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Wave Life Sciences

Second Quarter 2021 Earnings

August 5, 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
Paul Bolno, MD, MBA, President and CEO

Clinical development update
Michael Panzara, MD, MPH, Chief Medical Officer, Head of Therapeutics Discovery and Development

ADAR editing capability: Restoration of AAT protein *in vivo*
Paloma Giangrande, PhD, VP, Platform Discovery Sciences and Biology

2Q 2021 financial results
Kyle Moran, Chief Financial Officer

Continuous flow of data through 2022 to enable program decisions
Dr. Paul Bolno, MD, MBA, President and CEO

Q&A
All

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Second quarter and recent highlights

NEXT GENERATION CLINICAL PIPELINE ADVANCING

- Intrathecal dosing underway in FOCUS-C9 clinical trial of WVE-004 in ALS and FTD
- First clinical dosing of an oligonucleotide containing PN chemistry
- Recruitment ongoing for clinical trials in HD (WVE-003) and DMD (WVE-N531)

CLINICAL DATA TO DRIVE VALUE

- Innovative, adaptive clinical trials designed to provide rapid path to establish dose level, frequency, and ultimately clinical effects
- Data generation through 2022 provides the opportunity to confirm promising *in vivo* pre-clinical results utilizing Wave's novel PN chemistry backbone modifications, both intrathecally and systemically

LEADING ENDOGENOUS ADAR EDITING CAPABILITY

- ADAR editing demonstrates restoration of functional AAT protein *in vivo* in AATD program
- Progress illustrates ability to build upon foundational chemistry innovations of PRISM platform and enable novel therapeutic approaches

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AATD: Alpha-1 antitrypsin deficiency

Successfully advanced novel PN chemistry to clinic

Application *in vivo*

Improved pharmacological profile with PN backbone chemistry modifications

- **Potency**
- **Distribution**
- **Durability**

Expanded to pipeline programs

- Preclinical data in rodent and non-human primate models demonstrate improved profile that appears independent of sequence, tissue type, or modality

Advanced to clinic

- Three ongoing clinical trials
- Multiple therapeutic programs in collaboration with Takeda
- In-house GMP manufacturing to supply preclinical studies and clinical trials

Application of PN backbone modifications was a major advancement that emerged from PRISM

PRISM

Control over stereochemistry enabled application of PN and other drug design principles to oligonucleotides, advancing drug discovery and development

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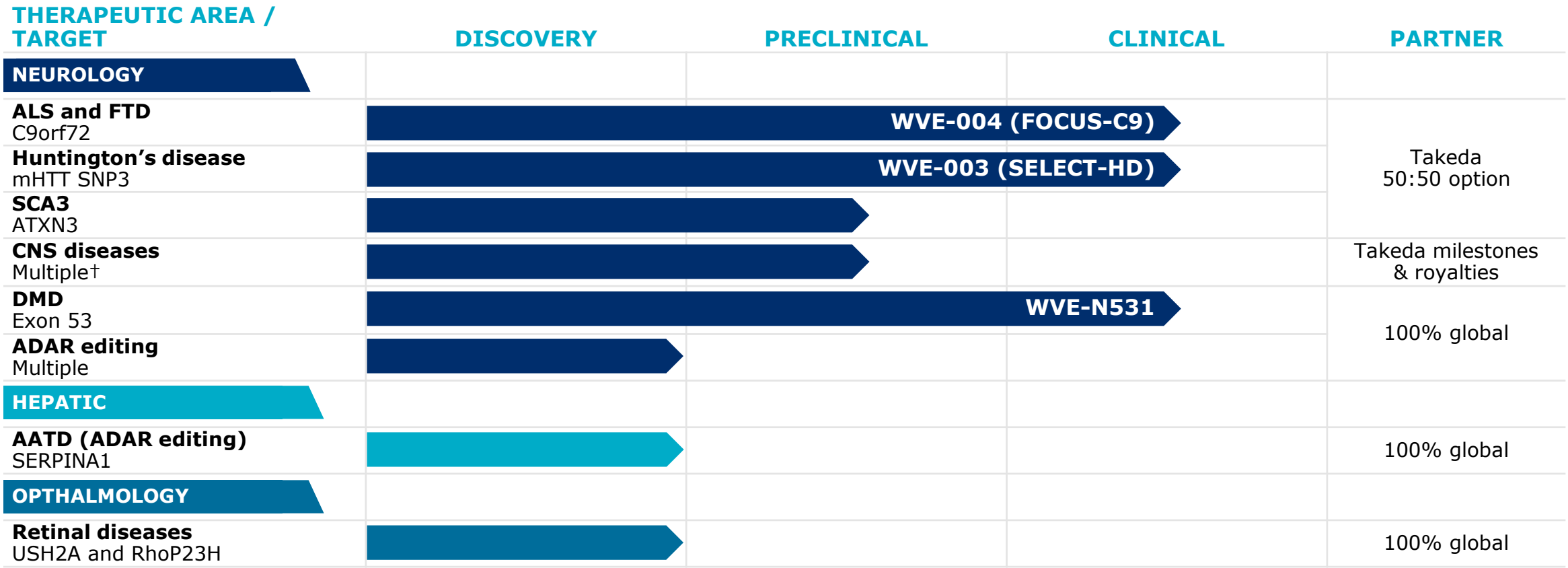
Robust portfolio of stereopure, PN-modified oligonucleotides



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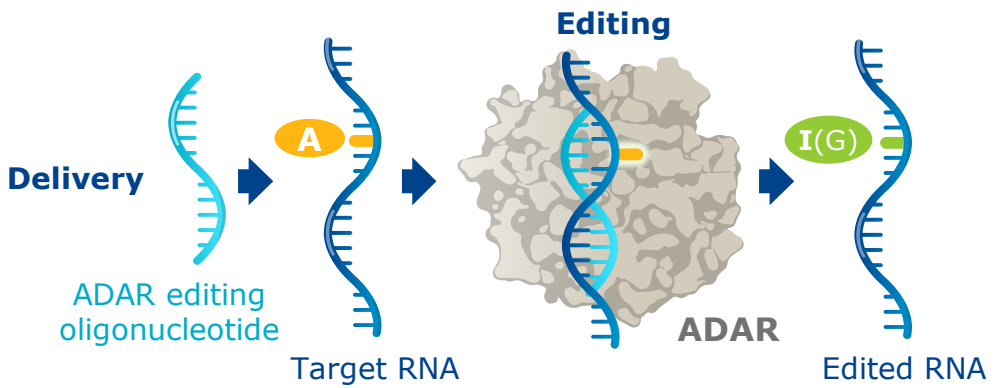
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system;
DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Leading ADAR RNA editing capability

Oligonucleotide chemistry experience
- Fully chemically modified to enhance stability
- Stereopure PN chemistry modifications

Simplified delivery
- Short, single-stranded
- No requirement for AAV / nanoparticles

Leverages endogenous ADAR
- No immunogenicity from exogenous proteins
- Avoids permanent off-target DNA edits



Opens many new therapeutic applications

- **Restore protein function**
- **Modify protein function**
- **Upregulate protein expression**

ADAR editing capability to be highlighted at Research Day September 28

Chen Biochemistry 2019

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Mike Panzara, MD, MPH

Chief Medical Officer,

Head of Therapeutics

Discovery and Development

Development of next generation candidates for intrathecal delivery to CNS targets

PN chemistry backbone modifications	Target engagement *in vivo*
WVE-004 (C9orf72)	✓ Prolonged knockdown of downstream mRNA and DPR proteins in CNS of transgenic animal model
WVE-003 (SNP3)	✓ Prolonged knockdown of mHTT mRNA in CNS of transgenic animal model
Additional CNS targets[1]	✓ Target engagement and widespread distribution in CNS of NHPs (e.g., **WVE-005**)

Preclinical *in vivo* studies support potential for **less frequent dosing** intervals than monthly in clinic

Potent and durable target engagement

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[1]Includes programs in collaboration with Takeda and wholly-owned Wave targets
DPR: dipeptide repeat protein CNS: central nervous system NHP: non-human primate

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

Establishing leadership through inclusion of patients with C9-associated disease across phenotypes

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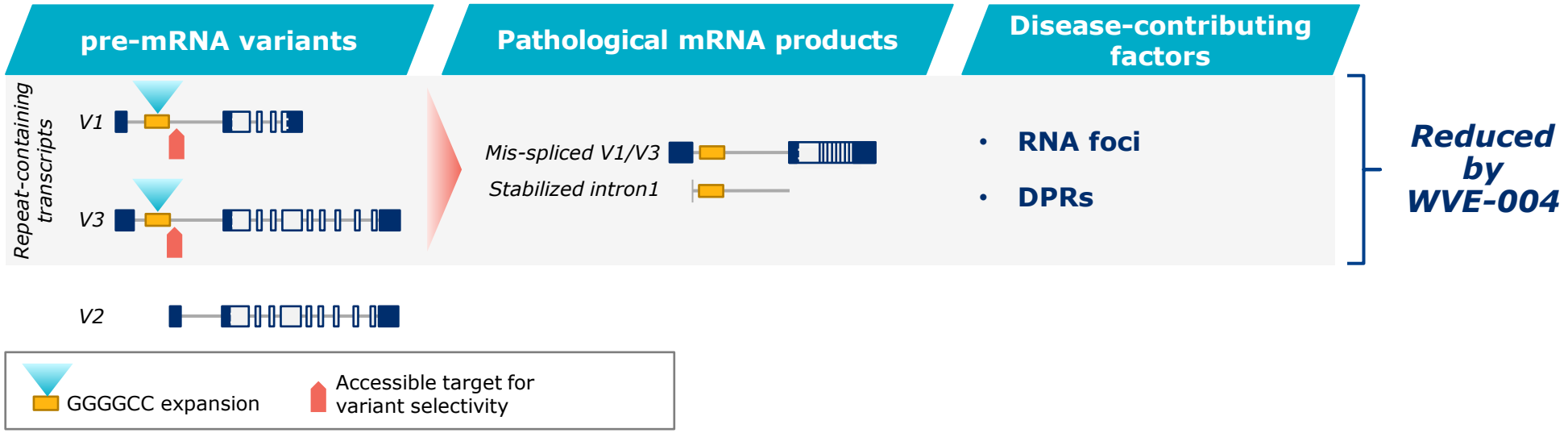
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

WVE-004 selectively targets repeat-containing transcripts to address multiple drivers of toxicity

WVE-004 (C9orf72)

- C9orf72 protein is important for normal regulation of neuronal function and the immune system
- WVE-004 targets hexanucleotide repeat containing transcript variants that lead to loss of normal C9orf72 function and production of pathological mRNA products and toxic dipeptide repeat (DPR) proteins
- Poly-GP is an important DPR transcribed from sense and antisense toxic mRNA transcripts
- Poly-GP is a sensitive biomarker of target engagement and reductions of mRNA transcripts and other toxic proteins by WVE-004
- Neurofilament Light-Chain (NfL) measurements will provide important insight into potential for neuroprotection



Liu et al, Nature Communications, 2021

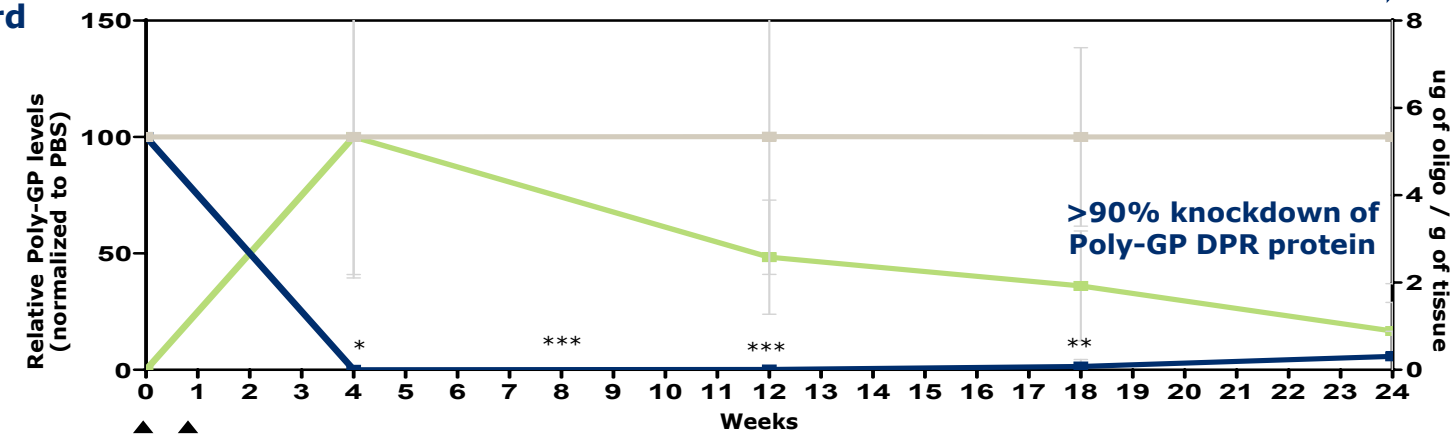
Durable reduction *in vivo* of Poly-GP in spinal cord and cortex; Preservation of C9orf72 protein

WVE-004 (C9orf72)

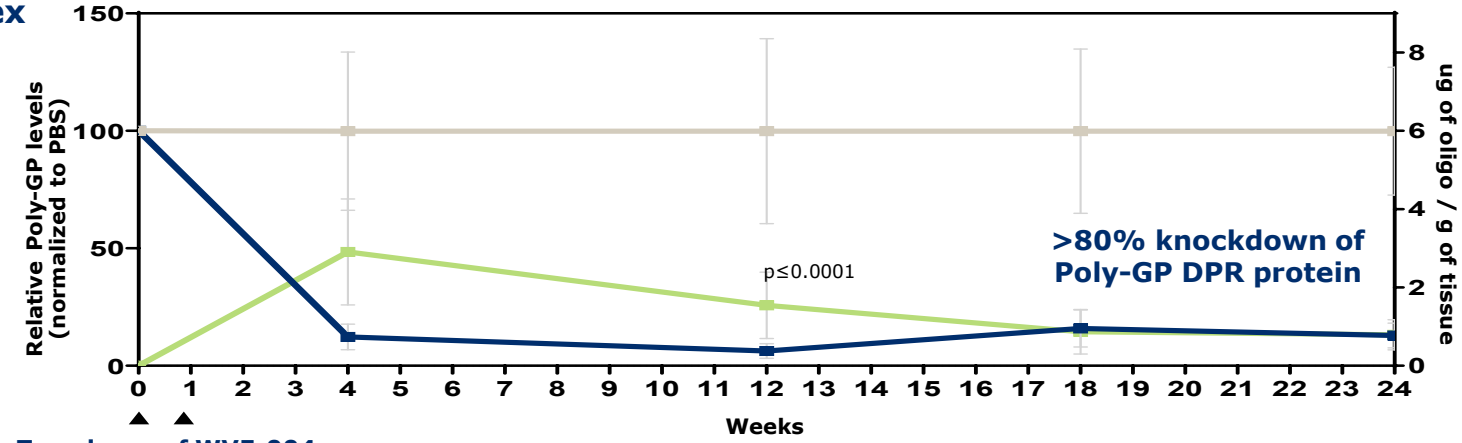
Preclinical *in vivo* results:

Six months

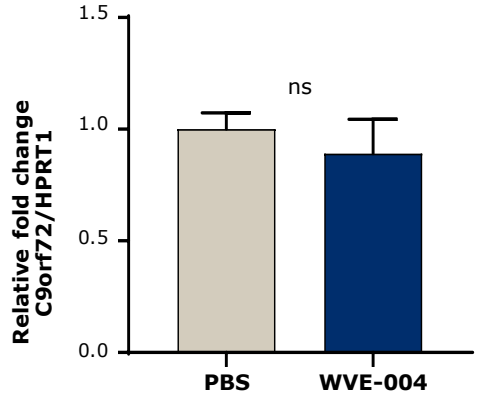
Spinal cord

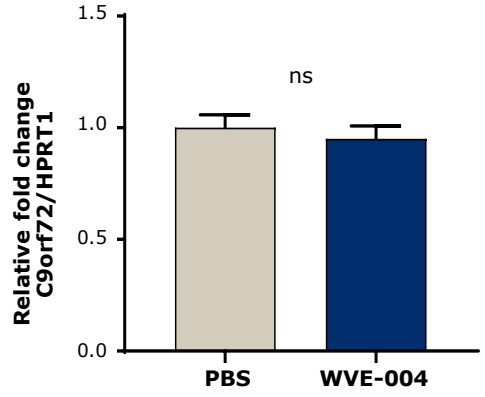


Cortex



C9orf72 protein unchanged at 6 months





Two doses of WVE-004

PBS | **WVE-004: Poly-GP DPR** | **WVE-004: Oligonucleotide concentration**

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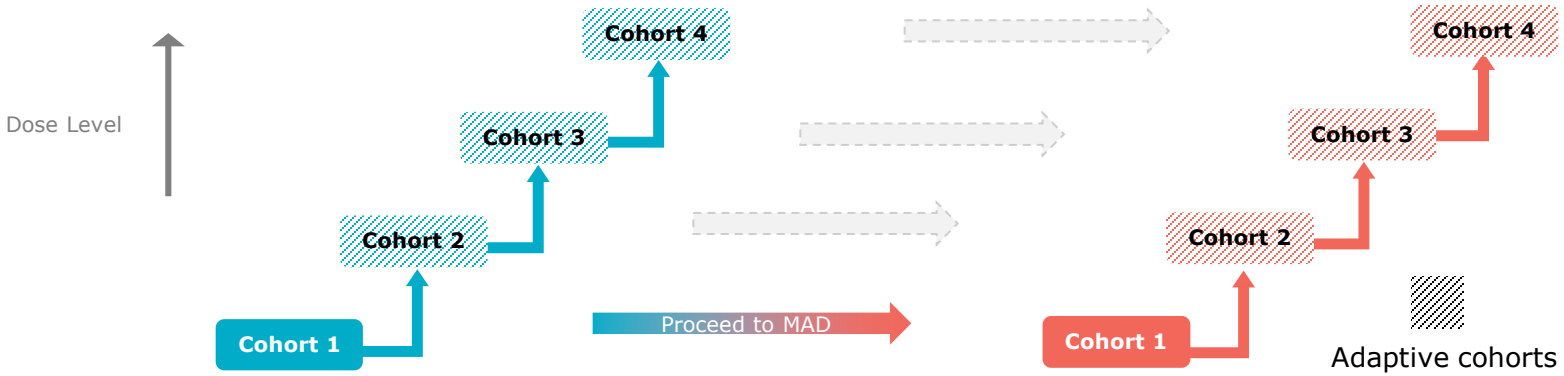
Full results presented at the 31st International Symposium on ALS/ MND (December 2020); 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. DPR: Dipeptide repeat protein

FOCUS-C9: Adaptive trial designed to assess target engagement and adjust dosing throughout the study

WVE-004 (C9orf72)

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



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
	Monthly or less frequent						
	●	●	●	●	●	●	●
	●	●	●	●	●	●	●

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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FOCUS C9

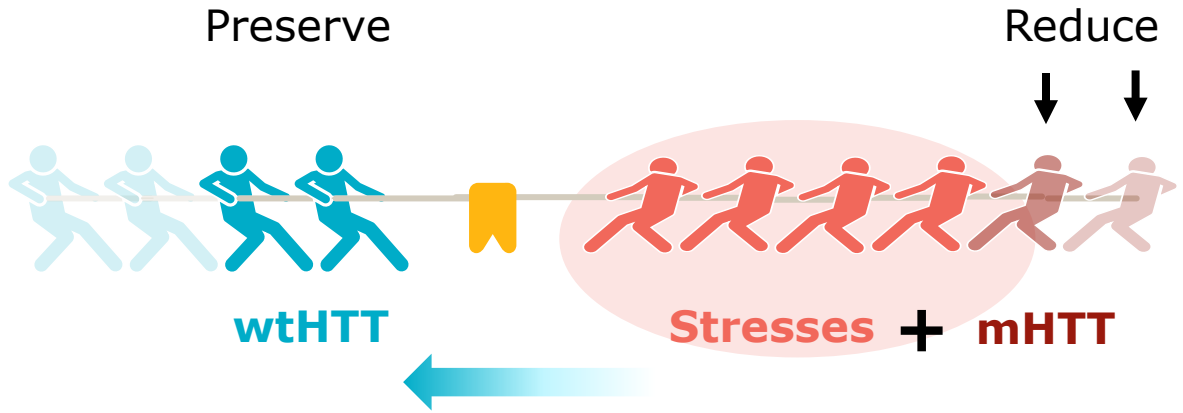
WVE-003 (SNP3)

WVE-003: Designed to address both toxic gain of function and loss of function drivers of HD progression

Selective lowering of mHTT transcript through SNP targeting; direct measurement of effects through CSF biomarkers

Goals:

- ✓ Reduce toxic mHTT protein
- ✓ Preserve neuroprotective effects of wtHTT protein
- ✓ Slow / halt neurodegeneration and disease progression



Allele-selective approaches seek to maintain beneficial effects of wtHTT to maximize effect of mHTT reduction

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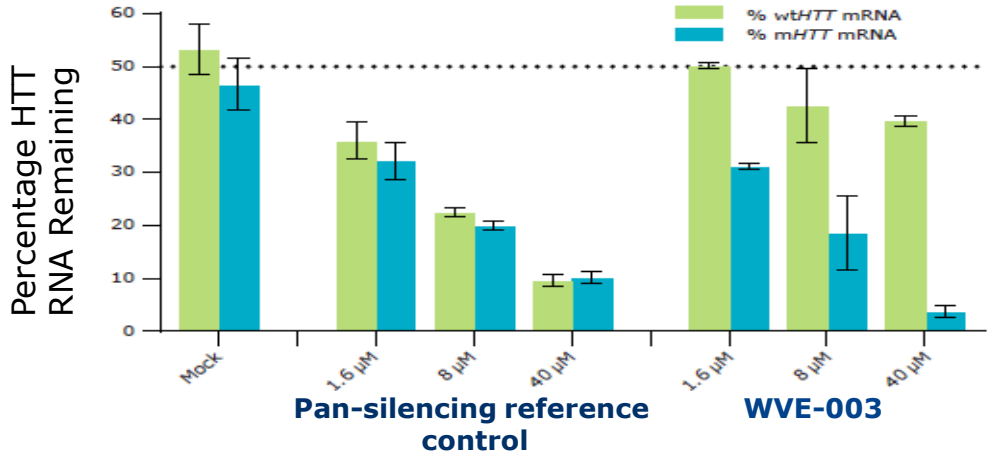
Selective, potent, durable mHTT knockdown achieved with WVE-003 in preclinical studies

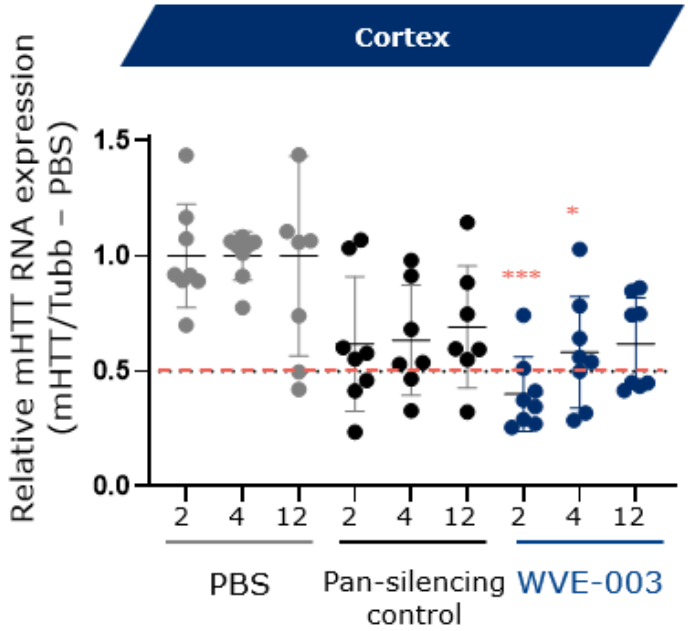
WVE-003 (SNP3)

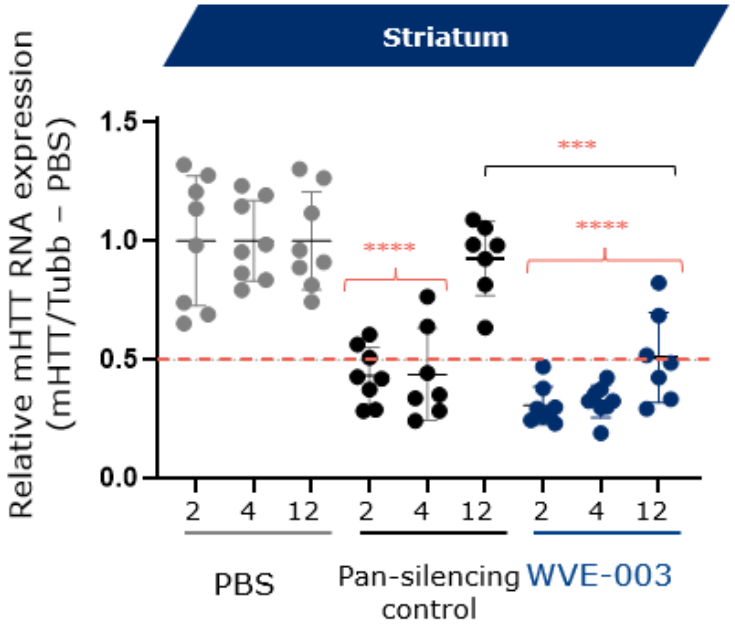
- ✓ **Selectivity**: Wild-type HTT is preserved even at high concentrations *in vitro*
- ✓ **Potency**: Maximum knockdown of 70-75% *in vivo*
- ✓ **Durability**: ~50% knockdown persisting for at least 3 months *in vivo*

Selective reduction of mHTT in HD motor neurons



mHTT knockdown *in vivo*





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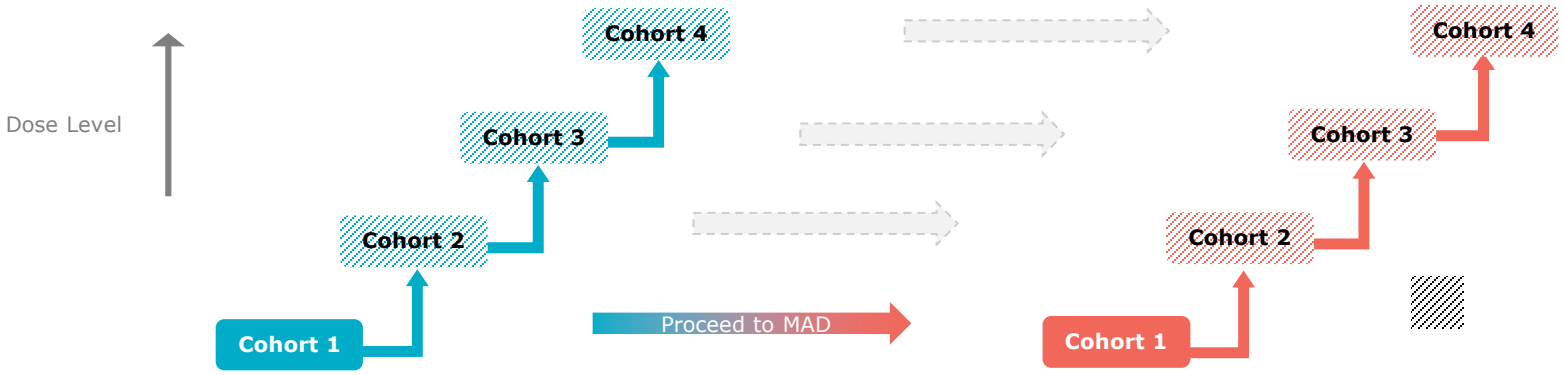
Results presented at the 27th Annual Meeting of the Huntington Study Group, October 2020, Virtual

WVE-003 (SNP3)

SELECT-HD: Adaptive trial designed to assess target engagement and adjust dosing throughout the study

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



Single-ascending dose (SAD)

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

Multi-ascending dose (MAD)

Week	1	2	4	8	12	16	20	24
	Monthly or less frequent							
	●	●	●	●	●	●	●	●
	●				●		●	

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

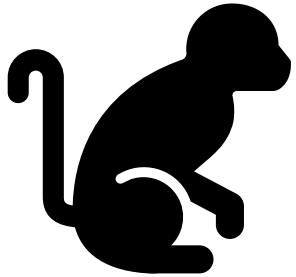
mHTT: mutant huntingtin; wtHTT: wild-type huntingtin; NfL: neurofilament light

Collaborative programs with Takeda allow assessment of CNS distribution and pharmacology across species

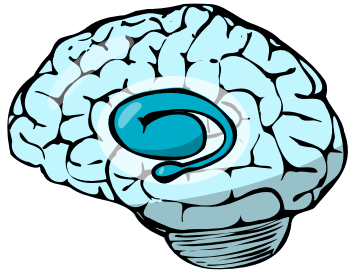
- Evaluate drug distribution and target engagement in a large animal species, using the clinical route of administration

Transgenic mouse model

NHP



Human



- Application of stereochemistry and PN chemistry backbone modifications enhances distribution throughout CNS

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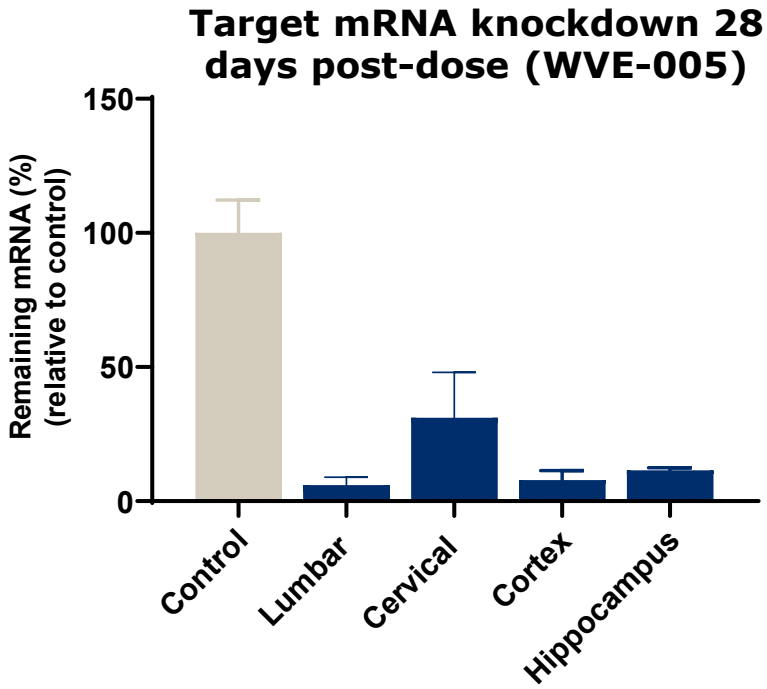
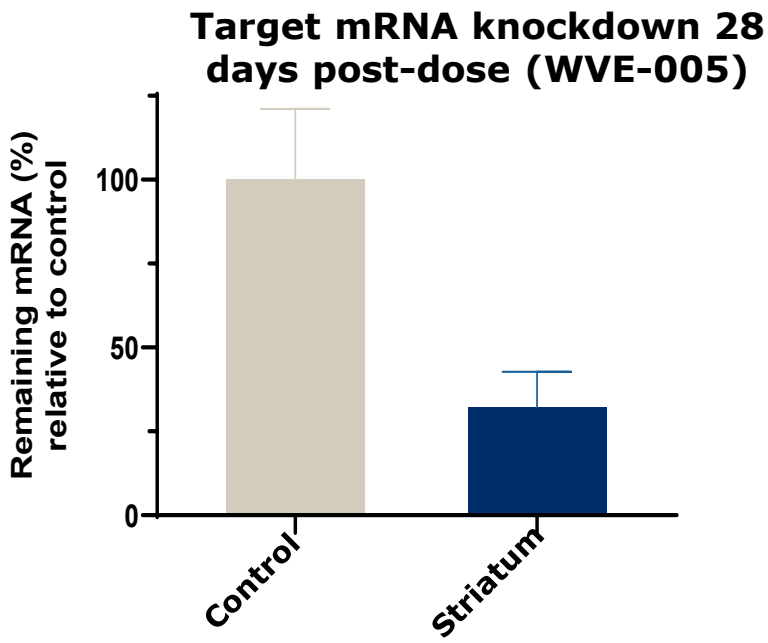
WVE-005: Single intrathecal dose in NHP leads to substantial and widespread target mRNA reduction throughout the CNS





Potential for infrequent IT administration, widespread CNS distribution of PN modified oligonucleotides, and availability of disease biomarkers facilitates development of differentiated CNS portfolio

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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

Advancing next generation chemistry to enhance splicing in muscle with systemic administration

PN chemistry backbone modifications	*in vivo* studies
WVE-N531 (exon 53 skipping)	✓ Survival benefit / dystrophin expression in dKO model with PN-modified exon-23 skipping surrogate oligonucleotide

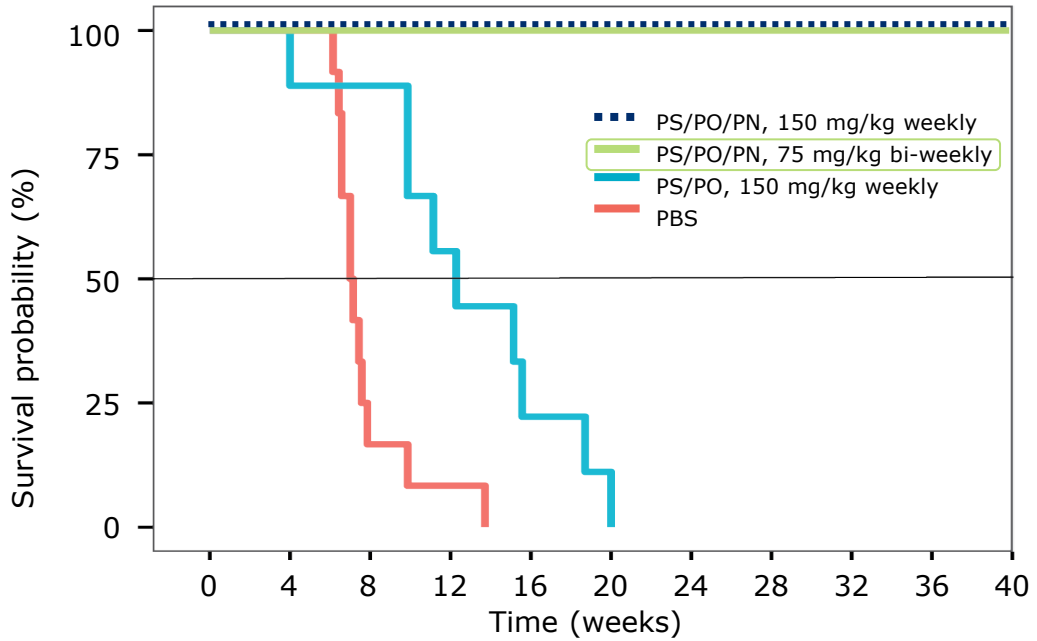
PN-modified oligonucleotide substantially more effective than PS-modified compound with identical sequence

dKO: Double Knockout

Dramatic increase in effect in dKO mouse model with stereopure ASO with PN-modified backbone versus stereopure compound with PS/PO modifications

WVE-N531 (Exon 53)

Treatment with PN-modified molecules led to 100% survival of dKO mice 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: First splicing candidate to use PN chemistry

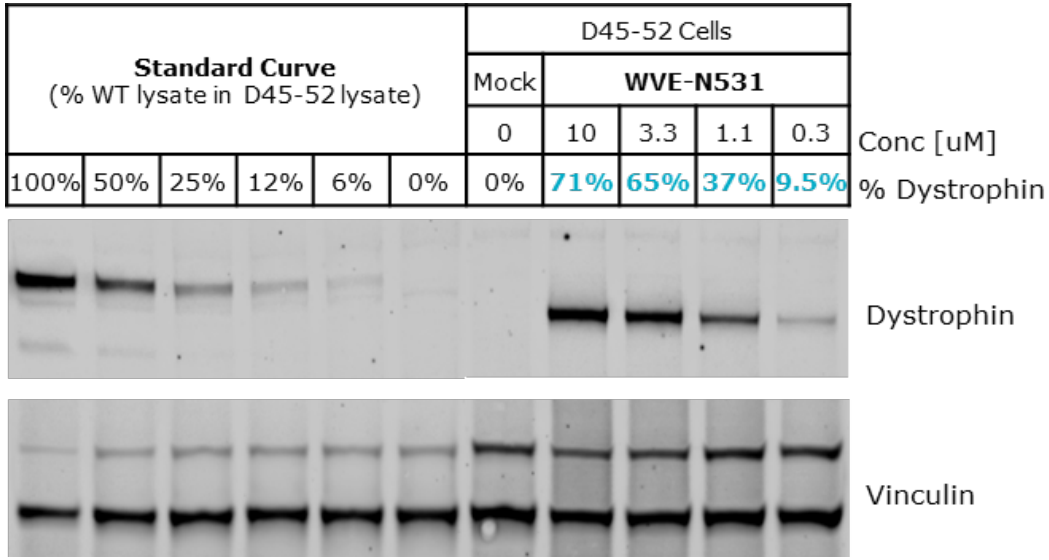
WVE-N531 (Exon 53)

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.

Dystrophin protein restoration of up to 71% *in vitro*

Western Blot normalized to primary healthy human myoblast lysate



Clinical trial of WVE-N531 underway

- Unmet need in DMD remains high
- Open-label clinical trial of up to 15 boys with DMD amenable to exon 53 skipping
  - Powered to evaluate change in dystrophin production
  - Includes assessment of drug concentration in muscle and initial safety
  - Study planned for every-other-week administration
- Potential to apply PN chemistry to other exons if successful

Dose escalation and frequency guided by independent committee

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DMD: Duchenne muscular dystrophy

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Paloma Giangrande, PhD

Vice President, Platform

Discovery Sciences, Biology

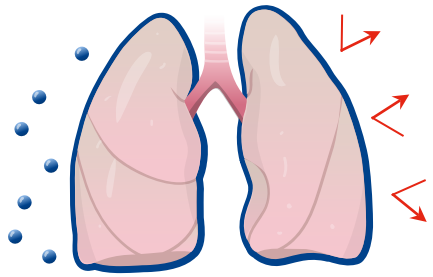
Leading RNA editing program provides optimal approach for treatment of AATD

AATD
ADAR editing

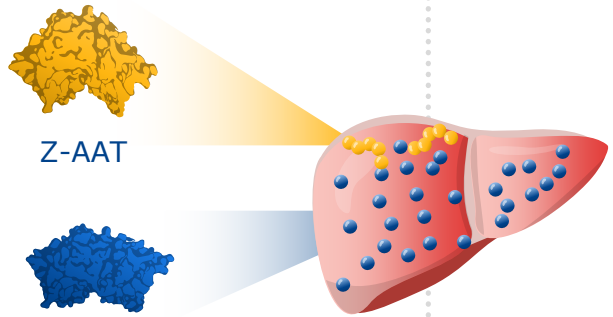
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

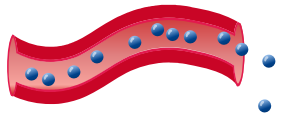
3) Retain M-AAT physiological regulation



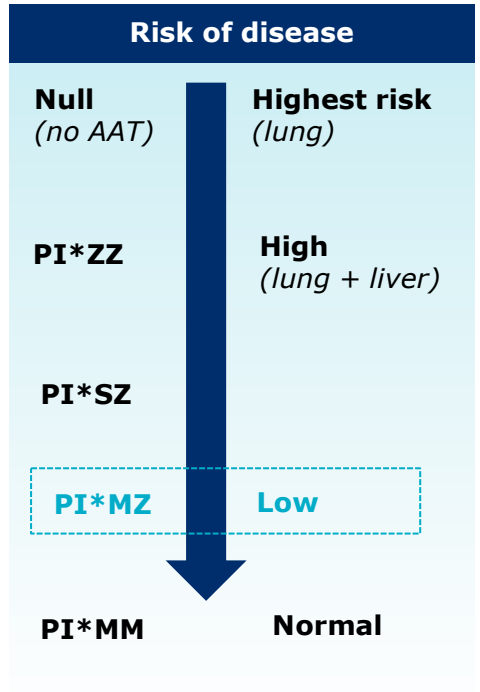
M-AAT reaches lungs to protect from proteases



Wild-type M-AAT protein replaces Z-AAT with RNA correction



M-AAT secretion into bloodstream



Wave ADAR editing approach addresses all goals of treatment

GalNAc-conjugated for subcutaneous delivery

~200K people in US and EU with mutation in *SERPINA1* Z allele (PI*ZZ)

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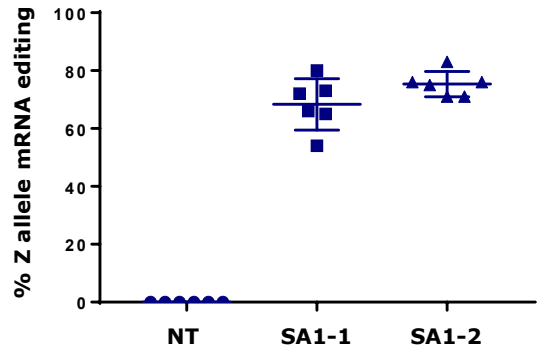
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017

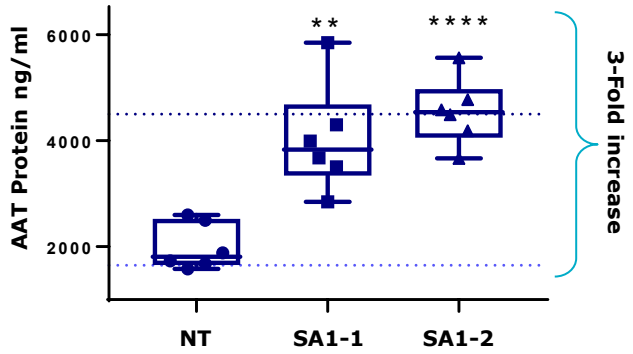
Focused on restoring wild-type M-AAT *in vivo*

In vitro proof of concept

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



In vivo proof of concept

AATD mouse

Genotype
✓ huSERPINA1-Pi*Z
Human Z-AAT protein expressed in liver

huADAR mouse

Genotype
✓ huADAR
Human ADAR expressed in all tissues

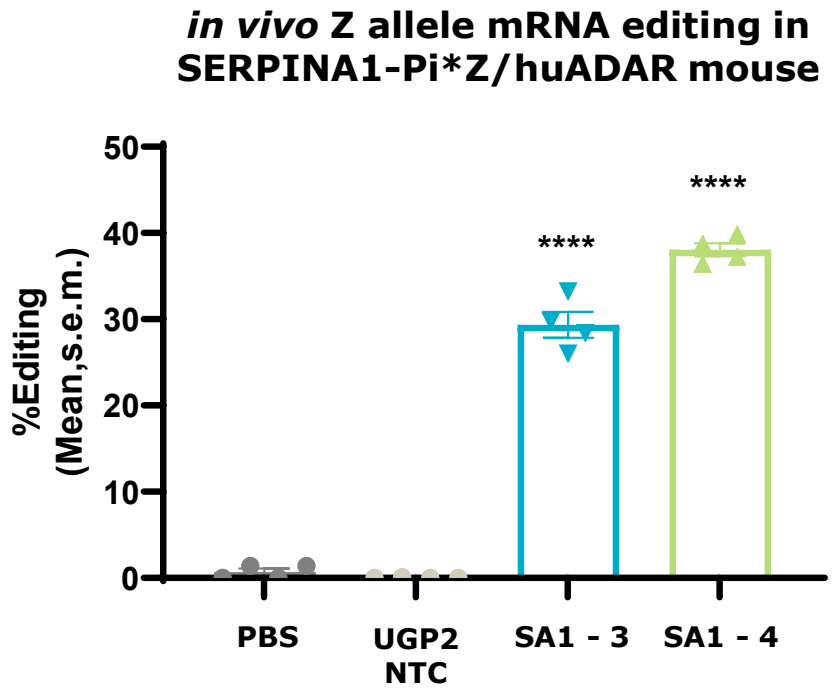
huADAR/AATD mouse

Genotype	Pathology
✓ huADAR	Liver pathology, Z-AAT protein in serum and liver
✓ huSERPINA1-Pi*Z	

AATD: Alpha-1 antitrypsin deficiency, Z-AAT: mutated protein, M-AAT: wild-type human AAT protein

Achieving 40% editing of Z allele mRNA at initial timepoint

SERPINA1 Z allele mRNA editing levels nearing correction to heterozygote (MZ)



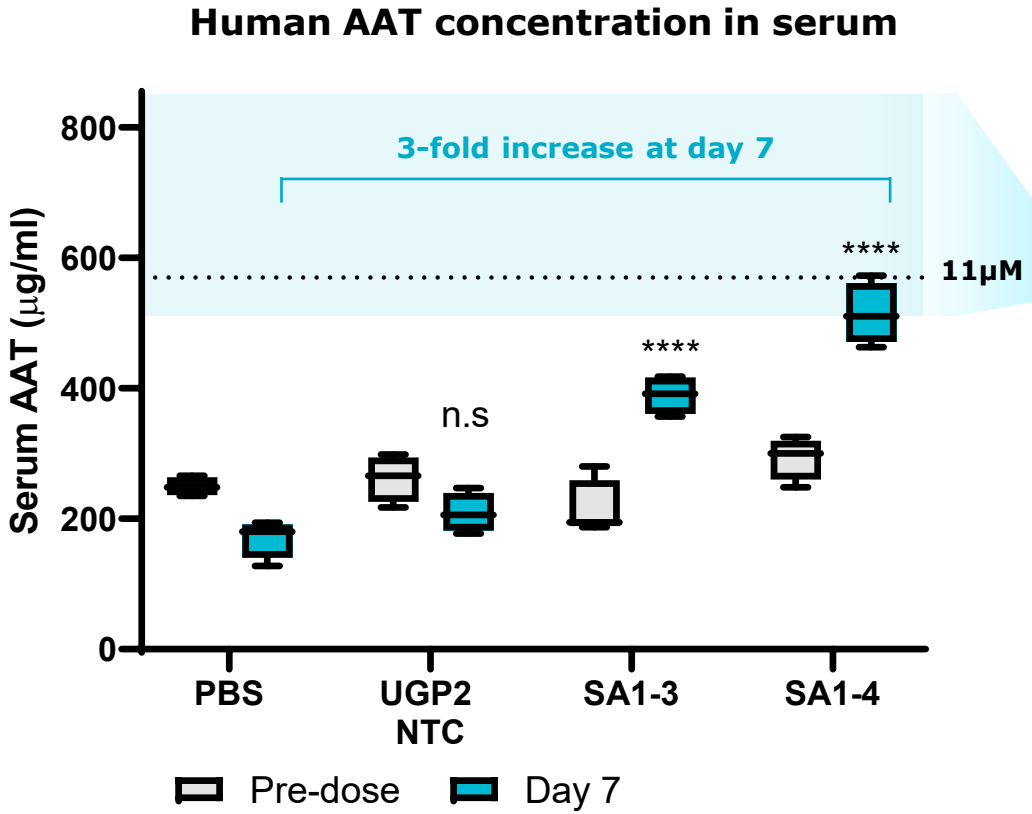
- GalNAc-conjugated compounds
- Up to 40% editing of Z allele mRNA in liver of transgenic human ADAR mice at day 7
- Highly specific editing (no bystander edits)

✓ **Z allele mRNA editing *in vivo*** | **AAT protein increase** | **Wild-type M-AAT functional**

Statistics: One-way ANOVA with correction for multiple comparisons (Dunnett's) was used to test for differences SERPINA1-Z allele editing in treated vs. PBS groups; 10 mg/kg dose administered day 0, 2, 4, sample collected on day 7; NTC: non-targeting control

Achieving therapeutically meaningful increases in circulating human AAT protein

3-fold increase in circulating human AAT as compared to PBS at initial timepoint



AAT serum levels by genotype

PI*MZ	~3 to 5-fold increase
PI*SZ	~2-fold increase
PI*ZZ	~3 – 7 uM

✓ Z allele mRNA editing *in vivo*

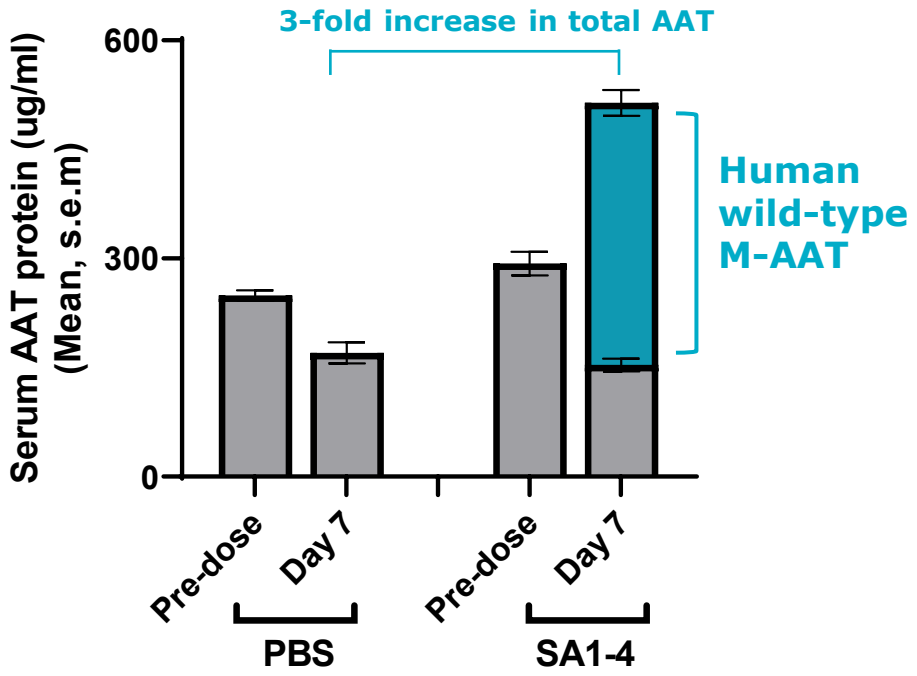
✓ AAT protein increase

Wild-type M-AAT functional

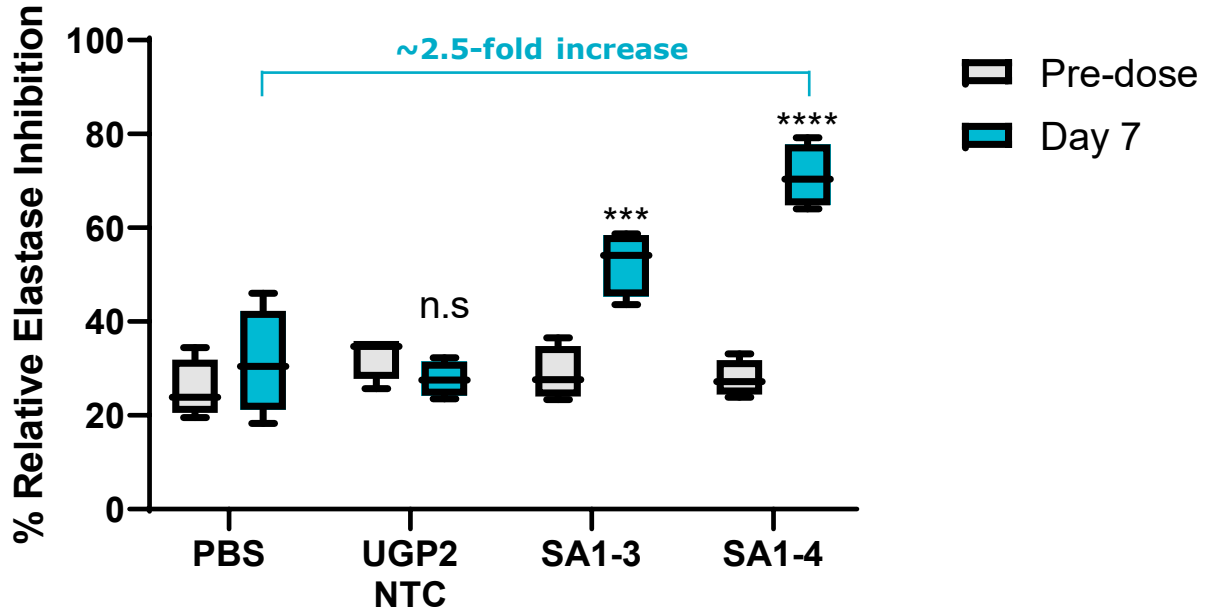
Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

ADAR editing restores circulating, functional M-AAT

Wild-type M-AAT detected with ADAR editing



Significant increase in neutrophil elastase inhibition with ADAR editing



✓ Z allele mRNA editing *in vivo*

✓ AAT protein increase

✓ Wild-type M-AAT functional

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Left: Mass spectrometry and ELISA Right: (Elastase inhibition): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in elastase inhibition activity in serum collected at day 7 vs pre-dose for each treatment group; NTC: non-targeting control

ADAR editing successfully corrects Z allele mRNA *in vivo* to restore functional M-AAT protein

Initial *in vivo* results

- Up to 40% editing of *SERPINA1* Z allele mRNA in liver at initial timepoint, nearing correction to heterozygotes (MZ)
- Initial Z allele mRNA editing resulted in therapeutically meaningful increase in circulating functional wild-type M-AAT protein *in vivo*

Ongoing studies

- Ongoing studies to assess duration of activity, dose response, PK / PD, reduction in Z-AAT protein aggregates, and changes in liver pathology
- Advancing optimized ADAR editing compounds with increased potency in new *in vivo* studies

Additional data on durability and dose response expected in 2H 2021

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Kyle Moran

Chief Financial Officer

Second quarter 2021 financial results

	Three Months Ended June 30, 2021	Three Months Ended June 30, 2020
Figures are in thousands, except per share amounts		
Revenue	$2,776	$3,027
Operating Expenses:		
Research and Development	31,635	31,478
General and Administrative	10,969	10,205
Total Operating Expenses	42,604	41,683
Loss from Operations	(39,828)	(38,656)
Total Other Income (Expense), Net	1,062	(1,872)
Net Loss	($38,766)	($40,528)
Net Loss per Share	**($0.78)**	**($1.15)**

As of June 30, 2021 | **Shares Outstanding:** 50.6 million | **Cash Balance:** $143.8 million

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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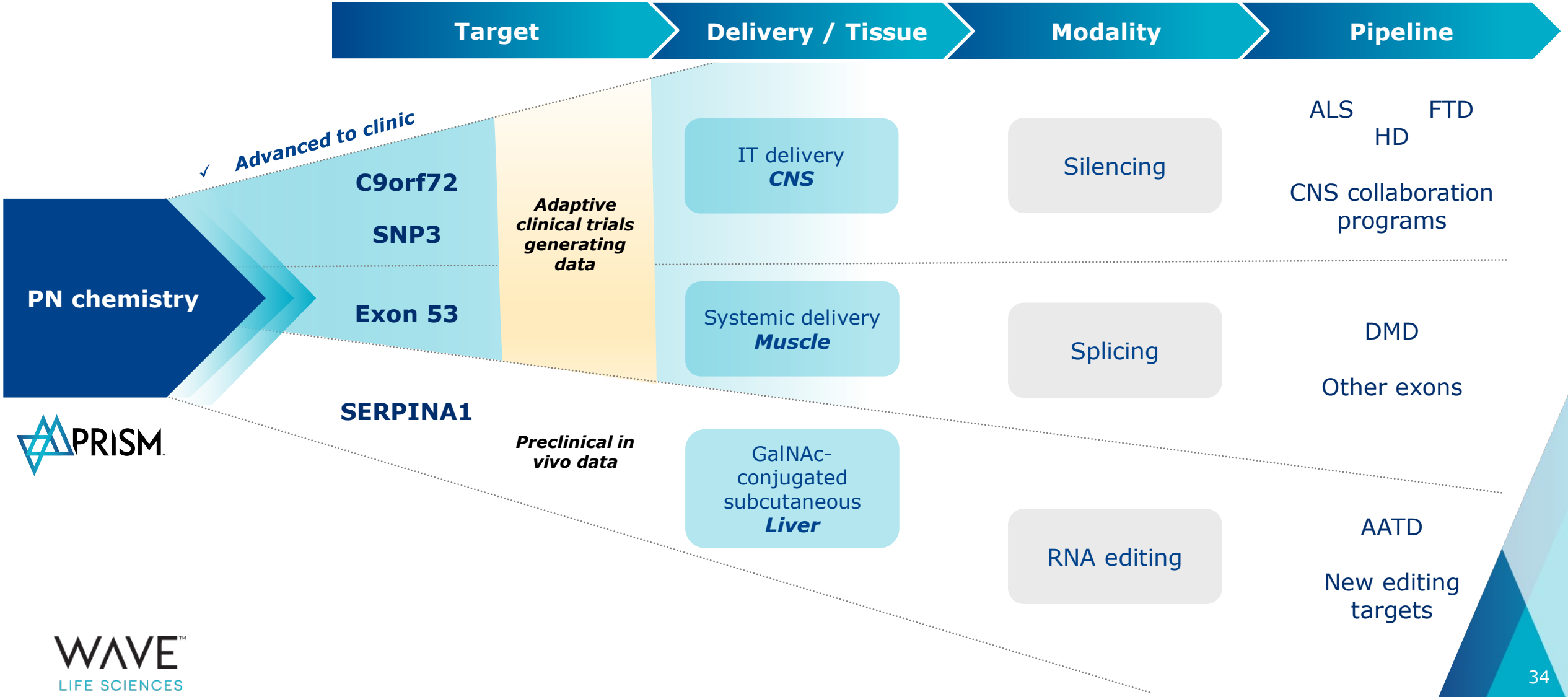
Paul Bolno, MD, MBA

President and CEO

Clinical data to unlock the potential of PN chemistry across different modalities and tissues



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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:

✓ SELECT-HD trial recruitment ongoing

• Dose first patient in SELECT-HD trial for patients with HD in 2021

WVE-N531:

✓ Clinical trial recruitment ongoing

• Dose first patient in clinical trial for patients with DMD in 2021

2022

Clinical data through 2022 to provide insights into the clinical effects of PN chemistry and enable decision making expected

Novel ADAR editing capability advancing

2021

Share data on durability and dose response from AATD program in 2H 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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Q&A

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Realizing a brighter future for people affected by genetic diseases

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