Forward-looking statements

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Building a leading genetic medicines company

INNOVATIVE PLATFORM
- Stereopure oligonucleotides
- Backbone modifications
- Allele-selectivity
- Novel modalities (ADAR)
- Foundational stereochemistry IP

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

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

MANUFACTURING
- Established internal manufacturing capabilities to produce oligonucleotides at scale
## Innovative pipeline led by neurology programs

<table>
<thead>
<tr>
<th>THERAPEUTIC AREA</th>
<th>TARGET</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>ESTIMATED U.S. PREVALENCE*</th>
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<td><strong>NEUROLOGY</strong></td>
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<td>Huntington’s disease</td>
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<td>ALS and FTD</td>
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<td>~1,800 (ALS)</td>
<td>Takeda 50:50 option</td>
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<td>~7,000 (FTD)</td>
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<td>CNS diseases</td>
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<td>Takeda milestones &amp; royalties</td>
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<td>Retinal diseases</td>
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<td>ADAR RNA-editing</td>
<td>Multiple</td>
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<td>100% global</td>
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</table>

*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington’s disease, numbers approximate manifest and pre-manifest populations, respectively.
†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; CNS: Central nervous system; OLE: Open-label extension
HD portfolio
Huntington’s Disease
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)

Recent 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

Presented by Dr. Frederic Saudou at Wave’s Analyst and Investor Research Day on October 7, 2019
Virlogeux et al., Cell Reports 2018

Status of the presynaptic compartment determines the integrity of the network
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

Selective reduction of mHTT mRNA & protein

**Reporter Cell Line***

![Graph showing mRNA and Protein levels](image)

*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 trial design

Two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101 and WVE-120102

<table>
<thead>
<tr>
<th>Study Day*</th>
<th>1</th>
<th>28</th>
<th>56</th>
<th>84</th>
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<td><strong>Dose</strong></td>
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<td>▲</td>
<td>▲</td>
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<td><strong>CSF sample</strong></td>
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</tbody>
</table>

**Single Dose (3:1)**

**Washout**

**Multidose Randomization 3:1**

**OLE**

- PRECISION-HD2 OLE: Initiated October 2019
- PRECISION-HD1 OLE: Initiated February 2020

**Multidose Cohorts**

N = 12 per cohort

- 2 mg
- 4 mg
- 8 mg
- 16 mg
- 32 mg

- PRECISION-HD2 data from 32 mg cohort expected in 2H 2020
- PRECISION-HD1 topline data, including 32 mg cohort, expected 2H 2020

OLE: Open label extension; CSF: cerebrospinal fluid *Study day may vary depending on patient washout period
## PRECISION-HD2 topline results

**Clinical trial ongoing**

<table>
<thead>
<tr>
<th>Doses</th>
<th>Safety</th>
<th>Biomarker Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>WVE-120102 2–16 mg (pooled)</td>
<td>Generally safe and well tolerated</td>
<td>Reduction in mHTT compared to placebo (-12.4%(^1), (p&lt;0.05)^2)</td>
</tr>
<tr>
<td>32 mg cohort initiated</td>
<td>Safety profile supports addition of higher dose cohorts</td>
<td>Analysis across groups suggests dose response at highest doses ((p=0.03)^3)</td>
</tr>
<tr>
<td>Assessing the potential for higher dose cohorts</td>
<td>Potential for greater mHTT reduction at higher doses</td>
<td>No change in tHTT compared to placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Larger reductions of mHTT expected to result in discernible impact on tHTT</td>
</tr>
</tbody>
</table>

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1 Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo; 2 Wilcoxon-Mann-Whitney non-parametric significance test; 3 Multiple Contrast Test (MCT)
Three allele-selective HD programs

Potential to address ~80% of HD patient population

% Huntington’s Disease Patient Population with SNP

- SNP1: ~50%
- SNP2: ~50%
- SNP3: ~40%
- SNP1 + SNP2: ~70%
- SNP1 + SNP2 + SNP3: ~80%

Intend to explore efficacy in early manifest and pre-manifest HD patient populations
SNP3 program approaching clinical development

**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 in 2H 2020

Data presented at CHDI Foundation’s 15th Annual HD Therapeutics Conference Feb 24-27, 2020; See poster for full dataset.

(Figure on right) Statistics: All oligo treatment groups statistically significantly different from PBS; One-way ANOVA ***, P<0.001. SNP3 Compound-1 and Compound-2 significantly different from pan-silencing active comparator at 8, 12 weeks ***, P<0.005; **P=0.001."
C9orf72 program

Amyotrophic Lateral Sclerosis (ALS)
Frontotemporal Dementia (FTD)
C9orf72: a critical genetic risk factor

- C9orf72 gene provides instructions for making protein found in various tissues, with abundance in nerve cells in the cerebral cortex and motor neurons.
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue.
- First pathogenic mechanism identified to be a genetic link between familial (inherited) ALS and FTD.
- Most common mutation identified associated with familial ALS and FTD.
- Availability of dipeptide biomarker in CSF has potential to accelerate drug development.

Amyotrophic lateral sclerosis

- Fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons in the brain and spinal cord
- Affects approximately 15,000-20,000 people in the US with a median survival of three years
- C9orf72 is present in approximately 40% of familial ALS and 8-10% of sporadic ALS; currently the most common demonstrated mutation related to ALS, far more so than SOD1 or TDP-43
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts; dominant trait with high penetrance

Frontotemporal dementia

- Progressive neuronal atrophy with loss in the frontal and temporal cortices characterized by personality and behavioral changes, as well as gradual impairment of language skills
- Affects approximately 55,000 people in the US
- Second most common form of early-onset dementia after Alzheimer’s disease in people under the age of 65
- Up to 50% of FTD patients have a family history of dementia, many inheriting FTD as an autosomal dominant trait with high penetrance
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts

C9orf72 program: Selective silencing in vivo of expanded C9orf72 repeat transcripts

- C9orf72 genetic mutations are the most common cause of familial Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of ALS and FTD; Hexanucleotide repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue.

- **Wave’s approach:** Selectively silence the repeat containing transcript while minimizing the impact on C9orf72 protein.

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

- **Protein preservation**

**Clinical development expected to initiate in 2H 2020**

Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot. Dipeptide repeat proteins were measured by Poly-GP MSD assay.
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.
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

Yellow spheres represent ‘S’ atoms
Importance of controlling stereochemistry

**Stereochemical diversity**

(Rp) (Sp)

Side view

Top view

Yellow spheres represent ‘S’ atoms

PS: Phosphorothioate

Number of PS linkages in oligonucleotide backbone

No. diastereomers

0 10 20 30 40 50

CRISPR guide

ADAR oligonucleotide

Antisense, exon skipping, ssRNAi

Number of PS linkages in oligonucleotide backbone

Exponential diversity arises from uncontrolled stereochemistry
PRISM platform enables rational drug design

Continuous Learning

Optimizing potency and durability across multiple tissues

**CNS**
Malat1 Transcript Knockdown in Mice
10 Weeks after single 100 µg ICV injection

**Eye**
MALAT1 Knockdown in Non-Human Primates
Single 450 µg IVT injection

**Liver**
Knockdown of Serum APOC3 Protein Levels in Mice
Two 5 mg/kg SC injections on Days 1&3

Data represented in this slide from in vivo studies. CNS: Central nervous system; PBS = phosphate buffered saline; Ctx = cortex; Str = striatum; Cb = cerebellum; Hp = hippocampus; SC = spinal cord. ICV = intracerebral; IVT = intravitreal; IV = intravenous; SC= subcutaneous.
ADAR-mediated RNA editing
RNA editing: A promising new therapeutic modality for treatment of genetic diseases

Potential benefits versus gene editing

- Ability to use endogenous proteins (e.g. ADAR)
- Ease of delivery
- Titration, repeatable dosing
- Reversible effects, avoids potential long-term risks associated with permanent off-target DNA editing

A-to-I(G) RNA editing opportunity is significant

- Nearly half of known human genetic pathogenic SNPs are G-to-A mutations\(^1\)
- Tens of thousands of potential disease variants A-to-I(G) editing could target\(^2\)

ADAR (adenosine deaminases acting on RNA)

- Endogenous proteins that catalyze A-to-I RNA editing
- Upon translation, I recognized as G, leading to A-to-G editing

Pathogenic human SNPs by base pair corrections

\(~48\%\)

\(>32,000\) pathogenic human SNPs\(^1\)

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

\(^1\) Gaudelli NM et al. Nature (2017).  \(^2\) ClinVar database
RNA editing can be used for several therapeutic applications and supplement Wave’s existing modalities.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Therapeutic Application</th>
<th>Silencing</th>
<th>Splicing</th>
<th>RNA Editing</th>
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<tbody>
<tr>
<td>Silence protein expression</td>
<td>Reduce levels of toxic mRNA/protein</td>
<td>✓</td>
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<tr>
<td>Alter mRNA splicing</td>
<td>Exon skipping/inclusion/restore frame</td>
<td></td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Fix nonsense mutations that cannot be splice-corrected</td>
<td>Restore protein expression</td>
<td></td>
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<td>✓</td>
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<tr>
<td>Fix missense mutations that cannot be splice-corrected</td>
<td>Restore protein function</td>
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<td>✓</td>
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<tr>
<td>Modify amino acid codons</td>
<td>Alter protein function</td>
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<td>✓</td>
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<tr>
<td>Remove upstream ORF</td>
<td>Increase protein expression</td>
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<td>✓</td>
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</table>

I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame.
Using PRISM to unlock ADAR-mediated RNA editing

- ADAR makes multiple contacts with oligonucleotide backbone, sugar and bases
- Using PRISM platform, rationally designed and screened oligonucleotides to optimize:
  - 2' sugar chemistry
  - Backbone chemistry and stereochemistry
  - Size and structure
  - Modified nucleobases

Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

~1,000 RNA editing oligonucleotides tested over the last year to develop SAR for editing format
Advantages of Wave ADAR-mediated RNA-editing platform

- Fully chemically modified to increase stability in vivo
- Chirally-controlled backbone to maximize in vitro activity
- 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
In vitro RNA editing demonstrated in non-human primate and human hepatocytes

**NHP Hepatocytes**

- % Actin A→G Editing
- Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

**Human Hepatocytes**

- % Actin A→G Editing
- Potent, dose-dependent RNA editing demonstrated via free uptake with GalNAc-conjugated stereopure oligonucleotides

NHP: non-human primate; ACTB: Beta-actin; nd= not determined

Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.
First non-human primate RNA editing

**In vivo – NHP**

Liver biopsies conducted at baseline and 2 days post last dose. RNA-editing efficiencies of up to 50% with GalNAc conjugate in liver of NHP.

<table>
<thead>
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<th>%Actin A→G Editing</th>
<th>ACTB 1</th>
<th>ACTB 2</th>
<th>ACTB 3</th>
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<td>Post-treatment</td>
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</table>

**Up to ~50% editing efficiency**

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 Right: % Editing quantified from Sanger sequencing using EditR program.
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

In vitro RNA Editing in Primary Human Hepatocytes

<table>
<thead>
<tr>
<th>Transcript</th>
<th>Percentage A → G editing</th>
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<tr>
<td>1</td>
<td>80 ± 2</td>
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<td>2</td>
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<tr>
<td>7</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>8</td>
<td>80 ± 9</td>
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Additional in vivo ADAR-mediated RNA-editing data and first RNA-editing program expected to be announced in 2020

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

Stereopure compound induces potent and durable MALAT1 knockdown in the eye

~50% MALAT1 knockdown at 9 months

In vivo duration of effect in the mouse retina

>90% knockdown of MALAT1 maintained for 4 months

In vivo duration of effect in the NHP retina

Mouse: Compound or PBS (1 x 50 mg 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. Statistics: Compound-2 Malat1 levels are significantly different from NTC at 36 weeks ***, P<0.001; **** P<0.0001, respectively. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control; Compound-1 and Compound-2 are stereopure MALAT1-targeting antisense oligonucleotide. NHP: Oligonucleotide or PBS (1 x 450 µg IVT) was delivered to NHP. Relative percentage of MALAT1 RNA in the retina to PBS-treated is shown at 1 week, 2 and 4 months, post-single injection. Compound-1 is a stereopure MALAT1-RNA-targeting antisense oligonucleotide.
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

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

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


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

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

**In vivo**

Collaborations in place for evaluation in transgenic human Rho P23H pig model

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**

- **2H 2020:** PRECISION-HD2 data from 32 mg cohort in Huntington’s disease
- **2H 2020:** PRECISION-HD1 topline data, including 32 mg cohort, in Huntington’s disease
- **2H 2020:** Initiate clinical development of SNP3 program in Huntington’s disease
- **2H 2020:** Initiate clinical development of C9orf72 program in ALS and FTD

**Ophthalmology**

- **2020:** Advance USH2A and RhoP23H programs

**Hepatic**

- **2020:** In vivo ADAR editing data
- **2020:** Additional in vivo ADAR-mediated RNA-editing data and announce first RNA-editing program
Realizing the potential of genetic medicines

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