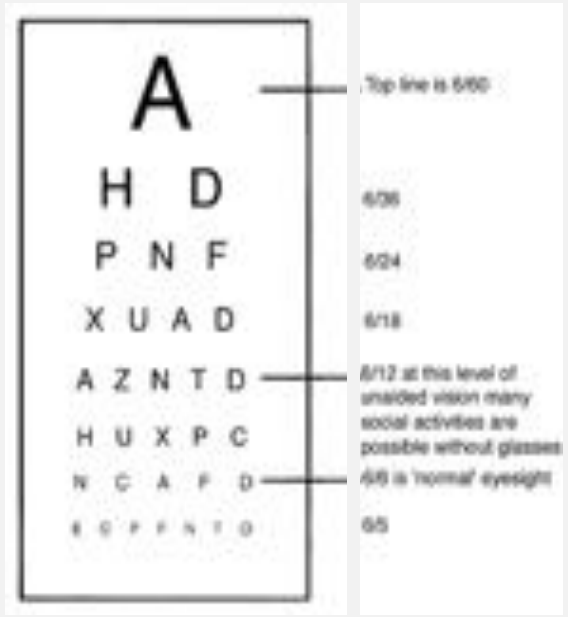
Visual Acuity

Only applicable in severe patients

Snellen Visual Acuity



- Snellen VA chart used in Clinical Practice

ETDRS/LogMAR Visual Acuity

- ETDRS Chart used as Gold Standard for assessing VA in Clinical Trials
- Alternative VA scales used for VA with low vision patients

Goals

- In responder analysis an improvement of -0.2 LogMAR (2 lines, or 10-letters) is considered meaningful by EMA
- In responder analysis an improvement of -0.3 LogMAR (3 lines, or 15-letters) is considered meaningful by FDA
- Noise of assay is likely 0.1 LogMAR (1 line, or 5-letters)

Some endpoints used in STELLAR (Ph 1/2 Trial)

*Patients with moderate disease**

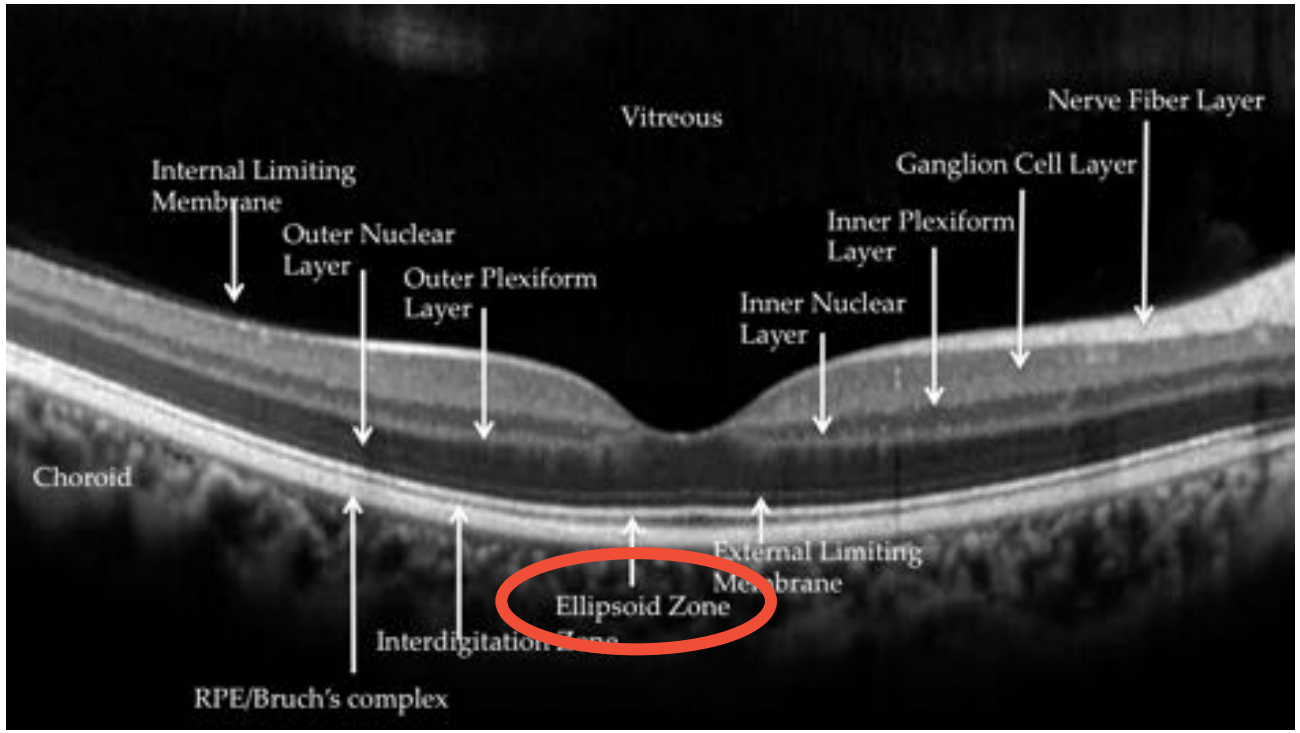
- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

*Patients with severe disease**

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- **OCT(EZ)**
- Patient Reported Outcomes

* Defined according to trial criteria

Ellipsoid Zone(EZ) on Optical Coherence Tomography(OCT)



- OCT is a non-invasive way of evaluating the retina cross-sectionally
- EZ represents one component of the photoreceptor layer
- EZ is important because:
  - EZ is easily identified on SD-OCT as objective biomarker
  - RP involves photoreceptor death
  - FDA accepts EZ as primary endpoint for trials
  - EZ width/area can be a biomarker for some retinal degenerative diseases e.g., RP (Ref: Birch et al*)
  - Clinically meaningful change=stat significant change from BL compared to Control

* *JAMA Ophthalmol*. 2013 September ; 131(9): 1143–1150

Summary

- Eye is ideal organ for RNA therapeutics(antisense oligonucleotides-ASO)
- ASO Treatment characteristics are ideal to treat eye diseases
  - Intra-vitreal delivery; relatively long half-life
- Many Inherited Retinal Diseases being investigated using ASO treatment
  - Ph 2/3 for LCA 10
  - Ph 1/2 for Ushers Type 2a(exon 13)
  - Ph 1/2 for Autosomal Dominant Retinitis Pigmentosa(anticipated end 2019)
- Many different endpoints/instruments being explored
- Many companies are working on trials for IRDs

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