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Wave Life Sciences

H.C. Wainwright 22nd Annual Global Investment Conference

September 14, 2020

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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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[1]

FOUNDATION OF NEUROLOGY PROGRAMS

- Huntington's disease
- ALS / FTD
- Ataxias
- Parkinson's disease
- Alzheimer's disease

PRISM

Wave's drug discovery and development platform

CLINICAL DEVELOPMENT EXPERTISE

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

MANUFACTURING

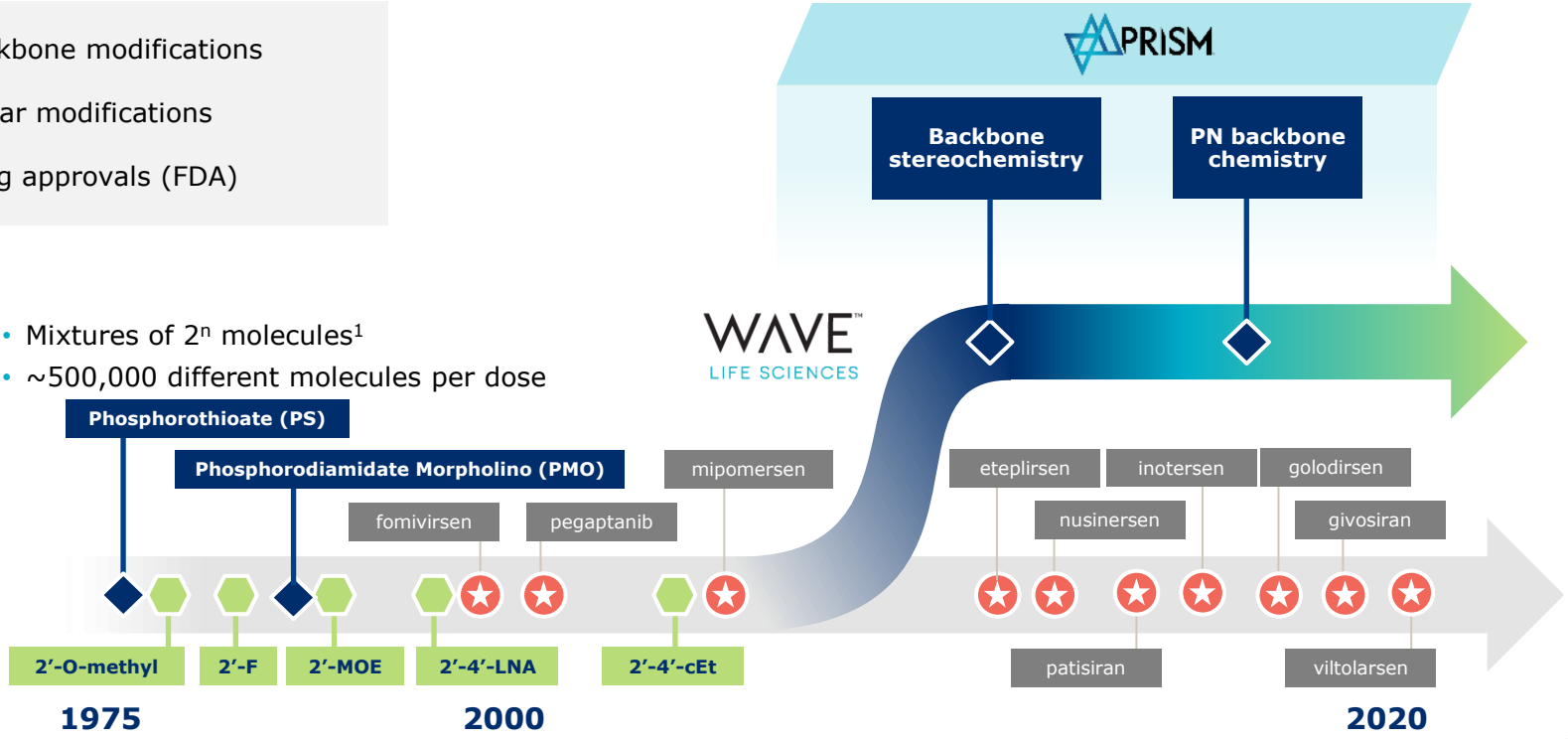
- Established internal manufacturing capabilities to produce oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia [1]stereopure 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



[1]n=number of chiral centers

PRISM platform enables rational drug design

Sequence

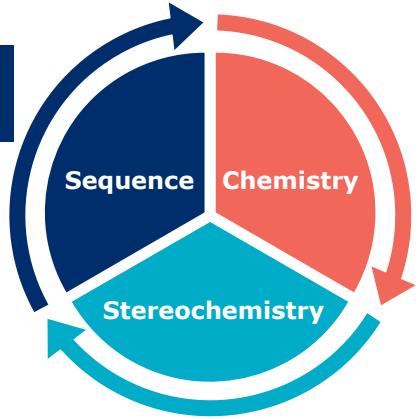
B: bases

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

Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



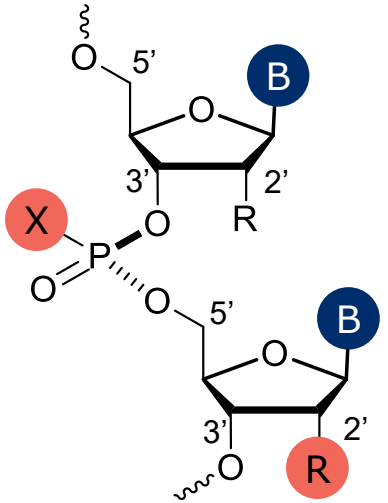
Chemistry

R: 2′ modifications

OMe, MOE, F,
other modifications

X: backbone chemistry

Phosphodiester (PO),
phosphorothioate (PS),
Phosphoramidate diester
(PN)



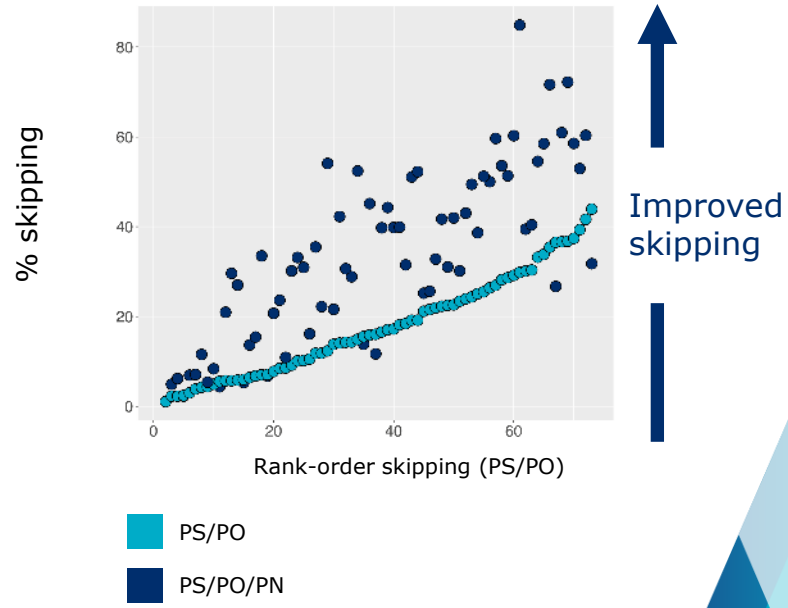
Rational design using PN chemistry backbone modification increases potency on average

Silencing

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

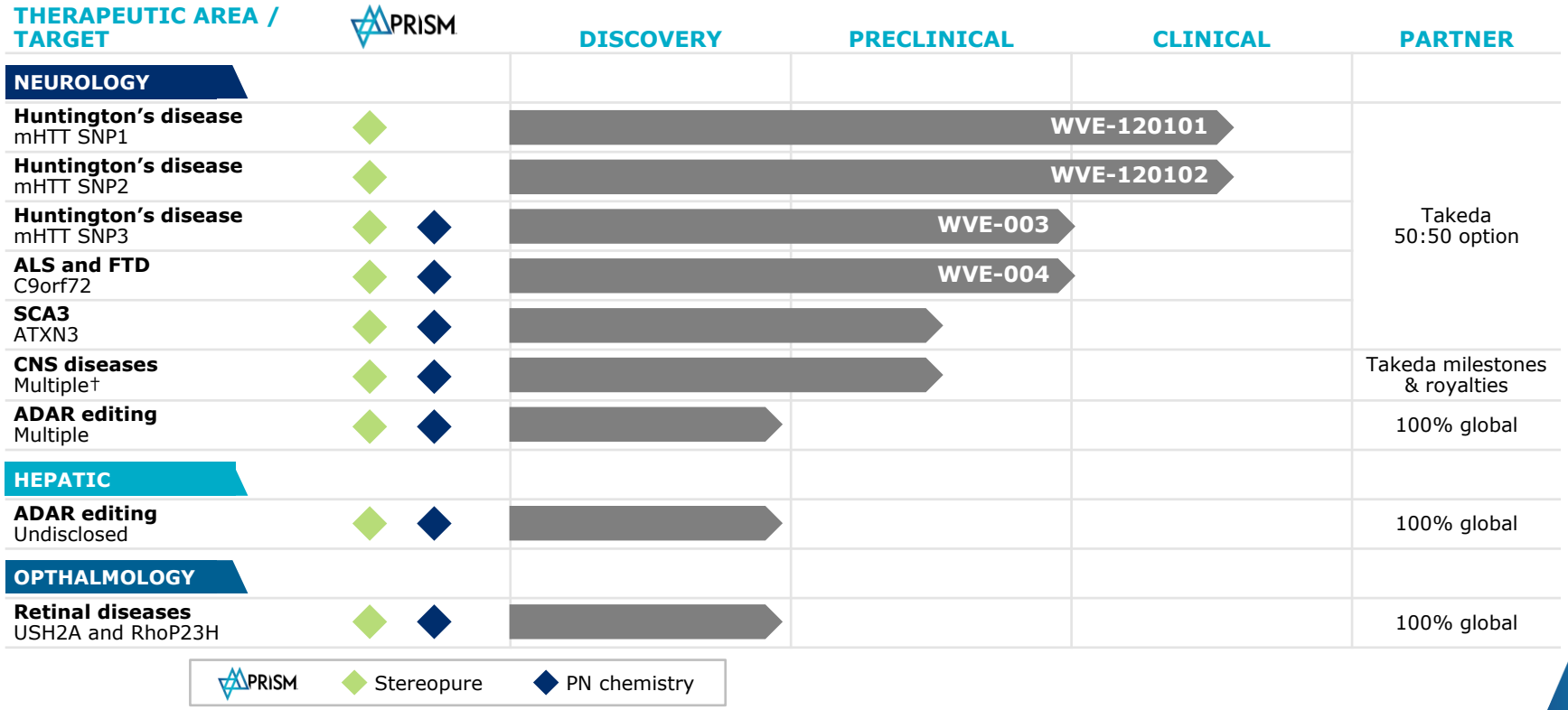
Splicing

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



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.

Innovative pipeline led by neurology programs



†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

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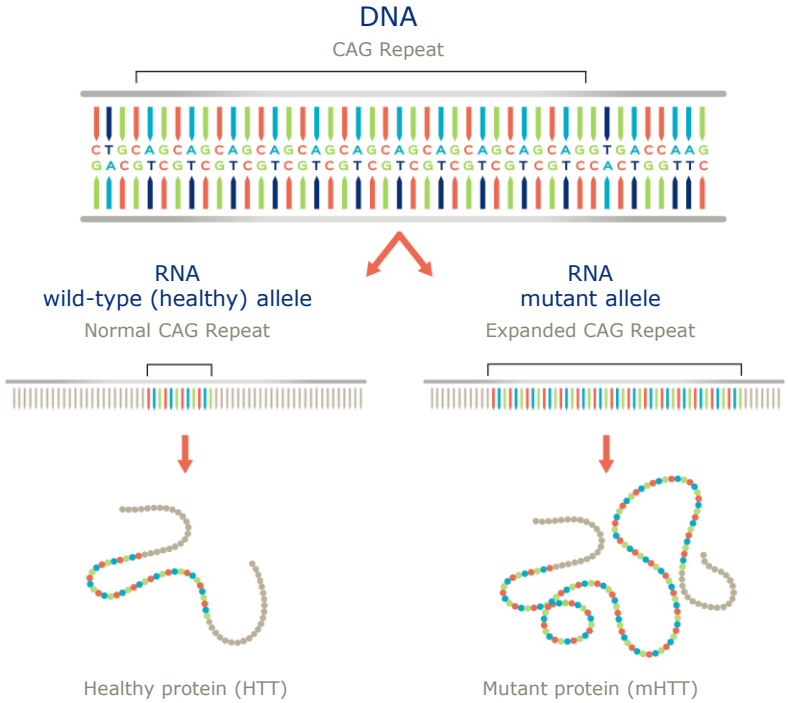
Huntington's disease: a hereditary, fatal disorder

- 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



Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem*. 2006;96:1121-1129. Nasir J, et al. *Cell*. 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet*. 1997;17:404-410. Zeitlin S, et al. *Nat Genet*. 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. HDSA 'What is Huntington's disease?' https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: 11/2/18.; Becanovic, K., et al., Nat Neurosci, 2015. 18(6): p. 807-16. Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005. 14(10): p. 1379-92.; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006. 7: p. 80.

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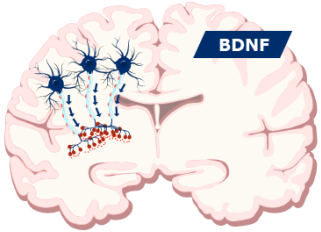
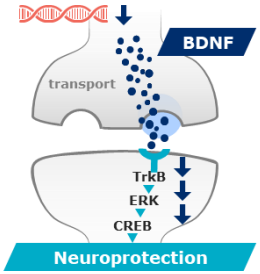
Importance of wild-type huntingtin (wtHTT) in HD

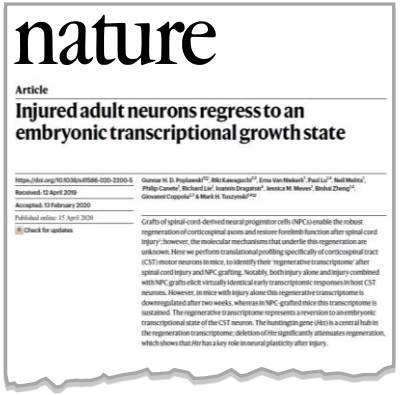
Huntington's disease (HD) may be caused by a dominant gain of function in mutant HTT *and* a loss of function of wtHTT protein





- 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)

"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"


nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

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Check for updates

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Grafts of spinal-cord-derived neural progenitor cells (NPCs) enable the robust regeneration of corticospinal axons and restore forelimb function after spinal cord injury; however, the molecular mechanisms that underlie this regeneration are unknown. Here we perform translational profiling specifically of corticospinal tract (CST) motor neurons in mice, to identify their 'regenerative transcriptome' after spinal cord injury and NPC grafting. Notably, both injury alone and injury combined with NPC grafts elicit virtually identical early transcriptomic responses in host CST neurons. However, in mice with injury alone this regenerative transcriptome is downregulated after two weeks, whereas in NPC-grafted mice this transcriptome is sustained. The regenerative transcriptome represents a reversion to an embryonic transcriptional state of the CST neuron. The huntingtin gene (*Htt*) is a central hub in the regeneration transcriptome; deletion of *Htt* significantly attenuates regeneration, which shows that *Htt* has a key role in neural plasticity after injury.

Sources: Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006; Becanovic, K., et al., Nat Neurosci, 2015; Saudou, F. and S. Humbert, The Biology of Huntingtin. Neuron, 2016; Gauthier, L.R., et al., Cell, 2004; Caviston, J.P. and E.L. Holzbaur, Trends Cell Biol, 2009; Ho, L.W., et al., J Med Genet, 2001, Zuccato et al., Science 2001; Zuccato et al., Brain Pathol 2007; Marullo et al. Genome Biol 2010; Squitieri et. al, Brain 2003

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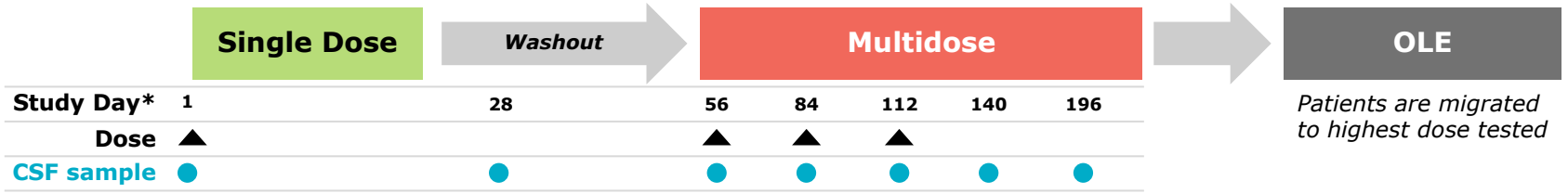
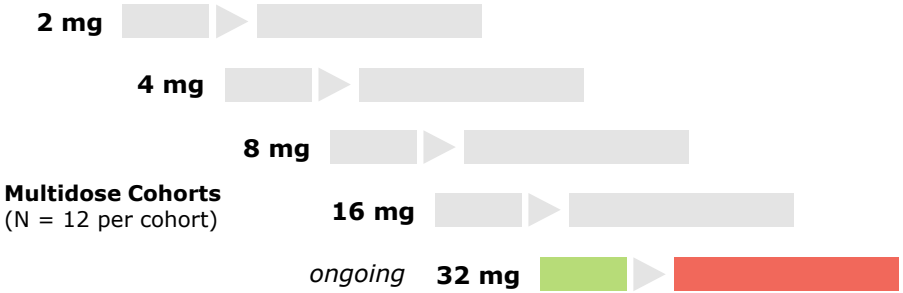
PRECISION-HD clinical trials

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%[1]); Analysis across groups suggests dose response at highest doses[3]
- **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); [3] Multiple Contrast Test (MCT), p=0.03; Interim data announced December 2019

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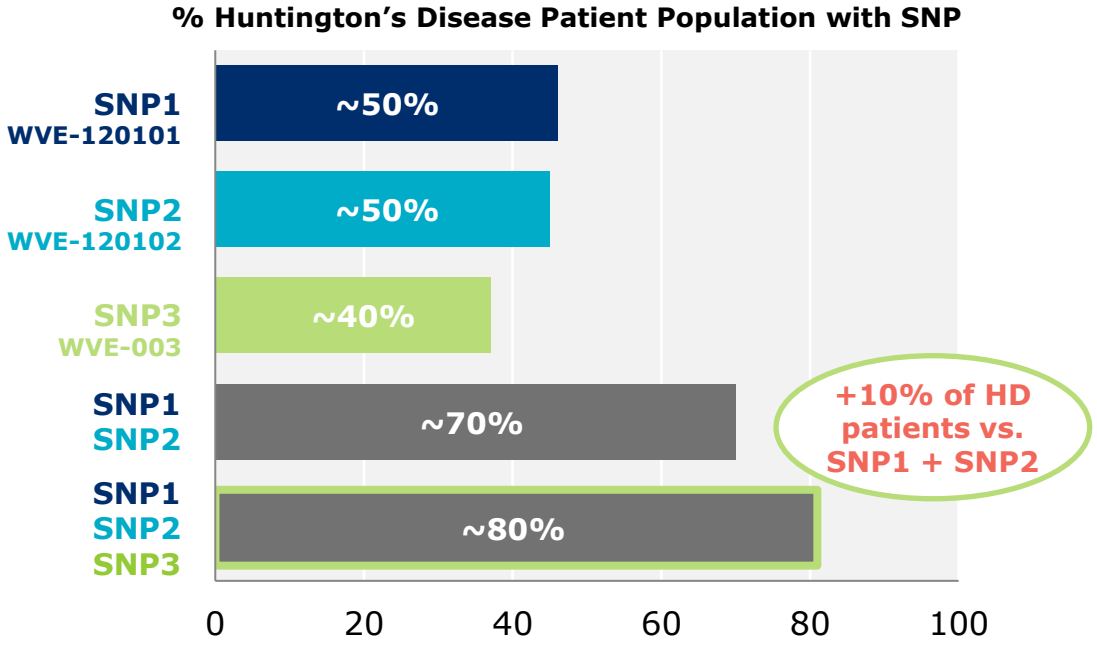
Three allele-selective HD programs

Potential to address ~80% of HD patient population



Intend to explore efficacy in early manifest and pre-manifest HD patient populations

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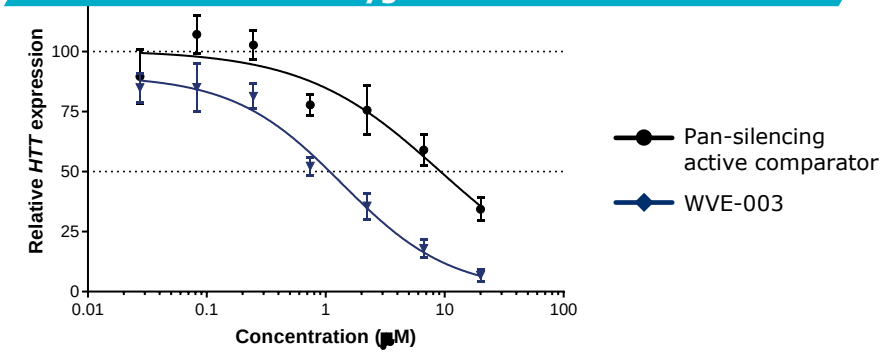
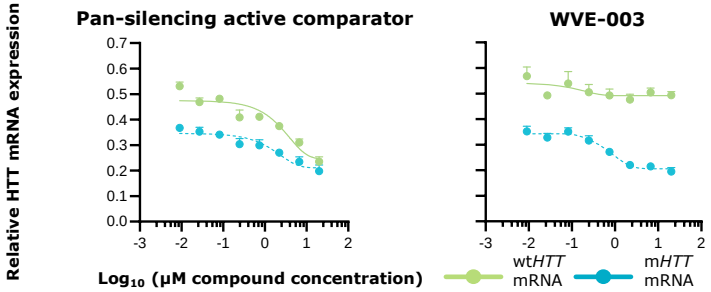
WVE-003 (SNP3) approaching clinical development

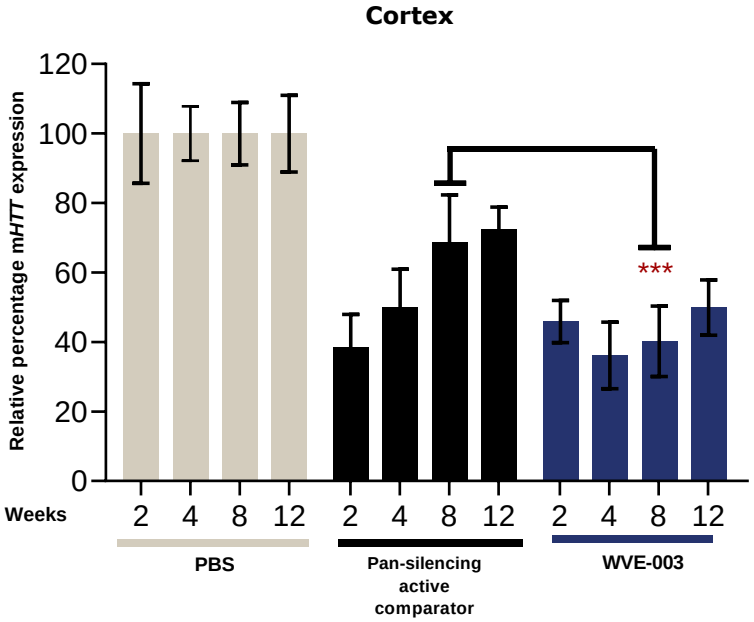
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



No loss of selectivity with increasing concentrations



Knockdown persists for 12 weeks in BACHD mouse model



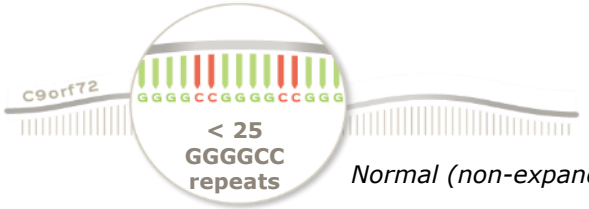
Similar knockdown achieved in striatum

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

CTA: clinical trial application; wtHTT: wild-type huntingtin; mHTT: mutant huntingtin

[Figure on right] Statistics: All oligo treatment groups statistically significantly different from PBS; ***, P<0.005

C9orf72 repeat expansions: A critical genetic driver of ALS and FTD



Normal (non-expanded) Allele

Expanded Allele

C9orf72 hexanucleotide repeat expansions (GGGGCC):

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

Two devastating diseases with a shared genetic basis

C9-ALS	• Fatal neurodegenerative disease • Progressive degeneration of motor neurons in brain and spinal cord	~2,000 (US patients)	3.1 years mean disease duration
C9-FTD	• Progressive neuronal atrophy in frontal/temporal cortices • Personality and behavioral changes, gradual impairment of language skills	~10,000 (US patients)	6.4 years Mean disease duration

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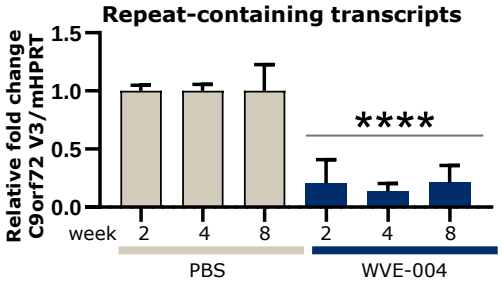
Sources: DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; Sources: Cammack et al, Neurology, October 2019. Moore et al, Lancet Neurology, February 2020

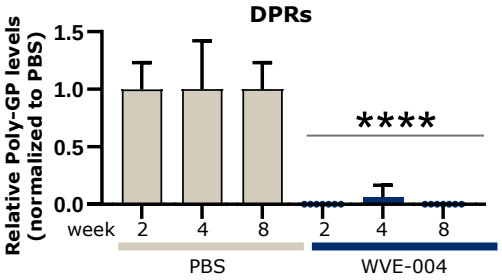
WVE-004: Potent and selective knockdown of repeat transcripts and DPRs

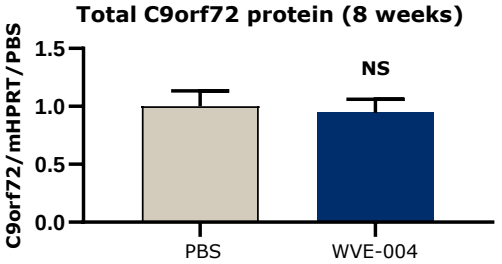
Potent *in vivo* knockdown of repeat containing transcripts and DPRs

Protein preservation

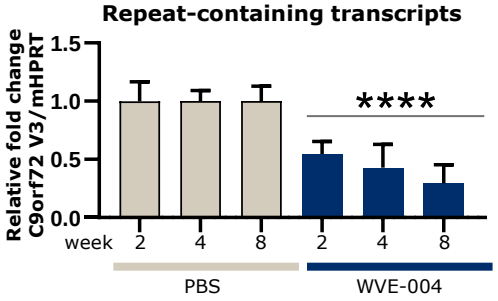
Spinal Cord

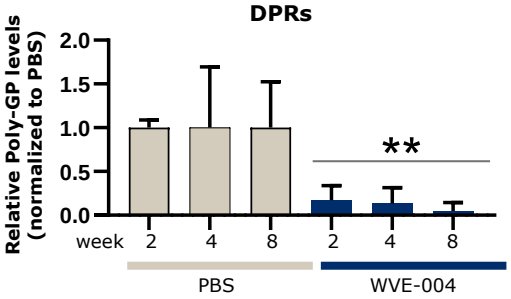


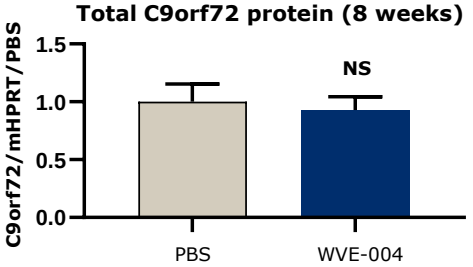




Cortex







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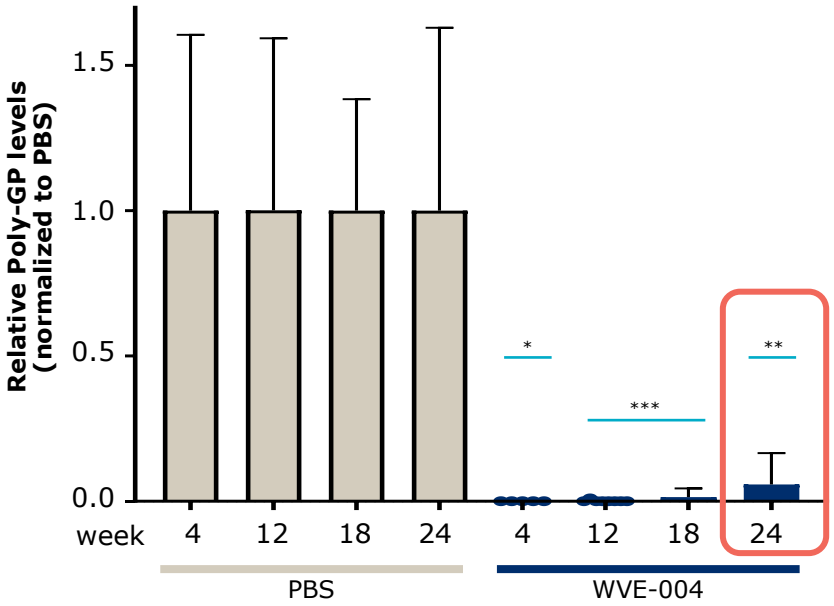
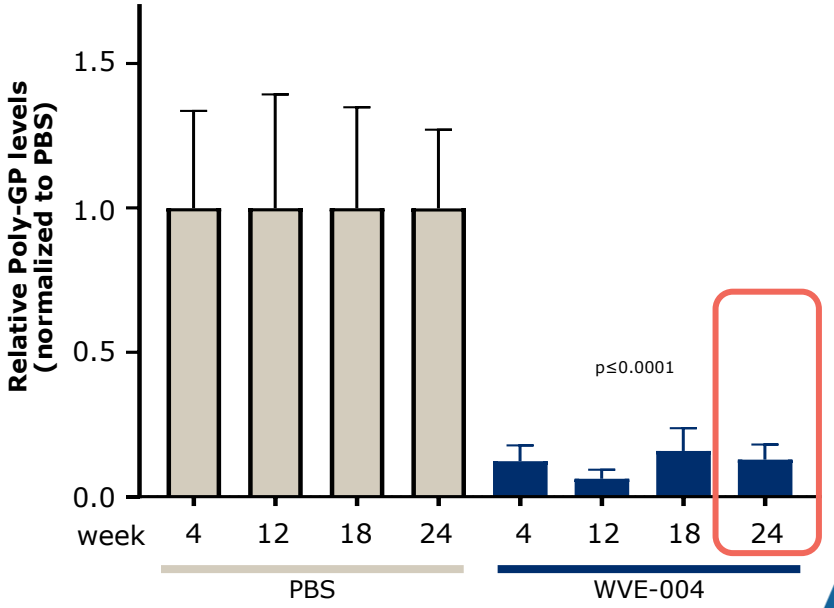
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Dipeptide repeat proteins were measured by Poly-GP MSD assay. Protein samples were measured by Western Blot. NS: not significant

WVE-004: Durable knockdown of DPRs *in vivo* after 6 months in spinal cord and cortex

Spinal cord



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

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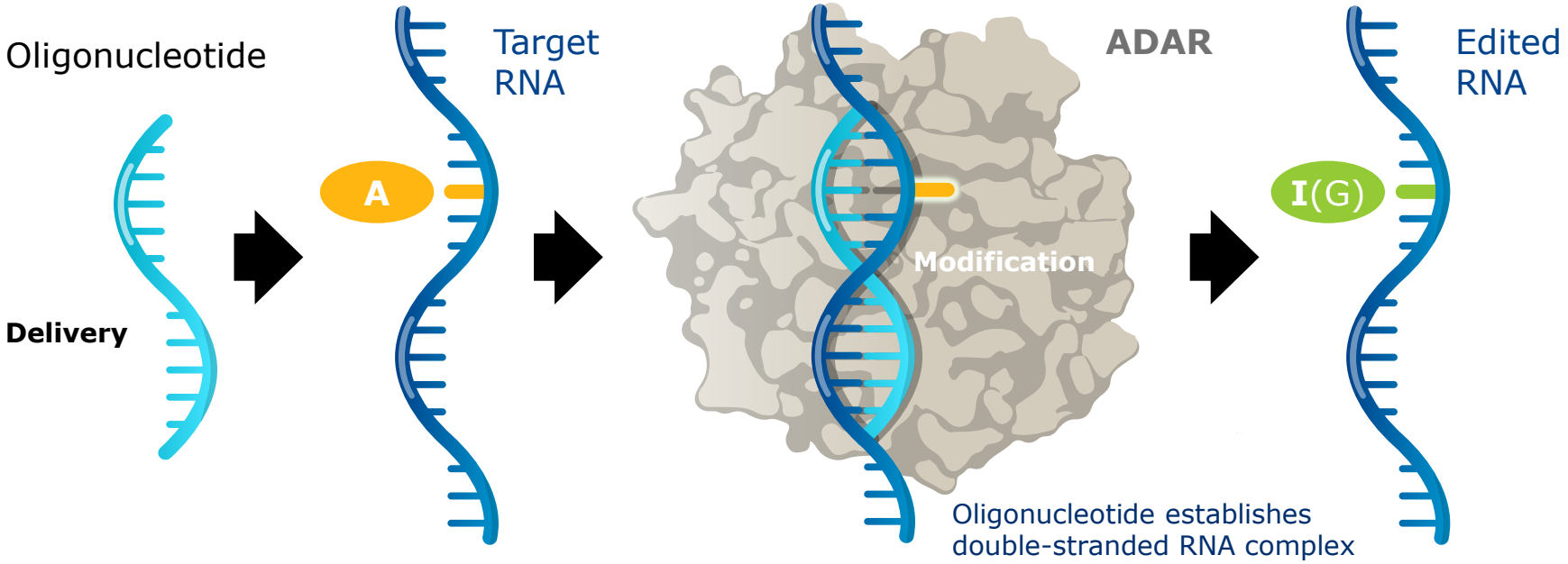
NfL: neurofilament light chain; ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration

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

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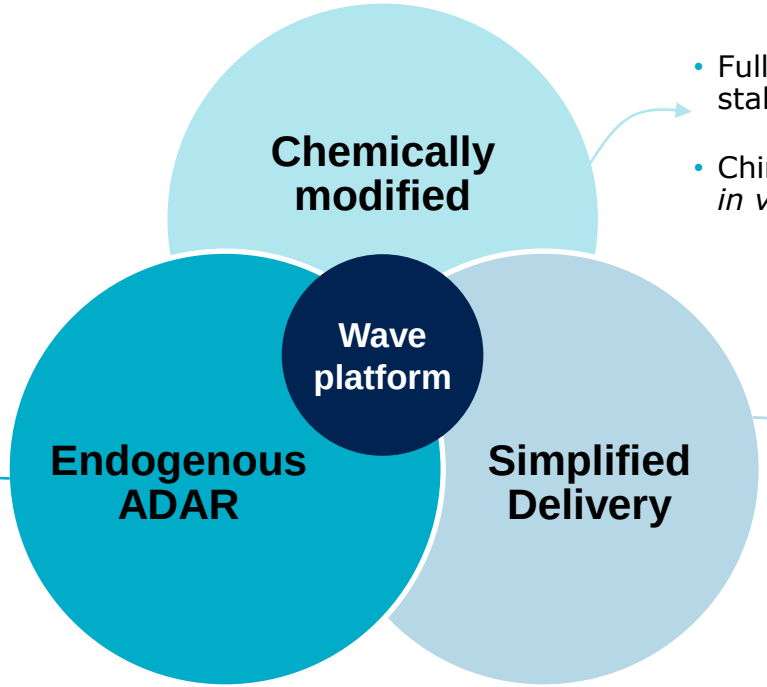
Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

Advantages of Wave ADAR-mediated RNA-editing platform



- Fully chemically modified to increase stability *in vivo*
- Chirally-controlled backbone to maximize *in vitro* activity

- No immunogenicity from exogenous proteins
- Reduced off-target effects[1]

- GalNAc-conjugated for targeted delivery into liver
- No requirement for AAV / nanoparticles

Building RNA-editing capability for PRISM platform

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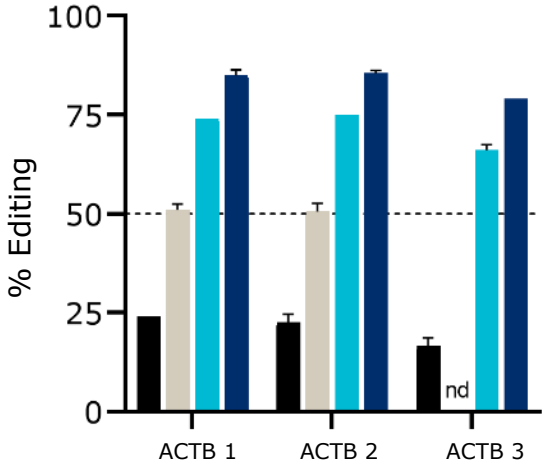
[1]Chen et al. Biochemistry 2019

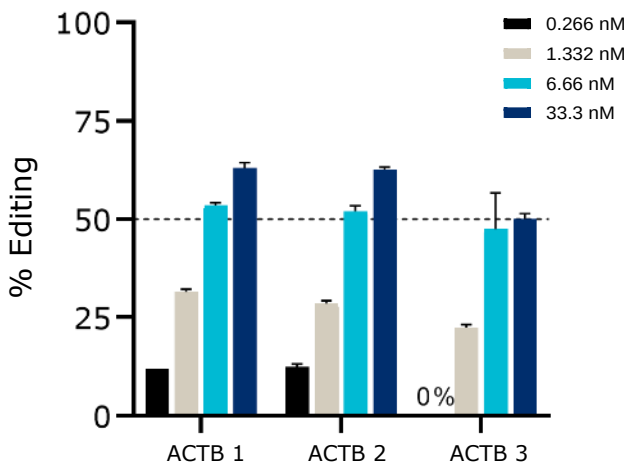
Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

ACTB GalNAc-conjugated oligonucleotides with stereopure PN chemistry modification

In vitro dose-response human hepatocytes



In vitro dose-response NHP hepatocytes

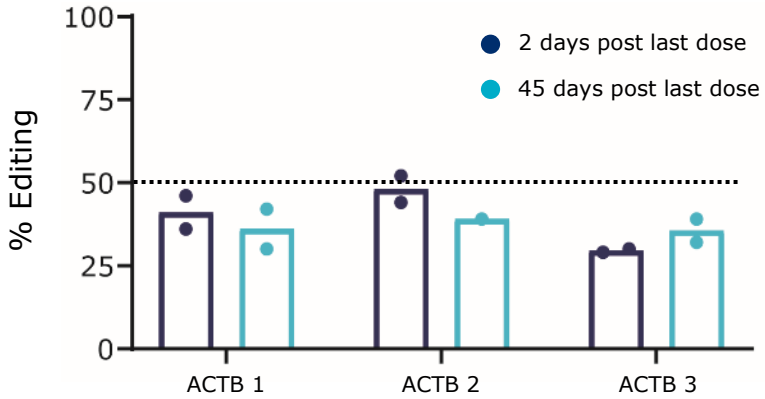


NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

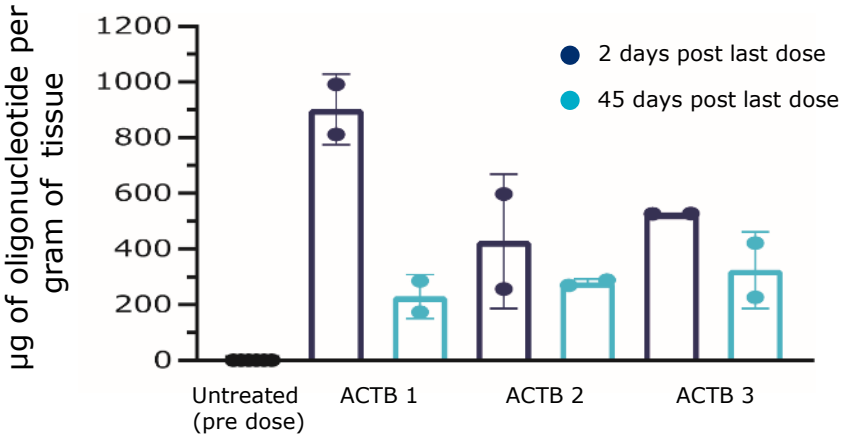
Efficient ADAR editing translated *in vivo* in non-human primate study

- 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



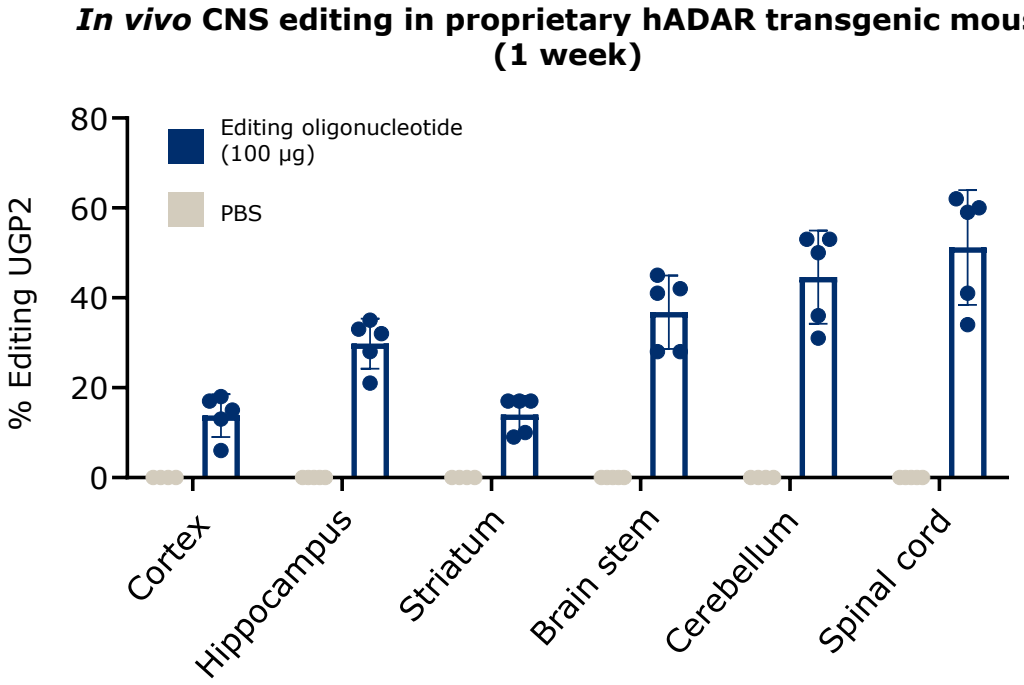
Oligonucleotide quantification in NHP following subcutaneous administration



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

Opening the door to ADAR editing in CNS

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



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.

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

PRISM

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)

WAVE LIFE SCIENCES

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CTA: clinical trial application; OLE: open-label extension

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