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Wave Life Sciences

First Quarter 2021 Earnings

May 13, 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

Agenda

Introduction and company update
Dr. Paul Bolno, MD, MBA, President and CEO

Clinical pipeline: WVE-004 (C9orf72), WVE-003 (SNP3), WVE-N531 (Exon 53)
Dr. Michael Panzara, MD, MPH, Chief Medical Officer, Head of Therapeutics Discovery and Development

ADAR editing capability: AATD (SERPINA1)
Dr. Paul Bolno, MD, MBA, President and CEO

Financial results
Kyle Moran, Chief Financial Officer

Q&A
All

Next generation of Wave

First quarter and recent highlights

Three RNA therapeutic candidates in clinic

- PN chemistry
- Silencing and splicing modalities
- Differentiated approaches

- Initiated clinical trials for WVE-004 in ALS / FTD and WVE-003 in HD
- Received regulatory approval for clinical trial of WVE-N531 in DMD

Rapid path to clinical proof-of-concept in 2022

- Innovative and adaptive clinical trial designs enabling decision making across three programs

Novel ADAR editing capability advancing

- ADAR editing capability and preclinical *in vivo* data highlighted at ASGCT 24th Annual Meeting
- On track to share *in vivo* data from AATD program in 1H 2021

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AATD: Alpha-1 antitrypsin deficiency, ASGCT: American Society of Gene & Cell Therapy

Rational drug design: Evolution of PRISM platform

Addressing the reality of stereochemistry

PRISM

First generation programs

- Stereopure oligonucleotides
- Silencing & splicing capabilities
- PN backbone chemistry modifications
- Novel *in vivo* models
- *In vivo* target engagement, including NHP
- Establish PK/PD and toxicology relationships
- Learnings of first-generation programs
- ADAR editing capability

Next generation of Wave

Choosing to control for stereochemistry enables Wave to apply principles of rational drug design to oligonucleotides

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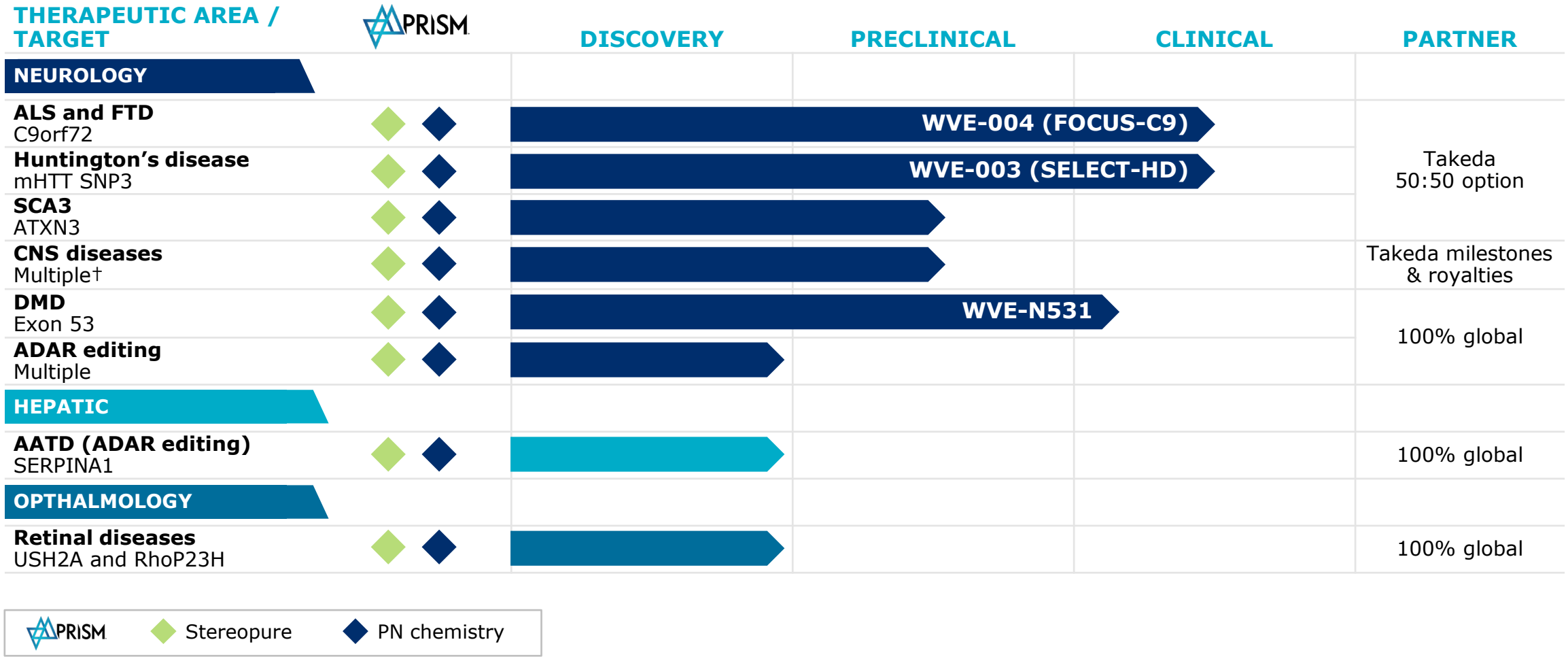
Mike Panzara, MD, MPH

Chief Medical Officer,

Head of Therapeutics

Discovery and Development

Innovative pipeline led by neurology programs



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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

Next generation clinical pipeline

- **Oligonucleotide innovation and optimization**
  - PN backbone chemistry modifications
  - Interactions between sequence, chemistry and stereochemistry
- ***In vivo* models**
  - Insight into PK / PD relationships
  - Novel model generation
- **Learnings of first generation programs**
  - Translational pharmacology
  - Adaptive clinical trial design

C9orf72

WVE-004

Variant-selective silencing candidate in ALS and FTD

SNP3

WVE-003

Allele-selective silencing candidate in HD

Exon 53

WVE-N531

Exon skipping candidate in DMD

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

C9orf72 repeat expansions: One of the most common genetic causes of ALS and FTD

WVE-004 (C9orf72)

Hexanucleotide (G_4C_2)- repeat expansions in C9orf72 gene are common autosomal dominate cause for ALS and FTD

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

- Fatal neurodegenerative disease
- Progressive degeneration of motor neurons in brain and spinal cord
- C9-specific ALS: ~2,000 patients in US

Frontotemporal Dementia (FTD)

- Progressive neuronal degeneration in frontal/temporal cortices
- Personality and behavioral changes, gradual impairment of language skills
- C9-specific FTD: ~10,000 patients in US

WVE-004 is the first therapy in clinical development for both C9-ALS and C9-FTD

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Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

WVE-004 durably reduced DPR protein *in vivo* in spinal cord and cortex, while preserving healthy protein

WVE-004 (C9orf72)

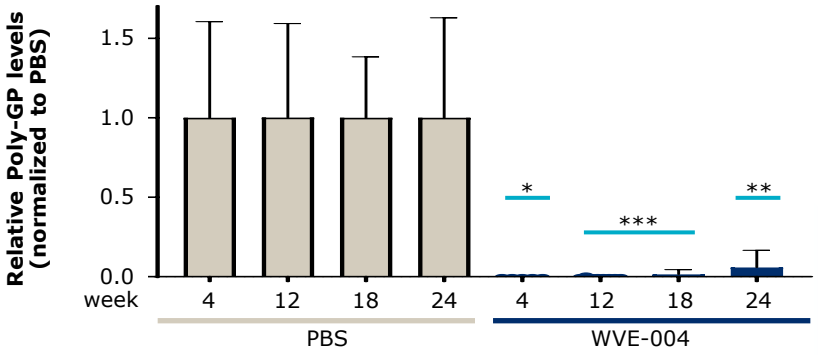
WVE-004 addresses multiple drivers of toxicity caused by C9orf72 mutations

1. **RNA mediated toxicity**: Accumulation of repeat containing RNA transcripts
   - ✓ **Reduce disease-causing RNA**
2. **DPR protein toxicity**: Accumulation of aberrantly translated DPR proteins (including polyGP)
   - ✓ **Reduce downstream DPR protein**
3. **Loss of function:** Insufficient levels of C9or72 protein
   - ✓ **Preserves C9orf72 protein**

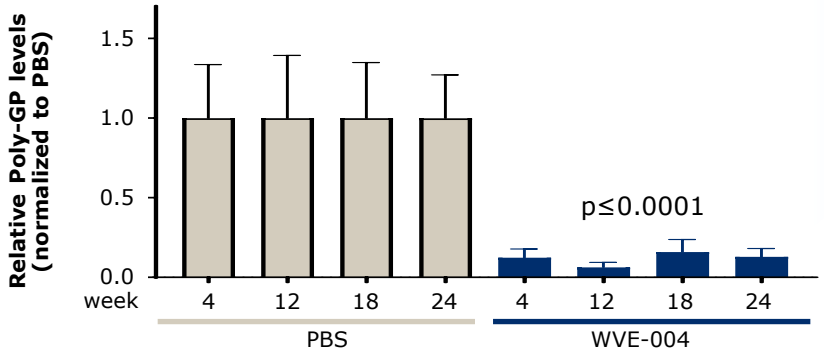
Novel variant selective targeting strategy published in *Nature Communications* – foundational work that led to development of WVE-004

Preclinical results: Durable reduction of DPR protein in spinal cord and cortex with WVE-004

Spinal cord



Cortex



Durable reduction of DPRs after six months with two doses of WVE-004 (day 0 and 7)

C9orf72 protein relatively unchanged at 6 months

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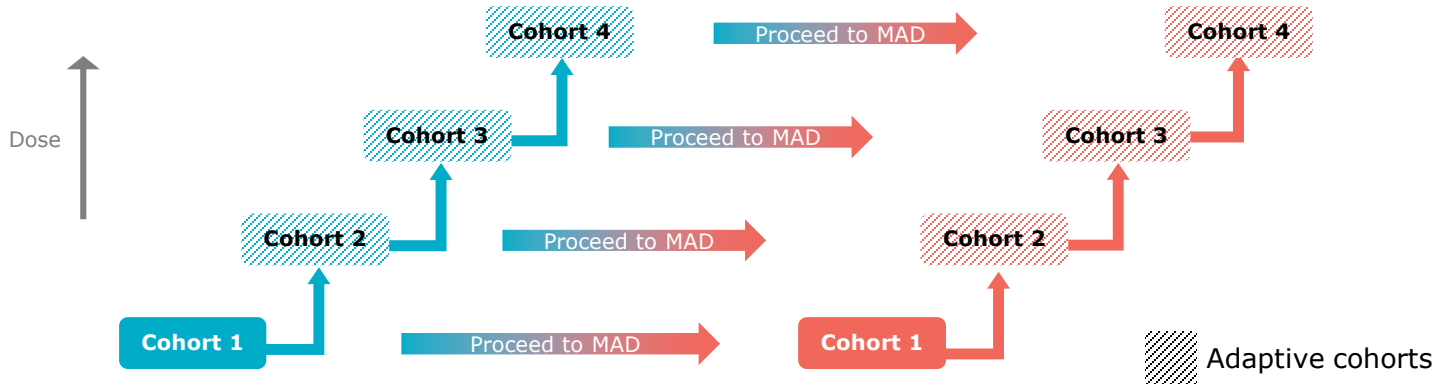
FOCUS-C9: Adaptive trial designed to enable rapid assessment of target engagement

WVE-004 (C9orf72)

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial

FOCUS MND C9

Targeting 50 patients with C9-ALS, C9-FTD or mixed phenotype



Single-ascending dose (SAD)

Day	1-3	15	29	57	85
Dose	▼				
Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●		●	●	●

Multi-ascending dose (MAD)

Week	1	4	8	12	16	20	24
	▼	▼	▼	▼			
	●	●	●	●	●	●	●
	●	●	●	●	●	●	●

Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma and CSF PK profile
- PolyGP in CSF

Exploratory objectives

Biomarkers:

- p75NTR^{ECD} in urine
- NfL in CSF

Clinical endpoints:

- ALSFRS-R
- CDR-FTDLD
- FVC
- HHD

Dose escalation and MAD dosing frequency guided by independent committee

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Recent CHDI conference reaffirms necessity for allele-selective approach to Huntington's disease

WVE-003 (SNP3)

Huntington's disease

- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT)
- Monogenic, autosomal dominant, fully penetrant genetic disease
- Huntington's disease affects entire brain

Wild-type HTT is critical protein for important functions in CNS

NEURONS

Promotes neuronal survival by protecting against stress

SYNAPSES

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

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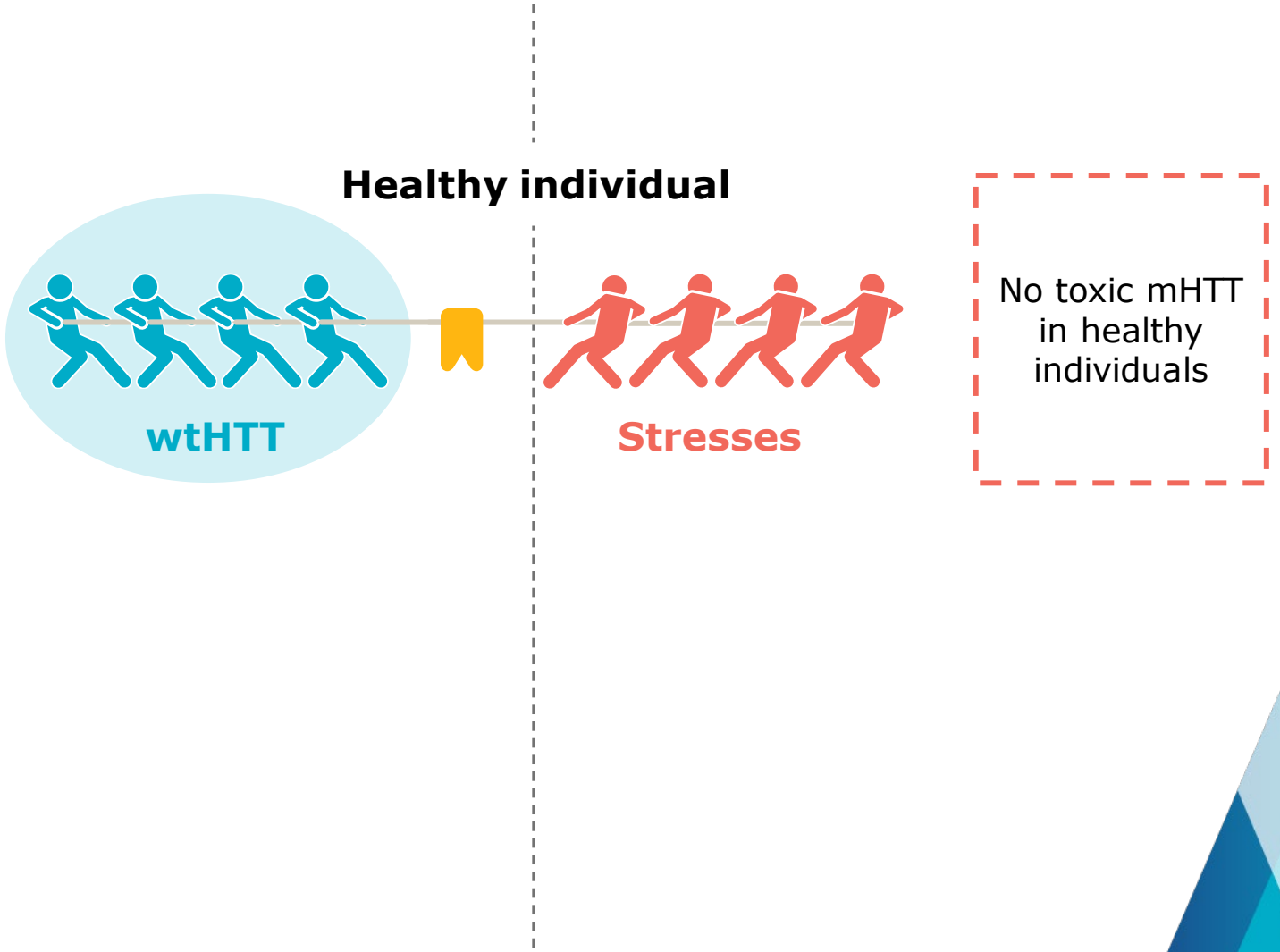
CSF: cerebrospinal fluid; BDNF, brain-derived neurotrophic factor Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. 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

Loss of wtHTT function in HD may contribute to progression of disease

WVE-003 (SNP3)

- Changes in wild-type HTT in healthy individuals or models that lack the effects of mutant HTT do not adequately represent the role of wild-type HTT in the context of Huntington's disease



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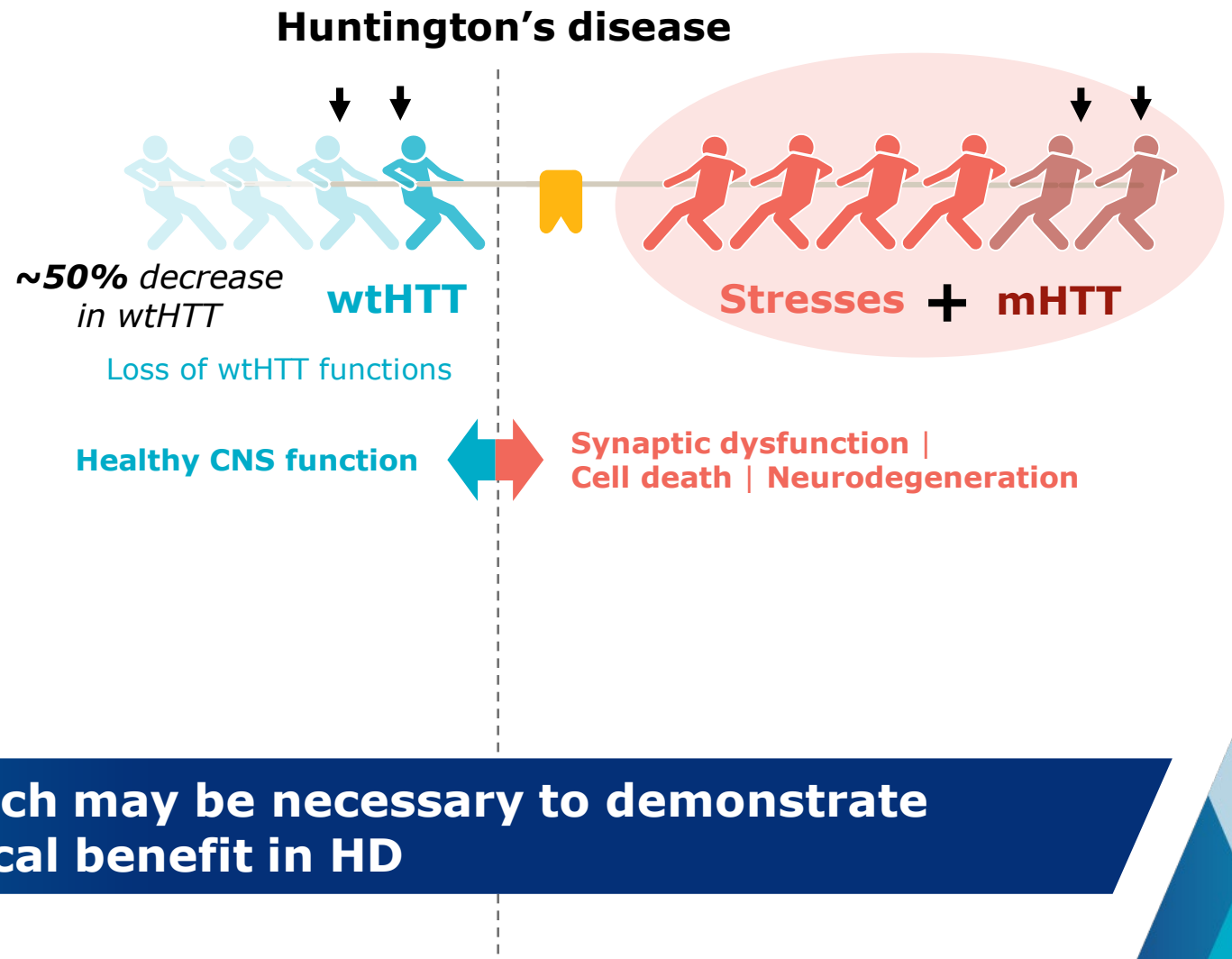
Loss of wtHTT function in HD may contribute to progression of disease

WVE-003 (SNP3)

- Depletion of wild-type HTT with mutant HTT (non-allele selective) could be expected to manifest as lack of effect or worsening of disease progression



Wild-type sparing approach may be necessary to demonstrate clinical benefit in HD

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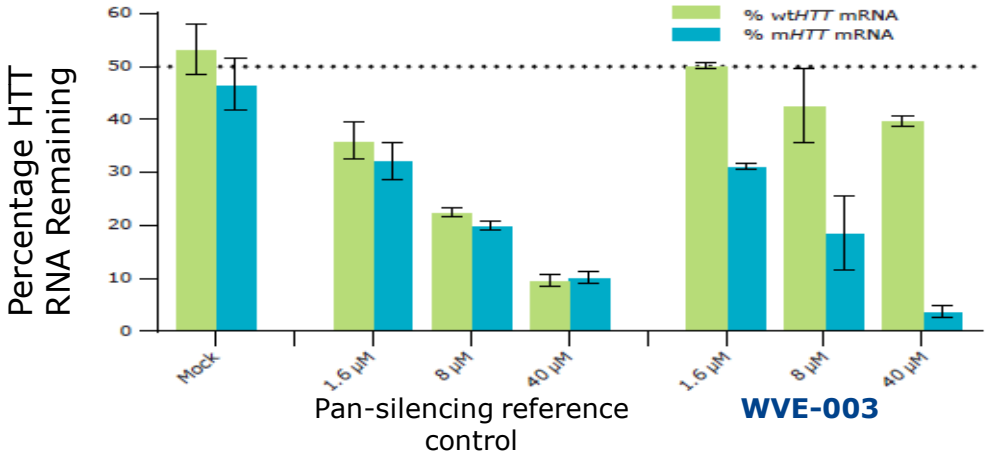
Selective, potent, durable mHTT knockdown achieved with WVE-003 in preclinical studies

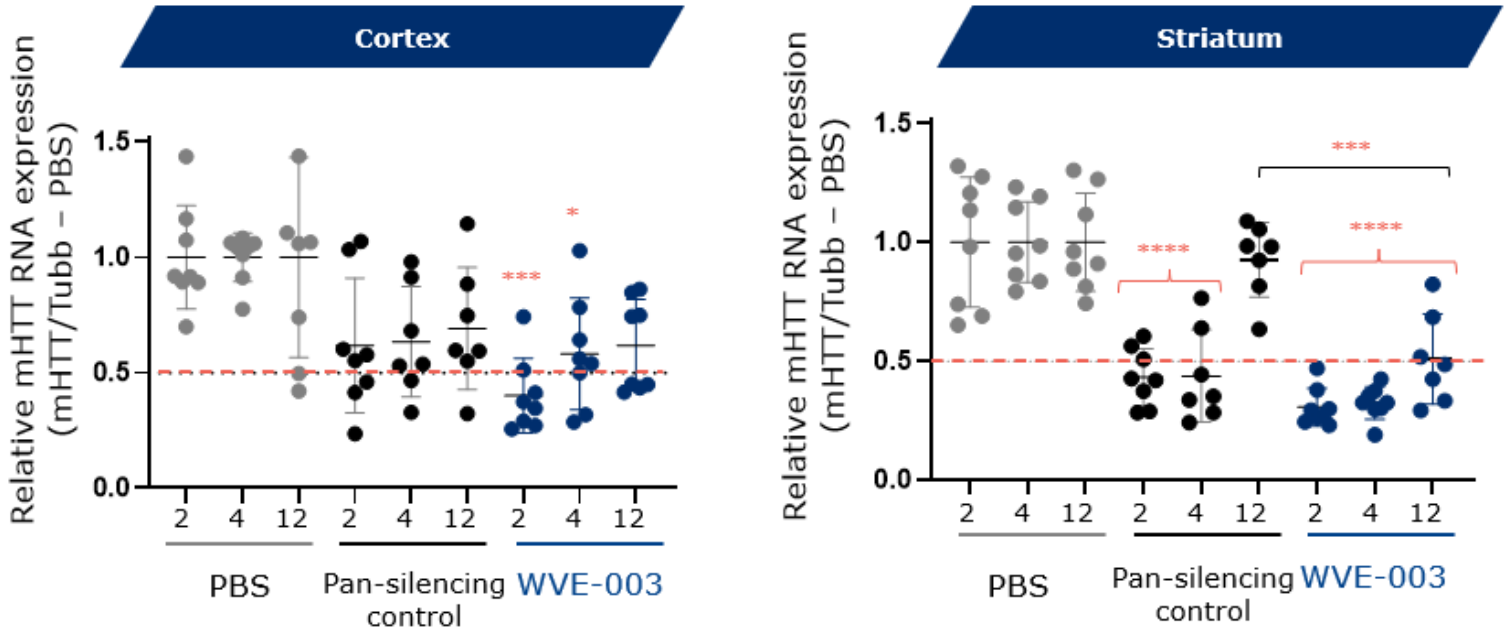
WVE-003 (SNP3)

- ✓ **Selectivity**: Wild-type HTT is preserved even at high concentrations *in vitro*
- ✓ **Potency**: Maximum knockdown of 70-75% *in vivo*
- ✓ **Durability**: ~50% knockdown persisting for at least 3 months *in vivo*

Selective reduction of mHTT in HD motor neurons



mHTT knockdown *in vivo*



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Results presented at the 27th Annual Meeting of the Huntington Study Group, October 2020, Virtual

WVE-003: *In vivo* studies support distribution to cortex and striatum in BACHD and NHPs

WVE-003 (SNP3)

BACHD model

Achieved maximum mHTT knockdown of 70-75% in **cortex** and **striatum** with ~50% knockdown persisting for at least 3 months with WVE-003

NHP

Achieved sufficient concentrations of WVE-003 in **cortex** and **striatum** for target engagement

Human

Anticipated mHTT knockdown in **cortex** and **striatum** based on PK-PD modeling

Clinical starting dose of WVE-003 informed by PK-PD modeling

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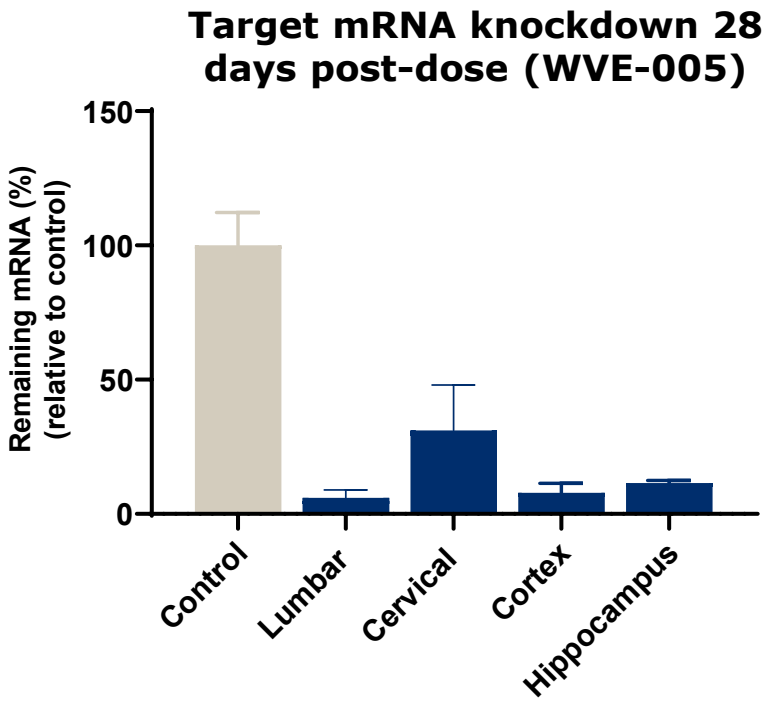
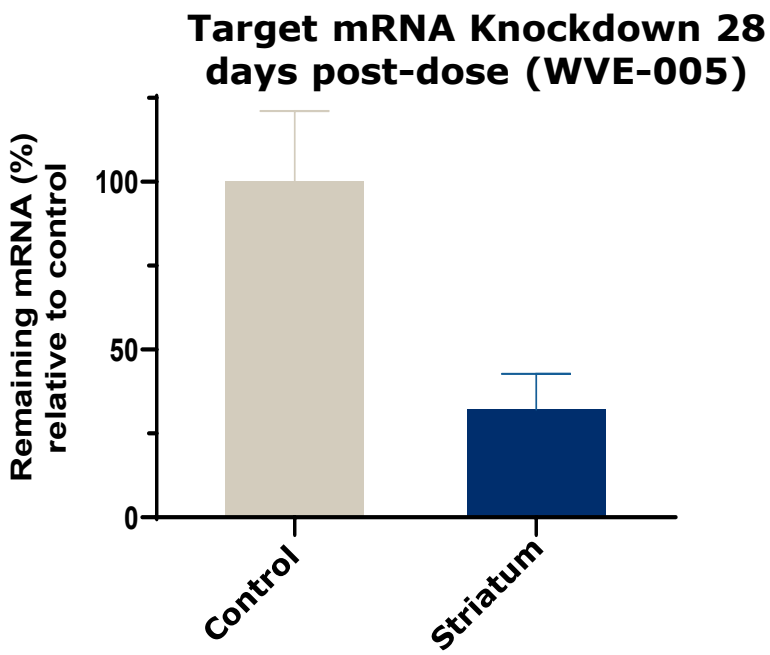
PK: pharmacokinetic PD: pharmacodynamic IC_{50}: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

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

CNS distribution





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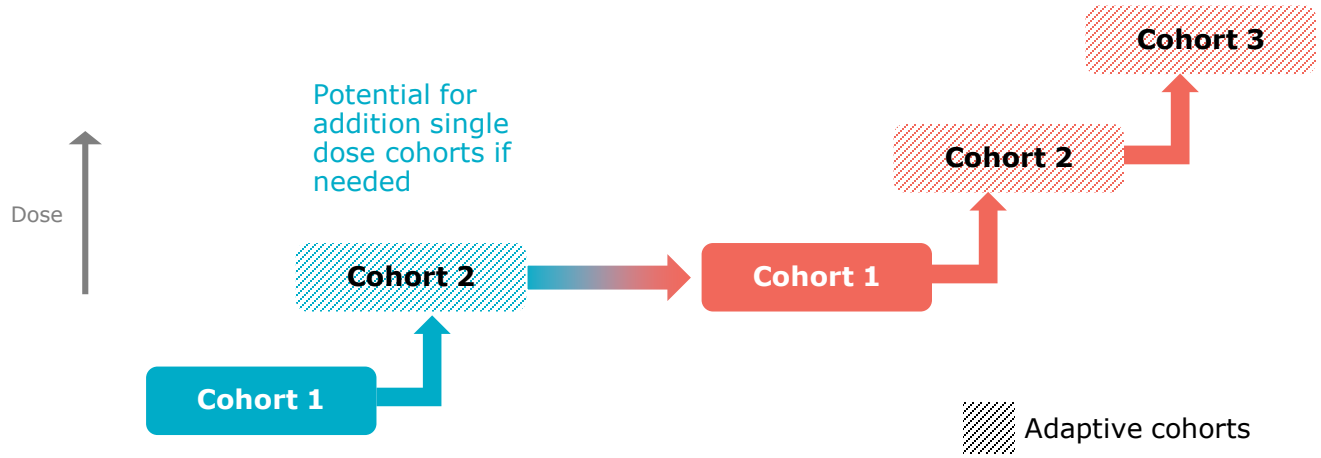
NHPs: Non-human primates
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.
WVE-005 is lead program in Takeda collaboration for an undisclosed CNS target

SELECT-HD: Adaptive trial designed to enable faster optimization of dose and frequency

WVE-003 (SNP3)

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial

Targeting 36 patients with early manifest HD diagnosis with SNP3 variant



Single-ascending dose (SAD)

Day	1-3	15	29	57	85
Dose	▼				
Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●				●

Multi-ascending dose (MAD)

Week	1	2	4	8	12	16	20	24
	▼	▼	▼	▼	▼			
	●	●	●	●	●	●	●	●
	●				●		●	

Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma PK profile
- CSF exposure

Exploratory objectives

Biomarkers:

- mHTT
- wtHTT
- NfL

Clinical endpoints:

- UHDRS

Dose escalation and MAD dosing frequency guided by independent committee

mHTT: mutant huntingtin; wtHTT: wild-type huntingtin; NfL: neurofilament light

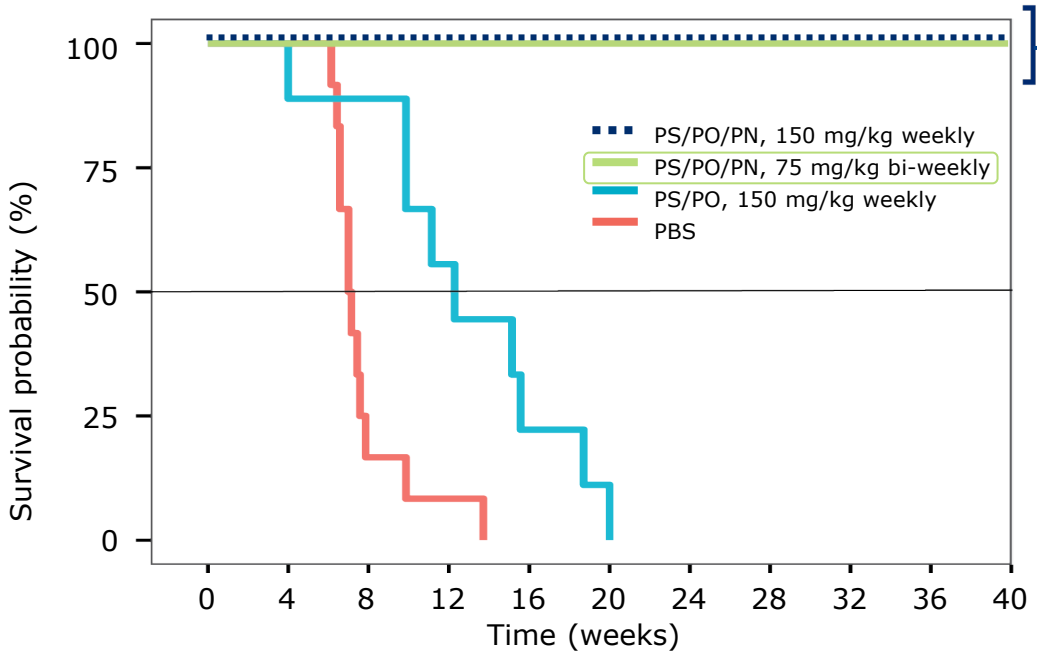
WVE-N531 (Exon 53)

WVE-N531: First splicing candidate to use PN chemistry

Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Current disease modifying treatments have demonstrated minimal dystrophin expression and clinical benefit has not been established.
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide.

Potential of PN chemistry demonstrated in preclinical study in dKO mouse 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

WVE-N531
(Exon 53)

Clinical trial of WVE-N531 to initiate in 2021

- Unmet need in DMD remains high
- CTA submitted in March 2021 to initiate clinical development
- Clinical trial powered to evaluate change in dystrophin production, and will assess 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

Dosing in clinical trial expected to initiate in 2021

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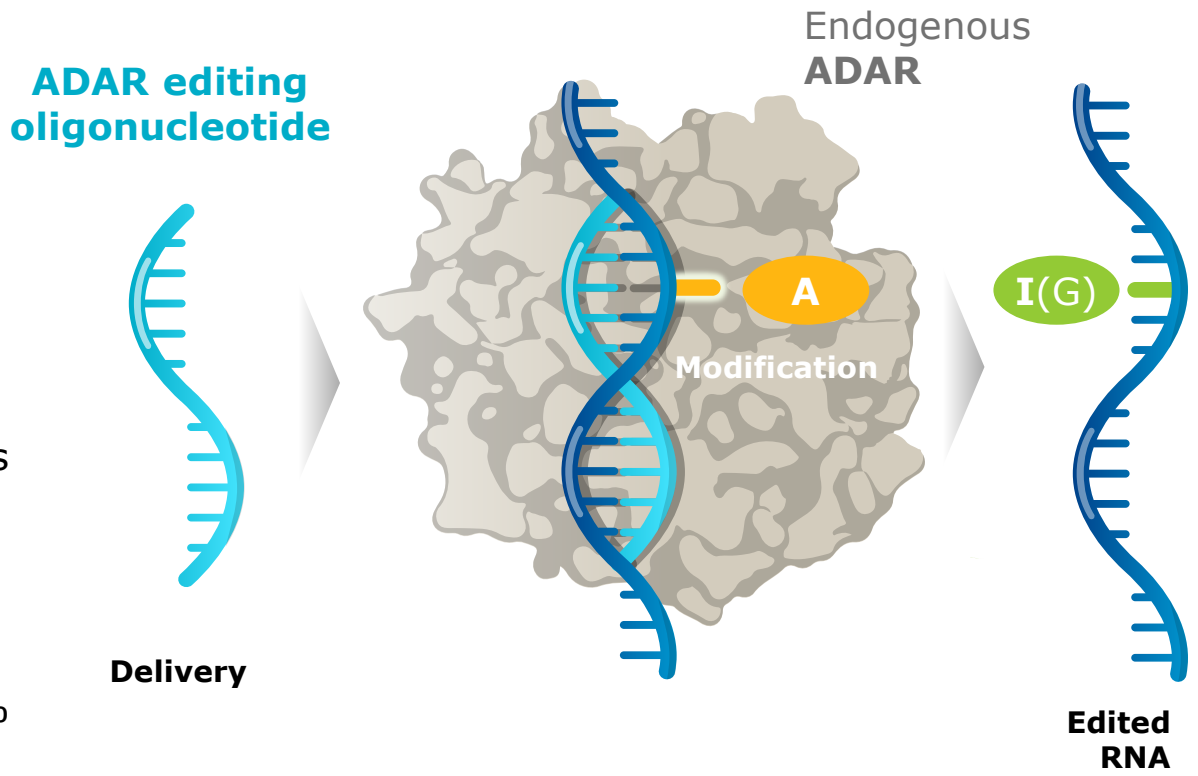
Paul Bolno, MD, MBA

President and CEO

Versatile platform for ADAR RNA editing

Wave advantage

- **Oligonucleotide chemistry experience**
  - Fully chemically modified to enhance stability
  - Stereopure PN chemistry modifications
- **Simplified approach**
  - Reversible / titratable
  - No requirement for AAV / nanoparticles or exogenous ADAR delivery
- **Breadth of *in vivo* proof-of-concept data**
  - Achieved successful and durable editing of up to 50% in NHPs with GalNAC-conjugated oligonucleotides
  - Developed proprietary transgenic model for PK/PD assessments



RNA editing opens many new therapeutic applications

ADAR editing

Restore protein function

- Fix nonsense and missense mutations that cannot be splice-corrected
- Remove stop mutations
- Prevent protein misfolding and aggregation

Examples:

Recessive or dominant genetically defined diseases

- Metabolic Liver Diseases
- Neurodevelopmental Disorders

Modify protein function

- Alter protein processing (e.g. protease cleavage sites)
- Protein-protein interactions domains
- Modulate signaling pathways

Examples:

Ion channel permeability

- Familial Epilepsies
- Neuropathic Pain

Protein upregulation

- miRNA target site modification
- Modifying upstream ORFs
- Modification of ubiquitination sites

Examples:

Haploinsufficient diseases

- Neuromuscular Disorders
- Dementias

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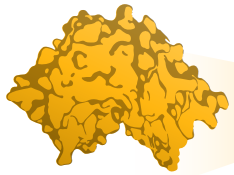
ADAR editing approach may simultaneously address lung and liver manifestation of AATD

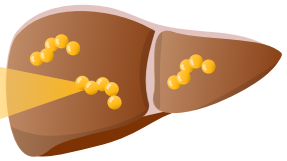
Alpha-1 antitrypsin deficiency (AATD)

Most common cause is mutation in *SERPINA1* Z allele

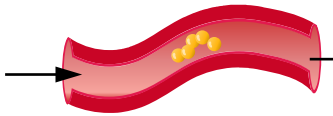


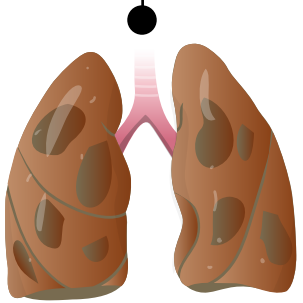
Z-AAT misfolded protein prone to aggregation

Dual Pathologies in AATD



Inability to secrete polymerized Z-AAT, leading to **liver damage/cirrhosis**



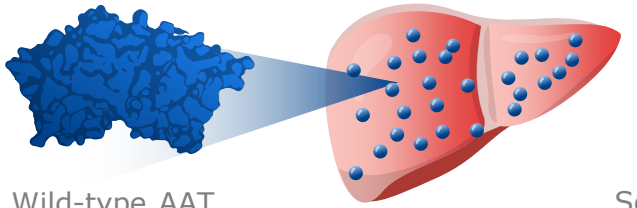


Open to unchecked proteases, leading to inflammation and **lung damage**

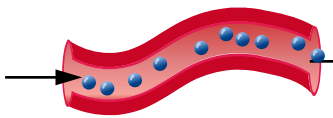
- **~200K people in US and EU** with homozygous ZZ genotype, most common form of severe AATD
- Approved therapies modestly increase circulating levels of wild-type AAT in those with lung pathology; no therapies address liver pathology

Wave's ADAR editing approach

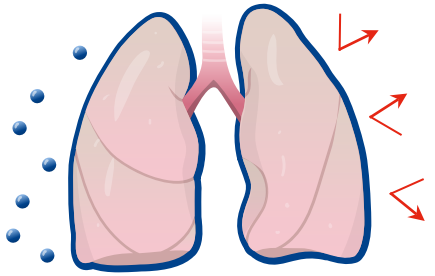
GalNAc oligonucleotide to correct *SERPINA1* Z allele mRNA



Wild-type AAT protein



Secretion into bloodstream



Lungs protected from proteases

✓ **Restores** wild-type AAT physiological regulation **in liver**, reducing Z-AAT protein aggregation

✓ Increases circulating, **lung-bound** wild-type AAT

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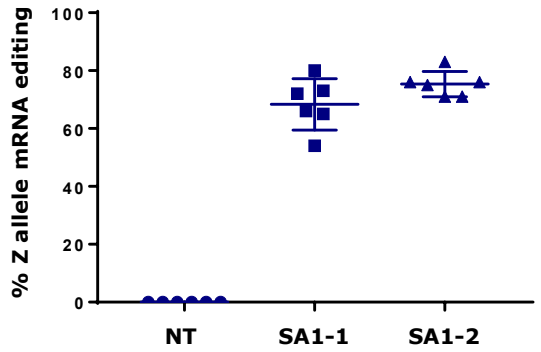
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017

AATD: Focused on delivering *in vivo* wild-type AAT protein restoration

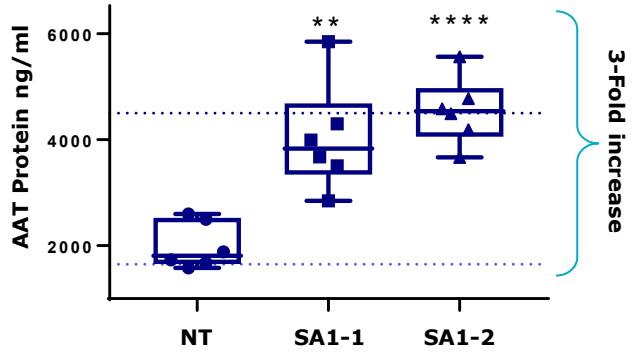
ADAR editing

✓ *In vitro* proof of concept

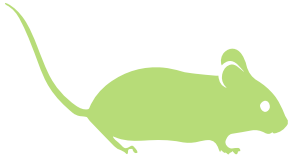
SERPINA1 Z allele mRNA editing



AAT protein concentration in media



✓ Transgenic model development



Protein	Pathology
✓ huADAR	Liver pathology, lower huSERPINA1 serum
✓ SERPINA1	

- Developed proprietary transgenic *in vivo* model to enable PK/PD assessment of human sequences
- Characterization ongoing

In vivo data

- Evaluated parameters expected to include:
  - SERPINA1-Z allele mRNA editing
  - Secretion and functionality of wild-type AAT protein in serum
  - Reduction in Z-AAT protein aggerates
- *In vivo* data to enable lead candidate optimization and inform preclinical development studies
- Expect to submit in vivo data for presentation at scientific congress in 2021

On track to share *in vivo* data in 1H 2021

AATD: Alpha-1 antitrypsin deficiency, Z-AAT: mutated protein

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Continuous flow of data to enable program decisions through 2022

Rapid path to clinical proof of concept

2021

WVE-004: Dose first patient in FOCUS-C9 trial for patients with ALS/FTD in 2021

WVE-003: Dose first patient in SELECT-HD trial for patients with HD in 2021

WVE-N531: Dose first patient in clinical trial for patients with DMD in 2021

2022

Clinical data to provide insights into PN chemistry and enable decision making expected in 2022

Novel ADAR editing capability advancing

2021

Share *in vivo* data from AATD program in 1H 2021

Validation of humanized mouse model in 1H 2021

Present additional *in vivo* ADAR editing data at scientific congress in 2021

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AATD: Alpha-1 antitrypsin deficiency

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Kyle Moran

Chief Financial Officer

First quarter 2021 financial results

	Three Months Ended Mar 31, 2021	Three Months Ended Mar 31, 2020
Figures are in thousands, except per share amounts		
Revenue	$0	$4,161
Operating Expenses:		
Research and Development	33,393	41,158
General and Administrative	10,078	12,996
Total Operating Expenses	43,471	54,154
Loss from Operations	(43,471)	(49,993)
Total Other Income, Net	1,007	2,500
Net Loss	($42,464)	($47,493)
Net Loss per Share	**($0.86)**	**($1.38)**

As of Mar 31, 2021 | **Shares Outstanding:** 49.9 million | **Cash Balance:** $148.5 million

In April 2021, Wave received an additional $30.0 million in committed research support under its collaboration with Takeda.

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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For more information:

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