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Wave Life Sciences

Fourth Quarter and Full Year 2020 Earnings

March 4, 2021

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, MD, MBA

President and CEO

Today’s agenda

Paul Bolno, MD, MBA
President and CEO

2020 Pipeline & Platform Achievements

Michael Panzara, MD, MPH
CMO, Head of Therapeutics Discovery and Development

Clinical Pipeline Expansion

Kyle Moran
CFO

4Q Financial Results

Q&A

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Wave Life Sciences: 2020 achievements

- ✓ Progressed four clinical trials (PRECISION-HD1, PRECISION-HD2 and OLEs) towards data readout
- ✓ Unveiled novel PN chemistry; WVE-003 (SNP3), WVE-004 (C9orf72), WVE-N531 (Exon 53) on track to advance into clinic
- ✓ Achieved several milestones within Takeda collaboration for CNS programs
- ✓ Advanced new ADAR editing modality and announced first program (AATD)
- ✓ Expanded peer-reviewed publications
- ✓ Strengthened balance sheet; Well-capitalized to execute on clinical and preclinical pipeline

OLE: open label extension; ADAR: AATD: Alpha-1 antitrypsin; CNS: Central nervous system

Robust dataset expected to enable a decision regarding potential Phase 3 clinical development

WVE-120102 (SNP2)

PRECISION-HD2 core

- Biomarker and safety data from all cohorts, including 32 mg

PRECISION-HD2 Open Label Extension (OLE)

- Initial biomarker and safety data from patients who received up to 16 monthly doses of 8 or 16 mg of WVE-120102

WVE-120101 (SNP1)

PRECISION-HD1 core

- Biomarker and safety data from all complete cohorts up to and including 16 mg

PRECISION-HD1 Open Label Extension (OLE)

- Initial biomarker and safety data from patients who received up to 9 monthly doses of 8 or 16 mg of WVE-120101

Biomarkers to be evaluated for all studies include mHTT, NfL, and wtHTT

PRECISION-HD core and OLE trial data expected end of 1Q 2021

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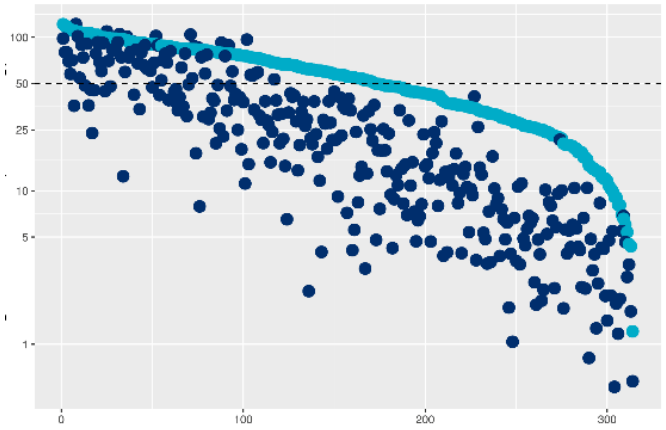
OLE: Open label extension; mHTT: mutant huntingtin; tHTT: total huntingtin; NfL: neurofilament light chain; wtHTT: wild-type huntingtin

PN chemistry increases potency in silencing, splicing, and editing preclinical studies

Silencing

Target knockdown (% remaining)



Ranked by potency of reference PS/PO compound

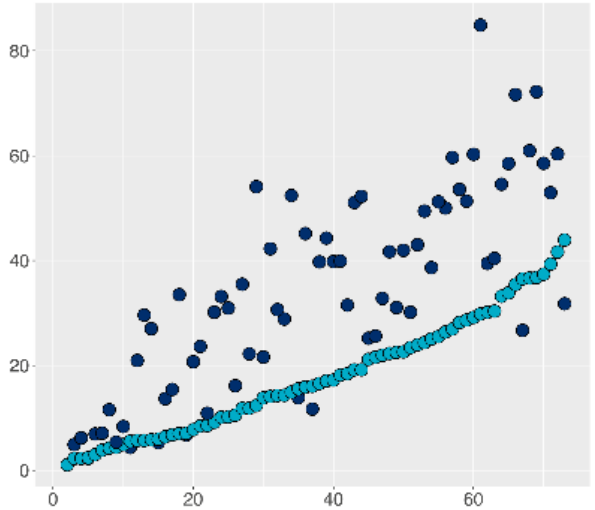
Improved knockdown

PS/PO reference compound

PS/PN modified compound

Splicing

% Skipping

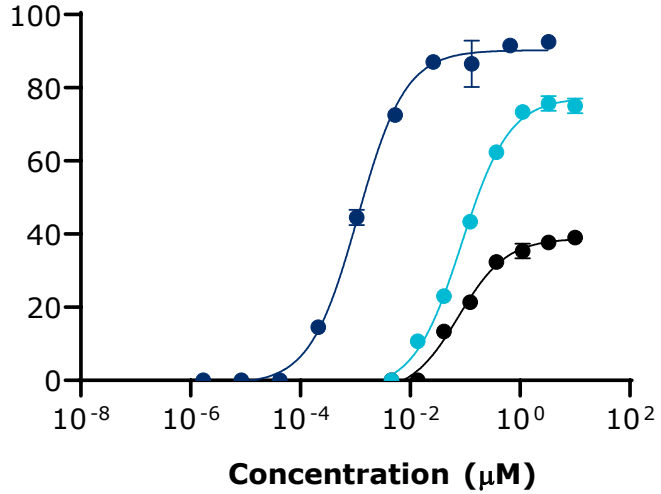


Ranked by potency of reference PS/PO compound

Improved skipping

Editing

% Editing



Improved editing

PS/PO/PN

PS/PO (Stereopure)

PS/PO (Stereorandom)

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Presented at Analyst & Investor Research Webcast on August 25, 2020; Right: Data from independent experiments

PRISM

Platform evolution reflected in three upcoming clinical trials to start in 2021

PRISM

Oligonucleotide optimization
- Stereopure backbone
- PN backbone chemistry modifications

***In vivo* disease models**
- Insight into PK / PD relationships
- Novel model generation

Leverage learnings of first generation programs
- Translational pharmacology
- Clinical trial design

SNP3

WVE-003

Allele-selective silencing candidate in HD

C9orf72

WVE-004

Variant-selective silencing candidate in ALS and FTD

Exon 53

WVE-N531

Exon skipping candidate for DMD

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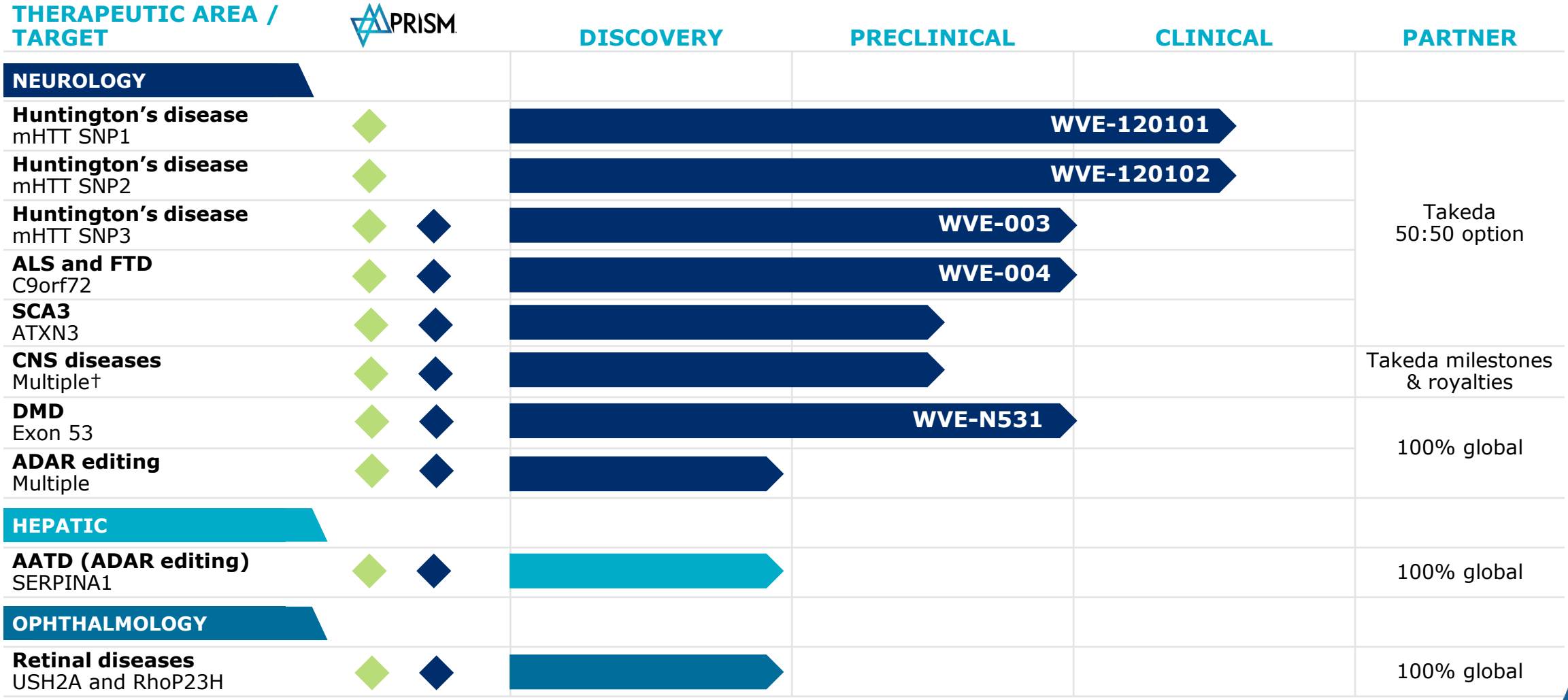
HD: Huntington's disease ALS: amyotrophic lateral sclerosis FTD: frontotemporal dementia DMD: Duchenne muscular dystrophy

Innovative pipeline of RNA therapeutics



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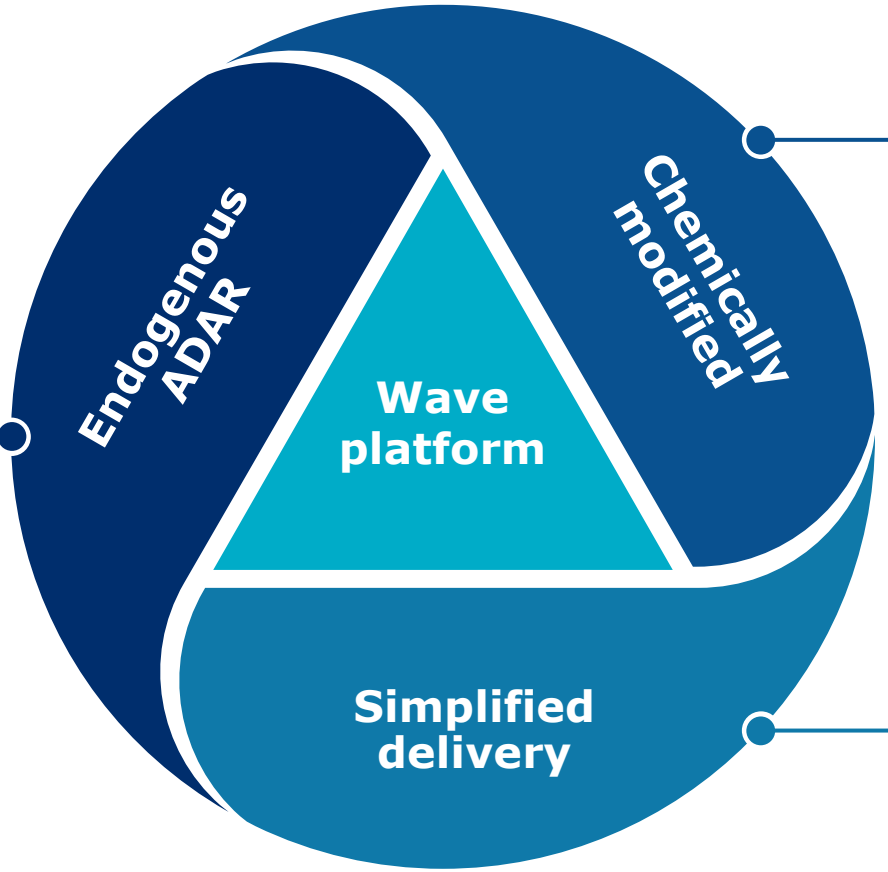
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system;
DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Advantages of Wave ADAR editing platform

- Avoids permanent off-target DNA edits
- No immunogenicity from exogenous proteins
- Reduced off-target effects



- Fully chemically modified to increase stability *in vivo*
- Chirally-controlled backbone to maximize *in vitro* activity
- PN backbone chemistry modification improves editing efficiency

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

Achieved durable *in vivo* editing in NHPs

Sources: Chen Biochemistry 2019; Shivalila OTS 2020.

Advancing Wave's first ADAR editing program in alpha-1 antitrypsin deficiency (AATD)

- Most common cause is a single G-to-A point mutation on the "Z" allele
- **~200K people in US and EU** with homozygous ZZ genotype, most common form of severe AATD
- Approved therapies modestly increase circulating levels of wild-type AAT in those with lung pathology; no therapies address liver pathology

Wave's approach may simultaneously address lung and liver manifestations by using ADAR editing to correct mutation:

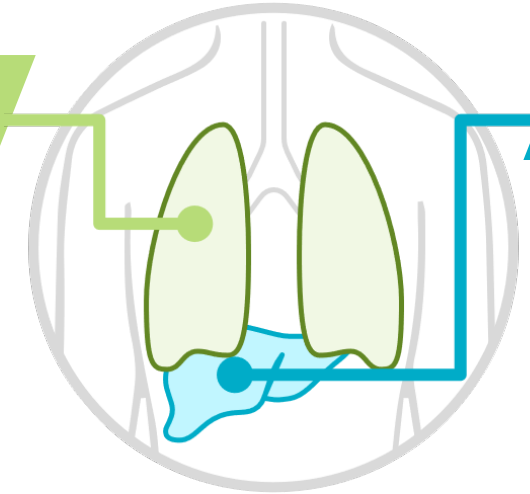
- Increase circulating levels of wild-type AAT protein
- Reduce aggregation of Z-AAT in liver
- Retain wild-type AAT physiological regulation

Dual pathologies in AATD

Loss of function in lung

Lack of functional AAT in serum:

- Insufficient levels to counteract protease levels, e.g., neutrophil elastase
- Lung damage due to unchecked proteolytic activity and inflammation
- Other tissues may be affected (e.g., skin)



Gain of function in liver

Misfolding of AAT in hepatocytes:

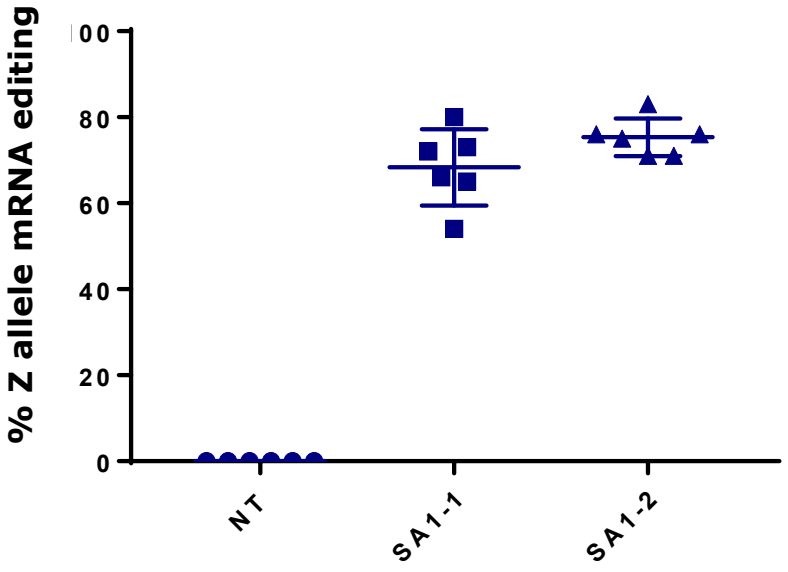
- Inability to secrete AAT
- AAT polymerizes in liver
- Liver damage/cirrhosis

Sources: Strnad 2020; Blanco 2017
AAT: Alpha-1 antitrypsin

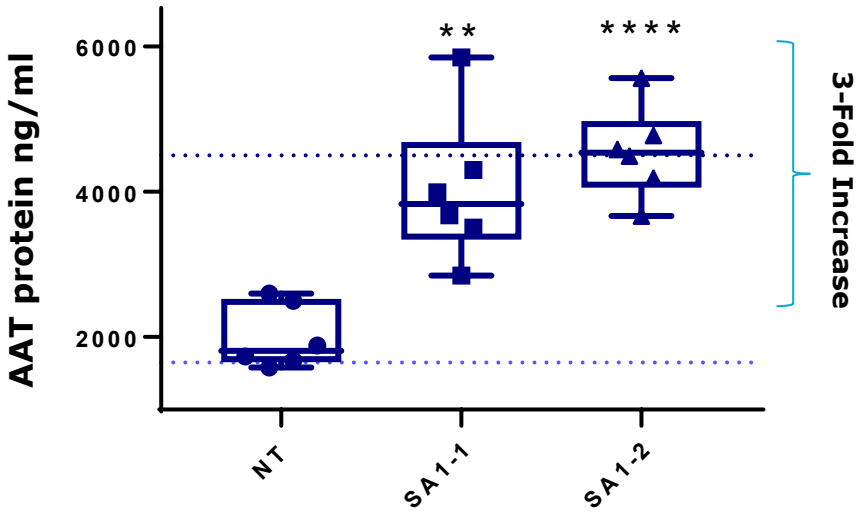
SERPINA1 Z allele mRNA editing increases edited AAT protein concentration *in vitro*

In primary hepatocyte *SERPINA1* Z cell model, editing the Z allele mRNA back to wild-type prevents protein misfolding and increases secretion of edited AAT protein from hepatocytes

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



Edited AAT protein analysis

- Wild-type AAT protein confirmed by mass spectrometry
- Function of secreted, edited AAT protein confirmed by neutrophil elastase inhibition assay

Model validation and *in vivo* data expected 1H 2021

AAT (alpha-1 antitrypson); Mouse primary hepatocytes that express SERPINA1 Z allele mRNA were transfected with 25 nanomolar (nM) of SERPINA1 (SA1-1 and SA1-2) targeting antisense oligonucleotides (ASOs) and a control non-targeting (NT) ASO. Media and RNA was collected at 5 days post transfection. AAT protein in media was quantified by Elisa Assay, RNA editing was quantified by RT/PCR/Sanger sequencing.

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Mike Panzara, MD, MPH

Chief Medical Officer,

Head of Therapeutics

Discovery and Development

Continued evolution of platform and portfolio with three new clinical trials dosing in 2021

SNP1

WVE-120101

Allele-selective silencing candidate in HD

SNP2

WVE-120102

Allele-selective silencing candidate in HD

SNP3

WVE-003

Allele-selective silencing candidate in HD

C9orf72

WVE-004

Variant-selective silencing candidate in ALS and FTD

Exon 53

WVE-N531

Exon skipping candidate for DMD

PRISM ◆ PS/PO backbone ◆ PS/PO/PN backbone

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HD: Huntington's disease ALS: amyotrophic lateral sclerosis FTD: frontotemporal dementia DMD: Duchenne muscular dystrophy

HD: Wild-type HTT is a critical protein for important functions in the central nervous system

NEURON

Promotes neuronal survival by protecting against stress

SYNAPSE

Plays essential role in transport of synaptic proteins to their correct location at synapses

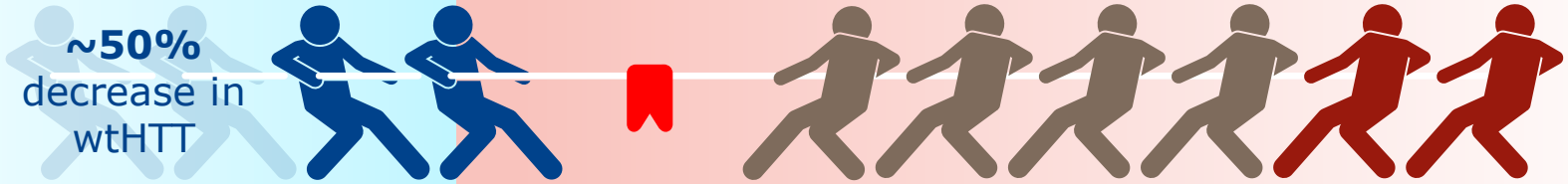
BRAIN CIRCUITS

Supplies BDNF to striatum to ensure neuronal survival and regulates synaptic plasticity, which underlies learning and memory

CSF CIRCULATION

Plays critical role in formation / function of cilia, which are needed to clear catabolites and maintain homeostasis

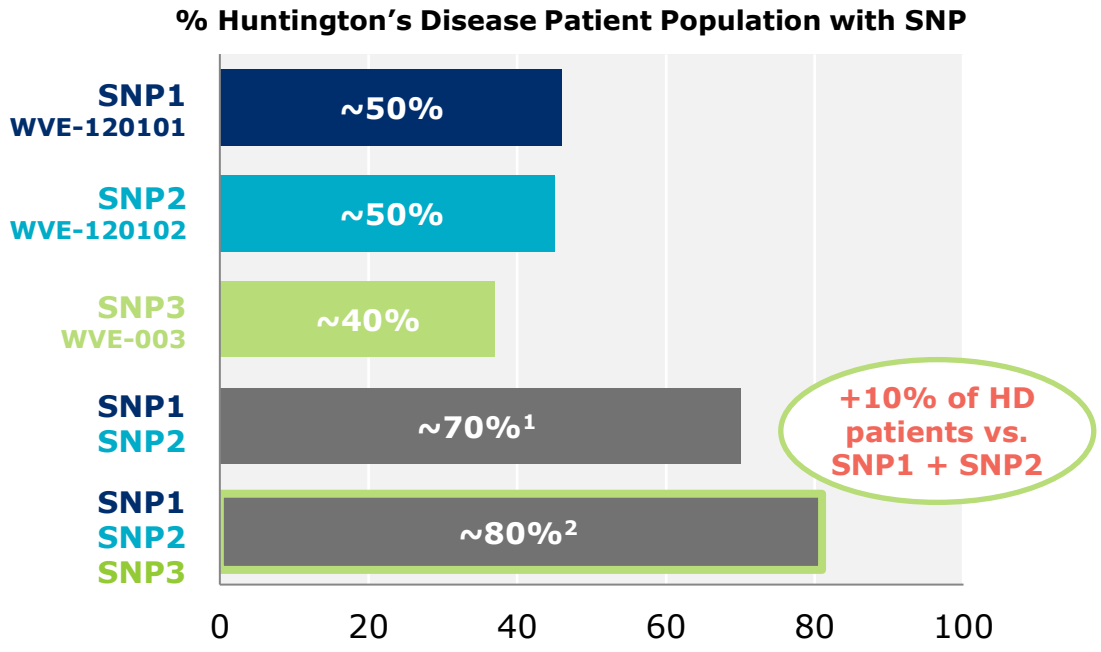
In HD, mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD



mHTT: mutant huntingtin wtHTT: wild-type huntingtin

Personalized approach to wild-type HTT sparing opens possibility of early treatment

Potential to address ~80% of HD patient population



Allele-selective treatments have potential to benefit many of those at-risk of HD

[1] Percentage of patient population with SNP1 and/or SNP2; [2] Percentage of patient population with SNP1, SNP2 and/or SNP3
Genotyping single nucleotide polymorphisms for allele-selective therapy in Huntington disease
Claassen et al. Neurol Genet Jun 2020; Carroll et al. Mol Ther. 2011 Dec; HDSA.org

Innovations towards developing personalized wild-type HTT sparing treatments

Rapid patient identification

- ✓ Novel SNP phasing assay deployed to accurately identify patients eligible for PRECISION-HD studies (Svrzikapa et al. 2020)
- ✓ First prospective study to establish proof of principle and confirm SNP frequency (Claassen et al. 2020)
- ✓ Partnership with Asuragen to expand capabilities to support multiple programs and eventual commercialization

CSF biomarkers to confirm target engagement, neuroprotection, and wild-type sparing

- ✓ mHTT
- ✓ NfL
- ✓ Novel approach to measure CSF wtHTT
  - ✓ Depletion of mHTT from patient CSF samples allows for direct measurement of wtHTT

WVE-003 (SNP3) program will leverage assay innovations

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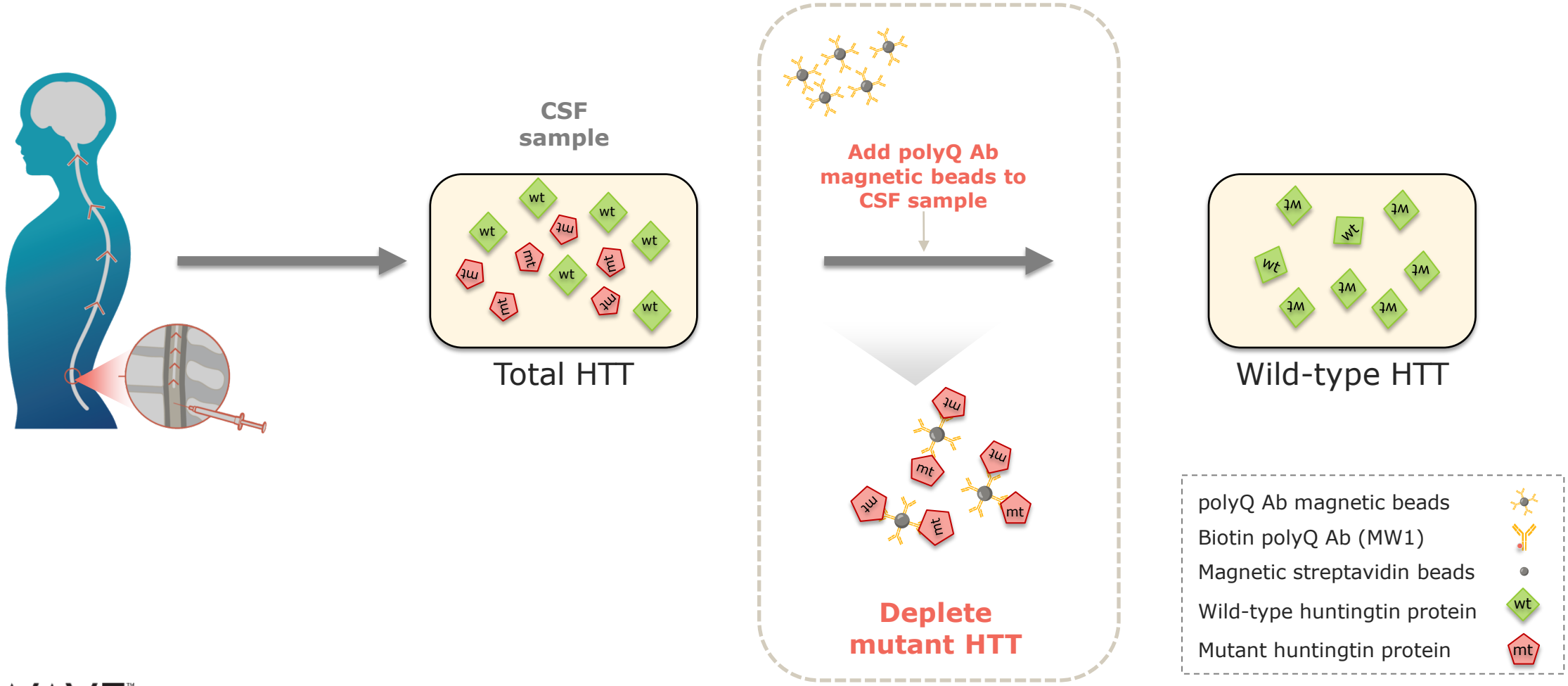
Ab: antibody; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; wtHTT: wild-type huntingtin; NfL: Neurofilament light chain

Assessment of wild-type protein in CSF

Depletion of mutant HTT key to ability to measure wild-type HTT protein



Ab: antibody CSF: cerebrospinal fluid HTT: huntingtin protein MW1: Wild et al. JCI 2015

WVE-003: Clinical trial to leverage experience and learnings in HD

Leveraging learnings from PRECISION-HD

- Starting dose informed by preclinical *in vivo* models
- Asuragen assay to improve efficiency of patient identification
- Drawing from experience of sites from PRECISION-HD1 and PRECISION-HD2 trials

Adaptive SAD/MAD design

- Patients with confirmed manifest HD diagnosis with SNP3 mutation (up to 40 patients planned)
- Dose escalation and dosing interval guided by independent DSMB
- Safety and tolerability
- Biomarkers
  - mHTT
  - NfL
  - wtHTT
- Clinical trial site activation ongoing

Dosing in Phase 1b/2a trial expected to initiate in 2021

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SAD: Single ascending dose MAD: Multiple ascending dose mHTT: mutant huntingtin NfL: neurofilament light chain wtHTT: wild-type huntingtin

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

	Disease	C9 specific US population	Mean disease duration	Standard of care
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 in US
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

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ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
Sources: Cammack et al, Neurology, October 2019. Moore et al, Lancet Neurology, February 2020

C9orf72 variant-selective targeting strategy published in *Nature Communications*

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-21112-8 OPEN

Variant-selective stereopure oligonucleotides protect against pathologies associated with *C9orf72*-repeat expansion in preclinical models

Yuanjing Liu[1,3], Jean-Cosme Dodart[1,3], Helene Tran[2,3], Shaunna Berkovitch[1], Maurine Braun[1], Michael Byrne[1], Ann F. Durbin[1], Xiao Shelley Hu[1], Naoki Iwamoto[1], Hyun Gyung Jang[1], Pachamuthu Kandasamy[1], Fangjun Liu[1], Kenneth Longo[1], Jörg Ruschel[1], Juili Shelke[1], Hailin Yang[1], Yuan Yin[1], Amy Donner[1], Zhong Zhong[1], Chandra Vargeese[1✉] & Robert H. Brown Jr.[2]

A large G_4C_2-repeat expansion in *C9orf72* is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Neuronal degeneration associated with this expansion arises from a loss of C9orf72 protein, the accumulation of RNA foci, the expression of dipeptide repeat (DPR) proteins, or all these factors. We report the discovery of a new targeting sequence that is common to all *C9orf72* transcripts but enables preferential knockdown of repeat-containing transcripts in multiple cellular models and C9BAC transgenic mice. We optimize stereopure oligonucleotides that act through this site, and we demonstrate that their preferential activity depends on both backbone stereochemistry and asymmetric wing design. In mice, stereopure oligonucleotides produce durable depletion of pathogenic signatures without disrupting protein expression. These oligonucleotides selectively protect motor neurons harboring *C9orf72*-expansion mutation from glutamate-induced toxicity. We hypothesize that targeting *C9orf72* with stereopure oligonucleotides may be a viable therapeutic approach for the treatment of *C9orf72*-associated neurodegenerative disorders.

[1] Wave Life Sciences Ltd., Cambridge, MA, USA. [2] Department of Neurology, University of Massachusetts, Worcester, MA, USA. [3] These authors contributed equally: Yuanjing Liu, Jean-Cosme Dodart, Helene Tran. ✉email: cvargeese@wavelifesci.com

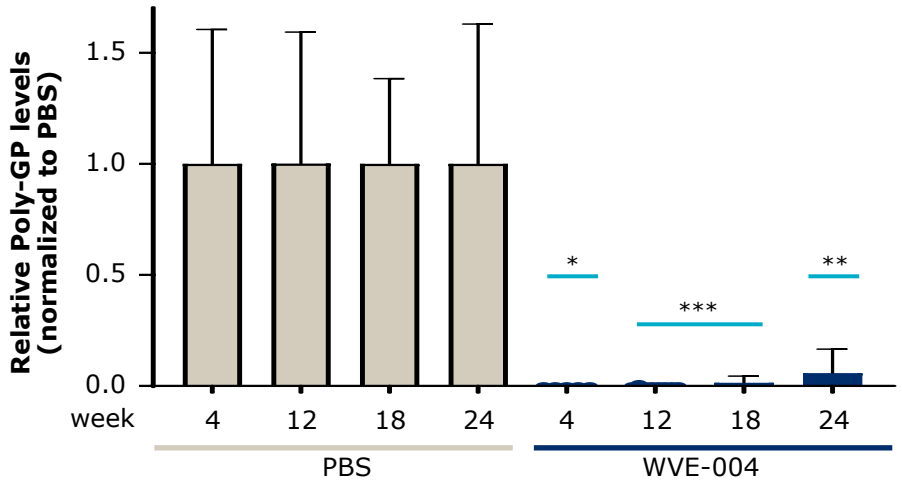
NATURE COMMUNICATIONS | (2021)12:847 | https://doi.org/10.1038/s41467-021-21112-8 | www.nature.com/naturecommunications 1

- *Nature Communications* paper reports novel targeting strategy to achieve variant-selective knockdown of expansion-containing C9orf72 transcript for ALS / FTD
- Publication describes the foundational work that led to the development of clinical candidate, WVE-004

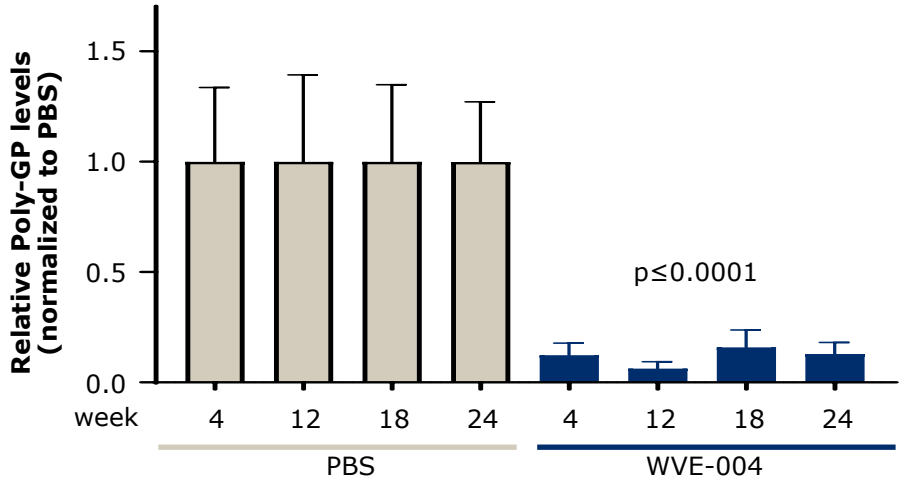
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia

WVE-004 demonstrates durable reduction of DPRs in vivo after 6 months in spinal cord and cortex

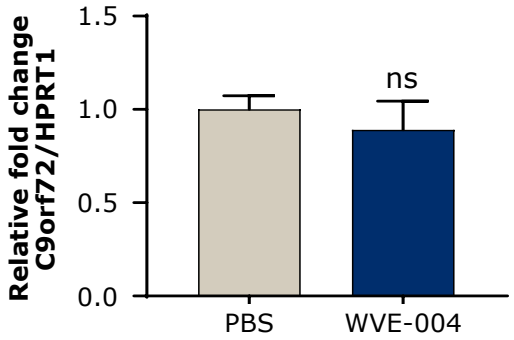
Spinal cord

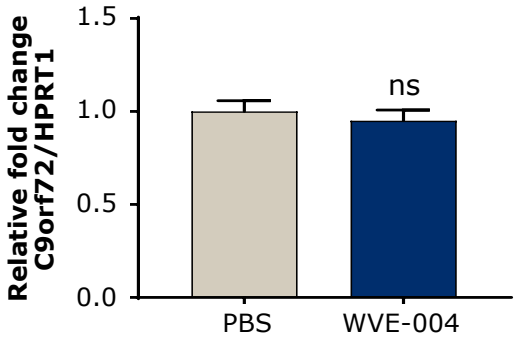


Cortex



Healthy C9orf72 protein relatively unchanged ~6 months after WVE-004 administration





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Full results presented at the 31st International Symposium on ALS/ MND (December 2020)
Top: 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. ICV: intracerebroventricular; DPR: Dipeptide repeat protein; Bottom: C9 BAC transgenic mice administered PBS or 50 ug WVE-004, ICV, (day 0, day 7). ns: not significant; PBS: phosphate-buffered saline

WVE-004: Adaptive SAD/MAD design to optimize dose level and frequency

- Patients with documented C9orf72 expansion and confirmed ALS, FTD, or mixed phenotype (up to 50 patients planned)
- Starting dose informed by preclinical *in vivo* models
- Dose escalation and dosing interval guided by independent DSMB
- Key biomarkers of target engagement and neurodegeneration will be assessed
  - PolyGP
  - NfL
- Key exploratory clinical outcome measures
  - ALSFRS-R and CDR-FTLD
- Clinical trial site activation ongoing

Dosing in Phase 1b/2a trial expected to initiate in 2021

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CTA: clinical trial application; NfL: neurofilament light chain; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale; CDRFTLD: Clinical Dementia Scale – frontotemporal lobar degeneration; PolyG: poly glycine-proline; SAD: Single ascending dose; MAD: Multiple ascending dose

WVE-N531: First splicing candidate to use PN chemistry

- First generation PS/PO chemistry reached muscle but not target likely due to poor intracellular access in dystrophic muscle
- Compelling preclinical data for WVE-N531 and PN-chemistry splicing compounds
  - Dose-dependent increase in dystrophin production (up to 71%) *in vitro* in patient-derived myoblasts
  - Higher concentrations and broader distribution in non-human primates with potential for every other week dosing
  - Rescue of double knockout (dKO) mouse model from rapidly fatal phenotype (median survival typically 7 weeks)

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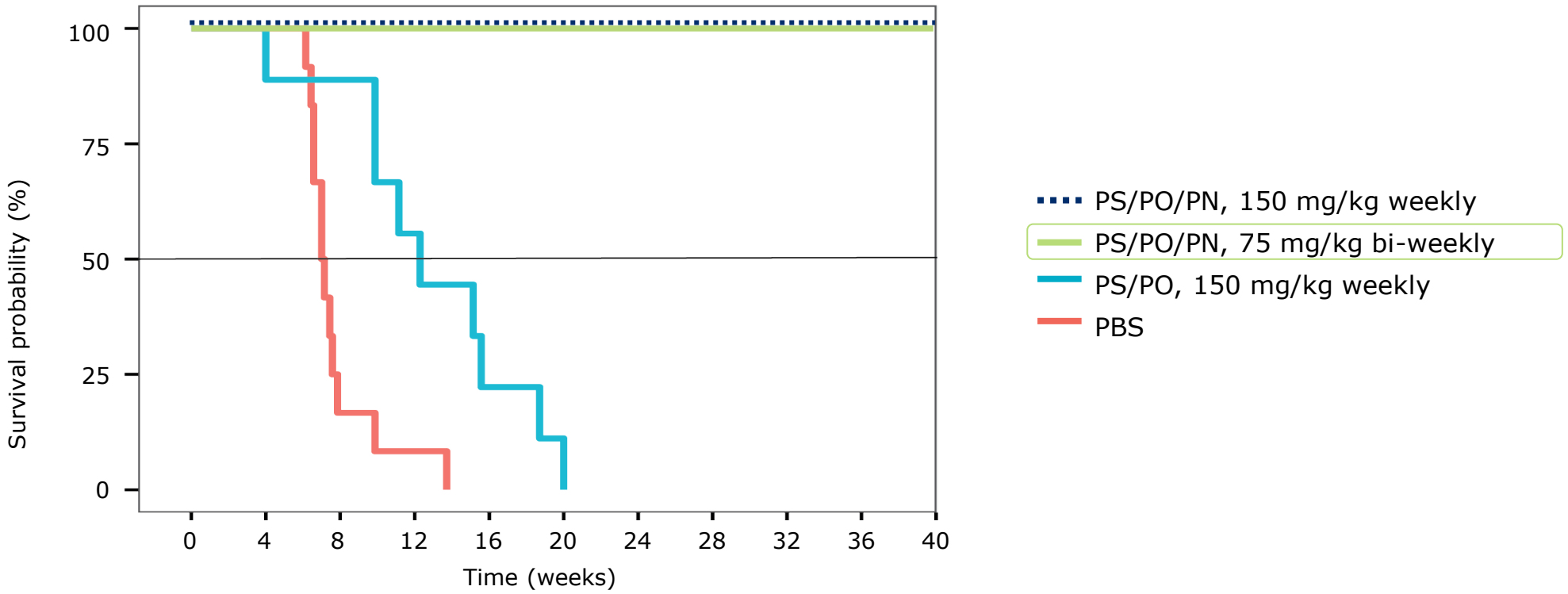
CTA: clinical trial application

PN chemistry led to overall survival benefit in dKO model

PN-containing molecules led to 100% dKO survival at time of study termination



Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

dKO; double knockout mice lack dystrophin and utrophin protein. mdx mice lack dystrophin. Left: Mice with severe disease were euthanized. dKO: PS/PO/PN 150 mg/kg n= 8 (p=0.0018); PS/PO/PN 75 mg/kg n=9 (p=0.00005); PS/PO n=9 (p=0.0024), PBS n=12 Stats: Chi square analysis with pairwise comparisons to PBS using log-rank test

Clinical trial of WVE-N531 to initiate in 2021

- Unmet need in DMD remains high
- Planned clinical trial designed to evaluate change in dystrophin production, drug concentration in muscle, and initial safety
  - Open-label study; targeting every-other-week administration in up to 15 boys with DMD
- Potential to apply PN chemistry to other exons if successful

CTA submission expected in 1Q 2021

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Kyle Moran

Chief Financial Officer

Fourth quarter 2020 financial results

	Three Months Ended Dec 31, 2020	Three Months Ended Dec 31, 2019
Figures are in thousands, except per share amounts		
Revenue	$9,439	$2,400
Operating Expenses:		
Research and Development	30,033	49,128
General and Administrative	9,719	13,805
Total Operating Expenses	39,752	62,933
Loss from Operations	(30,313)	(60,533)
Total Other Income, Net	683	3,763
Income Tax Benefit (Provision), Net	841	—
Net Loss	($28,789)	($56,770)
Net Loss per Share	**($0.59)**	**($1.65)**

As of Dec 31, 2020 | **Shares Outstanding:** 48.8 million | **Cash Balance:** $184.5 million

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Wave expects that its existing cash and cash equivalents, together with expected and committed cash from its existing collaboration, will enable the company to fund its operating and capital expenditure requirements into 2Q 2023.

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Paul Bolno, MD, MBA

President and CEO

Expected upcoming milestones

THERAPEUTIC AREA / TARGET	PRISM	Milestone
NEUROLOGY		
Huntington's disease mHTT SNP2	◆	**End of 1Q 2021:** PRECISION-HD2 data, including complete 32 milligram cohort, and initial data from OLE trial
Huntington's disease mHTT SNP1	◆	**End of 1Q 2021**: PRECISION-HD1 data, including complete 16 milligram cohort, and initial data from OLE trial
Huntington's disease mHTT SNP3	◆ ◆	**2021:** Dosing of first patient in clinical trial of WVE-003
ALS and FTD C9orf72	◆ ◆	**2021:** Dosing of first patient in clinical trial of WVE-004
Duchenne muscular dystrophy Exon 53	◆ ◆	**End of 1Q 2021:** CTA submission
ADAR editing Multiple	◆ ◆	**1H 2021**: Humanized mouse model validation
HEPATIC		
AATD (ADAR editing) SERPINA1	◆ ◆	**1H 2021:** *in vivo* AATD data

First clinical compounds with PN chemistry to begin dosing in 2021

PRISM ◆ Stereopure ◆ PN chemistry

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ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; AATD: Alpha-1 antitrypsin deficiency

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Q&A

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Realizing a brighter future for people affected by genetic diseases

For more information:
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617.949.4827