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Wave Life Sciences

Third Quarter 2020 Earnings

November 9, 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, MD, MBA

President and CEO

Today’s agenda

Paul Bolno, MD, MBA
President and CEO

Recent Achievements

PRECISION-HD Readout on Track

PN Chemistry Advancement

ADAR Editing (Alpha-1 antitrypsin)

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

WVE-003 (SNP3 in HD)

WVE-004 (C9orf72 in ALS/FTD)

WVE-N531 (Exon 53 in DMD)

David Gaiero
Interim CFO

Q3 Financial Results

Q&A

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Advancing clinical development and unlocking new programs

Clinical Pipeline

- PRECISION-HD data readouts expected in 1Q 2021
- CTA submission for WVE-003 (SNP3) expected in 4Q 2020
- CTA submission for WVE-004 (C9orf72) expected in 4Q 2020
- CTA submission for WVE-N531 (exon 53) expected in 1Q 2021

Discovery

- First ADAR editing program – Alpha-1 antitrypsin deficiency
- Neurology pipeline advancing through Takeda collaboration

PRISM Platform

- Novel PN backbone introduced into portfolio
- ADAR editing modality progressing in neurology

Cash Runway Extended

- Equity financing extended cash runway into 2Q 2023

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CTA: clinical trial application

PRECISION-HD and initial OLE results remain on track for 1Q 2021

Results expected to be reported in 1Q 2021

Studies and Cohorts	Results
• **PRECISION-HD1** data from all dose cohorts • **PRECISION-HD2** data from all dose cohorts • **PRECISION-HD1 Open-label Extension** initial data from patients who have received multiple doses of 8 or 16 mg of WVE-120101 • **PRECISION-HD2 Open-label Extension** initial data from patients who received multiple doses of 8 or 16 mg of WVE-120102	• **Safety and tolerability** • **Biomarkers** – mHTT – tHTT – NfL – Assay development work to measure wtHTT in CSF ongoing

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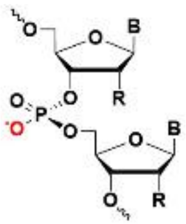
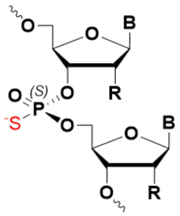
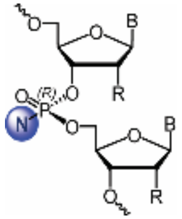
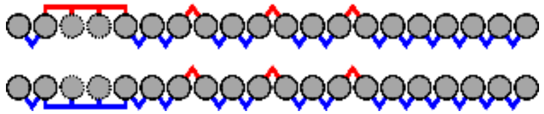
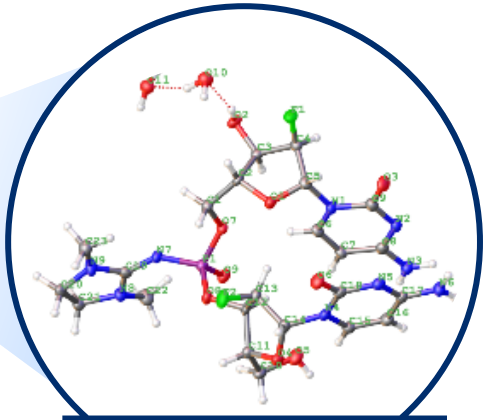
OLE: Open label extension; mHTT: mutant huntingtin; tHTT: total huntingtin; NfL: neurofilament light chain; wtHTT: wild-type huntingtin

Novel PN backbone chemistry introduced during Research Webcast

Backbone linkages

	PO	PS	PN
Backbone modification (X)	Phosphodiester 	Phosphorothioate 	Phosphoramidate diester 
Stereochemistry	Not chiral	Chiral ◇ Stereorandom PS backbone *Rp* PS backbone *Sp*	Chiral PN backbone Stereorandom PN backbone *Rp* PN backbone *Sp*
Charge	Negative	Negative	Neutral
Depiction			
PRISM backbone modifications	PO/PS	PO/PS	
	PO/PS/PN	PO/PS/PN	PO/PS/PN



Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

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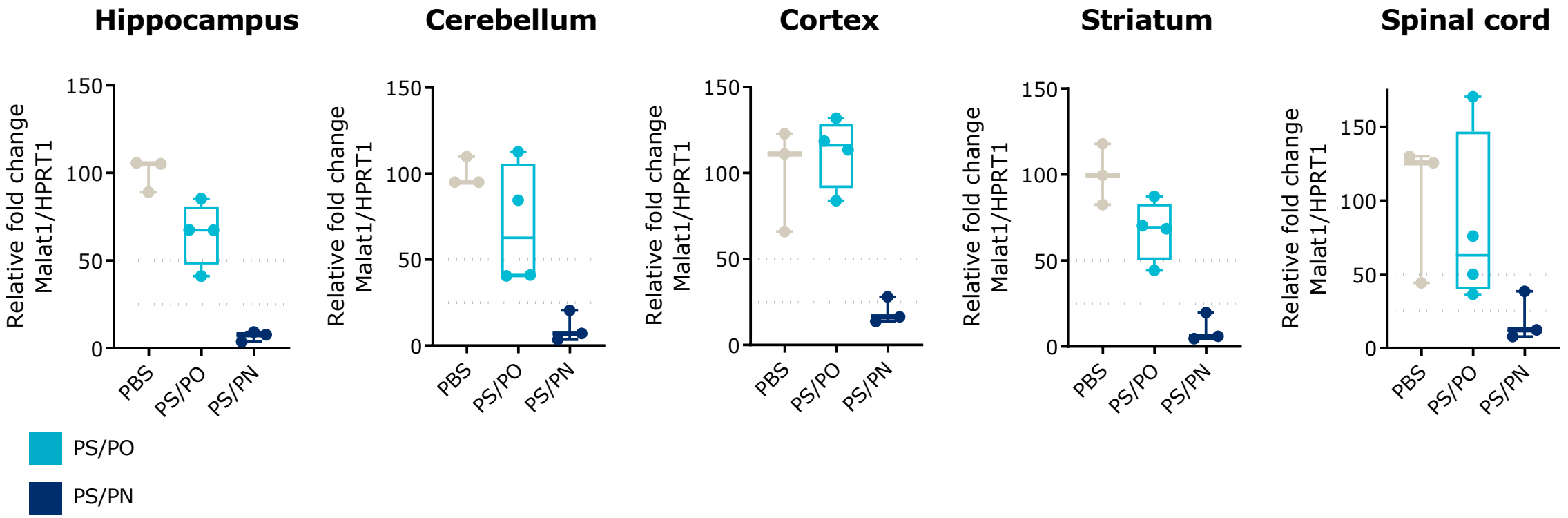
PN chemistry increases durability across CNS tissues

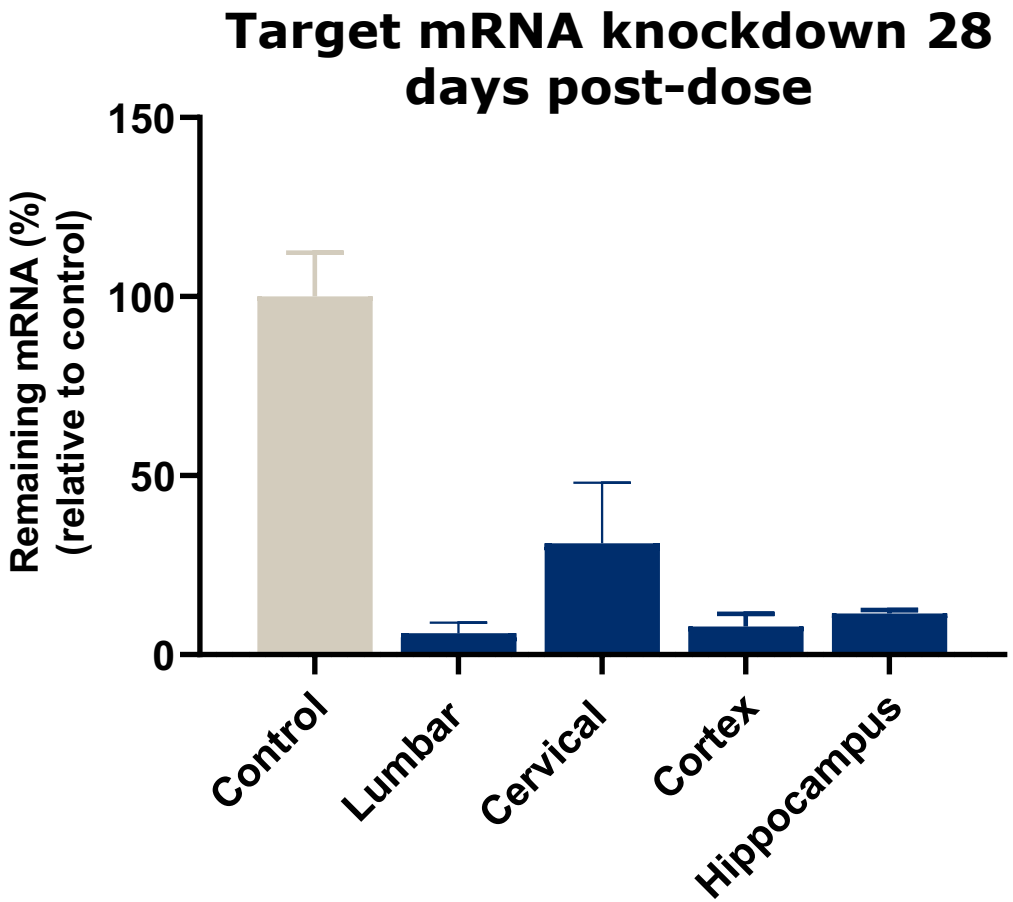
Malat1 knockdown at 10 weeks in CNS (100 µg)



Mice received a single 100 ug intracerebroventricular (ICV) injection (n=3 per group). Relative fold-change in MALAT1 expression is shown for the indicated tissues 10 weeks post-dose. MALAT1 expression levels are normalized to Hprt1. PBS, phosphate buffered saline

Lead program in Takeda collaboration reinforces potential of PN chemistry in the CNS

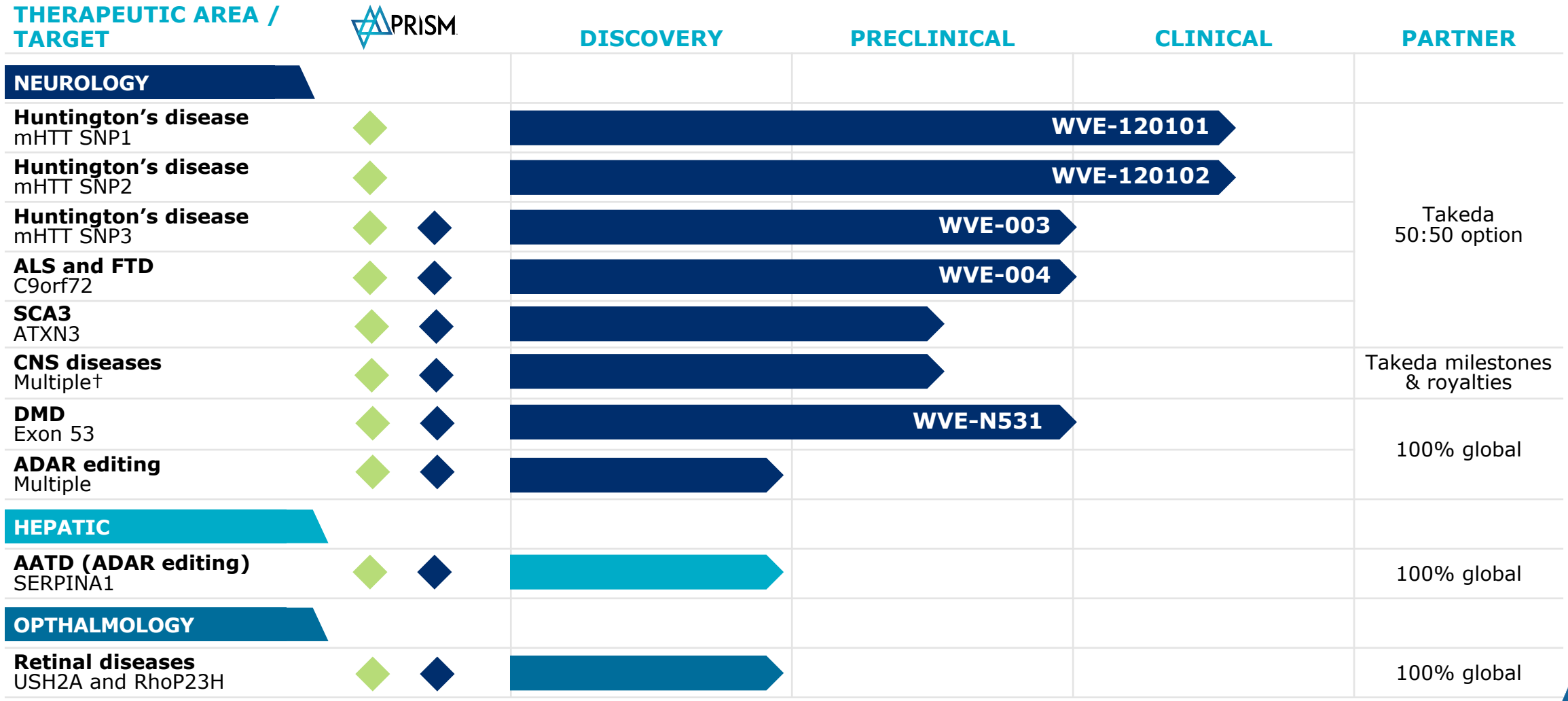
Substantial and widespread target mRNA reduction following single intrathecal dose in NHPs



- Single IT dose of 12 mg (n=3)
- Therapeutic candidate widely distributed across brain and spinal cord
- ~90% mRNA knockdown one-month following single dose

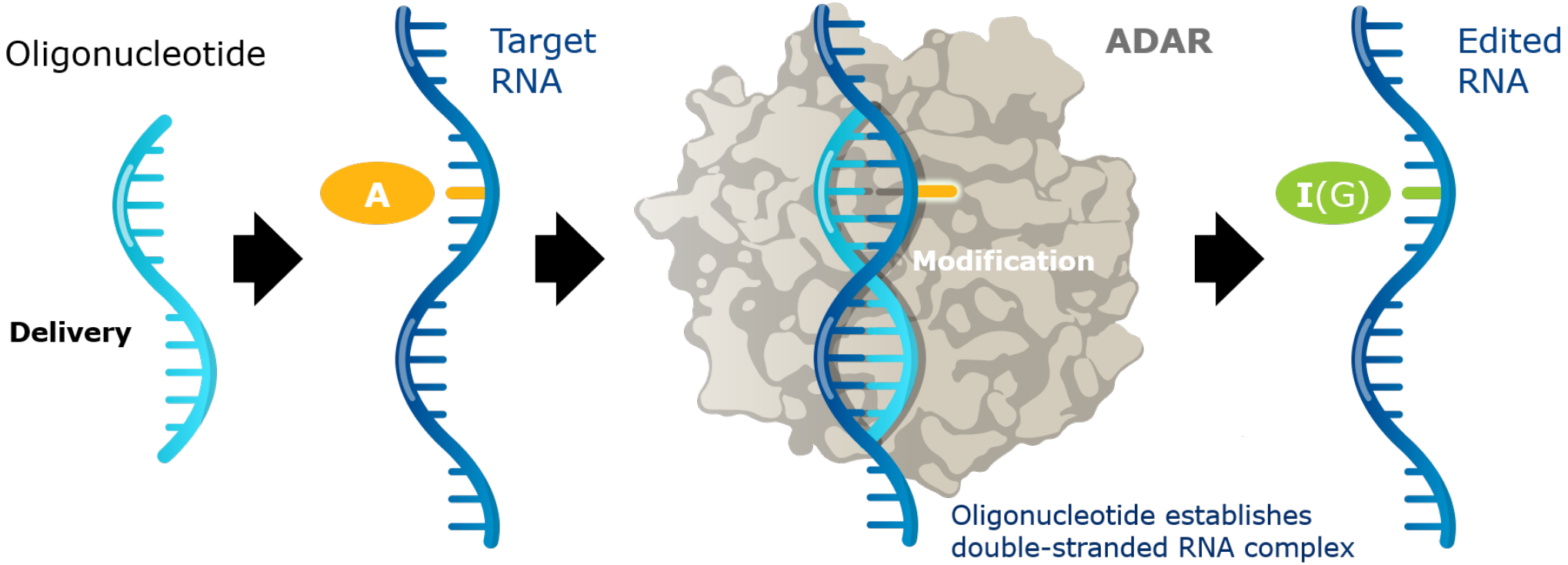
NHPs: Non-human primates; IT: intrathecal
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.

PN chemistry applied to all preclinical and discovery-stage 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; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

PRISM platform has unlocked ADAR editing

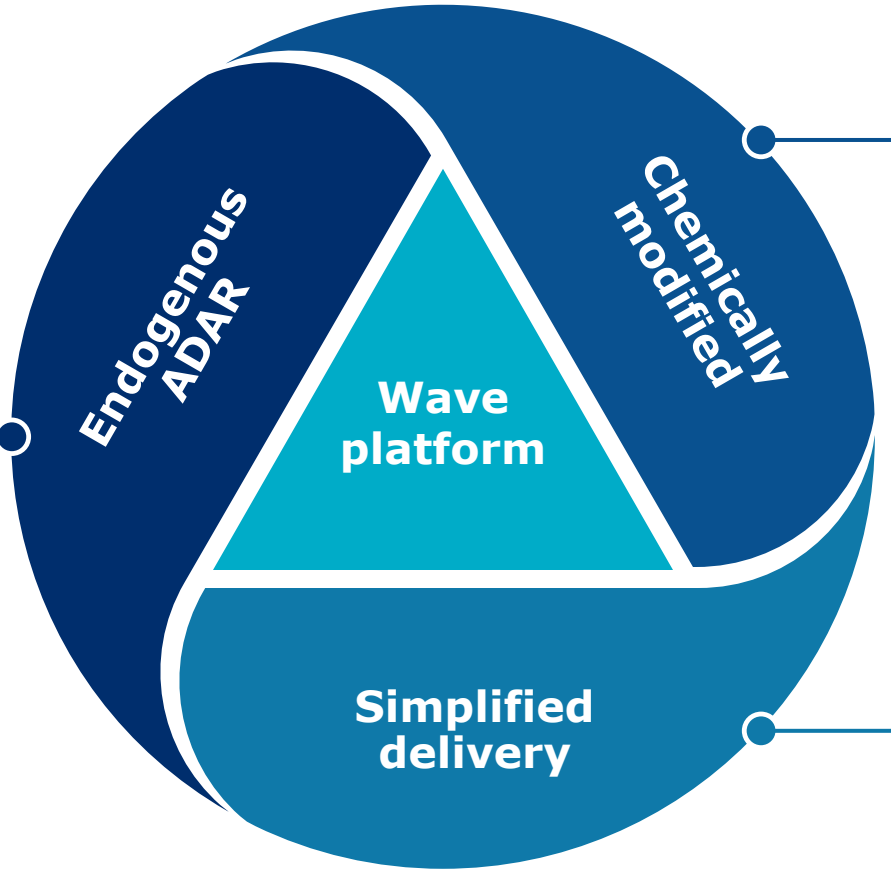


- **A**-to-**I(G)** editing is one of most common post-transcriptional modifications
- ADAR is ubiquitously expressed across tissues, including liver and CNS

A: adenosine; I: inosine; G: guanosine; 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 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

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Sources: Chen Biochemistry 2019; Shivalila OTS 2020.
NHPs: Non-human primates

Alpha-1 antitrypsin deficiency: One disease with two target organs

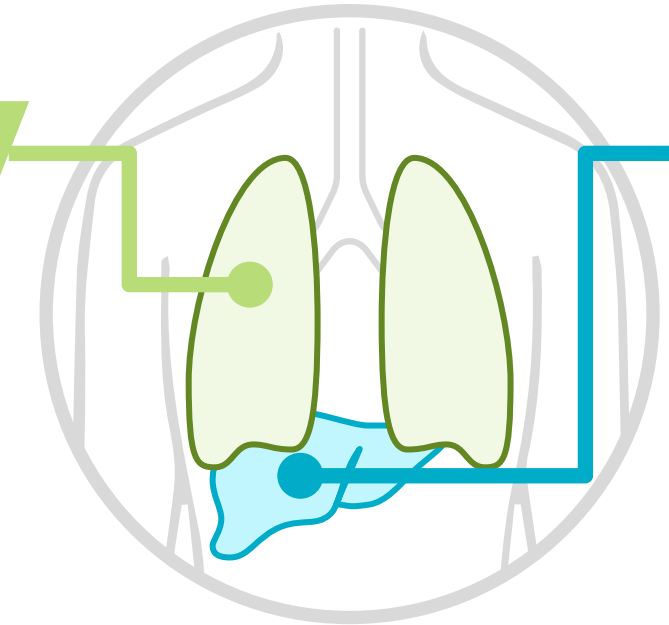
- Most common cause is a single G-to-A point mutation on the "Z" allele
- Patients who are homozygous for the Z allele are the most severe
- Current approved therapies modestly increase circulating levels of AAT in those with lung pathology; no therapies address liver pathology

ZZ genotype target population:
~250K people worldwide

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

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Sources: Strnad 2020; Blanco, 2017

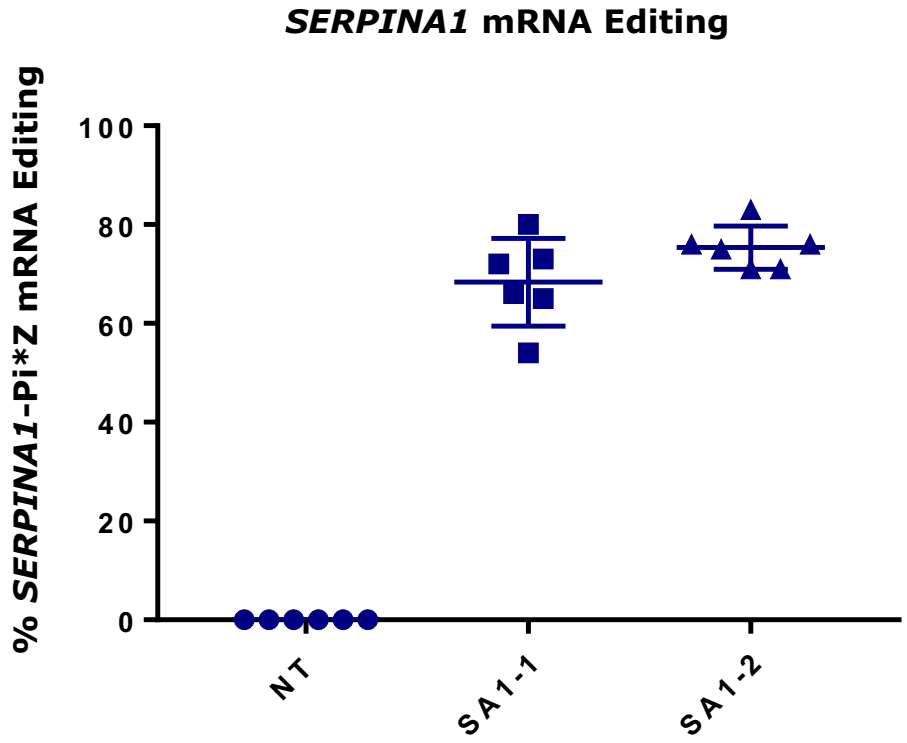
Building an optimal treatment approach in AATD

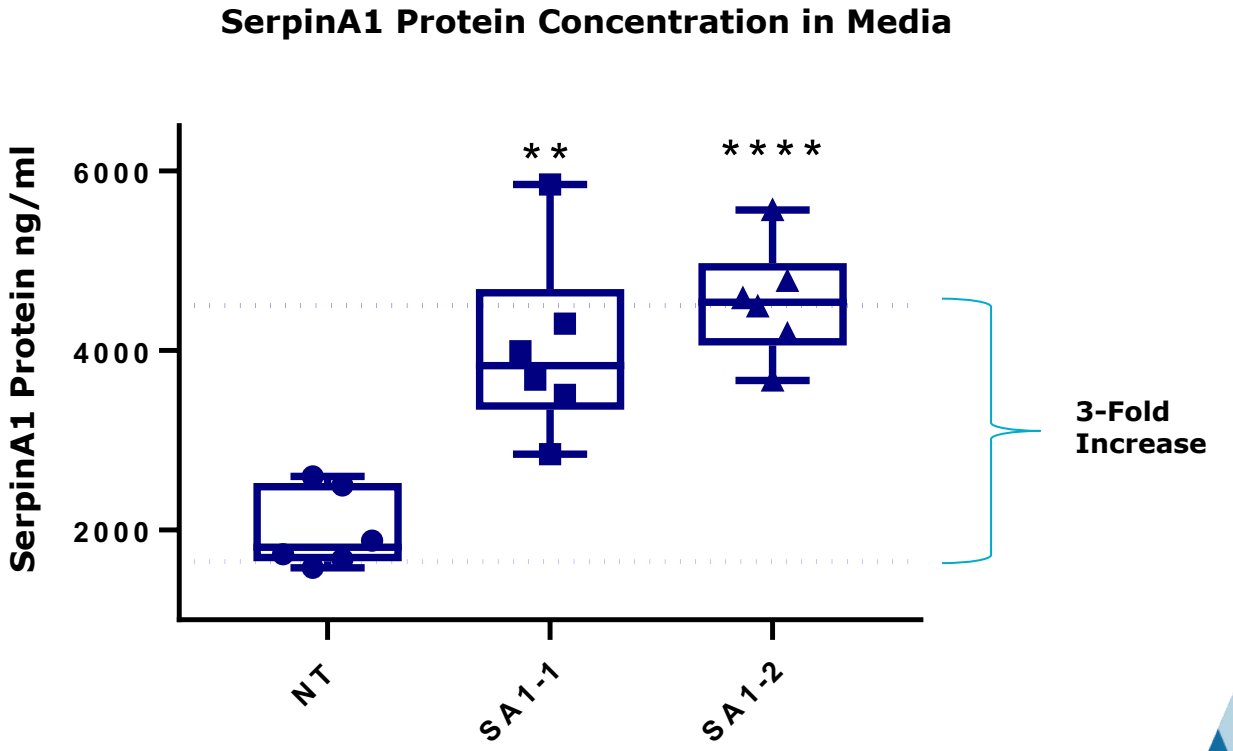
Target Attributes	Augmentation therapy	RNA silencing	Small molecule enhanced secretion	Wave editing approach
Restore wild-type AAT in the lungs	✓			✓
Reduce AAT aggregation in the liver		✓	✓	✓
Retain AAT physiological regulation			✓	✓

Sources: Strnad 2020; Huang 2016

SERPINA1 RNA editing increases protein concentration *in vitro*

In primary hepatocyte Pi*Z cell model, editing the Z transcript back to wild-type prevents protein misfolding and increases secretion from hepatocytes





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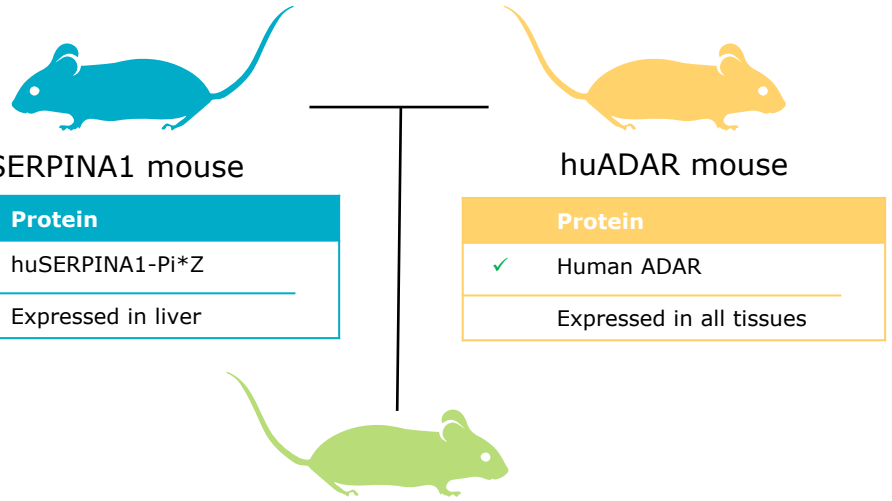
Mouse primary hepatocytes that express SERPINA1-PIZ allele were transfected with 25 nanomolar (nM) of SERPINA1 (SA1-1 and SA1-2) targeting antisense oligonucleotides (ASOs) and a control non-targeting (NT) ASO. Media and RNA was collected at 5 days post transfection. SerpinA1 Protein in media was quantified by Elisa Assay, RNA editing was quantified by RT/PCR/Sanger sequencing. All samples done at N=6 replicates.

Proprietary humanized mouse model developed to support ADAR platform



- Expression of huADAR in mouse is comparable to expression in human cells
- Expression of huADAR restores editing of endogenous targets in primary mouse cell types to levels seen in human primary cell types
- huADAR mouse model can be crossed with disease specific mouse models to provide model systems for use across Wave's ADAR editing programs

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

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Michael Panzara, MD, MPH

Chief Medical Officer,

Head of Therapeutics

Discovery and Development

Three clinical trials initiating in 2021

Programs all contain PN backbone chemistry modifications

SNP3	C9orf72	Exon 53
WVE-003	**WVE-004**	**WVE-N531**
Allele-selective silencing candidate in Huntington's disease (HD)	Variant-selective silencing candidate in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)	Exon skipping candidate for Duchenne muscular dystrophy (DMD)

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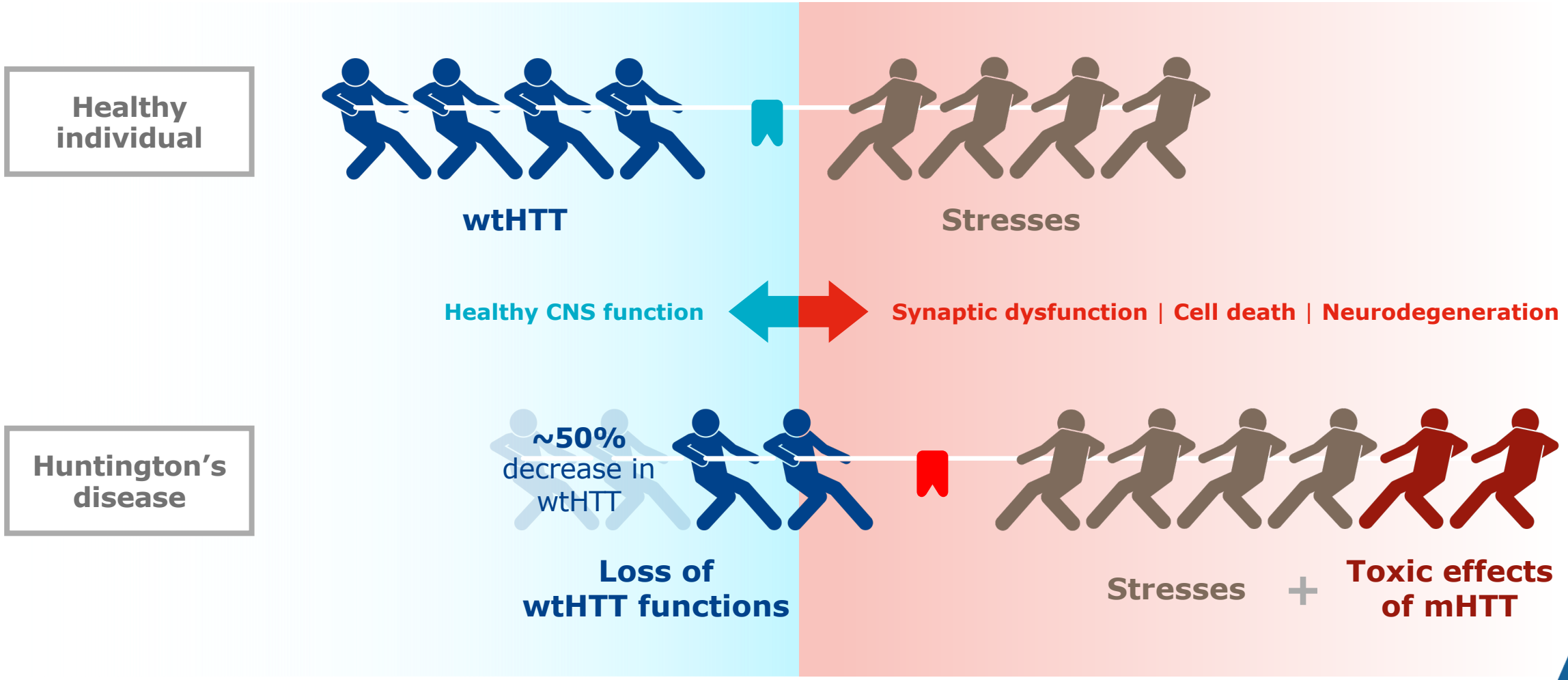
mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD

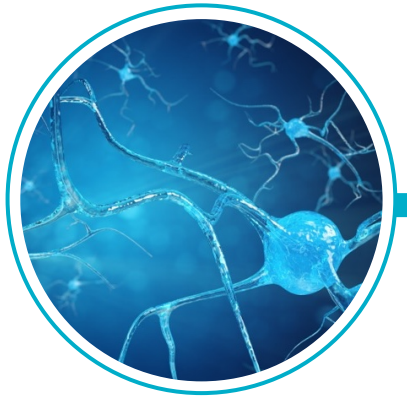


CNS, central nervous system; HD, Huntington's disease; HTT, huntingtin protein; mHTT, mutant huntingtin protein; wtHTT, wild-type huntingtin protein.

1. Ross CA, Tabrizi SJ. *Lancet Neurol*. 2011;10(1):83-98. 2. Saudou F, Humbert S. *Neuron*. 2016;89(5):910-926. 3. Cattaneo E, et al. *Nat Rev Neurosci*. 2005;6(12):919-930. 4. Milnerwood AJ, Raymond LA. *Trends Neurosci*. 2010;33(11):513-523.

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

NEURON



Promotes neuronal survival by protecting against stress (e.g., excitotoxicity, oxidative stress, toxic mHTT aggregates)[1-8]

SYNAPSE

Plays an essential role in the transport of synaptic proteins—including neurotransmitters and receptors—to their correct location at synapses[9-12]

BRAIN CIRCUITS

Supplies BDNF to the striatum to ensure neuronal survival[13-16]

Regulates synaptic plasticity, which underlies learning and memory[17-22]

CSF CIRCULATION

Plays a critical role in formation and function of cilia—sensory organelles that control the flow of CSF—which are needed to clear catabolites and maintain homeostasis[23]

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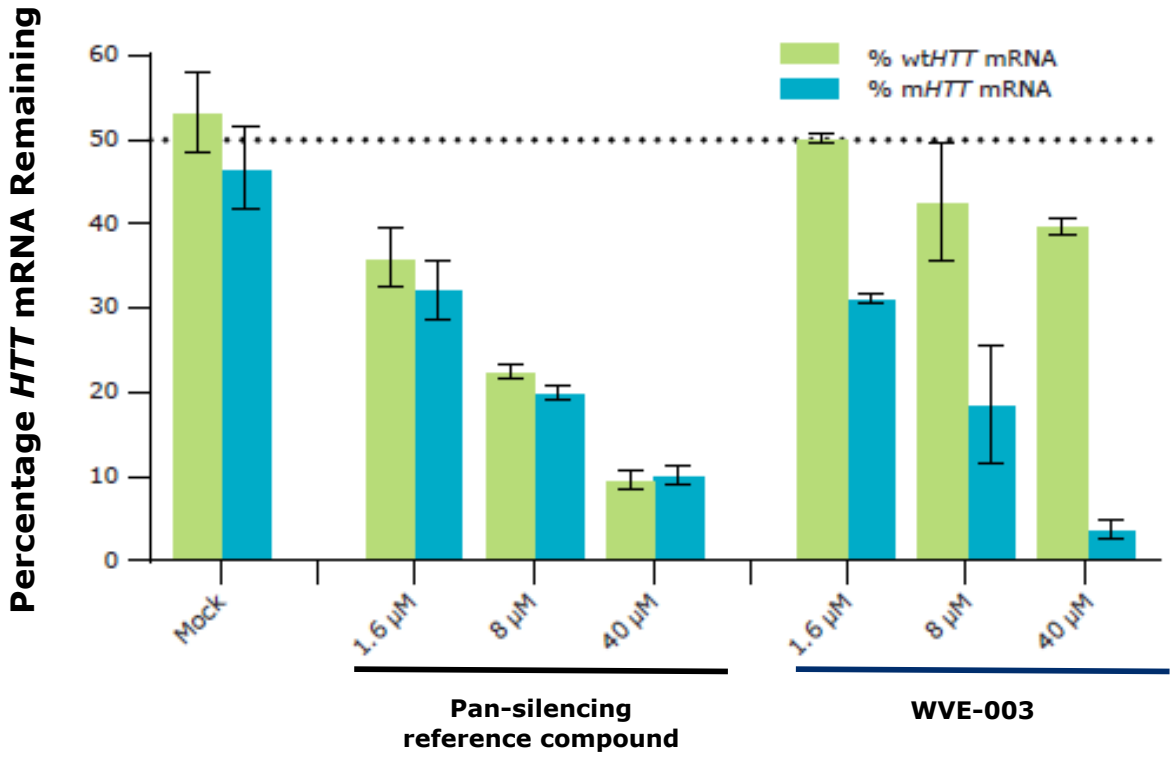
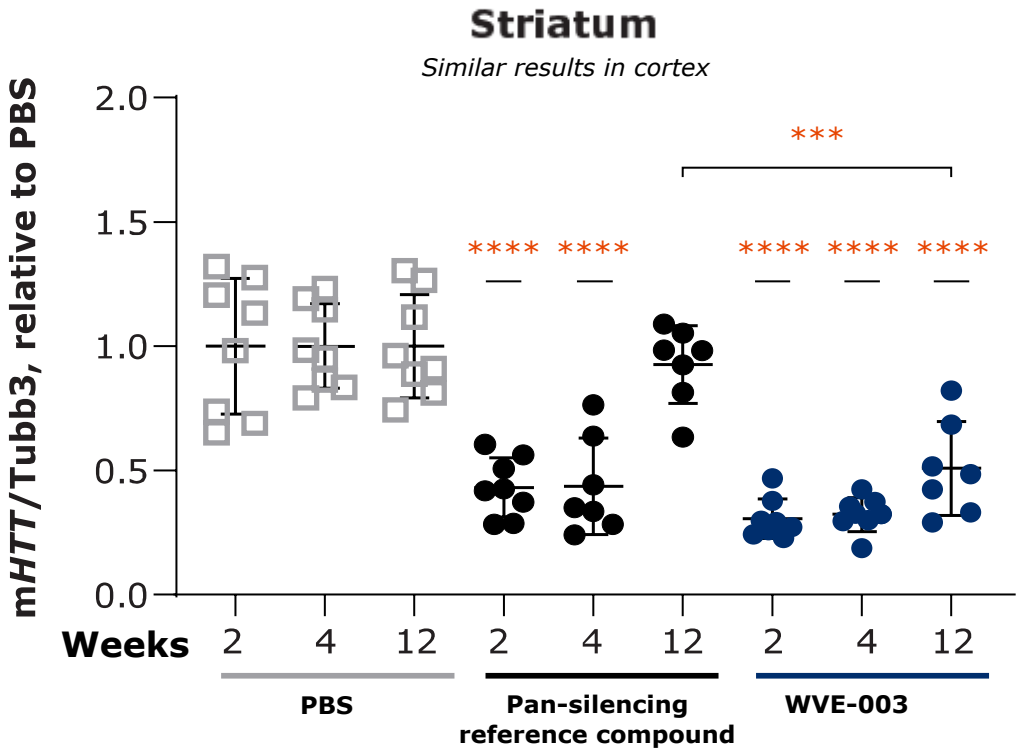
BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015

WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

Selectively reduces mHTT mRNA in HD iPSC neurons in vitro



Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model



CTA submission expected in 4Q 2020

Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1
Oligonucleotide or PBS [100 µg ICV injections through a cannula on days 1, 3, and 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS unless otherwise noted).
HPRT1, hypoxanthine-guanine phosphoribosyl transferase; iPSC, induced pluripotent stem cell; ICV, intracerebroventricular; PBS, phosphate-buffered saline

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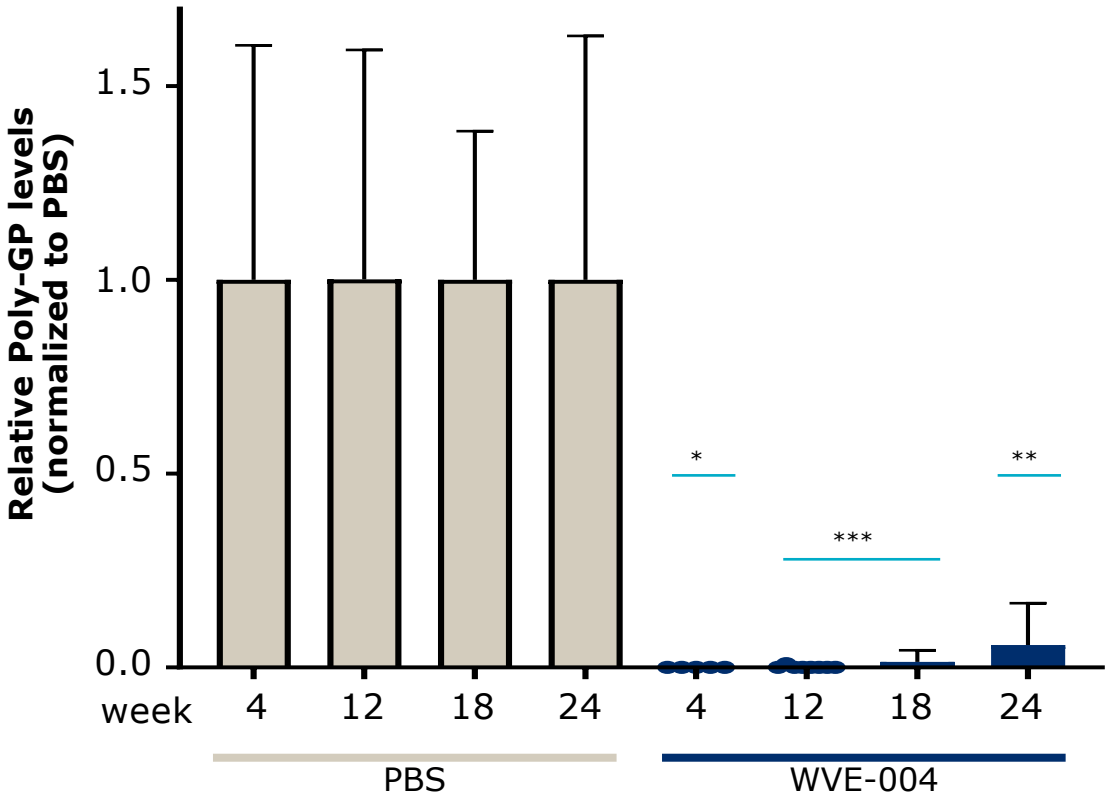
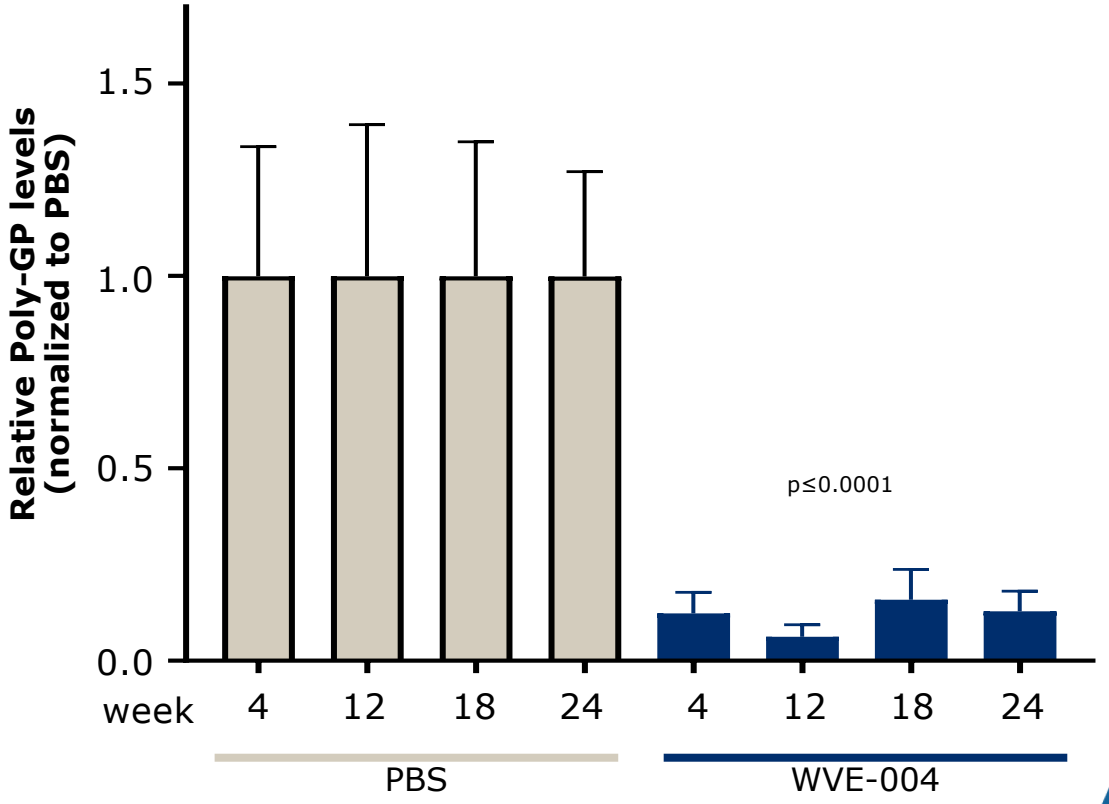
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
Sources: Cammack et al, Neurology, October 2019. Moore et al, Lancet Neurology, February 2020

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

Spinal cord



Cortex



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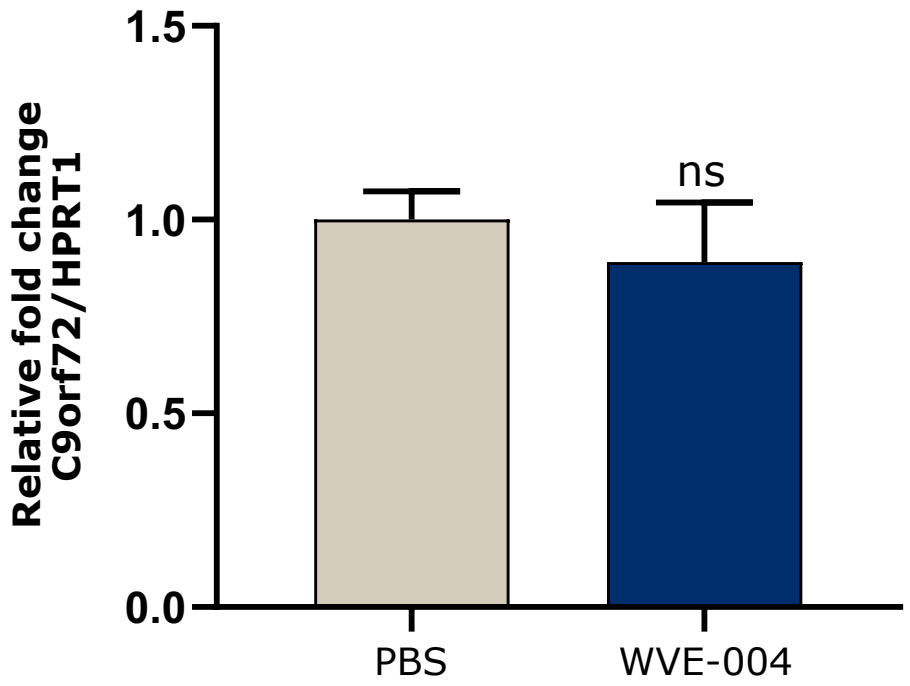
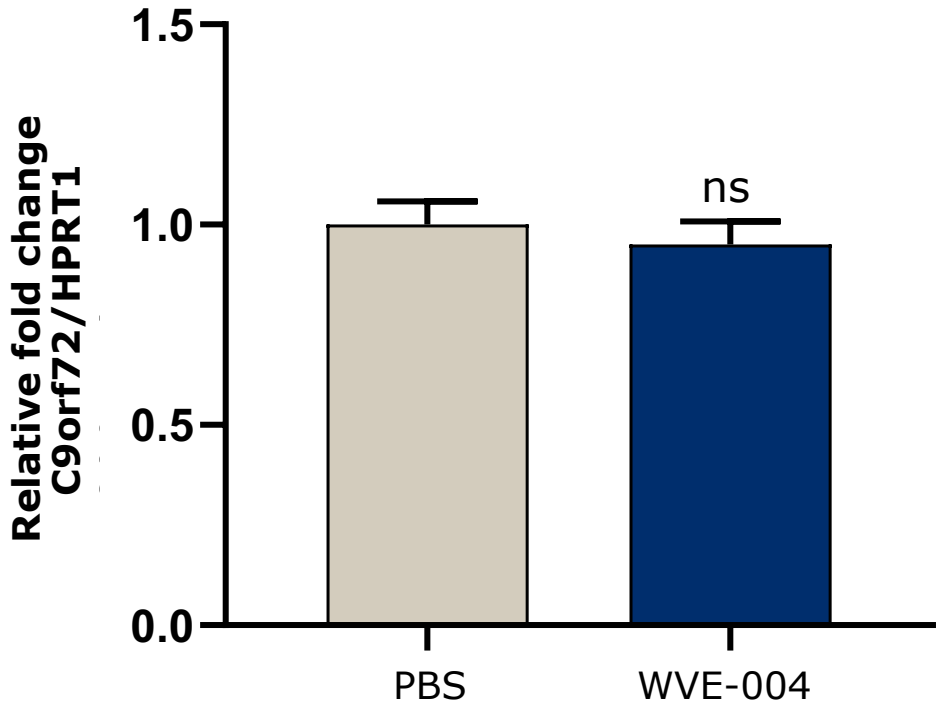
Experimental description: 2 x 50 ug on day 0 and day 7 dosed ICV; DPRs were measured by Poly-GP MSD assay.
*: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001
ICV: intracerebroventricular; Dipeptide repeat proteins: DPRs

Healthy C9 protein relatively unchanged ~6 months after WVE-004 administration

Spinal cord



Cortex



C9 BAC transgenic mice were administered PBS or 50 ug WVE-004, ICV, on day 0 and again on day 7. Relative fold change of total human C9orf72 to mouse Hprt1 protein in the spinal cord *(left)* and cortex (*right*) shown at 24 weeks after first administration. Data show mean ± SD (n=7). ns, not significant; PBS, phosphate-buffered saline; ICV: intracerebroventricular

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

CTA submission expected in 4Q 2020

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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

DMD: Exploring splicing in muscle with PN chemistry

Background

- WVE-N531 CTA previously on track for planned submission in late 2019 to initiate clinical development for exon 53-amenable DMD patients
  - Based upon compelling preclinical data
    - Dose-dependent increase in dystrophin production (up to 71%) *in vitro* in patient-derived myoblasts
    - Higher potency, durability and broader distribution with exon skipping in non-human primates with potential for every other week dosing following application of PN chemistry
- Held submission pending a full review of suvodirsen data
- Suvodirsen review indicated no target engagement in patients, likely due to poor intracellular access in dystrophic muscle

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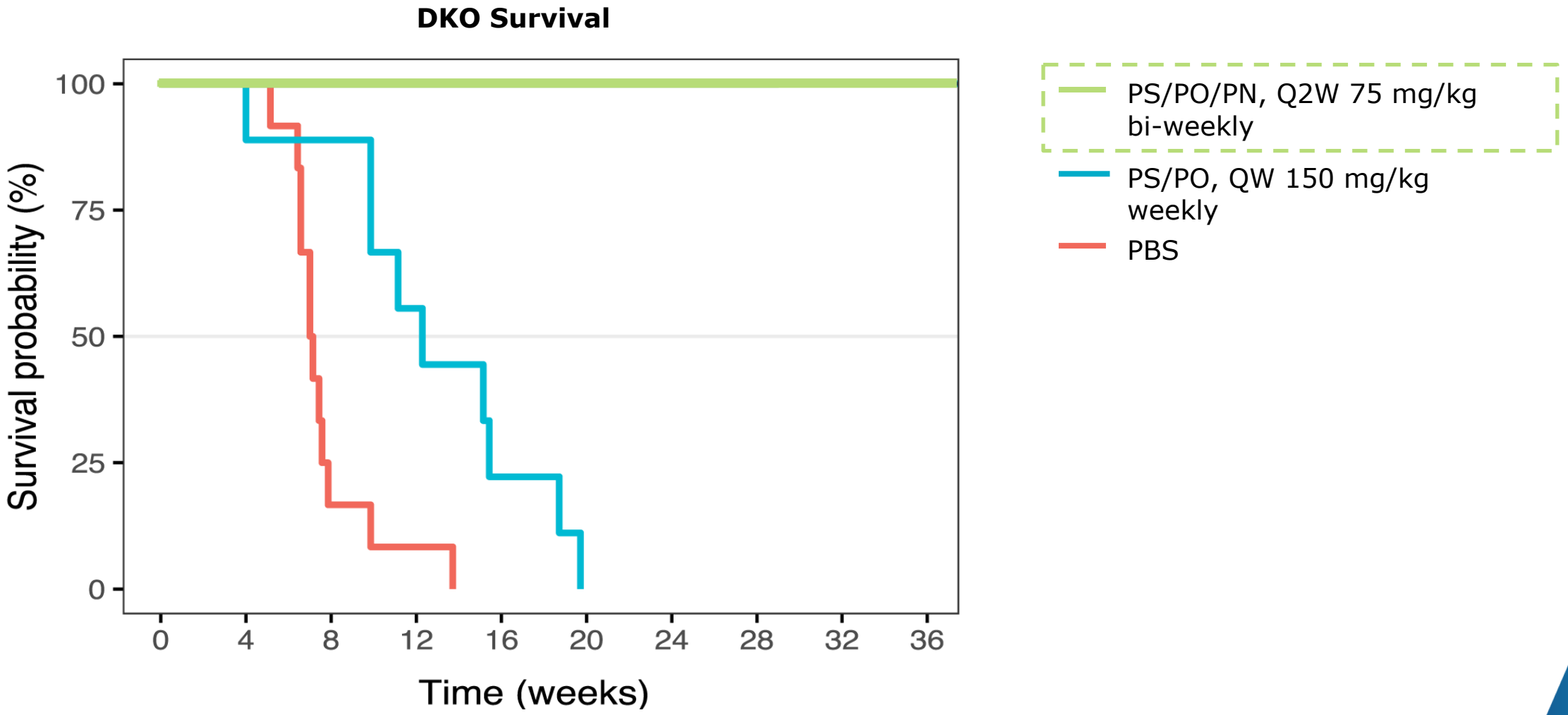
CTA: clinical trial application

Substantial increase in survival observed in DKO model using PN chemistry (study ongoing)



Double knock-out (DKO) mice lack dystrophin and utrophin protein and have a severe phenotype. *Mdx/utr-/-* mice received weekly subcutaneous (SC) 150 mg/kg dose of PS/PO or bi-weekly SC 75 mg/kg PS/PO/PN stereopure oligonucleotide beginning at postnatal day 10. Age-matched *mdx/utr-/-* littermates were treated with PBS, and *mdx* mice were not treated. Mice with severe disease were euthanized. DKO: PS/PO/PN 75 mg/kg n=9; PS/PO n=9, PBS n=12

Planning underway for clinical trial investigating WVE-N531 in DMD

- DKO data and previously generated preclinical data support advancing WVE-N531 to the clinic
- Unmet need in DMD remains high
  - Support from DMD advocacy community to explore possibility to improve efficiency of exon skipping with novel therapeutic approaches such as PN chemistry
- Planned clinical trial adequately powered 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
  - Trial planned to be conducted in Europe
- Potential to apply PN chemistry to other exons if successful

CTA submission expected in 1Q 2021

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David Gaiero

Interim Chief Financial Officer

Third quarter 2020 financial results

	Three Months Ended Sep 30, 2020	Three Months Ended Sep 30, 2019
Figures are in thousands, except per share amounts		
Revenue	$3,450	$2,929
Operating Expenses:		
Research and Development	28,275	44,585
General and Administrative	9,590	12,523
Total Operating Expenses	37,865	57,108
Loss from Operations	(34,415)	(54,179)
Total Other Income, Net	1,315	3,453
Net Loss	($33,100)	($50,726)
Net Loss per Share	**($0.86)**	**($1.48)**

As of Sep 30, 2020 | **Shares Outstanding:** 48.8 million | **Cash Balance:** $216.4 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

Huntington's disease

- **4Q 2020**: CTA submission for WVE-003 (SNP3)
- **1Q 2021**: PRECISION-HD1 data, including 32 mg cohort, and initial data from OLE trial
- **1Q 2021**: PRECISION-HD2 data, including 32 mg cohort, and initial data from OLE trial

Amyotrophic lateral sclerosis and frontotemporal dementia

- **4Q 2020**: CTA submission for WVE-004 (C9orf72)

Duchenne muscular dystrophy

- **1Q 2021**: CTA submission for WVE-N531 (exon 53)

ADAR editing (Alpha-1 antitrypsin deficiency)

- **1H 2021**: Humanized mouse model validation and *in vivo* data

Dosing in three new clinical trials expected in 2021

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

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Q&A

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Realizing a brighter future for people affected by genetic diseases

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