Forward-looking statements

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Building a leading genetic medicines company

**INNOVATIVE PLATFORM**
- Stereopure oligonucleotides
- Novel backbone modifications (PN chemistry)
- Allele-selectivity
- Multiple modalities (silencing, splicing, ADAR editing)
- Strong IP position

**FOUNDATION OF NEUROLOGY PROGRAMS**
- Huntington’s disease
- ALS / FTD
- Ataxias
- Parkinson’s disease
- Alzheimer’s disease

**CLINICAL DEVELOPMENT EXPERTISE**
- Multiple global clinical trials ongoing across eight countries
- Innovative trial designs

**MANUFACTURING**
- Established internal manufacturing capabilities to produce oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia

1stereopure oligonucleotides and novel backbone chemistry modifications
PRISM has unlocked novel and proprietary advances in oligonucleotide design

- Backbone modifications
- Sugar modifications
- Drug approvals (FDA)

- Mixtures of $2^n$ molecules\(^1\)
- ~500,000 different molecules per dose

Phosphorothioate (PS)

Phosphorodiamidate Morpholino (PMO)

- fomivirsen
- pegaptanib
- mipomersen
- eteplisren
- inotersen
- golodirsen
- nusinersen
- givosiran
- patisiran
- viltolarsen

PN backbone modification chemistry

1975

2000

2020

1\(^n\)=number of chiral centers
2oligonucleotide therapies approved by the FDA across the industry
Innovative pipeline led by neurology programs

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<th>THERAPEUTIC AREA / TARGET</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
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**Note:** During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.

ALs: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3 CNS: Central nervous system
WVE-120101
WVE-120102
WVE-003

Huntington’s Disease Portfolio
Huntington’s disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; evidence suggests wild-type HTT loss of function plays a role in Huntington’s disease
- 30,000 people with Huntington’s disease in the US; another 200,000 at risk of developing the condition

Importance of wild-type huntingtin (wtHTT) in HD

Huntington’s disease (HD) may be caused by a dominant gain of function in mutant HTT and a loss of function of wtHTT protein

• Evidence suggests wild-type or healthy HTT is neuroprotective in an adult brain
  – Transport of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are regulated by wtHTT levels

• Relative proportion of wild-type to mutant protein is critical
  – Increased amount of wild-type protein relative to mutant HTT may result in slower disease progression (measured by age-at-onset)
  – Patients with lack of wild-type have significantly more severe disease (measured by disease progression after symptom onset)

Nature publication contributes to weight of evidence on importance of wild-type huntingtin

- Conditional knock-out of Htt in 4-month old mice (post-neuronal development)

- Results suggest that:
  1) Htt plays a central role in the regenerating transcriptome (potentially influencing genes such as NFKB, STAT3, BDNF)
  2) Htt is essential for regeneration

"Indeed, conditional gene deletion showed that Htt is required for neuronal repair. Throughout life, neuronal maintenance and repair are essential to support adequate cellular functioning.\"
Increasing evidence on the importance of wtHTT in HD pathogenesis, CNS and systemic health

Recent publications on wtHTT LoF as a likely driver of HD pathogenesis

- Striatum-specific defect in synaptic vesicle endocytosis that was not corrected by total lowering of HTT
- Corrected by overexpression of wild-type protein

- Striatal projection neurons require HTT for motor regulation, synaptic development, cell health, and survival during aging
- Loss of HTT function could play a critical role in HD pathogenesis

wtHTT in HD highlighted at CHDI 15th Annual HD Therapeutics Conference:

HTT LOWERING: EXPLORING DISTRIBUTION, TIMING, AND SAFETY (LOSS OF FUNCTION)

Key points discussed at meeting:

- wtHTT has numerous critical functions throughout life (e.g., intracellular trafficking, cell-cell adhesion, BDNF transport)
- Near elimination of mouse wtHtt detrimental regardless of when suppression begins
- Specific brain regions, e.g., STN, may be particularly vulnerable to wtHTT lowering
- Mouse Htt lowering can lead to thalamic, hepatic, pancreatic toxicity
- HTT LoF mutations highly constrained in human population, suggesting selection against LoF mutations

LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington’s disease; STN: subthalamic nucleus
Wild-type HTT in the cortex appears critical for striatal health

<table>
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<tr>
<th>Neuron Type</th>
<th>Genetic Status</th>
<th>Compartment</th>
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<tr>
<td>Cortical</td>
<td>WT</td>
<td>HD</td>
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<tr>
<td>Striatal</td>
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</table>

<table>
<thead>
<tr>
<th>Network Status</th>
<th>Functional</th>
<th>Dysfunctional</th>
</tr>
</thead>
</table>

Status of the presynaptic compartment determines the integrity of the network

Presented by Dr. Frederic Saudou at Wave’s Analyst and Investor Research Day on October 7, 2019
Virlogeux et al., Cell Reports 2018
Wave approach: novel, allele-selective silencing
Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington’s disease (HD)

- Potential to provide treatment for up to 80% of HD population

WVE-120101: Selective reduction of mHTT mRNA and protein

Reporter Cell Line*


*These results were replicated in a patient-derived cell line.
Demonstrated delivery to brain tissue

- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection

PRECISION-HD clinical trials
Two Phase 1b/2a clinical trials for WVE-120101 and WVE-120102

PRECISION-HD2 interim data (2-16 mg cohorts pooled)
• Safety profile supported addition of higher dose cohorts

Biomarker Effects
• Reduction in mHTT (~12.4%); Analysis across groups suggests dose response at highest doses
• No change in total HTT
• Not all patients had reached Day 140 at interim analysis

PRECISION-HD2 and PRECISION-HD1 data, including 32 mg cohorts and OLE data, expected in 1Q 2021

OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; wtHTT: wild-type HTT; tHTT: total HTT
* Study day may vary depending on patient washout period
1 Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo, p<0.05 (Wilcoxon-Mann-Whitney non-parametric significance test); 2 Multiple Contrast Test (MCT), p=0.03; Interim data announced December 2019

Dose

CSF sample

Study Day*
1
28
56
84
112
140
196

Washout

Multidose

OLE

Patients are migrated to highest dose tested

2 mg

4 mg

8 mg

Multidose Cohorts
(N = 12 per cohort)

16 mg

ongoing

32 mg
### Three allele-selective HD programs

Potential to address ~80% of HD patient population

<table>
<thead>
<tr>
<th>SNP</th>
<th>WVE</th>
<th>% Population</th>
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<tbody>
<tr>
<td>SNP1</td>
<td>120101</td>
<td>~50%</td>
</tr>
<tr>
<td>SNP2</td>
<td>120102</td>
<td>~50%</td>
</tr>
<tr>
<td>SNP3</td>
<td>003</td>
<td>~40%</td>
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<td>SNP1</td>
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<tr>
<td>SNP1</td>
<td>SNP2</td>
<td>~80%</td>
</tr>
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</table>

1. Percentage of patient population with SNP1 and/or SNP2
2. Percentage of patient population with SNP1, SNP2 and/or SNP3
WVE-003 (SNP3) approaching clinical development
Incorporates PN modified backbone chemistry

- Potent mutant HTT knockdown activity in homozygous iCell neurons
- Knockdown persists for 12 weeks in BACHD mouse model
- No loss of selectivity with increasing concentrations

Clinical development expected to initiate with CTA submission in 4Q 2020
WVE-004

Amyotrophic Lateral Sclerosis (ALS)
Frontotemporal Dementia (FTD)
C9orf72 repeat expansions: A critical genetic driver of ALS and FTD

- C9orf72 hexanucleotide repeat expansions (GGGGCC) are the strongest known risk factor for sporadic and inherited forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)
- The C9orf72 repeat expansions also lead to accumulation of repeat-containing transcripts, nuclear sequestration of RNA binding proteins and synthesis of toxic dipeptide-repeat (DPR) proteins
- The C9orf72 repeat expansions lead to reduced expression of wild-type C9orf72 and to cellular changes that reduce neuronal viability

## C9-ALS and C9-FTD: Manifestations of a clinical spectrum

<table>
<thead>
<tr>
<th>Disease</th>
<th>C9 specific US population</th>
<th>Mean disease duration</th>
<th>Standard of care</th>
</tr>
</thead>
</table>
| **C9-ALS** | • Fatal neurodegenerative disease  
• Progressive degeneration of motor neurons in brain and spinal cord | ~2,000 | 3.1 years | Significant unmet need despite two approved therapies |
| **C9-FTD** | • Progressive neuronal atrophy in frontal/temporal cortices  
• Personality and behavioral changes, gradual impairment of language skills | ~10,000 | 6.4 years | No approved disease modifying therapies |

Two devastating diseases with a shared genetic basis

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
C9orf72 repeat expansions: Mechanisms of cellular toxicity

• C9-ALS and C9-FTD may be caused by multiple factors:
  – Insufficient levels of C9orf72 protein
  – Accumulation of repeat-containing RNA transcripts
  – Accumulation of aberrantly translated DPR proteins

• Recent evidence suggests lowering C9orf72 protein exacerbates DPR-dependent toxicity

Variant-selective targeting could address multiple potential drivers of toxicity

C9orf72 targeting strategy spares C9orf72 protein

- Normal C9orf72 allele produces three mRNA transcripts (~80% are V2, ~20% are V1 and V3)
- **Pathological allele** with expanded repeat leads to healthy V2 and pathological V1 and V3 transcript by-products

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**pre-mRNA variants**

- V1
- V3
- V2

**Pathological mRNA products**

- Mis-spliced V1/V3
- Stabilized intron1

**Disease-causing factors**

- RNA foci
- Dipeptide repeat proteins (DPRs)

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**WVE-004 reduces**

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Wave C9orf72 candidate targets only V1 and V3 transcripts, sparing V2 transcripts and healthy C9orf72 protein
PN backbone chemistry: Improved potency among C9orf72-targeting oligonucleotides *in vivo*

Mice received 2 x 50 µg ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.
WVE-004: Potent and selective knockdown of repeat-containing transcripts in vitro

In vitro activity in C9 patient-derived neurons

IC50: 201.7nM

In vitro selectivity in C9 patient-derived neurons

C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gynnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC= non-targeting control.
WVE-004: Potent and selective knockdown of repeat transcripts and DPRs in vivo

Incorporates PN modified backbone chemistry

**Potent in vivo knockdown of repeat containing transcripts and DPRs**

**Protein preservation**

Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Dipeptide repeat proteins were measured by Poly-GP MSD assay. Protein samples were measured by Western Blot. NS: not significant
WVE-004 reaches target brain regions and cell types in vivo

In situ hybridization of WVE-004 in spinal cord and cortex at 8 weeks

Red = viewRNA hybridization with WVE-004; blue = nucleus staining with Hematoxylin. 40X magnification.

C9 BAC transgenic mice were administered PBS or 50 ug of WVE-004, ICV, on day 0 and day 7. Mice were euthanized at 8 weeks after the first injection.
Durable knockdown of repeat transcripts *in vivo* after 6 months in spinal cord and cortex

**Experimental description:** 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay)
WVE-004: Durable knockdown of DPRs *in vivo* after 6 months in spinal cord and cortex

**Experimental description:** 2 x 50 ug on day 0 and day 7 dosed ICV; Dipeptide repeat proteins were measured by Poly-GP MSD assay.

*: p ≤ 0.05 **: p ≤ 0.01; ***: p ≤ 0.001
WVE-004 proof-of-concept study to include both ALS and FTD patients

- Patients with documented C9orf72 expansion and confirmed ALS or FTD diagnosis
- Single and multiple ascending doses to be explored
- Safety and tolerability
- Pharmacodynamic effects on key biomarkers while on treatment
  - PolyGP
  - NfL
- Key exploratory clinical outcome measures
  - ALSFRS-R and CDR-FTLD

Clinical trial application expected to be submitted in 4Q 2020

NfL: neurofilament light chain; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration
Wave’s discovery and drug development platform
Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

Through iterative analysis of *in vitro* and *in vivo* outcomes and artificial intelligence-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

**Multiple modalities**
- Silencing
- Splicing
- ADAR editing
PRISM platform enables rational drug design

**Sequence**

**B**: bases

A, T, C, mC, G, U, other modified bases

**Stereochemistry**

Chiral control of any stereocenter

5’ modifications, backbone modifications

**Chemistry**

**R**: 2’ modifications

OMe, MOE, F, other modifications

**X**: backbone chemistry

Phosphodiester (PO), phosphorothioate (PS), Phosphoramidate diester (PN)
Expanding repertoire of backbone modifications with novel PN backbone chemistry

Backbone linkages

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<th>Backbone modification (X)</th>
<th>PO</th>
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<th>PRISM backbone modifications</th>
<th>PO/PS</th>
<th>PO/PS/PN</th>
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</table>

Molecule structure illustrative of backbone modification patterns
Rational design using PN chemistry backbone modification increases *in vitro* potency in most cases

**Silencing**

*In vitro* knockdown of PS/PO containing compounds compared to PS/PN compounds with same sequence and PS stereochemistry

**Splicing**

*In vitro* skipping efficiency of PS/PO containing compounds compared to PS/PO/PN compounds with same sequence and PS stereochemistry

Presented at Analyst & Investor Research Webcast on August 25, 2020; Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Right: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. PS/PO compounds are rank-ordered on X-axis.

- Target knockdown (% remaining)
- Improved knockdown
- % skipping
- Improved skipping
PRISM enables optimal placement of backbone stereochemistry

Crystal structure confirms phosphate-binding pocket of RNase H binds 3’-SSR-5’ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

Target RNA  Stereopure Oligonucleotide (C9orf72 compound)  RNase H

Yellow spheres represent ‘S’ atoms
Importance of controlling stereochemistry

Stereochemical diversity

(Rp) \hspace{1cm} (Sp)

Side view

Top view

Yellow spheres represent ‘S’ atoms

PS: Phosphorothioate

Number of PS linkages in oligonucleotide backbone

Exponential diversity arises from uncontrolled stereochemistry

No. diastereomers

CRISPR guide

ADAR oligonucleotide

Antisense, exon skipping, ssRNAi

Number of PS linkages in oligonucleotide backbone
ADAR editing
PRISM platform has unlocked ADAR editing

- **A-to-I** editing is one of most common post-transcriptional modifications
- ADAR is ubiquitously expressed across tissues, including liver and CNS

PRISM enables practical approach to RNA editing without need for viruses or exogenous protein

Wave ADAR-editing Oligonucleotides

- Extracellular space
- Intracellular

Endogenous ADAR

- Unedited RNA
- Edited RNA

Alternative Base-Editing Systems

- Delivery vehicles
- Genetic construct or foreign protein
- Exogenous ADAR or other base editors

Protein release/ expression

- Edited RNA
Advantages of Wave ADAR-mediated RNA editing platform

- Fully chemically modified to increase stability \textit{in vivo}
- Chirally-controlled backbone to maximize \textit{in vitro} activity
- PN backbone modification chemistry improves editing efficiency
- GalNAc-conjugated for targeted delivery into liver
- No requirement for AAV / nanoparticles
- No immunogenicity from exogenous proteins
- Reduced off-target effects\(^1\)

\(^1\)Chen et al. Biochemistry 2019
ADAR amenable diseases represent a sizeable opportunity

- Nearly half of known human SNPs associated with disease are G-to-A mutations
- Tens of thousands of potential disease variants A-to-I(G) editing could target\(^1\)

Potentially pathogenic human SNPs by base pair corrections

- A-to-C
- C-to-A
- A-to-G
- A-to-T
- C-to-G
- C-to-T

\(~48\%\) 

\(>32,000\) potentially pathogenic human SNPs\(^2\)

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SNP: single nucleotide polymorphism  
A: Adenosine  
I: Inosine  
G: Guanosine

\(^1\)ClinVar database  
RNA editing opens many new therapeutic applications

**Restore protein function**
- Fix nonsense and missense mutations that cannot be splice-corrected
- Remove stop mutations
- Prevent protein misfolding and aggregation

**Modify protein function**
- Alter protein processing (e.g. protease cleavage sites)
- Protein-protein interactions domains
- Modulate signaling pathways

**Protein upregulation**
- miRNA target site modification
- Modifying upstream ORFs
- Modification of ubiquitination sites

**Examples:**
- **Recessive or dominant genetically defined diseases**
- **Ion channel permeability**
- **Haploinsufficient diseases**
PN chemistry improves editing efficiency

PN backbone modification increased both potency and editing efficiency \textit{in vitro}

ACTB editing in primary human hepatocytes using GalNAc-mediated uptake

Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing.
Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

ACTB GalNAc-conjugated oligonucleotides with stereopure PN chemistry modification

**In vitro dose-response**

**human hepatocytes**

**In vitro dose-response**

**NHP hepatocytes**

Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

NHP: non-human primate; ACTB: Beta-actin; nd = not determined
Efficient ADAR editing translated *in vivo* in non-human primate study

- Up to 50% editing efficiency observed at Day 7, 2 days post last dose
- Substantial and durable editing out to at least Day 50, 45 days post last dose

*In vivo* editing in NHP following subcutaneous administration

![Diagram showing % Editing vs. Time for ACTB 1, ACTB 2, and ACTB 3](Diagram)

- 2 days post last dose
- 45 days post last dose

Oligonucleotide quantification in NHP following subcutaneous administration

![Diagram showing µg of oligonucleotide per gram of tissue vs. Time for ACTB 1, ACTB 2, and ACTB 3](Diagram)

- 2 days post last dose
- 45 days post last dose

NHP: non-human primate; ACTB: Beta-actin; Left: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing) & eASO Exposure: Day 7
Sustained editing *in vivo* in non-human primates after 45 days

Efficient and potent editing of ACTB demonstrated with Sanger sequencing

Baseline

Post-treatment (2 days post-last dose)

Post-treatment (45 days post-last dose)

% Editing quantified from Sanger sequencing using EditR program.
ADAR editing is highly specific

RNA editing within ACTB transcript (human hepatocytes)

Genome coordinates

Editing site

Mock

Editing oligonucleotide

Coverage

ACTB

% Editing

Confidence (LOD score)

Human hepatocytes were dosed with 1um oligonucleotide, 48 hours later RNA was collected and sent for RNA sequencing. RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing in primary human hepatocytes; plotted circles represent sites with LOD>3
Efficient and potent editing observed in neurons and astrocytes

ACTB editing in iCell Neurons

ACTB editing in human iCell Astrocytes

Concentration (µM)

% Editing

EC50:
~200-250nM

Gymnotic uptake; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing.
Opening the door to ADAR editing in CNS

First in vivo study in proprietary transgenic model yields efficient editing across all tissues

In vivo CNS editing in proprietary hADAR transgenic mouse (1 week)

Editing oligonucleotide (100 µg)
PBS

% Editing UGP2

Cortex, Hippocampus, Striatum, Brain stem, Cerebellum, Spinal cord

hADAR: human ADAR; UGP2: Glucose Pyrophosphorylase 2; CNS: central nervous system; Editing observed across all tested tissues of human-ADAR-transgenic mice by ICV injection. 5 mice in each group were injected with PBS or a single 100uG dose on day 0. Animals were necropsied on day 7. RNA was harvested and editing measured by Sanger sequencing.
RNA editing design applicable across targets

- Editing achieved across several distinct RNA transcripts
- Supports potential for technology to be applied across variety of disease targets

Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020); See poster for full dataset
Ophthalmology
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

• Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
• Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of MALAT1 is a surrogate for an ASO mechanism of action

• Widely expressed in many different cell types
• Only expressed in the nucleus

Intravitreal injection

Durable Malat1 knockdown through 9 months with PN chemistry

~50% Malat1 knockdown at 36 weeks in the posterior of the eye

Compound or PBS (1 x 50 µg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control.
Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood

- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors

- No approved disease-modifying therapies

- ~5,000 addressable patients in US

Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

**Enhanced potency over a stereorandom reference compound (*in vitro*)**

- Reference Compound: EC_{50}=8.73 µM
- Compound-1: EC_{50}=2.20 µM

**Target engagement in NHP and human retinas (*ex vivo*)**

<table>
<thead>
<tr>
<th>PBS</th>
<th>NTC</th>
<th>Compound-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
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<td>20</td>
<td>10</td>
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</tr>
<tr>
<td>1</td>
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<td>1 [µM]</td>
</tr>
</tbody>
</table>

Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. USH2A transcripts were normalized to SRSF9. Data are mean±s.d., n=2. Reference Compound: van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide. Right: Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 µM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by 48 hrs later by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m.
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **Retinitis pigmentosa (RP):** group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure

- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)

- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells

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**In vivo: Collaborations in place for evaluation in transgenic human Rho P23H pig model**

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Ferrari et al., *Current Genomics.* 2011;12:238-249.; Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.
Anticipated upcoming Wave milestones

**NEUROLOGY**

**Huntington’s disease**
- **4Q 2020**: Initiate clinical development with CTA filing of SNP3 program
- **1Q 2021**: PRECISION-HD2 data from 32 mg cohort and data from OLE trial
- **1Q 2021**: PRECISION-HD1 data, including 32 mg cohort, and data from OLE trial

**ALS and FTD**
- **4Q 2020**: Initiate clinical development with CTA filing of C9orf72 program in ALS and FTD

**ADAR editing**
- *In vivo* ADAR-mediated RNA editing data
- **August 2020**: Additional *in vivo* ADAR editing data at Research webcast
  - **2020**: Announce first ADAR editing program in a hepatic indication

**PRISM platform updates in 2020**
- Research webcast held August 25 (introduced PN chemistry)

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CTA: clinical trial application; OLE: open-label extension
Realizing a brighter future for people affected by genetic diseases

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