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Wave Life Sciences

Jefferies Virtual Healthcare Conference

June 2, 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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Building a leading genetic medicines company

INNOVATIVE PLATFORM

- Stereopure oligonucleotides
- Novel backbone modifications (PN chemistry)
- Allele-selectivity
- Multiple modalities (silencing, splicing, ADAR editing)
- Strong IP position[1]

FOUNDATION OF NEUROLOGY PROGRAMS

- ALS / FTD
- Huntington's disease
- Neuromuscular diseases
- Ataxias
- Parkinson's disease
- Alzheimer's disease

PRISM

Wave's discovery and drug development platform

CLINICAL DEVELOPMENT EXPERTISE

- Multiple global clinical trials
- Innovative trial designs

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

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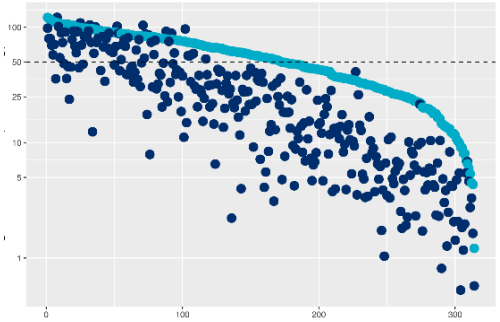
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
[1]stereopure oligonucleotides and novel backbone chemistry modifications

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

Silencing

Target knockdown (% remaining)

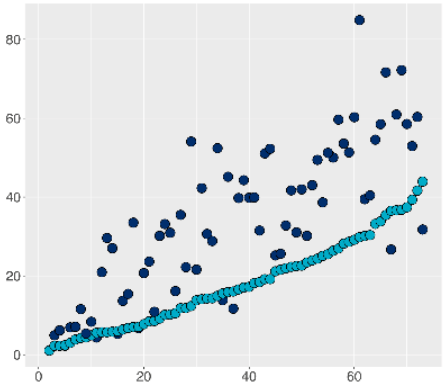


Ranked by potency of reference PS/PO compound

Improved knockdown

Splicing

% Skipping

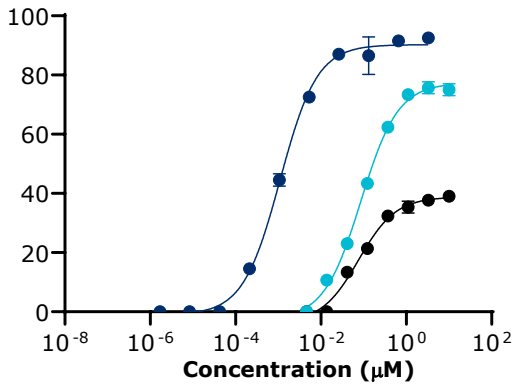


Ranked by potency of reference PS/PO compound

Improved skipping

Editing

% Editing



Improved editing

PS/PO/PN

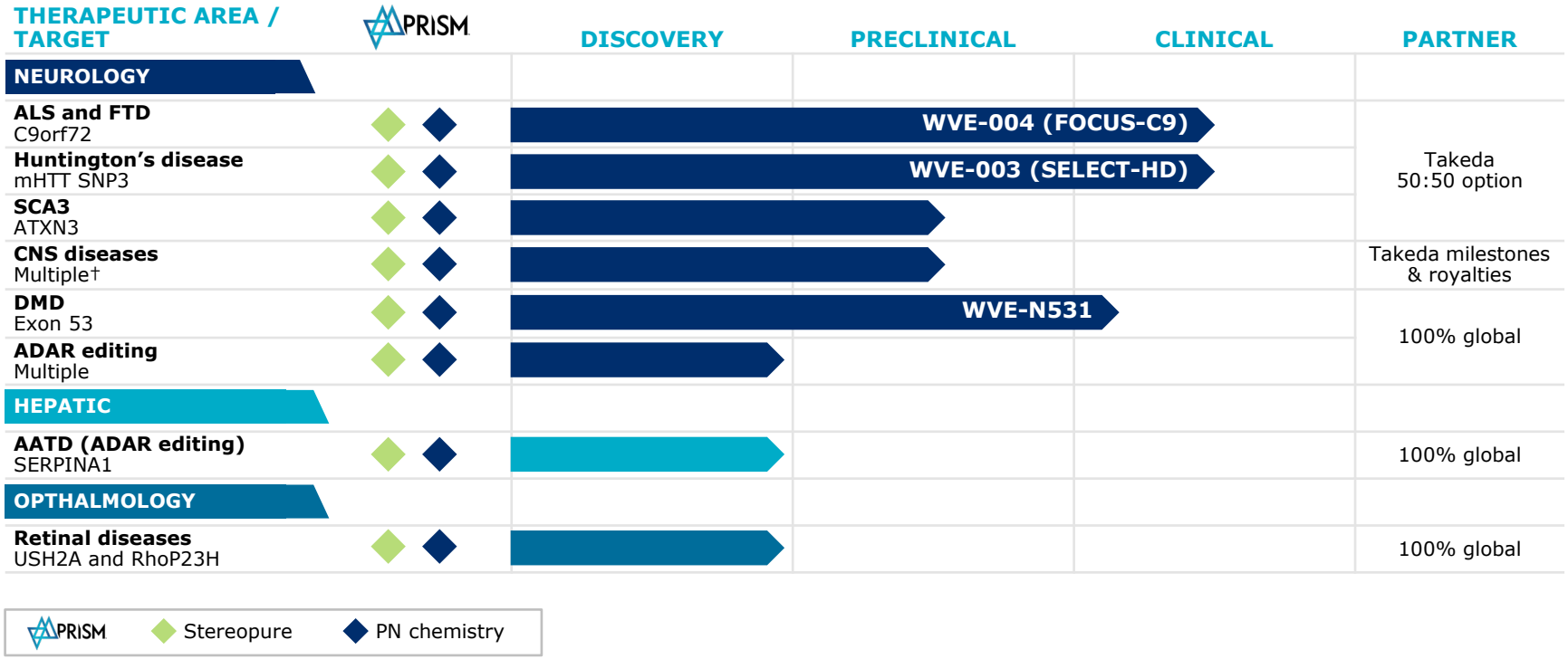
PS/PO (Stereopure)

PS/PO (Stereorandom)

PS/PO reference compound

PS/PN modified compound

Innovative pipeline led by neurology 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

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

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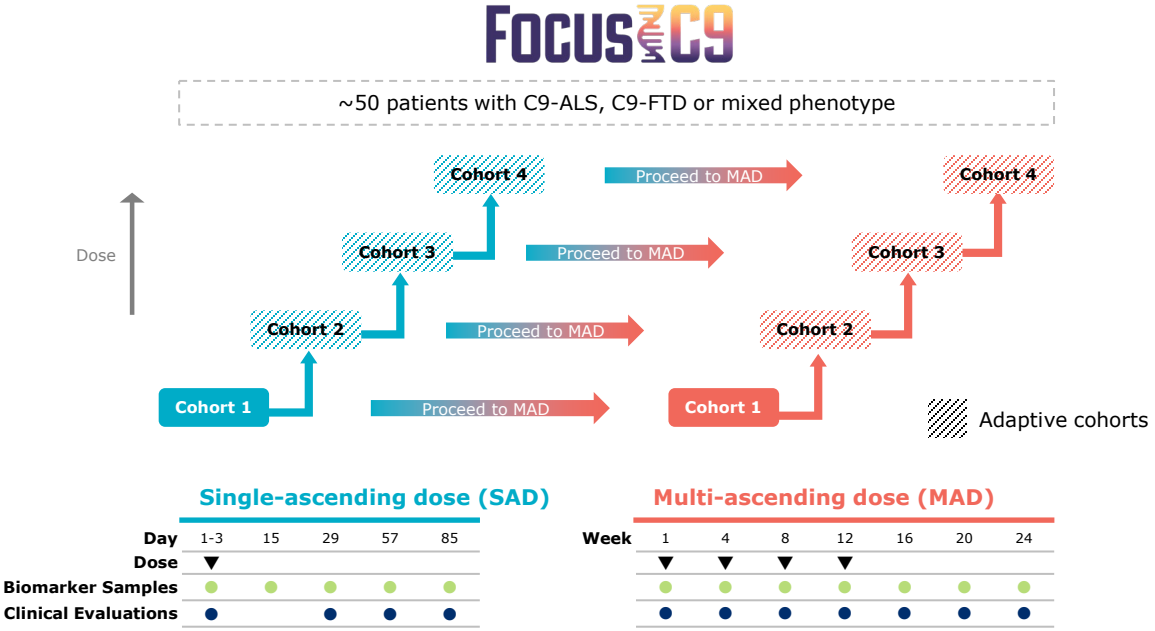
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

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

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



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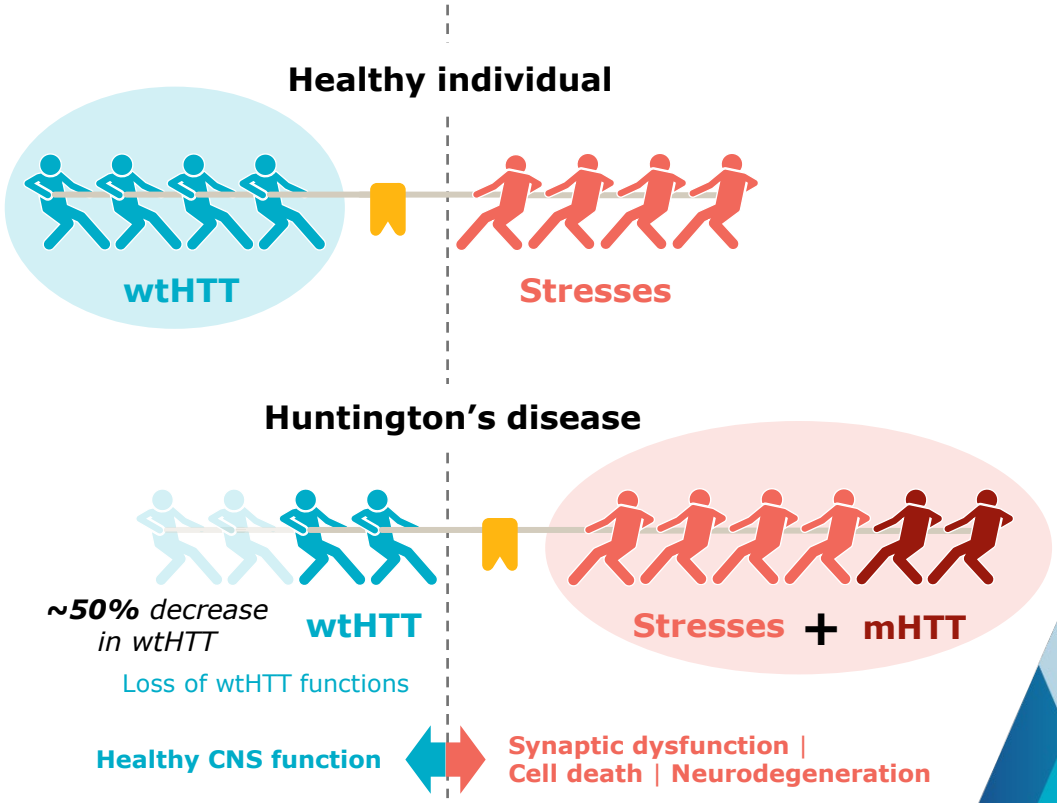
mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD

- Monogenic autosomal dominant genetic disease; fully penetrant
- Wild-type HTT is critical for normal neuronal function
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein
- Huntington's disease affects entire brain



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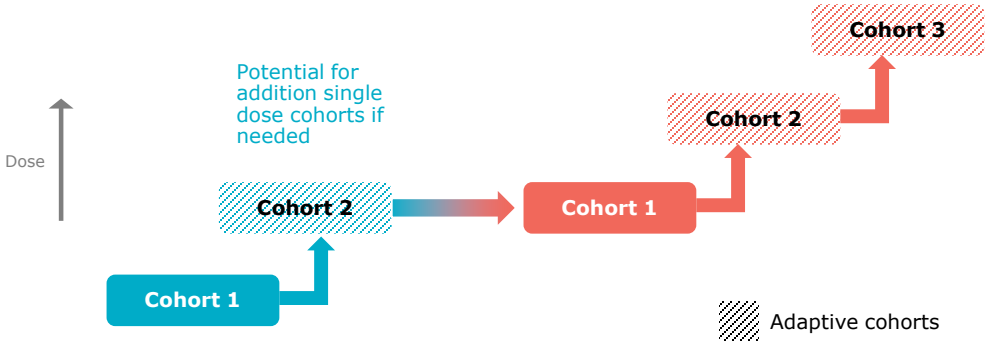
SELECT-HD: Adaptive trial designed to enable faster optimization of dose and frequency

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

~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

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

Clinical trial of WVE-N531 for DMD (Exon 53)

- 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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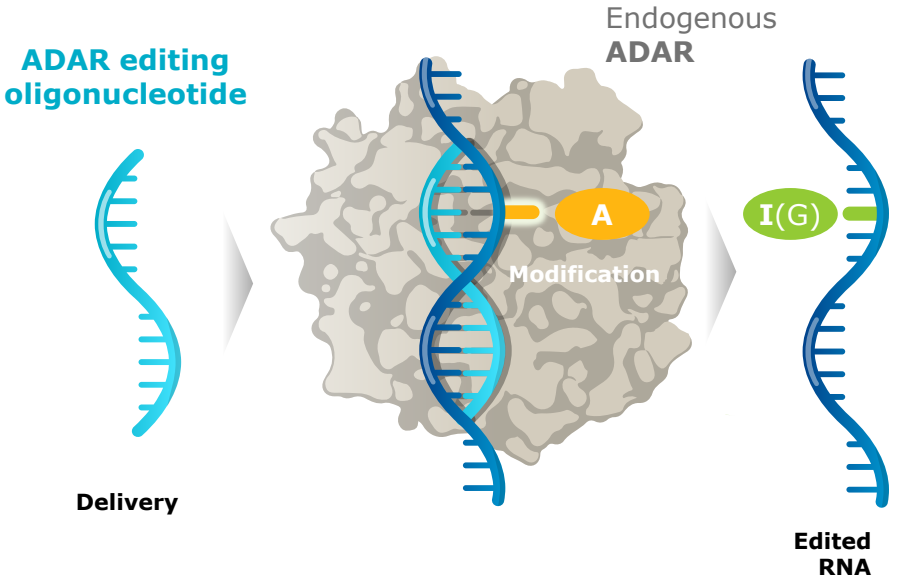
Potential best-in-class ADAR RNA editing platform

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
  - Proprietary transgenic model for PK/PD assessments



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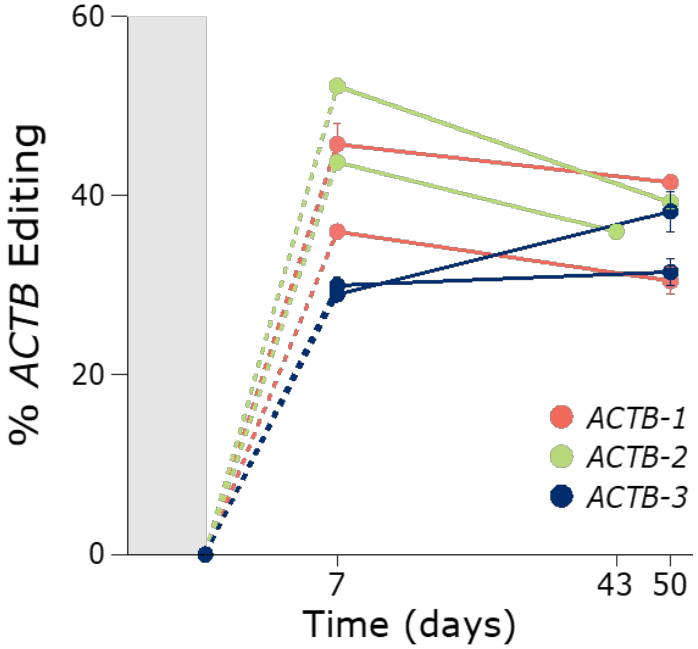
Potent and durable RNA editing *in vivo* in NHP

Substantial and durable editing out to 45 days post last dose

In vivo editing in NHP liver following SC administration with GalNAc conjugate

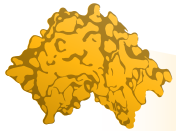


Data presented at Analyst and Investor Research Day 2020 and ASGCT 24th Annual Meeting 2021; GalNAc-conjugated oligo was administered once daily on days 1-5. Liver biopsies were collected on days 7 and 50. NHP: nonhuman primate; ACTB β-actin; SC subcutaneous

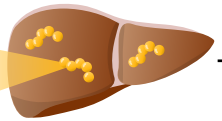
An ADAR editing approach to correct alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency (AATD)

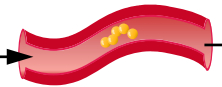
Most common cause is mutation in *SERPINA1* Z allele (PI*ZZ)



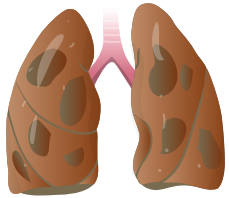
Z-AAT
misfolded protein prone to aggregation



Inability to secrete polymerized Z-AAT
liver damage/cirrhosis



☒ No M-AAT

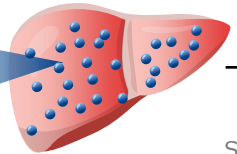


Open to unchecked proteases
inflammation / lung damage

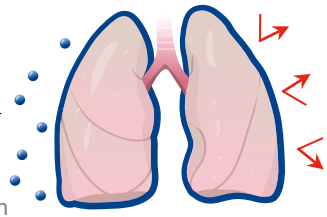
Wave's ADAR editing approach

Correct Z allele mRNA to healthy M allele

M-AAT
Wild-type AAT protein



Secretion into bloodstream



Lungs protected from proteases

- ✓ Restores M-AAT physiological regulation in liver
- ✓ Reducing Z-AAT protein aggregation
- ✓ Restores circulating, lung-bound M-AAT

Risk of disease

Null *(no AAT)*	**Highest risk** *(lung)*
PI*ZZ	**High** *(lung + liver)*
PI*SZ	
PI*MZ	**Low**
PI*MM	**Normal**

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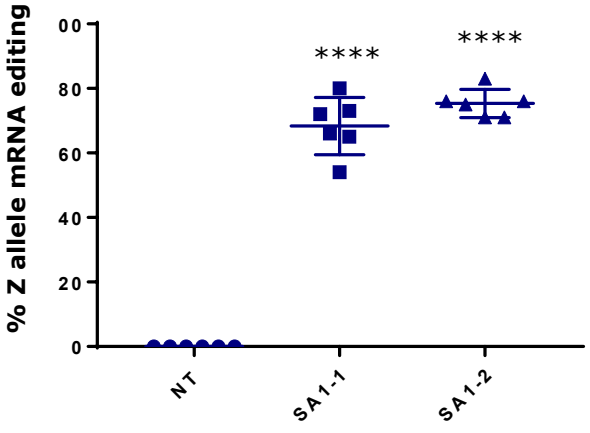
Fregonese, Respir Med, 2008, Strnad, NEJM, 2020

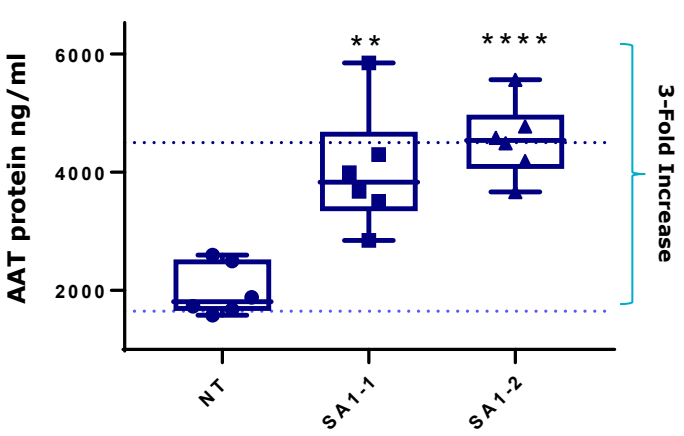
SERPINA1 Z allele mRNA editing restores wild-type M-AAT protein concentration *in vitro*

Editing Z allele mRNA back to wild-type prevents protein misfolding and restores secretion of wild-type M-AAT protein from hepatocytes

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



Wild-type M-AAT protein analysis

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

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AAT (alpha-1 anti-trypsin); 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.

First proof-of-concept study to restore M-AAT protein with ADAR editing *in vivo*

- Goals of first *in vivo* proof-of-concept study:
  - Editing of SERPINA1 Z allele mRNA in liver to approach heterozygous (MZ) phenotype
  - Restore wild-type human M-AAT protein in serum
  - Demonstrate functionality of wild-type human M-AAT protein

SERPINA1 mouse

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

huADAR mouse

Genotype
✓ huADAR
Human ADAR expressed in all tissues

SERPINA1-Pi*Z/huADAR

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

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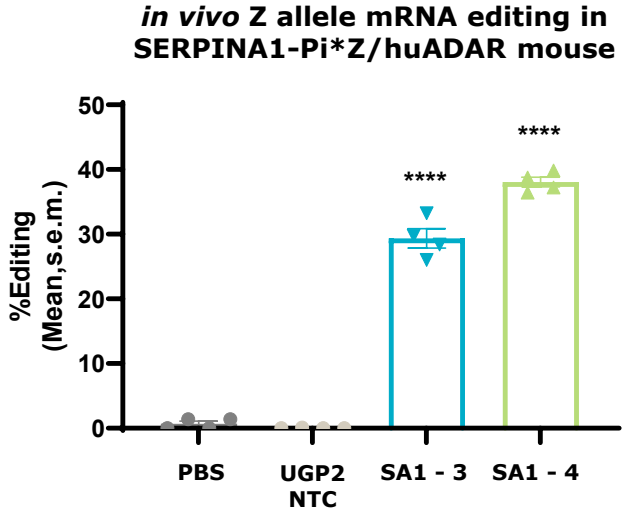
Achieving 40% editing of Z allele mRNA at single timepoint

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



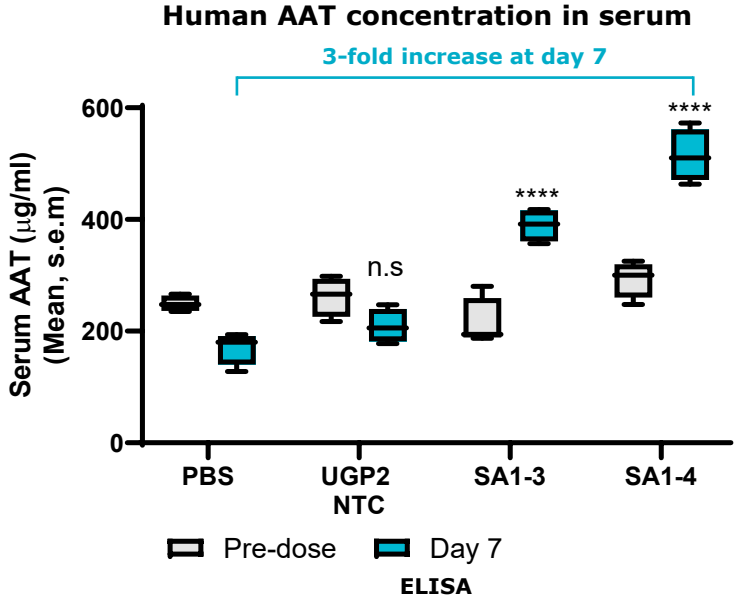
- GalNAc-conjugated compounds
- Up to 40% editing of Z allele mRNA in liver of transgenic human ADAR mice at day 7
- Highly specific editing (no bystander edits)

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 single 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

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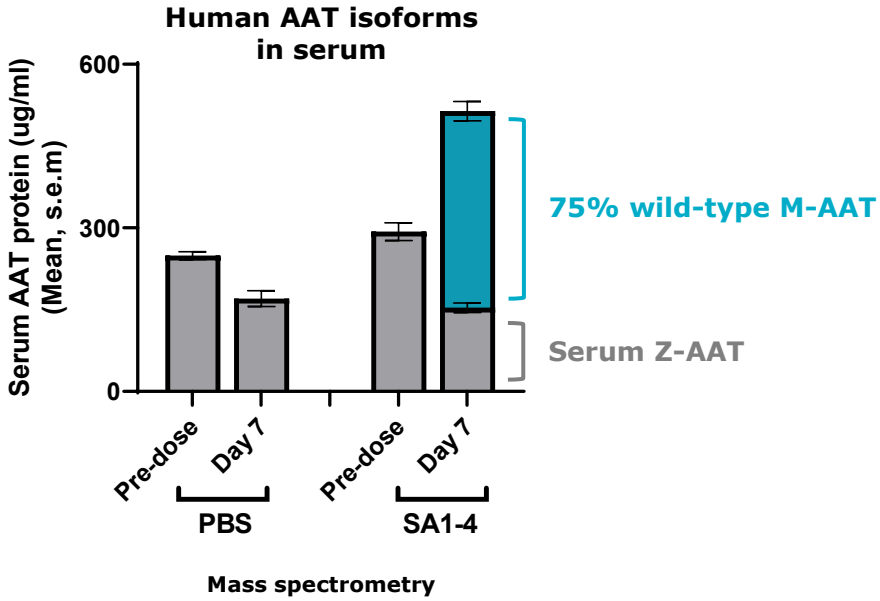
Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

Restoring circulating wild-type M-AAT

ADAR editing restores wild-type M-AAT, suggesting reduction of Z-AAT in liver and serum



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

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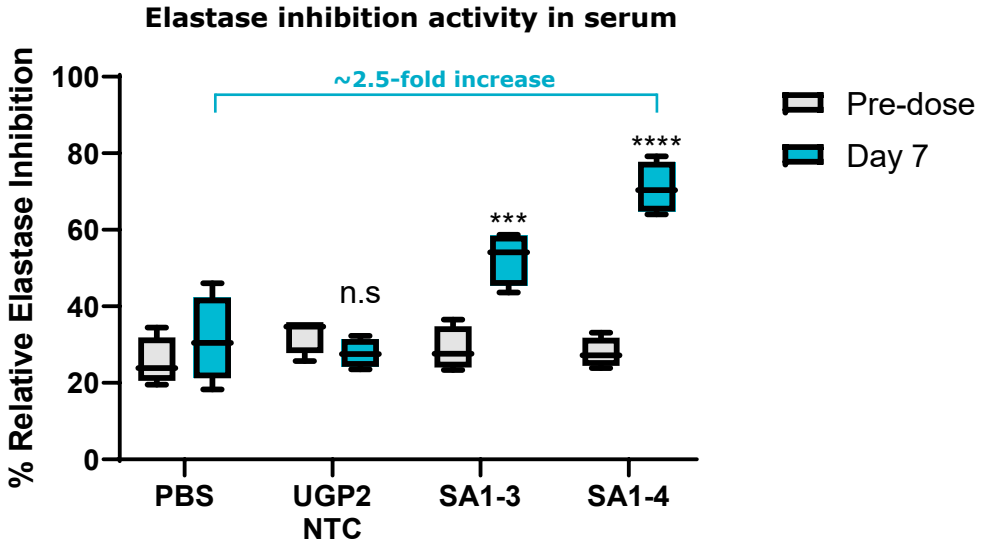
Secreted wild-type M-AAT protein is functional

Significant increase in neutrophil elastase inhibition with wild-type M-AAT protein



✓ Z-allele mRNA editing *in vivo*

✓ AAT protein increase

✓ Wild-type M-AAT functional

(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

- Results support use of human transgenic mouse model to evaluate ADAR editing compounds for additional targets
- Up to 40% editing of *SERPINA1 Z* allele mRNA in liver at single 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*
- Restoration of wild-type M-AAT suggests reduction of mutant Z-AAT protein in liver and serum
- Ongoing studies to assess duration of activity, dose response, PK/PD, reduction in Z-AAT protein aggregates to provide insight into wild-type M-AAT secretion levels over time and changes in liver pathology

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

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

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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Realizing a brighter future for people affected by genetic diseases

For more information:
Kate Rausch, Investor Relations
krausch@wavelifesci.com
617.949.4827