An antisense oligonucleotide for the treatment of RP due to USH2A exon 13 mutations

Date: April 30, 2019
Presenter: Hester van Diepen
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.
QR-421a for Usher syndrome

Designed to treat genetic 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 for USH2A exon 13

Unmet need

- For USH2A exon 13 no therapy available

- RNA is established modality in eye
- Strong preclinical proof of concept in patient retinal model
- Orphan drug designation
- Fast track designation
- First patient dosed

STELLAR Phase 1/2 trial

- Expect safety and efficacy results in mid-2019
- Expect results from multiple dose adaptive trial in 2021
RP associated with Usher Syndrome

Genetic cause of combined deafness and blindness

From Sandberg et al. 2008

Normal

Symptoms: Pale optic nerve, thin vessels

USH2A

Normal EZ-line

Normal retina has functioning central and peripheral retina (presence of ONL and EZ-line)

RP

Macula EZ-line only

RP patients have slower degeneration starting in the peripheral retina and then progressing to the macula (presence of ONL and macular EZ-line) retina defect is in peripheral retina
**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.
Targeting Strategy

In frame removal of Ex13 (642nt)

Many pathogenic mutations in exon 13, including the two most common variants

- G2299del (frameshift), causing Usher
- G2276T (Cys759Phe), causing RP

mRNA remains in frame (removal of 642 nt) Removes 4 laminin-EGF repeat domains (214 aa)

Strict requirement to show truncated (exon-13 deleted) mRNA leads to functional protein

Lamin-type EGF like domain 4

Lamin-type EGF like domain 8

A USH2A  Usherin (5 213 aa)
QR-421a mediated USH2A exon 13 skip in optic cups

QR-421a treated optic cups from USH2A c.2299delG homozygous patient
Restoration of usherin protein in exon 13 mutant zebrafish

RT-PCR in zebrafish retina

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
</table>

Usherin protein (in red) in zebrafish retina

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>Ush2a&lt;sup&gt;rmc1&lt;/sup&gt;</th>
<th>Treated with oligo</th>
</tr>
</thead>
</table>

Co-staining with anti-centrin Ab showed Usherin localized at the connecting cilium

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands
Restoration of usherin protein and ERG amplitude in exon 13 mutant zebrafish

Usherin protein (in red) in zebrafish retina

<table>
<thead>
<tr>
<th>With usherin protein</th>
<th>Without usherin protein</th>
<th>Treated with oligo</th>
</tr>
</thead>
</table>

ERG with light stimulus in zebrafish

- Exon 13 mutant zebrafish without treatment
- Treated exon 13 mutant zebrafish

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands
Pharmacokinetics in non human primates

Rapid clearance from vitreous with prolonged retention and activity in retina

Pharmacokinetics

Retina

Vitreous humor

mean concentration (μg/g)

mean concentration (μg/ml)

days

days

19μg/eye QR-421a

72μg/eye QR-421a
In vivo uptake and retention of QR-421a in the Outer Nuclear Layer of mouse retina
QR-421a Phase 1/2 trial in Usher 2a patients

**STELLAR Phase 1/2 trial**
- Single dose, double-masked, randomized, controlled trial
- Goals include safety and efficacy PoC and dose interval
- ~18 adult patients with moderate to severe eye disease
- 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, data expected in mid-2019
ProQR® IT’S IN OUR RNA