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Wave Life Sciences

Fourth-quarter and full year 2019

March 2, 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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Paul Bolno
President and CEO

Building a leading genetic medicines company

INNOVATIVE PLATFORM

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

FOUNDATION OF CNS PROGRAMS

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

PRISM™

CLINICAL DEVELOPMENT EXPERTISE

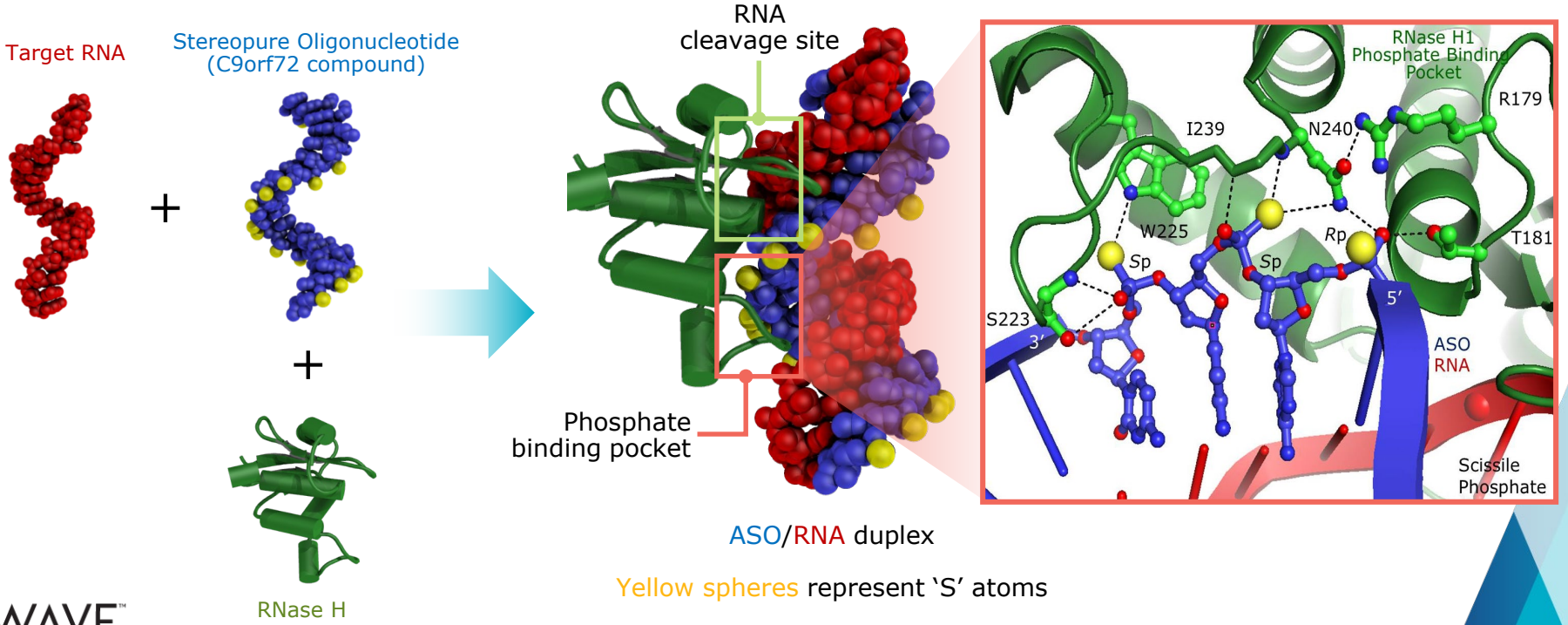
- Multiple global clinical trials ongoing across eight countries
- Innovative trial designs

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

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



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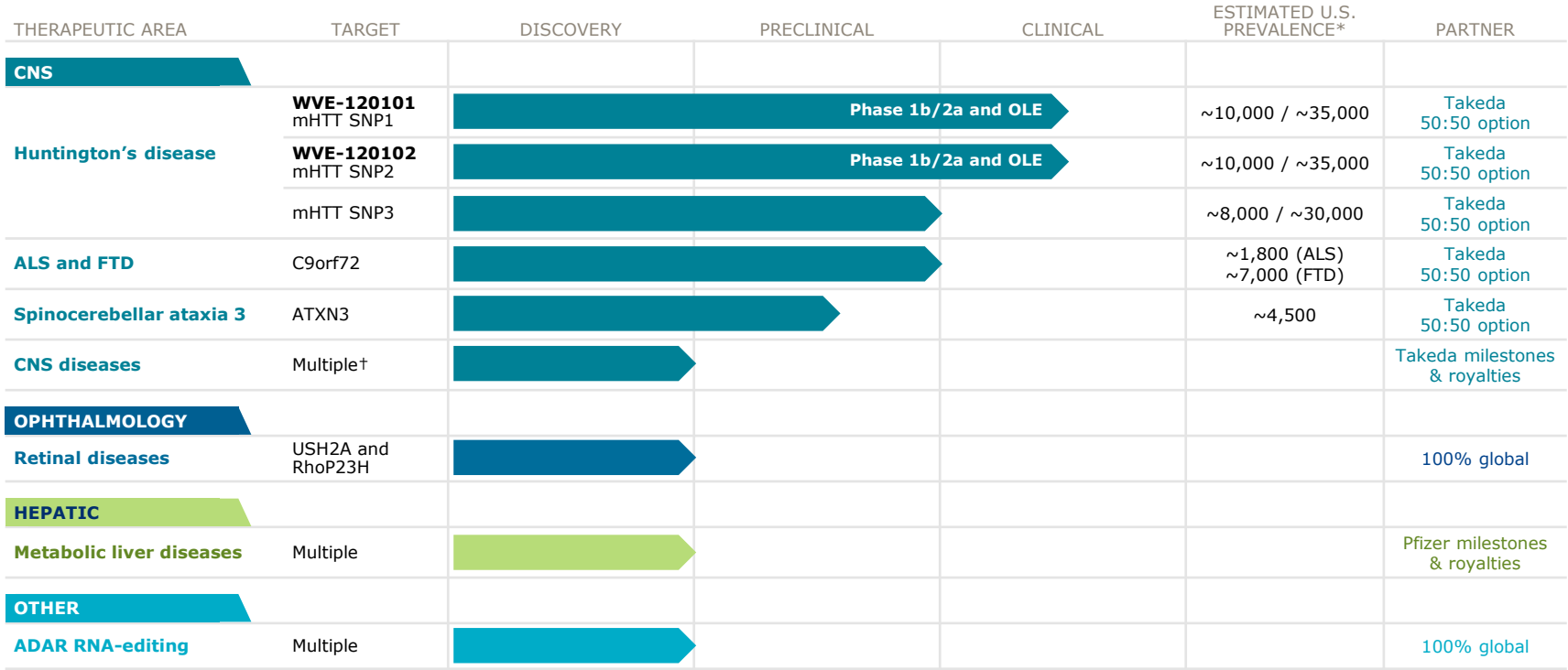
Innovative pipeline led by CNS programs



*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

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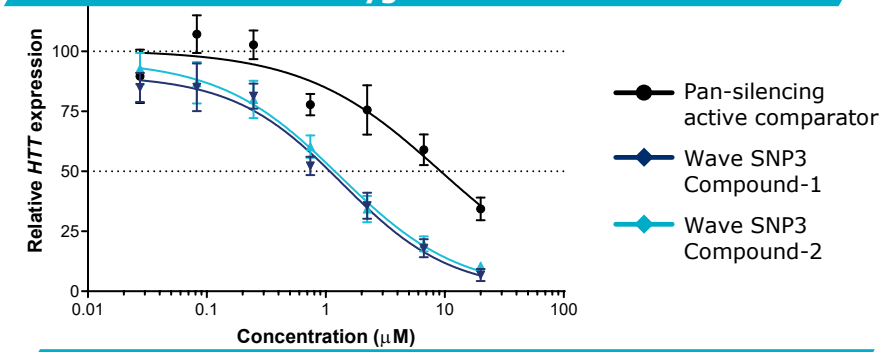
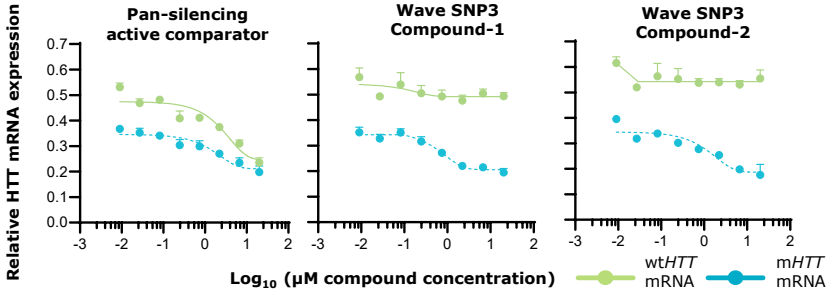
SNP3 program approaching clinical development

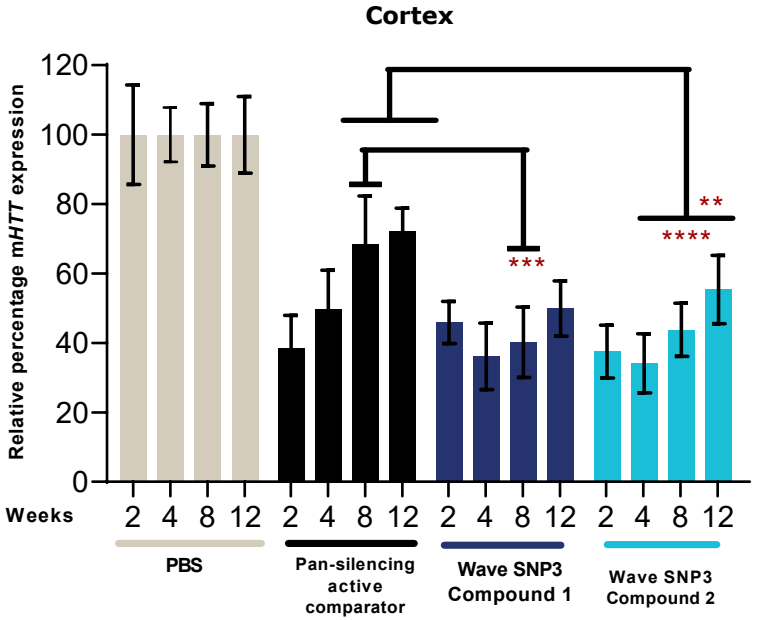
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



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 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≤0.0001. SNP3 Compound-1 and Compound-2 significantly different from pan-silencing active comparator at 8, 12 weeks ***, P<0.005; **P=0.001."

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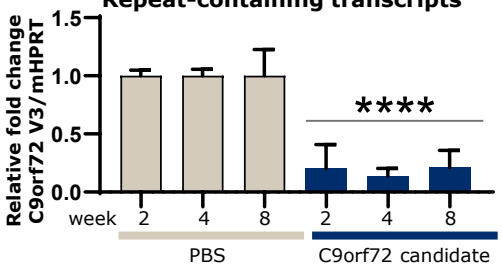
C9orf72 program: Selective silencing *in vivo* of expanded C9orf72 repeat transcripts

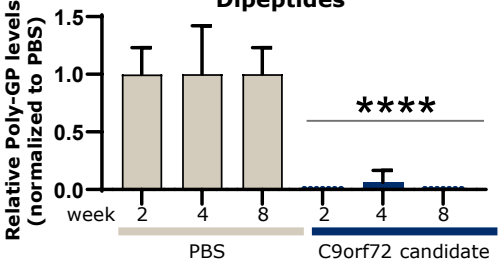
- C9orf72 genetic mutations are the most common cause of familial Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of ALS and FTD; Hexanucleotide repeat drives the formation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

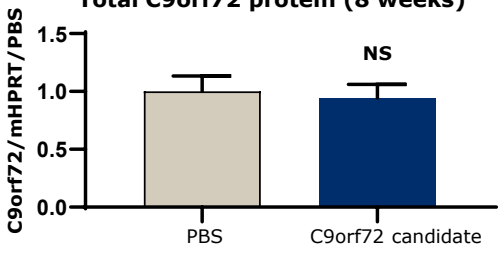
Potent *in vivo* knockdown of repeat containing transcripts and dipeptides

Protein preservation

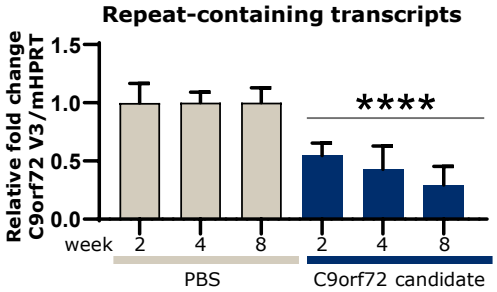
Spinal Cord

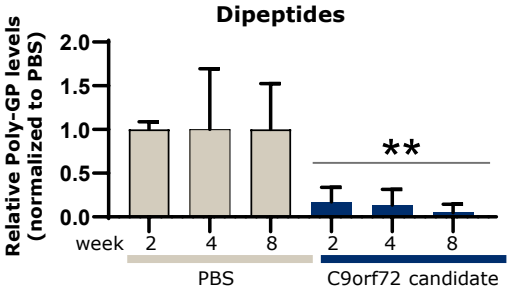


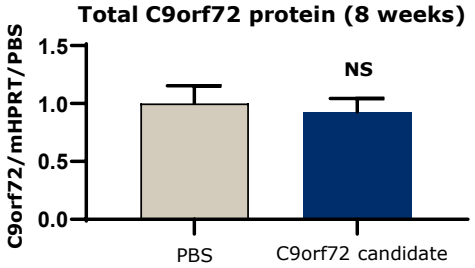




Cortex







Clinical development expected to initiate in 2H 2020

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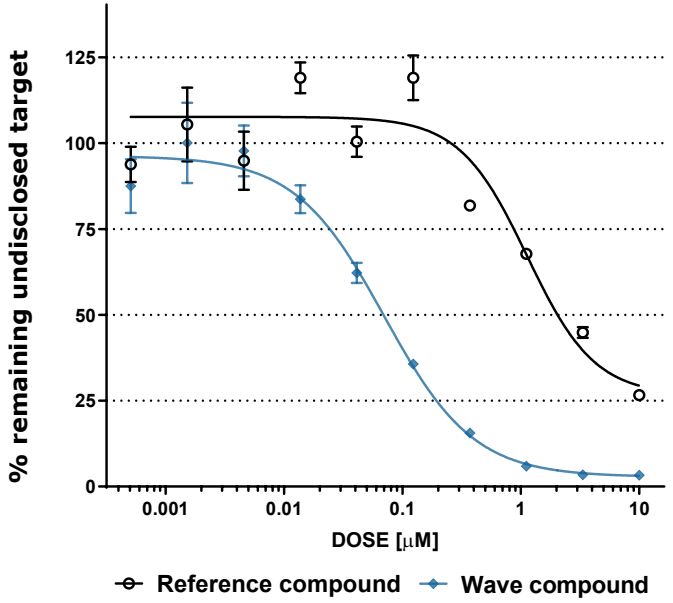
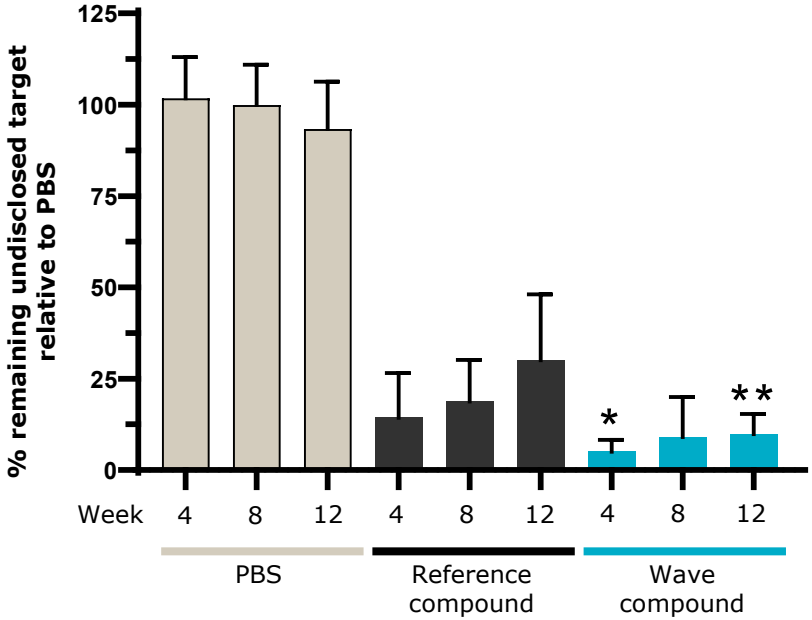
Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot. Dipeptide repeat proteins were measured by Poly-GP MSD assay.

Chemistry innovations transferable to new CNS targets within Takeda collaboration

16-fold more potent *in vitro* versus reference compound



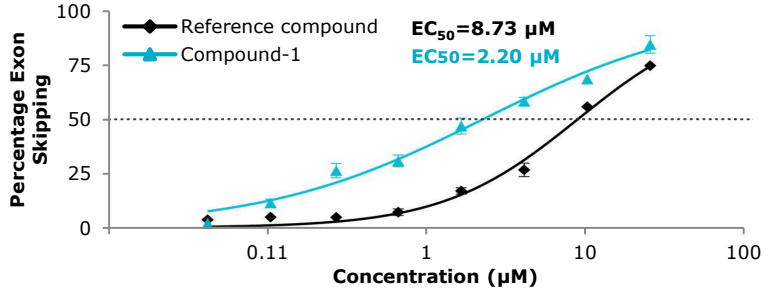
Potent and durable knockdown *in vivo* in transgenic mouse model brain



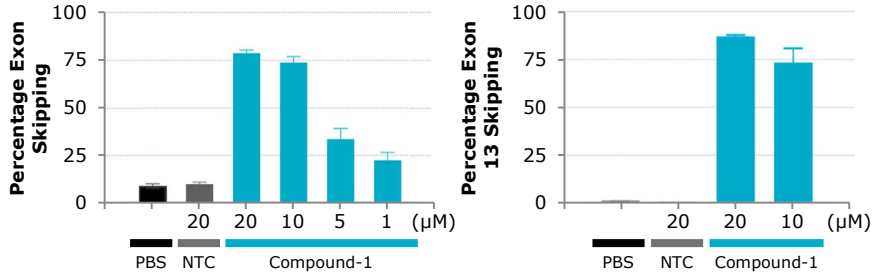
Ophthalmology: USH2A and RhoP23H

USH2A

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



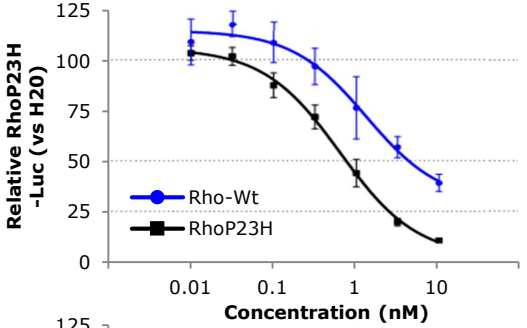
Target engagement in NHP (left) and human retinas (right) *ex vivo*



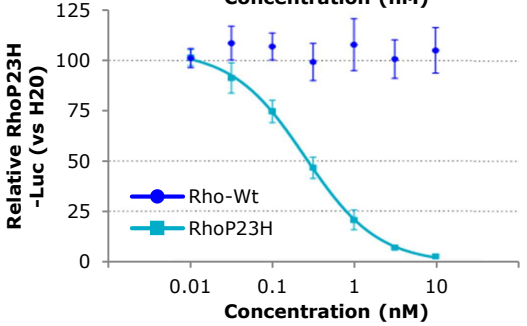
RhoP23H

Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

Stereorandom
(Reference compound)



Stereopure



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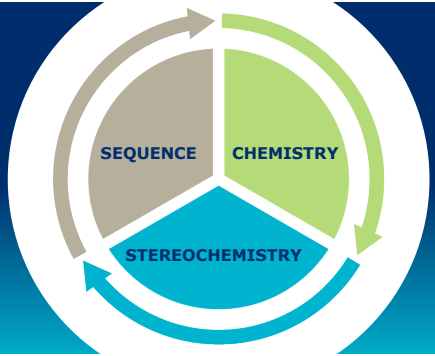
USH2A: Data presented at 15th Annual Meeting of the Oligonucleotide Therapeutics Society, October 2019; See poster for full dataset
RhoP23H: Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

PRISM™

Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

DESIGN

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile



OPTIMIZE

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

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

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Dave Gaiero
Interim Chief Financial Officer

Q4 2019 Financial Results

	Three Months Ended Dec 31, 2019	Three Months Ended Dec 31, 2018
Figures are in thousands		
Revenue	$2,400	$3,620
Operating Expenses:		
Research and Development	49,128	39,809
General and Administrative	13,805	12,754
Total Operating Expenses	62,933	52,563
Loss from Operations	(60,533)	(48,943)
Net Loss	(56,770)	(37,887)
Net Loss per Share	**($1.65)**	**($1.29)**

As of Dec 31, 2019 **Shares Outstanding:** 34.3 million **Cash Balance:** 147.2 million

Wave expects that its existing cash and cash equivalents, together with expected and committed cash from existing collaborations, will enable Wave to fund its operating and capital expenditure requirements into 3Q 2021.

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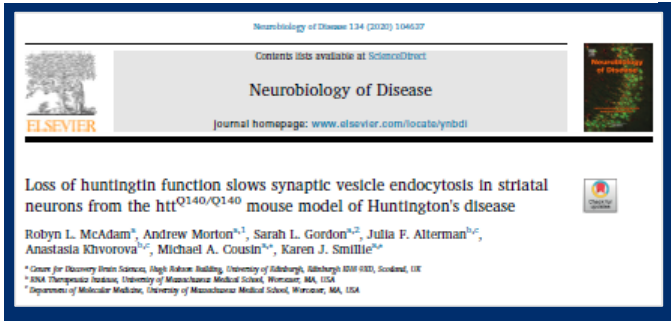
Mike Panzara
Chief Medical Officer

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


Neurobiology of Disease 134 (2020) 104637

Contents lists available at ScienceDirect

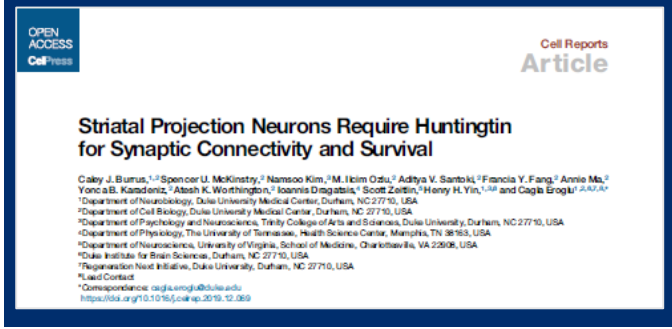
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Loss of huntingtin function slows synaptic vesicle endocytosis in striatal neurons from the htt$^{Q140/Q140}$ mouse model of Huntington's disease

Robyn L. McAdam[a], Andrew Morton[a,1], Sarah L. Gordon[a,2], Julia F. Alterman[b,c], Anastasia Khvorova[b,c], Michael A. Cousin[a,*], Karen J. Smillie[a,*]

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


OPEN ACCESS CellPress

Cell Reports

Article

Striatal Projection Neurons Require Huntingtin for Synaptic Connectivity and Survival

Caley J. Burrus,[1,2] Spencer U. McKinstry,[2] Namsoo Kim,[3] M. Ilcim Ozlu,[2] Aditya V. Santoki,[2] Francia Y. Fang,[2] Annie Ma,[2] Yonca B. Karadeniz,[2] Atesh K. Worthington,[2] Ioannis Dragatsis,[4] Scott Zeitlin,[5] Henry H. Yin,[1,6,8] and Cagla Eroglu[1,2,6,7,9,*]

- 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

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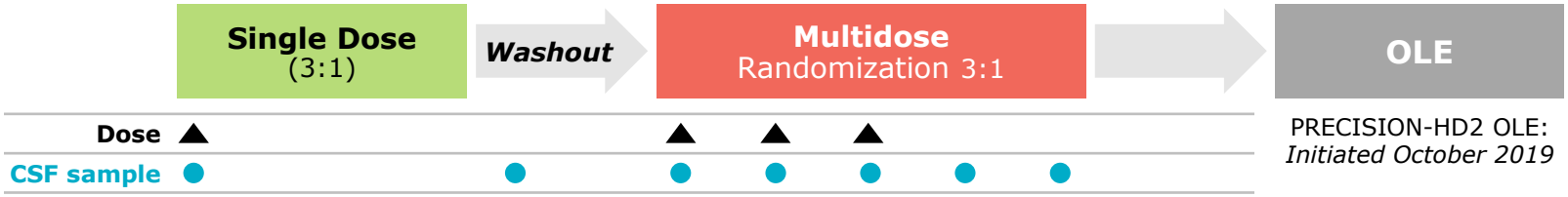
LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington's disease; STN: subthalamic nucleus

PRECISION-HD2 ongoing trial

Multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120102



Multidose Cohorts

N = 12 per cohort

Initial clinical data
(doses 2–16mg pooled)

- Generally safe and well tolerated
- Reduction in mHTT compared to placebo (-12.4%[1], p<0.05[2])
- Analysis across groups suggests dose response at highest doses (p=0.03)[3]
- No change in tHTT compared to placebo

PRECISION-HD2 data from 32 mg cohort expected in 2H 2020

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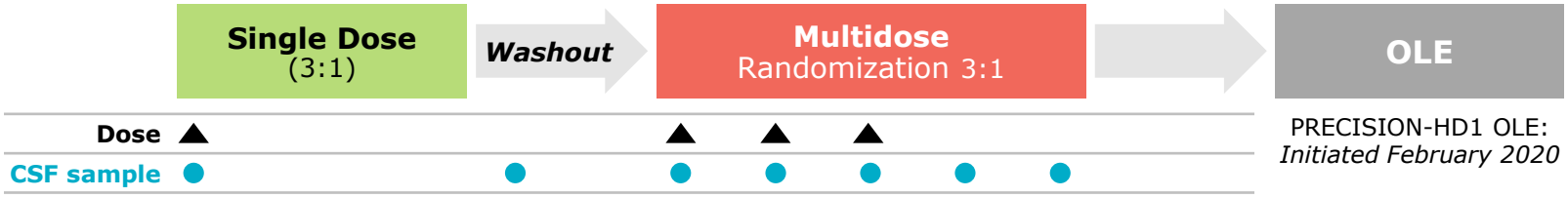
OLE: Open label extension; CSF: cerebrospinal fluid; [1] Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo; [2] Wilcoxon-Mann-Whitney non-parametric significance test; [3] Multiple Contrast Test (MCT).

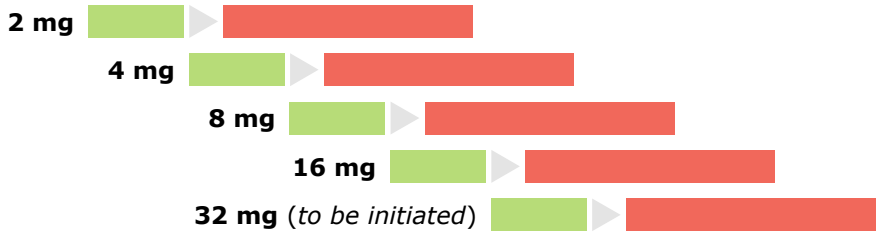
PRECISION-HD1 ongoing trial

Multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101



Multidose Cohorts

N = 12 per cohort



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

OLE: Open label extension; CSF: cerebrospinal fluid.

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Paul Bolno
President and CEO

Wave's ADAR approach has several potential advantages over existing technologies

Existing RNA editing technologies		Wave's RNA editing platform
Use unmodified RNA	Stability	Fully chemically-modified stereopure oligonucleotides
Require AAV or lipid nano particle delivery	Delivery	Free uptake into tissues
Require exogenous protein (e.g. CAS13 or chimeric ADAR)	Editing	Uses endogenous ADAR for editing

Single oligonucleotide through free uptake is sufficient for editing

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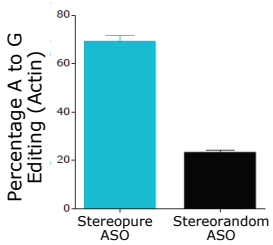
RNA Editing with Endogenous ADAR Achieved Across Multiple Primary Human Cell Types

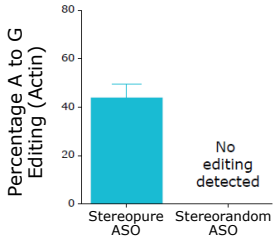
Editing of Up to 70% Achieved *In Vitro*

Editing UAG Site in Actin mRNA in Primary Human Cell Lines

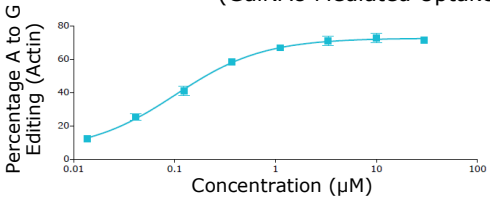
Hepatocytes
(Gymnotic Uptake)



Bronchial Epithelial Cells
(Gymnotic Uptake)



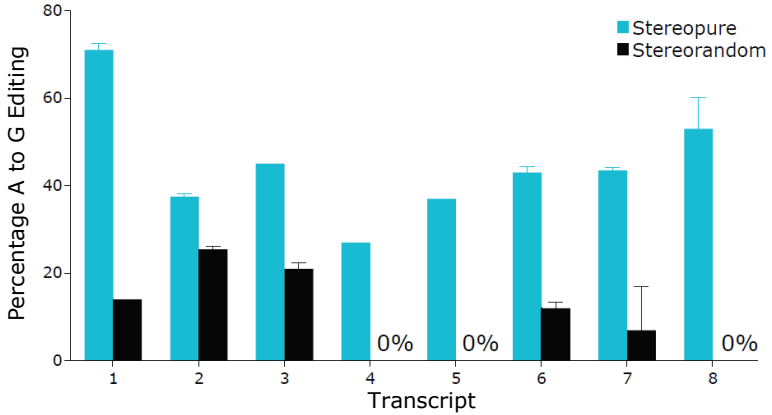
Targeting Editing in Primary Human Hepatocytes
(GalNAc-Mediated Uptake)



- Dose dependent RNA editing with EC_{50} of ~100 nM

Technology Validated Across Multiple Sequences *In Vitro*

Editing in Primary Human Hepatocytes

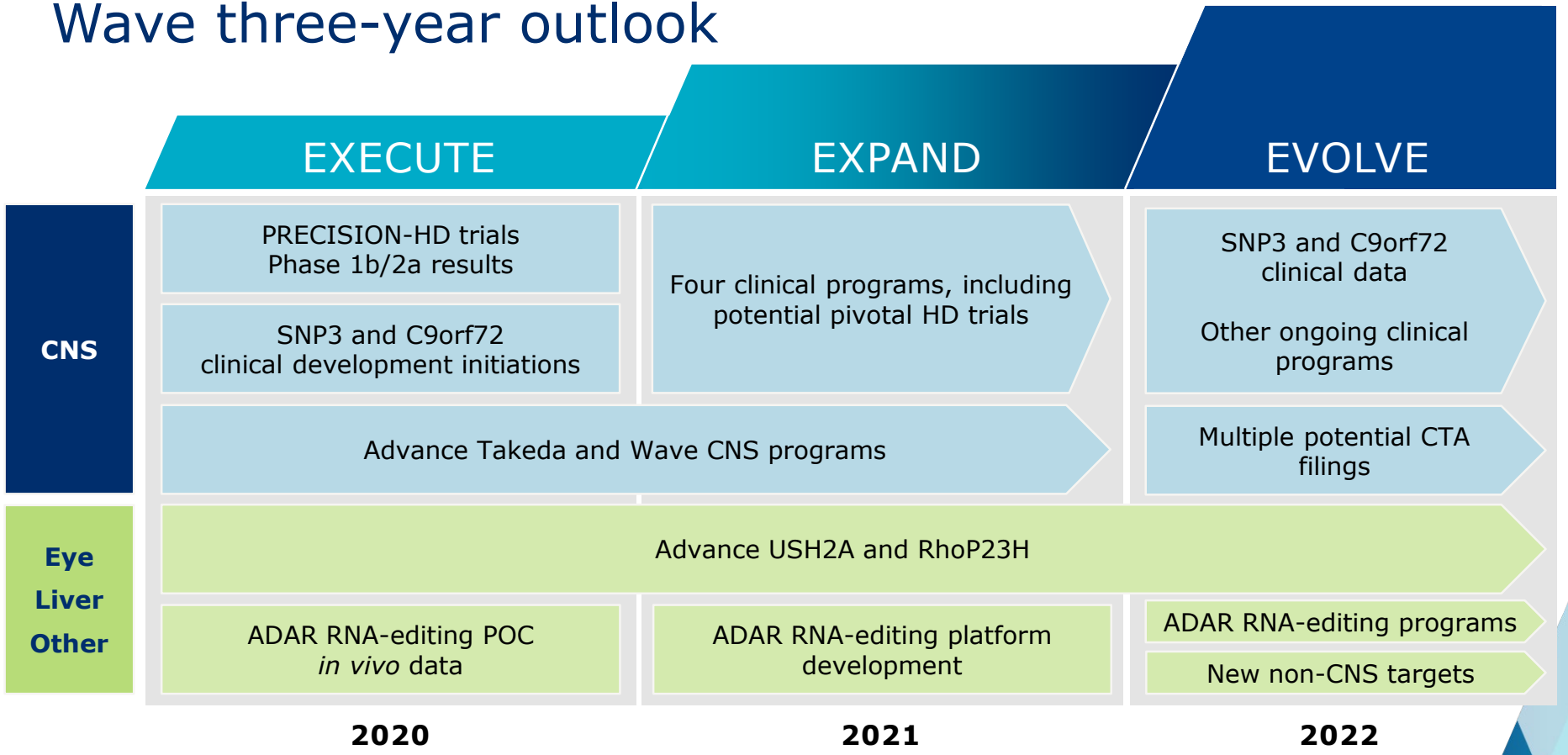


- Editing achieved across several distinct RNA transcripts

In vivo editing data with fully modified stereopure oligonucleotides expected in 2020

Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020); See poster for full dataset

Wave three-year outlook



PRISM **Chemistry innovations transferred to new programs**

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POC: proof of concept

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Q&A

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Realizing the potential of genetic medicines

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