UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 15, 2022

WAVE LIFE SCIENCES LTD.
(Exact name of registrant as specified in its charter)

Singapore	**001-37627**	**00-0000000**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

7 Straits View #12-00, Marina One East Tower Singapore	**018936**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +65 6236 3388

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol	Name of each exchange on which registered
$0 Par Value Ordinary Shares	**WVE**	**The Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

From time to time, Wave Life Sciences Ltd. (the "Company") presents and/or distributes slides and presentations to the investment community to provide updates and summaries of its business. On November 15, 2022, the Company updated its corporate presentation, which is available on the "For Investors & Media" section of the Company's website at http://ir.wavelifesciences.com/. This presentation is also furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information in this Item 7.01 is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference into any registration statement or other filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibit relating to Item 7.01 is furnished and not filed:

Exhibit No.	Description
99.1	Corporate Presentation of Wave Life Sciences Ltd. dated November 15, 2022
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

WAVE LIFE SCIENCES LTD.

By: */s/ Paul B. Bolno, M.D.*
Paul B. Bolno, M.D.
President and Chief Executive Officer

Date: November 15, 2022

Exhibit 99.1

Wave Life Sciences
Corporate Presentation

November 15, 2022

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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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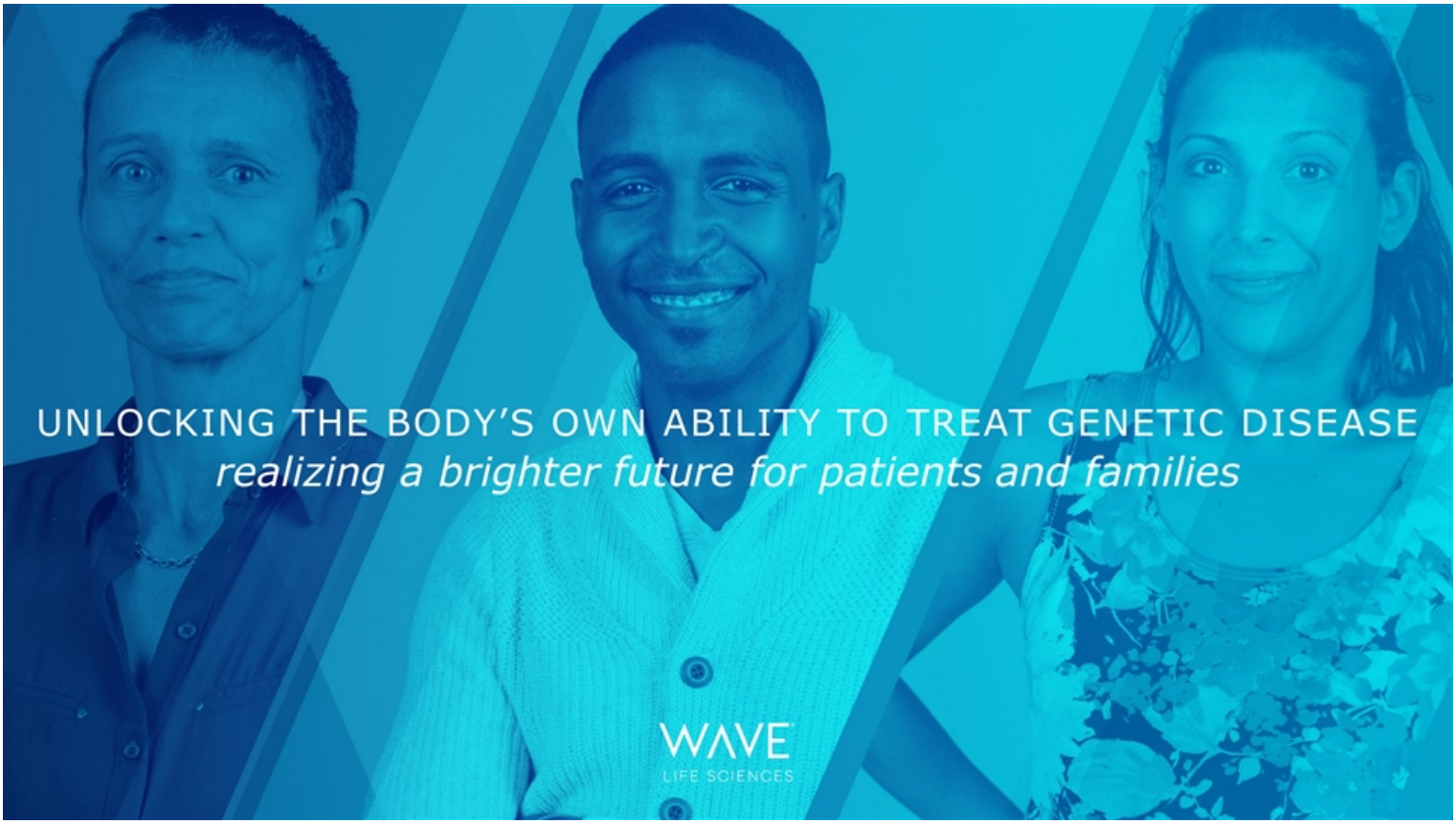
UNLOCKING THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE
realizing a brighter future for patients and families
WAVE
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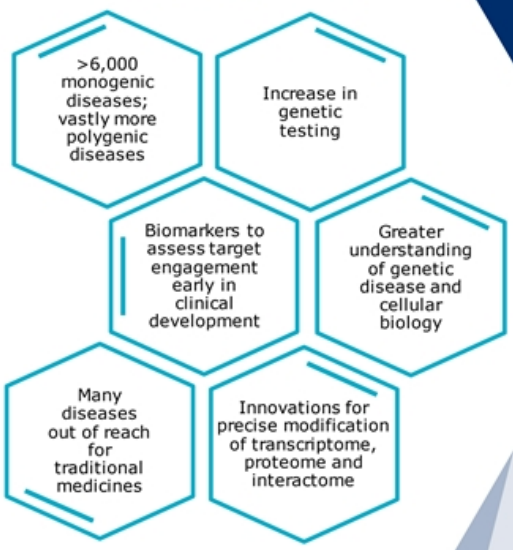
Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



WAVE LIFE SCIENCES

TARGETING THE TRANSCRIPTOME TO UNLOCK THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE

PRISM

Innovative Platform

Stereopure oligonucleotides

Novel backbone modifications (PN chemistry)

Silencing, splicing, and editing modalities

Strong and broad IP position[1]

Diversified Pipeline

CNS: ALS, FTD, HD

Muscle: DMD

Hepatic diseases: AATD

Clinical Expertise

Multiple global clinical trials

Innovative trial designs

GMP Manufacturing

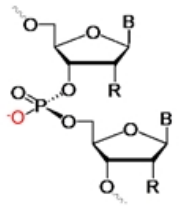
Internal manufacturing capable of producing oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency
[1]stereopure oligonucleotides and novel backbone chemistry modifications

Wave's ability to rationally design oligonucleotides enables access to unique disease targets

PRISM backbone linkages

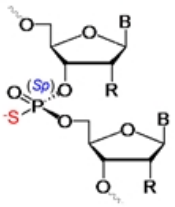
PO



Chirality
None

Negative charge

PS

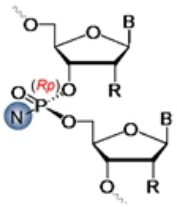


Chirality

PS backbone *Rp*
PS backbone *Sp*

Negative charge

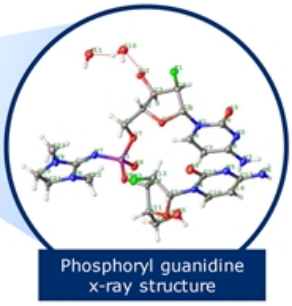
PN



Chirality

PN backbone *Rp*
PN backbone *Sp*

Neutral charge



Phosphoryl guanidine x-ray structure

example

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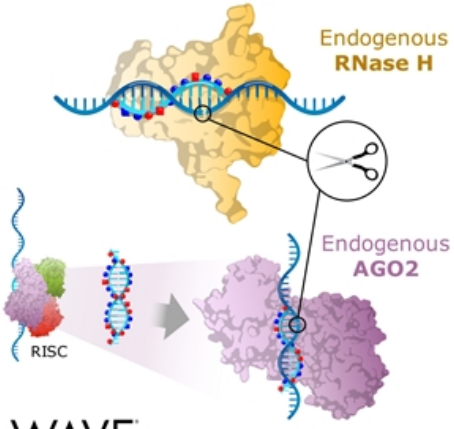
PO: phosphodiester PS: phosphorothioate

Harnessing the biological machinery in our cells to treat genetic diseases

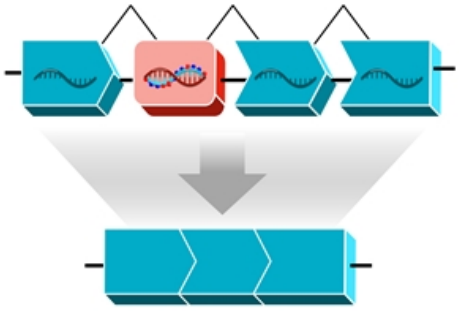
Silencing

- Degradation of RNA transcripts to **turn off** protein production



Splicing

- Restore RNA transcripts and **turn on** protein production



RNA Base Editing

- Efficient editing of RNA bases to **restore** or **modulate** protein production

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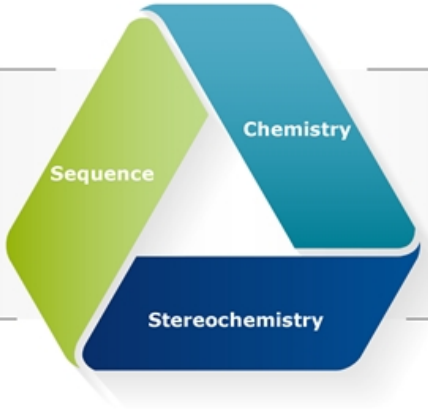
PRISM Unlocking the body's own ability to treat genetic disease

DESIGN

Unique ability to construct stereopure oligonucleotides and control three structural features to efficiently engage biological machinery



OPTIMIZE

Provides the resolution to observe this structural interplay and understand how it impacts key pharmacological properties

Built-for-Purpose Candidates to Optimally Address Disease Biology

Silencing | Splicing | RNA Editing

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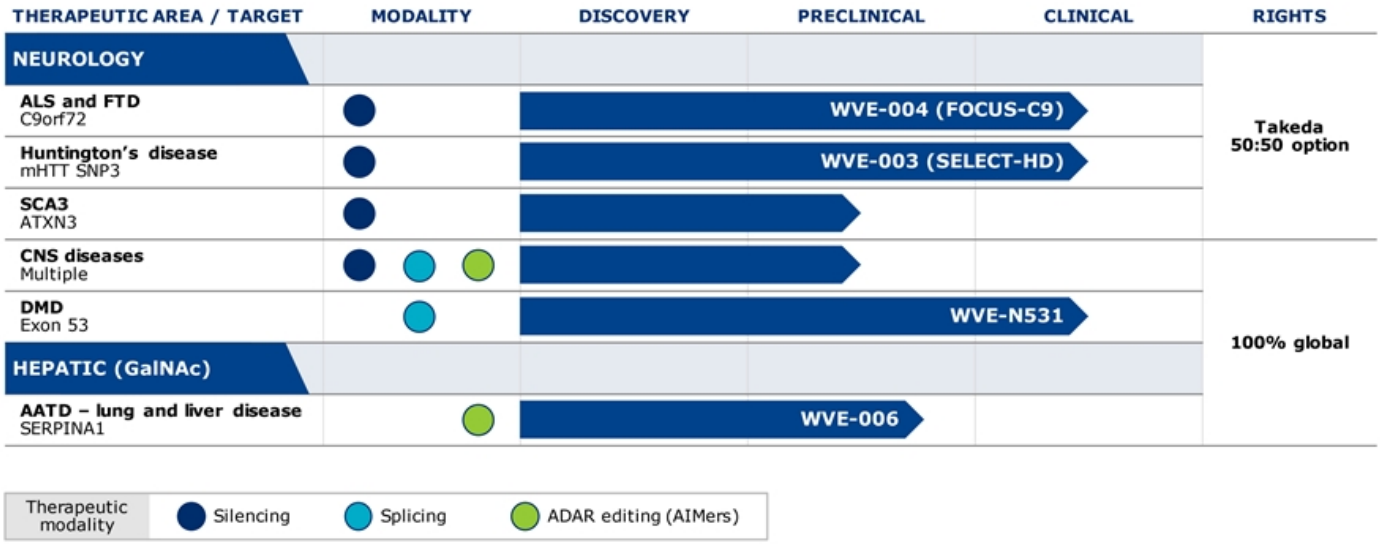
Robust portfolio of stereopure, PN-modified oligonucleotides



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ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

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WVE-004

Amyotrophic Lateral Sclerosis (ALS)
Frontotemporal Dementia (FTD)

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)	Frontotemporal Dementia (FTD)
• Fatal neurodegenerative disease	• Progressive neuronal degeneration in frontal / temporal cortices
• Progressive degeneration of motor neurons in brain and spinal cord	• Personality and behavioral changes, gradual impairment of language skills
• C9-specific ALS: ~2,000 patients in US	• C9-specific FTD: ~10,000 patients in US

Including patients with C9-associated ALS, FTD or both

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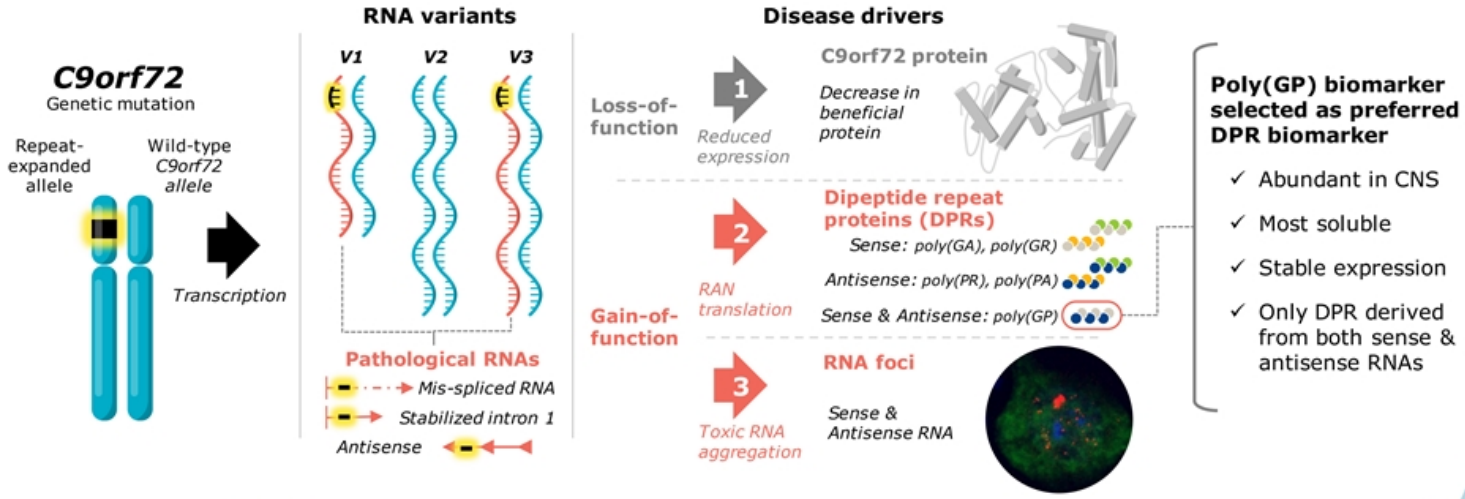
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

WVE-004 addresses each biological aspect of *C9orf72*-associated ALS and FTD



WVE-004 is designed to affect multiple drivers of toxicity

Variant-selective oligonucleotide, lowering V1 & V3 in preclinical studies[1]

Preserves C9orf72 protein expression; does not exacerbate potential loss-of-function driver of disease

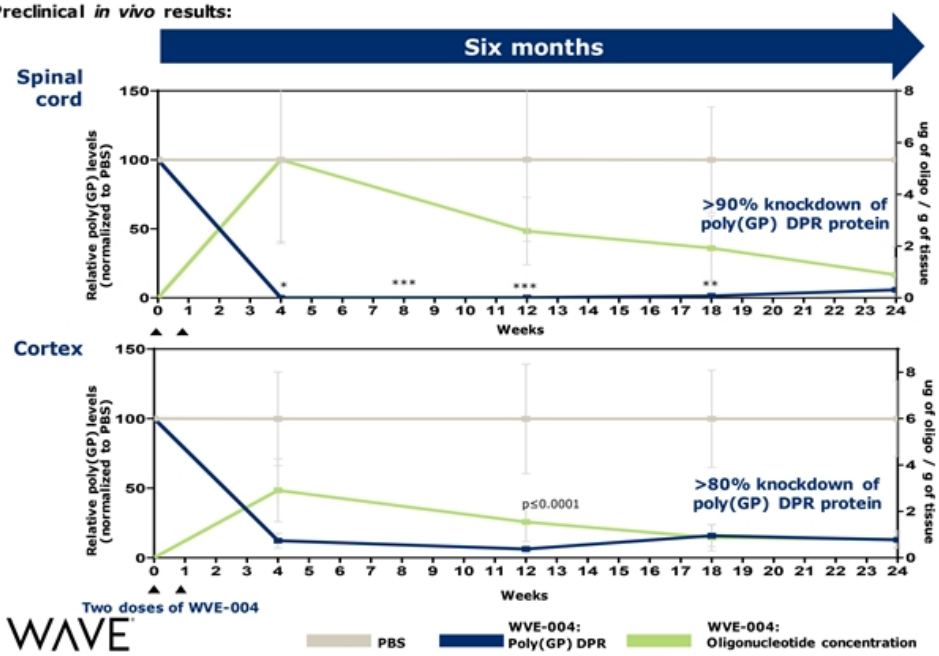
Reduces toxic gain-of-function drivers of disease (RNA foci, DPRs)

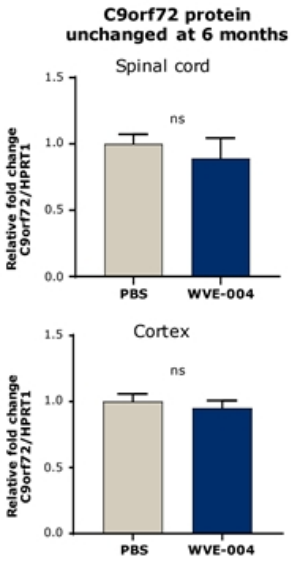
FOCUS ON C9 WAVE LIFE SCIENCES

[1]**Liu et al., 2022** *Mol Ther Nuc Acids* doi: 10.1016/j.omtn.2022.04.007

Preclinical studies with WVE-004 demonstrated durable reduction of poly(GP) in spinal cord and cortex 6 months after two doses

Preclinical *in vivo* results:





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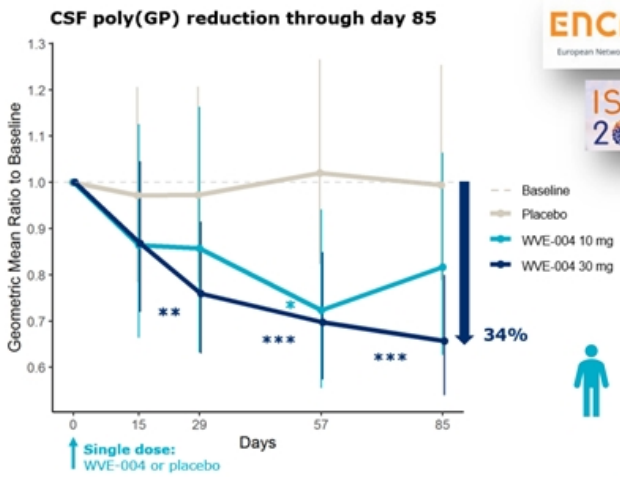
Liu *et al., 2022 Molecular Therapy Nucleic Acids* doi: 10.1016/j.omtn.2022.04.007; 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by poly(GP) MSD assay.
*: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. DPR: Dipeptide repeat protein

WVE-004 clinical data demonstrate successful translation of preclinical approach to clinic

PK/PD modeling using preclinical *in vivo* models predicted pharmacodynamically active starting dose

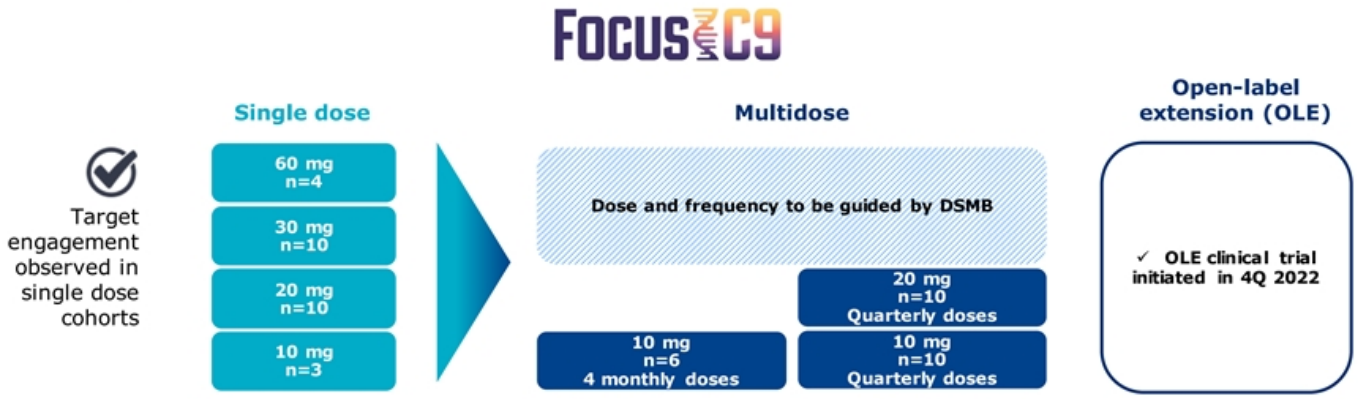
- ✓ Poly(GP) reduction in cortex and spinal cord in transgenic mice with WVE-004
- ✓ Sufficient concentrations of WVE-004 in cortex and spinal cord of NHP for target engagement

Target engagement confirmed in patients supports advancing FOCUS-C9 clinical study



PK: pharmacokinetic PD: pharmacodynamic; Right: Mixed model for repeated measures used to estimate geometric mean ratio to baseline via least squares mean and to calculate p-values. P-values represented by asterisks are for within-dose group geometric mean ratios. *p≤0.05, **p≤0.01, ***p≤0.001. Poly(GP) assay: Wilson et al., 2022 J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2021-328710. Data presented at ENCALS Meeting (June 1-3, 2022) and International Congress on Frontotemporal Dementias (Nov. 2 – 5, 2022)

Dosing ongoing in FOCUS-C9 clinical trial with multiple doses of WVE-004



Data from all cohorts in the FOCUS-C9 trial are expected in 1H 2023

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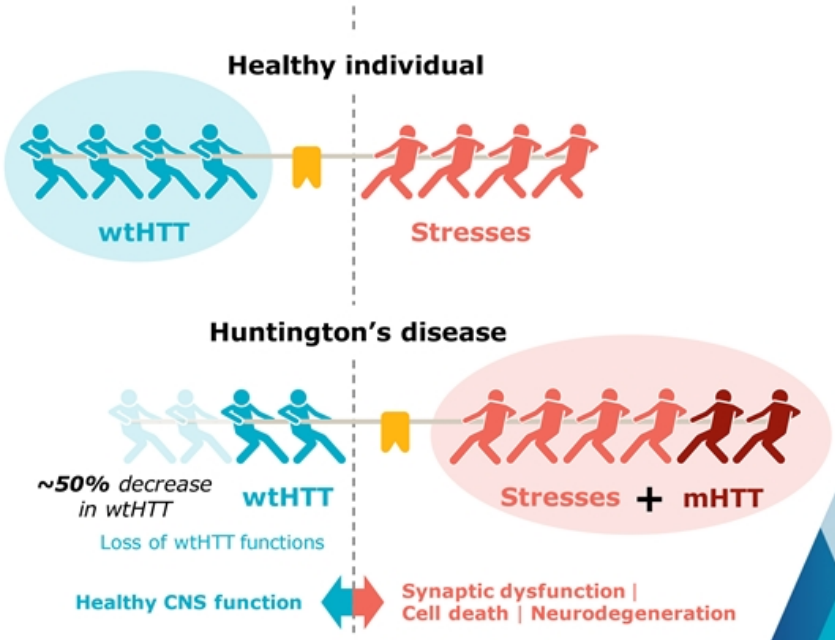
WVE-003

Huntington's Disease

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

Huntington's disease (HD)

- Wild-type HTT (wtHTT) is critical for normal neuronal function*
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT)
- HD is a monogenic autosomal dominant genetic disease; fully penetrant and affects entire brain
- Fatal disease characterized by cognitive decline, psychiatric illness, and chorea
- 30,000 people with HD in the US and more than 200,000 at risk of developing HD



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WVE-003: Only investigational HD therapy in clinical development designed to lower mHTT while sparing wtHTT

wtHTT supports healthy brain function, especially in the context of stress

Regulates synaptic plasticity

Supports synaptic protein transport

Promotes neuronal survival

Supports cilia and CSF circulation

WVE-003

- **Unique and innovative wildtype HTT-sparing oligonucleotide**
- **Delivered to CNS without invasive surgical procedures**
- **No complex delivery vehicles required (e.g. AAV)**
- **Designed with next-generation PN chemistry**

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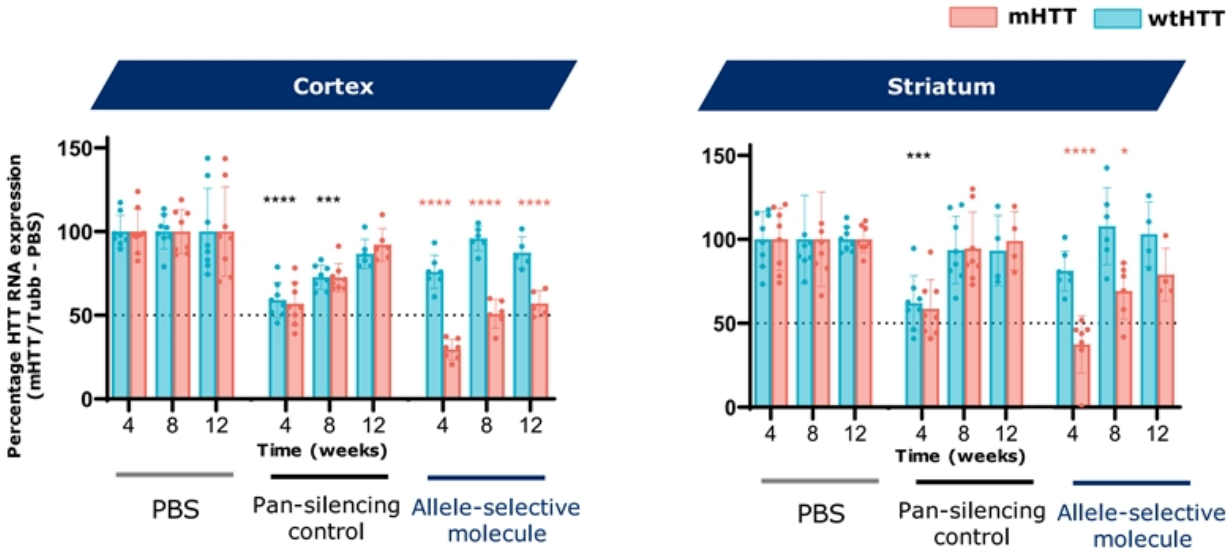
mHTT, mutant HTT; wtHTT, wild-type HTT; PO, phosphodiester; PS, phosphorothioate; PN, phosphoryl guanidine; wtHTT literature sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. 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

Allele-selective molecule decreases mHTT, spares wtHTT; Pan-silencer uniformly decreases both

Allele-selective activity in CNS of Hu97/18 mice

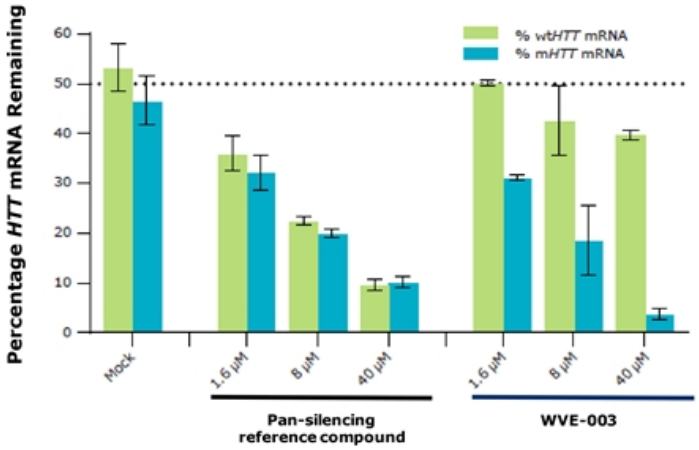


Hu97/18 mouse

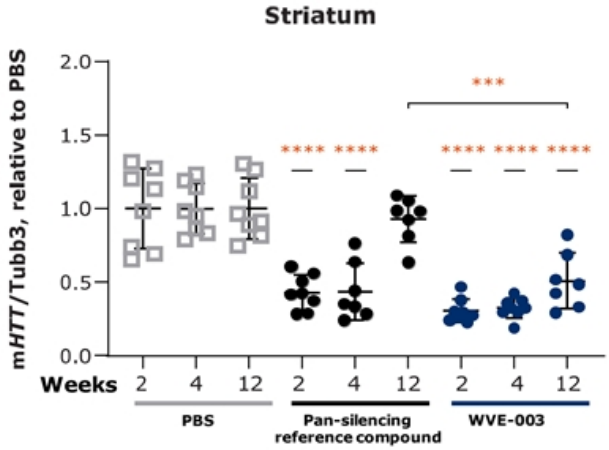
Hu97/18 mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: ns non-significant, *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus PBS by 1-way ANOVA. mHTT, mutant HTT; wtHTT, wild-type HTT; Tubb, tubulin

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



Similar results in cortex

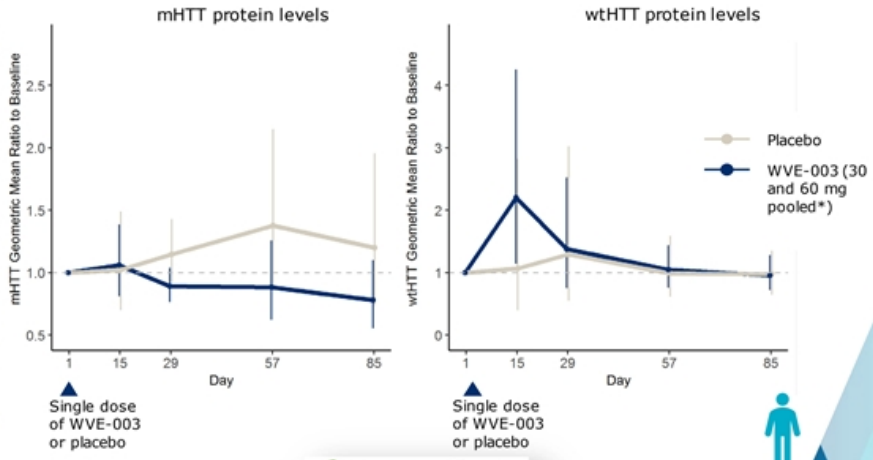
Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1. Oligonucleotide or PBS [100 µg ICV injections through cannula on days 1, 3, 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS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

Initial clinical results indicating allele-selective target engagement suggests translation of preclinical data

PK/PD modeling using preclinical *in vivo* models

- ✓ Allele selectivity (Hu97/18 mice)
- ✓ mHTT reduction in cortex and striatum (transgenic mice)
- ✓ Concentrations in NHP brain tissues sufficient for target engagement

Reductions in mean CSF mHTT and preservation of wtHTT observed in pooled analysis of single dose cohorts in SELECT-HD clinical study



HSG 2022 ANNUAL MEETING TAMPA, FLORIDA

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mHTT: mutant huntingtin protein wtHTT: wild-type huntingtin protein *Pooled considering no apparent dose response between 2 cohorts

Expanding single dose cohorts to optimize dose level based on initial clinical results

- mHTT protein reductions observed in single dose cohorts
- wtHTT protein levels appear consistent with allele-selectivity
- Generally safe and well-tolerated

- Adapting clinical trial to optimize dose level

SELECT HD

- **90 mg** *Expanding cohort*
- **60 mg** *Expanding cohort*
- **30 mg** *Expanding cohort*

Adding patients to each cohort

Additional single-dose biomarker and safety data are expected in 1H 2023

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mHTT: mutant huntingtin wtHTT: wild-type huntingtin


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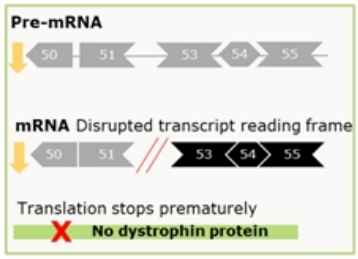
WVE-N531
Duchenne muscular dystrophy

Duchenne muscular dystrophy

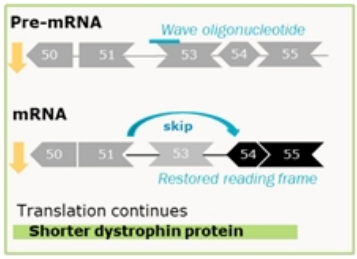
Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function.
- Dystrophin protein established by FDA as surrogate endpoint reasonably likely to predict benefit in patients[1] for accelerated approval in DMD
  - Confirmatory studies ongoing
  - Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for patients
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide.

Dysfunctional splicing (Disease)



Exon skipping (Partial Restoration)



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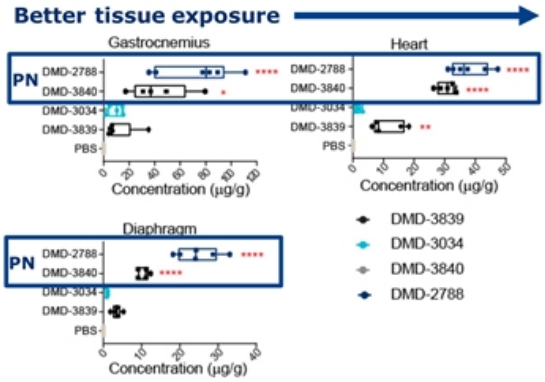
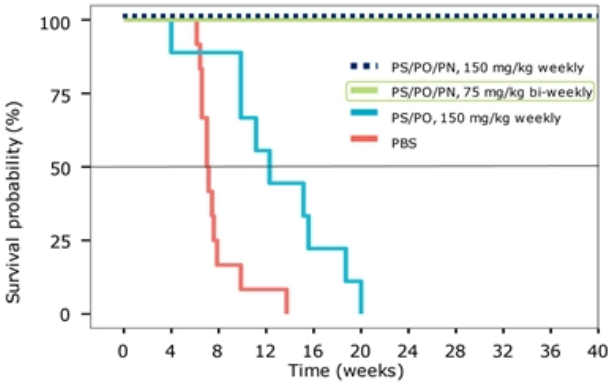
[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

PN chemistry improved muscle exposure and survival in preclinical mouse models

PN boosted muscle concentrations after single dose, which correlated with exon-skipping activity



Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination

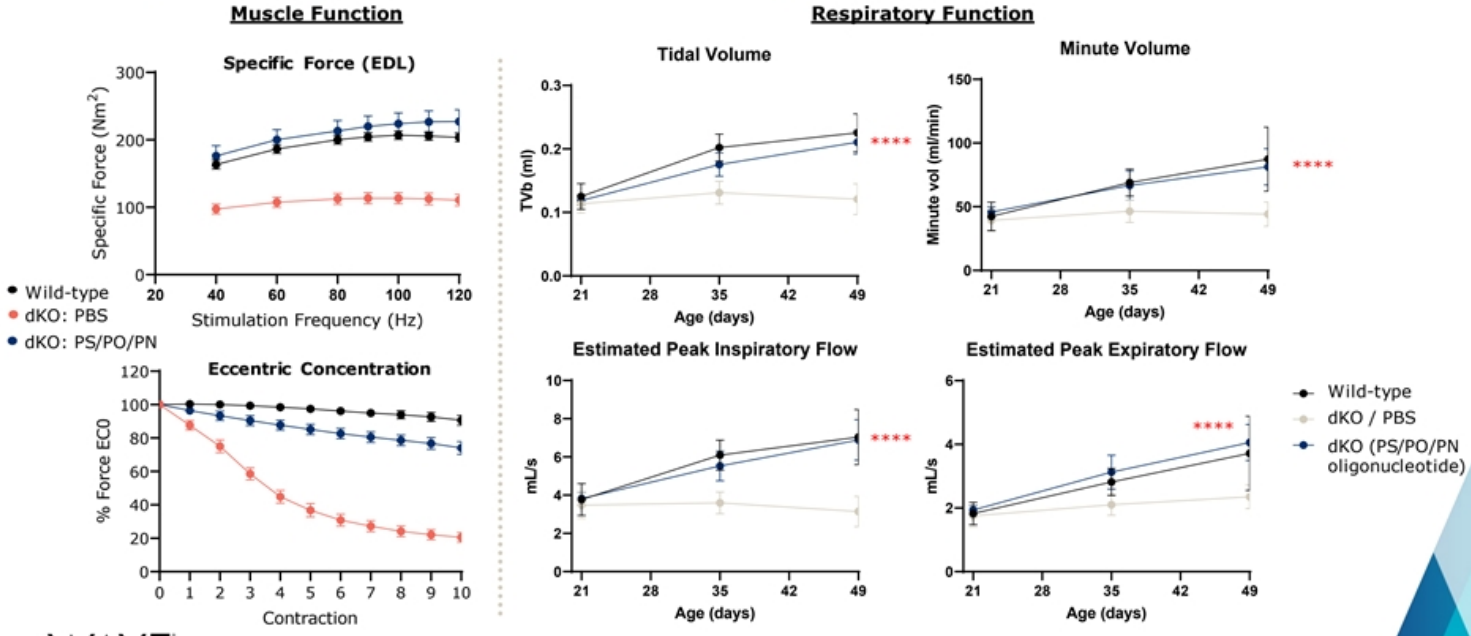


Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

WAVE LIFE SCIENCES

Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

PS/PO/PN splicing compound restores muscle and respiratory function to wild-type levels in dKO mice



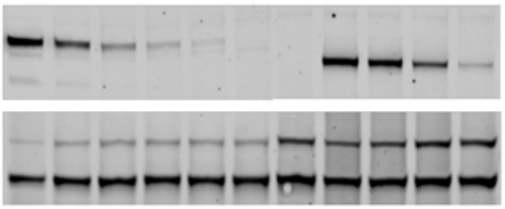
Left: *Mdx/utr-/-* mice received weekly subQ 150 mg/kg dose of PS/PO/PN stereopure oligonucleotide (postnatal day 10). Age-matched *mdx/utr-/-* littermates treated with PBS, *wild-type C57BL10* mice not treated. Wild-type, dKO PBS mice: 6 wks old; dKO PS/PO/PN: 28 – 41 wks old; Electrophysiology performed at Oxford University based on Goyenvalle et al., 2010 Mol Therapy; Right: Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

WVE-N531: Dystrophin restoration *in vitro* and enhanced muscle distribution in NHPs

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

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells					
						Mock	WVE-N531				
						0	10	3.3	1.1	0.3	Conc [uM]
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%	% Dystrophin



Enhanced muscle distribution in NHPs

Plasma and tissue concentrations of WVE-N531 (PS/PO/PN) significantly higher than suvodirsen (1st-gen PS/PO) in multiple NHP studies

- ✓ Substantially higher muscle concentrations (including heart and diaphragm) as compared to suvodirsen
- ✓ Higher plasma Cmax, AUC and Ctrough

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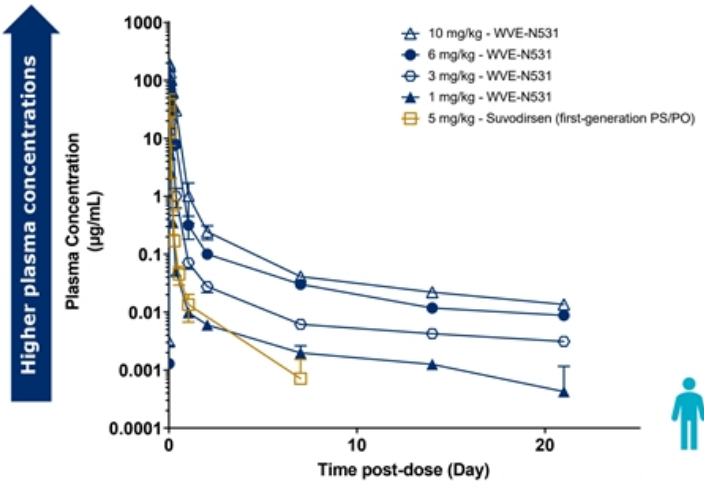
Top doses evaluated represent human-equivalent level in the range explored in preclinical dKO mouse

dKO mouse model

- ✓ Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination

Plasma WVE-N531 concentrations compared to plasma suvodirsen concentrations



Pharmacokinetic data demonstrate unique and distinct pharmacological profile with WVE-N531 as compared to first-generation chemistry

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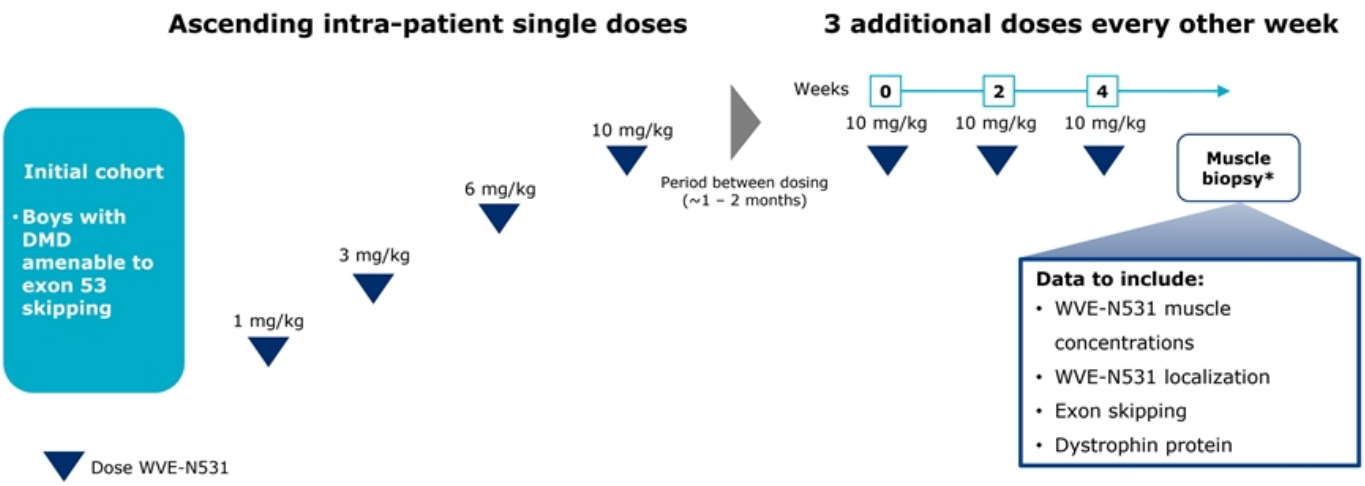
WVE-N531 open-label clinical trial (NCT04906460)

Dosing underway with multiple doses of WVE-N531



Clinical data, including muscle biopsies, expected in 4Q 2022

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*Biopsies to be taken at least six weeks after initiation of multidosing

WVE-006

Alpha-1 antitrypsin deficiency (AATD)

WVE-006: Designed to correct mutant SERPINA1 transcript to address both liver and lung manifestations of AATD

WVE-006 designed to correct Z allele mRNA to enable M-AAT protein to be produced

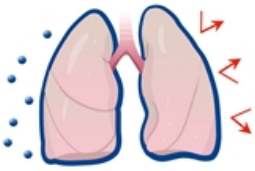
SERPINA1 Z allele mRNA encodes Z-AAT protein with E342K mutation

WVE-006 (GalNAc-conjugated AIMer)

Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

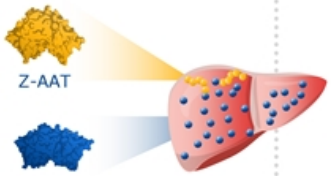
WVE-006 ADAR editing approach to address key goals of AATD treatment:

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



M-AAT reaches lungs to protect from proteases

2) Reduce Z-AAT protein aggregation in liver



RNA correction replaces mutant Z-AAT protein with wild-type M-AAT protein

3) Retain M-AAT physiological regulation

M-AAT secretion into bloodstream

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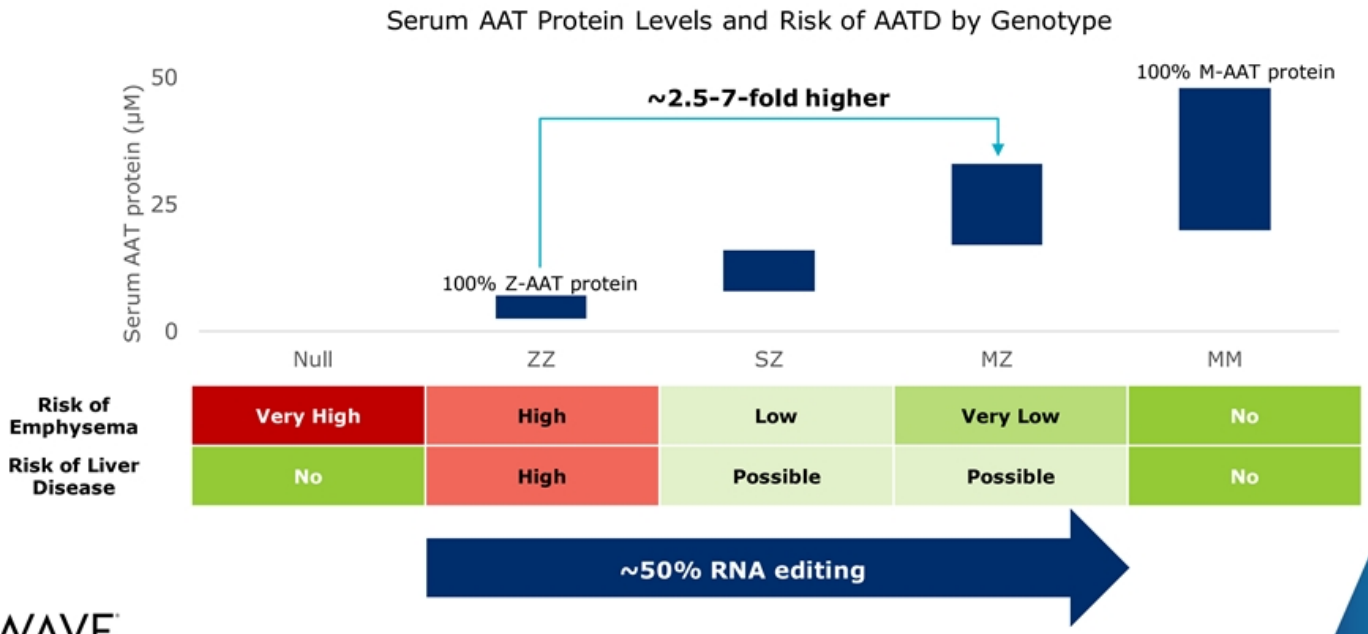
AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

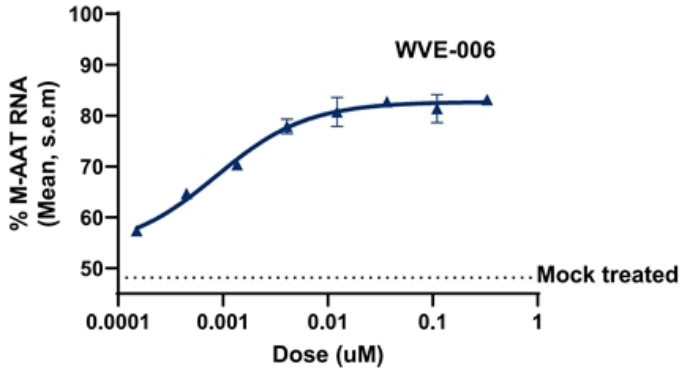
~50% RNA editing expected to increase PI*ZZ patient serum AAT levels to PI*MZ levels, with low risk of disease



1. Brode, et al. 2012 CMAJ 184:1365-1371; 2. ATS/ERS. 2003 Am J Respir Crit Care Med 168:818–900.

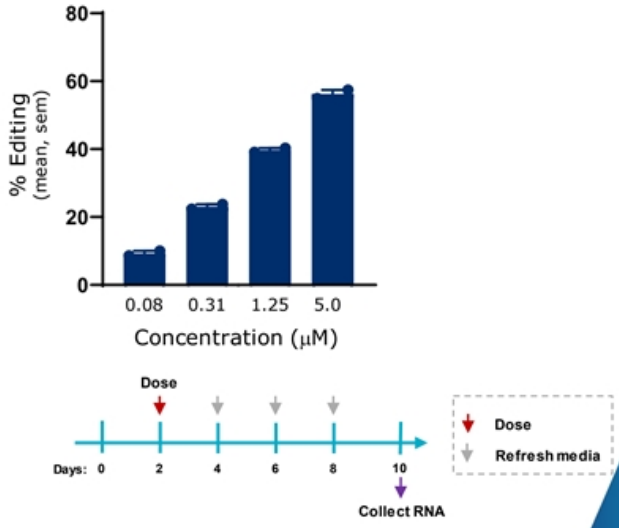
WVE-006 supports dose-dependent RNA editing in human preclinical model systems

Efficient SERPINA1 editing in donor-derived primary human hepatocytes with WVE-006 (MZ genotype)



Note: Due to MZ genotype, Y-axis ranges from ~50-100%

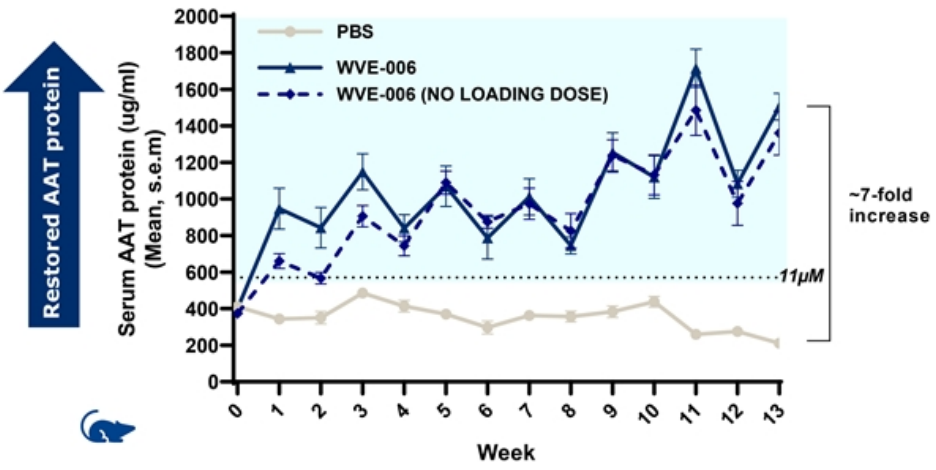
iPSC-derived human hepatocytes (ZZ genotype)



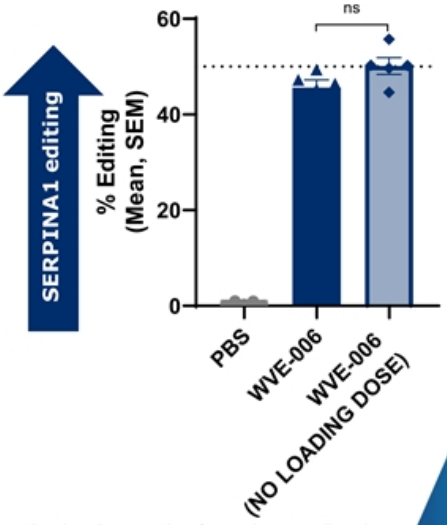
Left: MZ-donor derived primary human hepatocytes treated with WVE-006 at indicated concentrations for 48 hours
Right: Patient-iPSC derived hepatocytes (ZZ genotype) plated on day 0 and treated on day 2 with WVE-006 at indicated concentrations. Media refreshed every 2 days (days 4, 6, 8). RNA was collected on day 10. In each experiment, RNA editing was quantified by Sanger sequencing (n=2 biological replicates)

WVE-006 results in circulating AAT protein levels 7-fold above PBS control, well above established 11µM threshold

WVE-006 treatment results in serum AAT protein levels >11 uM in AATD mouse model (NSG-PiZ mice)



SERPINA1 mRNA editing in liver of AATD mouse model (NSG-PiZ mice) (Week 13)

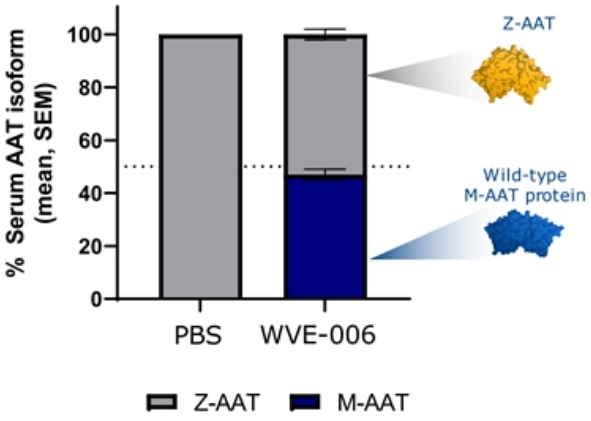


WVE LIFE SCIENCES

WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at week 13 (one week after last dose) and SERPINA1 editing was quantified by Sanger sequencing; Stats: One-way ANOVA with adjustment for multiple comparisons (Tukey); Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

WVE-006 leads to restoration of confirmed, wild-type M-AAT protein in serum

Overall percentages of serum AAT protein isoforms in NSG-PiZ mice
(Week 13)



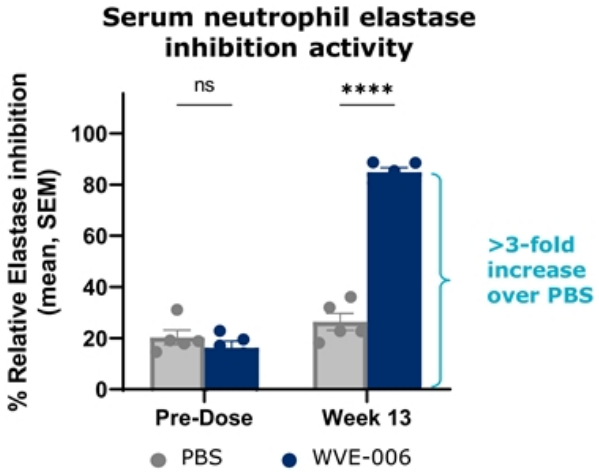
- Mass spectrometry confirms restoration of circulating healthy M-AAT protein *in vivo* after WVE-006 treatment
- Consistent with RNA editing of mutant transcript

WVE-006 administered in 7-week old NSG-PiZ mice (n=5 per group). Relative proportion of M- vs. Z-AAT protein in serum collected from animals at week 13 (one week after last dose) was measured by mass spectrometry

Significant increase in neutrophil elastase inhibition activity indicates restored M-AAT protein is functional

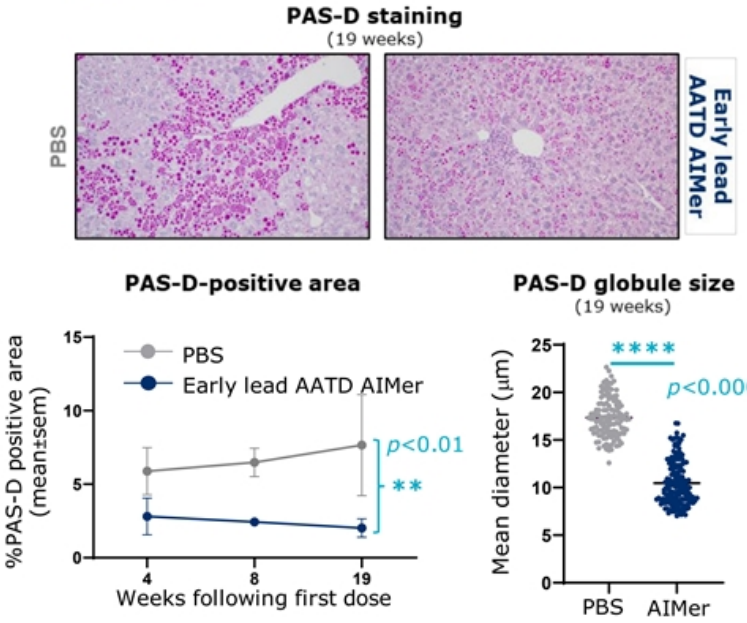
Increased neutrophil elastase inhibition activity demonstrates functionality of AAT protein

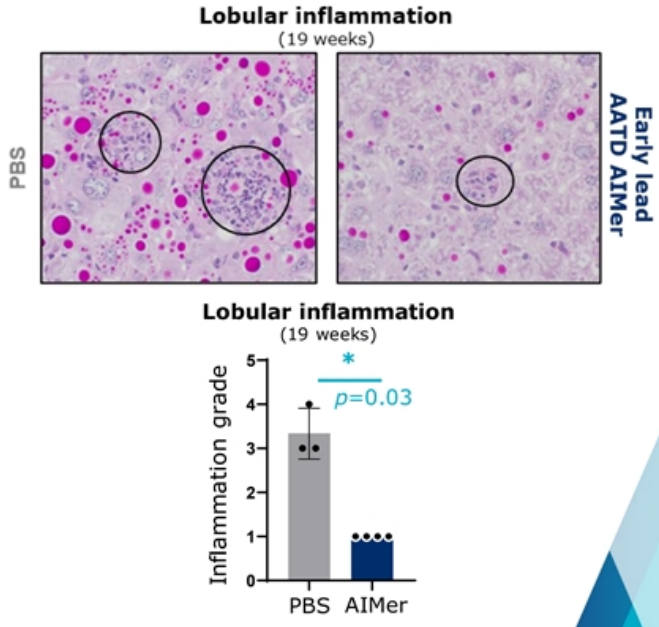
- Increases in neutrophil elastase, a proteolytic enzyme, may cause emphysema and damage the surrounding lung tissue
- Main function of AAT protein is to neutralize/control neutrophil elastase



GalNAc-conjugated AIMers administered in 7-week old NSG-PiZ mice (n=5 per group). Serum collected from mice was tested for ability to inhibit fixed concentration of neutrophil elastase in an *in vitro* reaction. Stats: Two-way ANOVA with adjustment for multiple comparisons (Bonferroni)

Early lead (pre-optimization) AATD AIMer reduces aggregation of Z-AAT and inflammation in mouse liver





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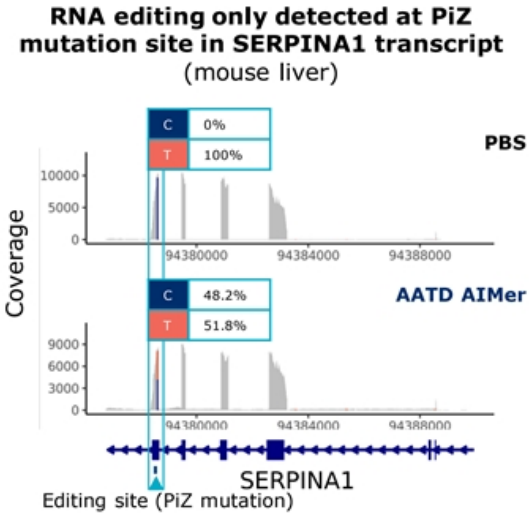
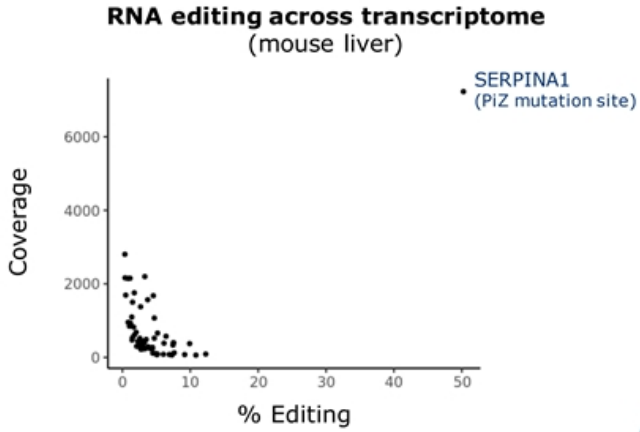
Early lead pre-optimization AATD AIMer (SA1-5) administered in hu*ADAR/SERPINA1* mice (8–10 wKs old); lower left: 20x liver images PAS-D stained, 19 weeks; Quantification of PAS-D positive staining, Stats 2-way ANOVA; Right: Quantification lobular inflammation grade (Grade based on # of inflammatory foci in lobules: Grade 0: 0; G1 1-5; G2 6-10; G3 11-15; G4 ≥16) and mean globular diameter (40 largest globules/ animal) with HALO. Stats Wilcox rank-sum tests

AIMer-directed editing is highly specific in mice

No bystander editing observed on SERPINA1 transcript





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Dose 3x10 mg/kg (days 0, 2, 4) SC with AATD AIMer (SA1 – 4). Liver biopsies day 7. RNA-seq to quantify on-target SERPINA1 editing, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4), SERPINA1 edit site is indicated

WVE-006 is a potential first- and best-in-class candidate for AATD

- **Correct Z-allele mRNA to replace mutant Z-AAT protein with functional wild-type M-AAT protein**
  - RNA editing levels show potential to support conversion of a patient from ZZ to MZ mRNA expression
  - M-AAT protein can address lung disease
  - Reduction of Z-AAT protein enables clearance of protein aggregates in liver
- **M-AAT protein produced with WVE-006 would remain under physiological regulation**
- **mRNA editing is highly specific**
- **Potentially applicable across AATD patient subpopulations**
- **Convenience of subcutaneous administration**

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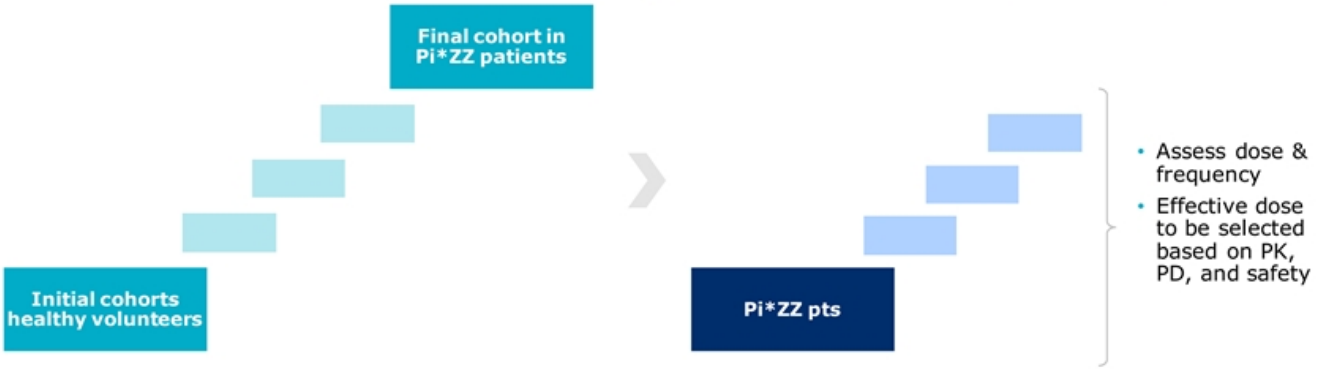
Planning for clinical development for WVE-006 underway

Phase 1/2 placebo-controlled study to establish dose and evaluate target engagement

Single-ascending dose (SAD) cohorts

Multiple-ascending dose (MAD) cohorts



Safety, tolerability, PK, change in relevant biomarkers, including serum AAT

CTA submissions for WVE-006 expected in 2023

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WAVE
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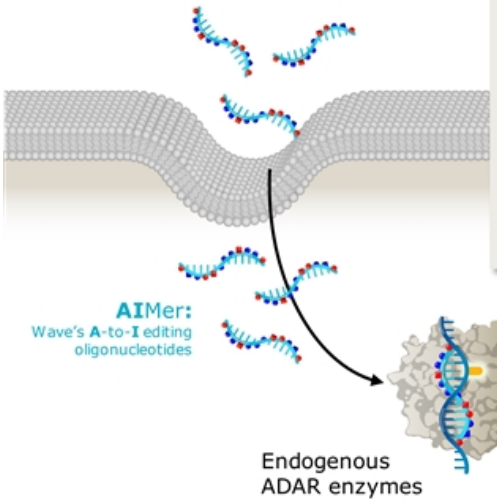
AIMers
RNA base editing capability

Unlocking RNA editing with PRISM platform to develop AIMers: A-to-I editing oligonucleotides

Free-uptake of chemically modified oligonucleotides
(No need for LNPs or viral vectors)

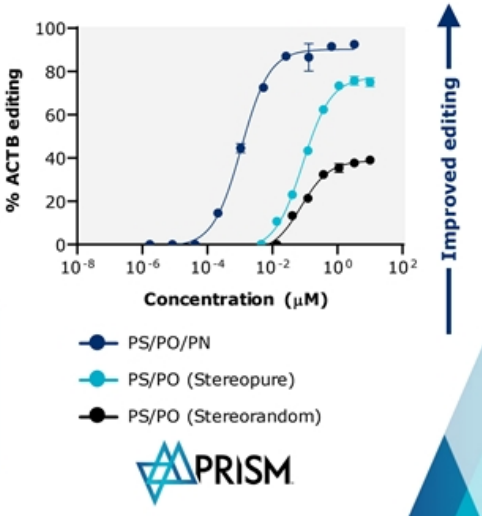


ADAR enzymes

- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- Catalyze conversion of A-to-I (G) in double-stranded RNA substrates
- A-to-I (G) edits are one of the most common post-transcriptional modifications
- ADAR1 is ubiquitously expressed across tissues, including liver and CNS

- ✓ Learnings from biological concepts
- ✓ Applied to ASO structural concepts
- ✓ Applied PRISM chemistry

Stereochemistry and PN chemistry enhance potency and editing efficiency of GalNAc AIMers in primary human hepatocytes



PRISM

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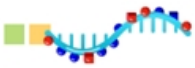
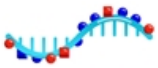
[1] Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995; Right: Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

AIMers: Realizing potential of therapeutic RNA editing by harnessing endogenous ADAR

Solved for key therapeutic attributes for potential best-in-class RNA editing therapeutics

Efficient ADAR recruitment	Stability	Delivery and intracellular trafficking	Beyond liver
• AIMer design principles • SAR developed to design AIMers for different targets	• Decade of investment and learnings to improve stability of single-stranded RNAs	• GalNAc compatible for targeted liver delivery • Endosomal escape and nuclear uptake	• AIMer design also works for delivery to CNS and other tissue types
Potent and specific editing *in vivo*	**Potential for infrequent dosing**	**Subcutaneous dosing**	**IT, IVT, systemic dosing**





- **Systematized AIMer design enables rapid advancement of new targets**
- **Strong and broad IP in chemical and backbone modifications, stereochemistry patterns, novel and proprietary nucleosides**

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SAR: structure-activity relationship

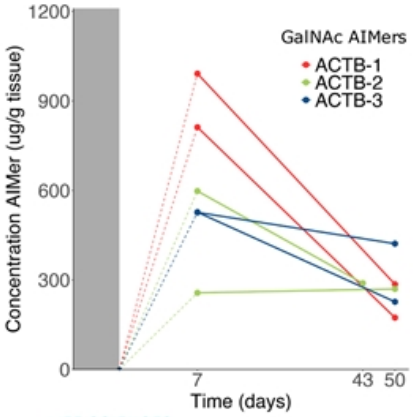
Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature biotechnology ARTICLES

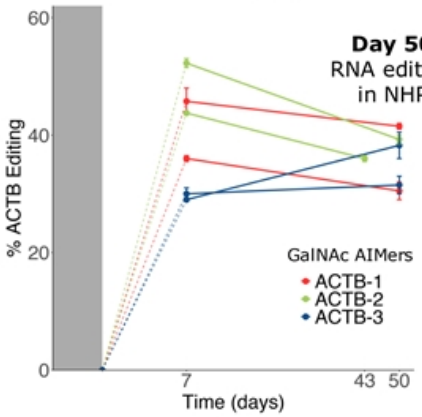
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- Specificity *in vitro* & *in vivo* (NHPs)
- *In vitro-in vivo* translation (NHPs)
- GalNAc conjugation
- Foundational AIMer SAR

AIMers detected in liver of NHP at Day 50 (PK)

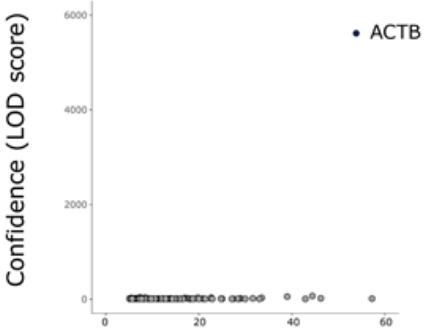


Substantial and durable editing in NHP liver *in vivo* (PD)



ADAR editing with ACTB AIMer is highly specific

RNA editing within full transcriptome (primary human hepatocytes)



LIFE SCIENCES Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1
SAR structure-activity relationship

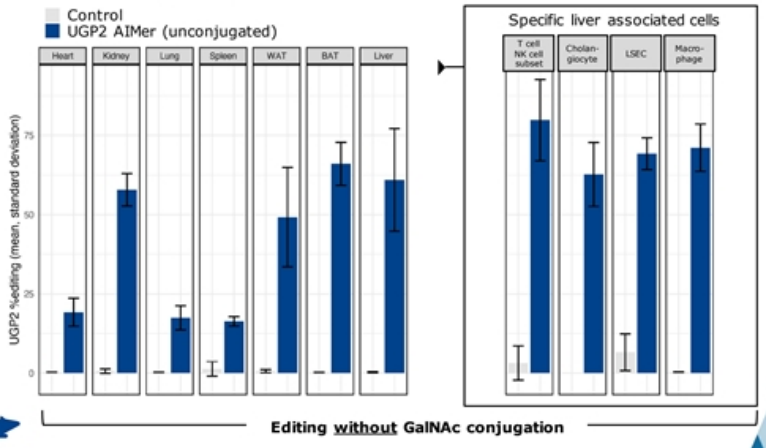
Systemic *in vivo* editing without delivery vehicles

Editing: Potent, durable, specific A → I (G) RNA editing

Delivery: Efficient RNA editing in preclinical *in vivo* models:

- ✓ Targeted delivery (GalNAc)
- ✓ Systemic delivery
- ✓ Local delivery (IT, IVT, others)

Substantial RNA editing across multiple tissues following single subcutaneous dose of UGP2 AIMer



Potential to accelerate timelines to candidate with AIMer pipeline expansion

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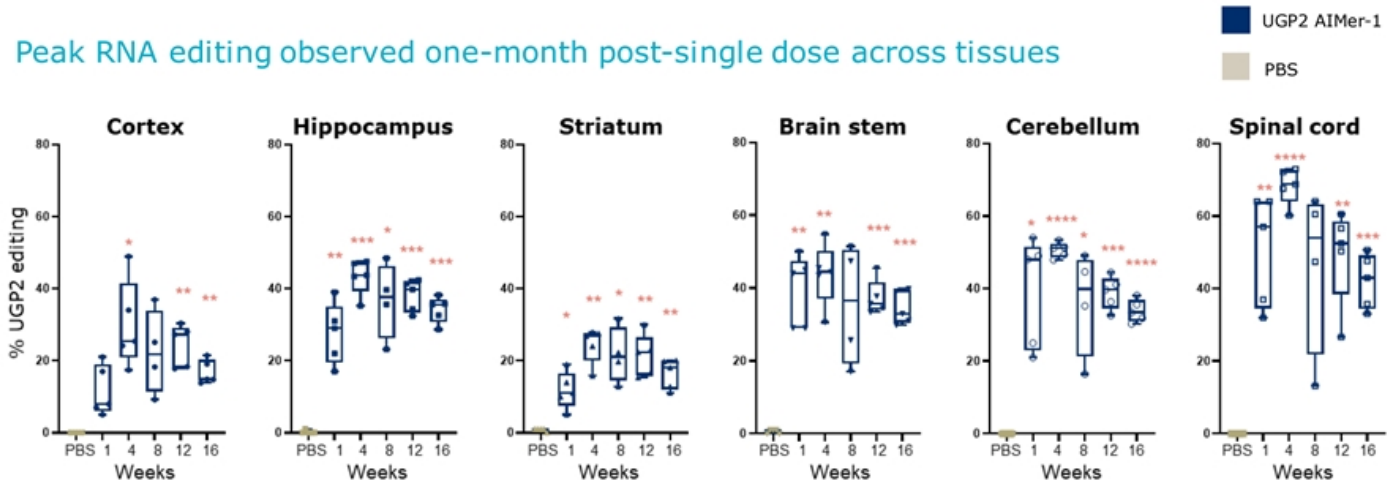
Right: Single dose of 100mg/kg unconjugated UGP2 AIMer, seven days post dose; WAT: White adipose tissue; BAT: Brown adipose tissue; CD3+: T-cells and subset of NK cells; EpCAM+(Epithelial cell adhesion molecule): mainly cholangiocytes within liver; LSEC cells (Liver Sinusoidal Endothelial Cells); M0 cells: macrophages

Substantial *in vivo* editing without delivery vehicles in CNS tissues

Peak RNA editing observed one-month post-single dose across tissues



Peak editing	30%	>40%	25%	>40%	50%	>65%

Potential CNS editing targets to benefit from learnings taken from clinical CNS silencing programs

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Transgenic huADAR mice administered 100 μg AIMer or PBS on day 0 and evaluated for UGP2 editing across CNS tissues at 1, 4, 8, 12, and 16-weeks post dose. Percentage UGP2 editing determined by Sanger sequencing. Stats: 2-way ANOVA compared to PBS (n=5 per time point per treatment) *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. ICV intracerebroventricular; PBS phosphate buffered saline

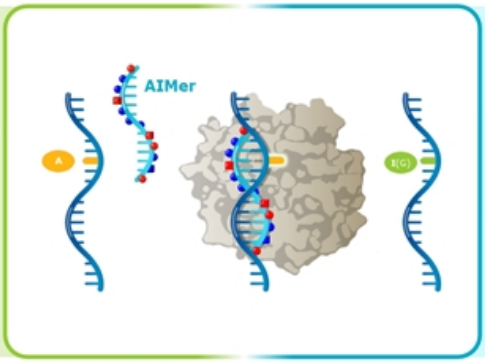
Expanding addressable disease target space using AIMers to activate pathways and upregulate expression

Correct G-to-A driver mutations with AIMers

Restore or correct protein function ☑

WVE-006 (GalNAc AIMer)
AATD

Modulate protein interactions with AIMers



- ☑ **Modulate protein-protein interaction** *Achieved POC*
- ☑ **Upregulate expression** *Achieved POC*
- ☐ Modify function
- ☐ Post-translational modification
- ☐ Alter folding or processing

AIMers provide dexterity, with applications beyond precise correction of genetic mutations, including upregulation of expression, modification of protein function, or alter protein stability

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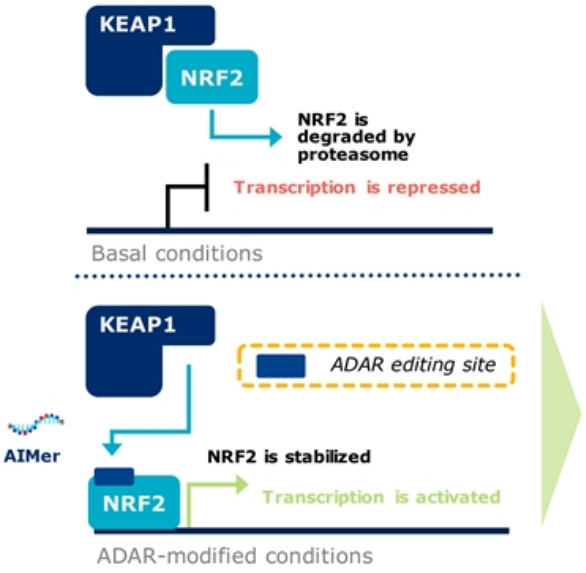
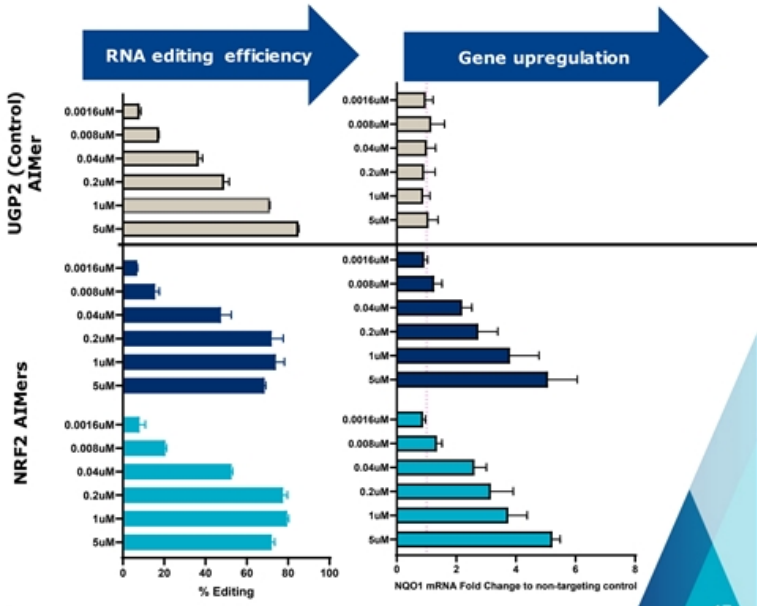
POC: proof of concept

Dose dependent modulation of protein/protein interactions



Dose-dependent gene upregulation (NQO1) *in vitro* following Nrf2 editing to disrupt protein/protein interaction



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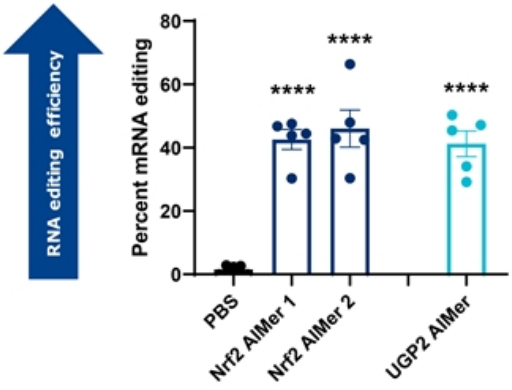
n=2; Primary hepatocytes 48h of treatment with the indicated dose concentration of AIMers

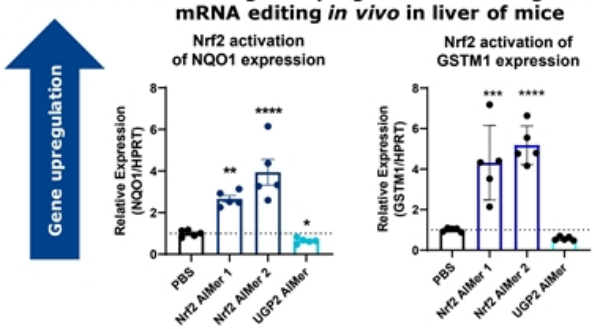
AIMers enable activation of gene pathway *in vivo* with single edit

Nrf2 mRNA editing *in vivo* in liver of mice with GalNAc AIMers

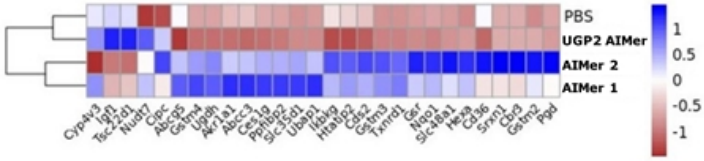


Note: Editing percentage for UGP2 control AIMer indicates editing of UGP2 mRNA

NRF2 downstream gene upregulation following GalNAc AIMer mRNA editing *in vivo* in liver of mice



RNAseq transcriptome analysis confirms disruption of Nrf2 protein interaction with upregulation of key factors



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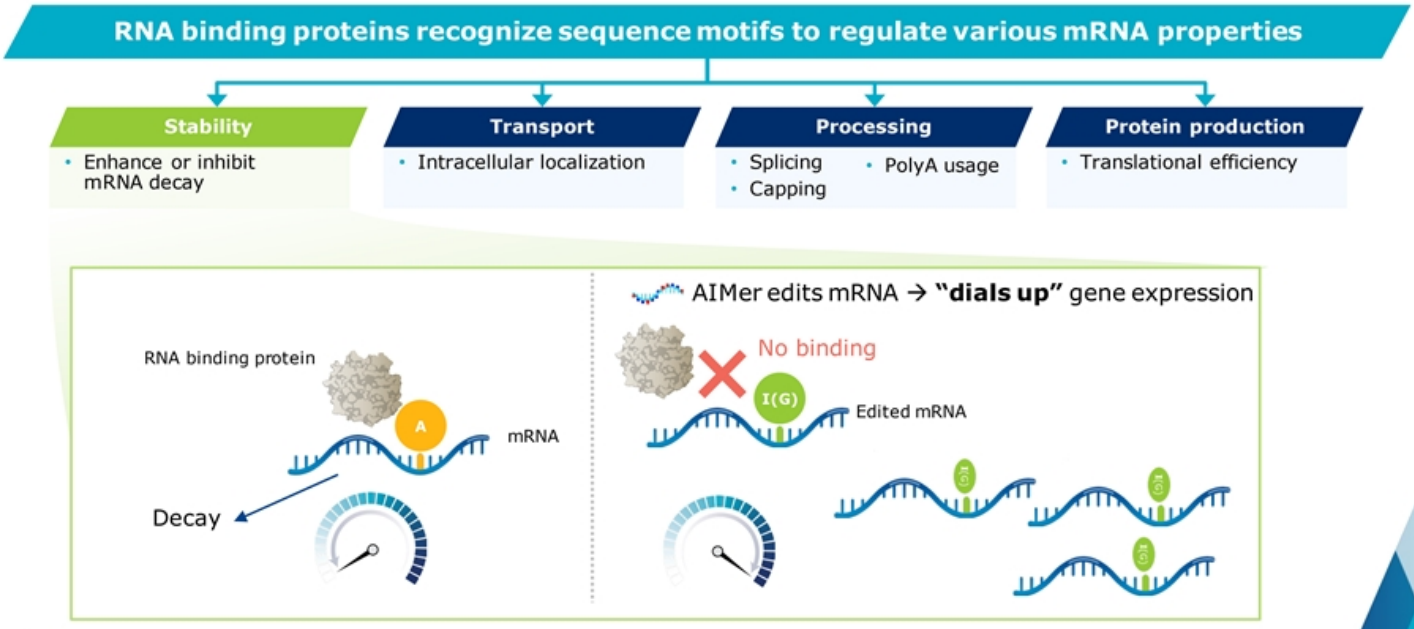
Methods: hADAR C57BL/6 mice dosed subQ (days 0, 2, 4) at 10mg/kg GalNAc-conjugated AIMers. Livers harvested (day 7), analyzed for editing and NQO1 expression via Sanger sequencing or qPCR, respectively. Data analyzed via One-way ANOVA with Tukey's multiple comparison test. Asterisks indicate statistical significance to PBS-treated animals as follows: * = p<0.05; ** = p<0.01; *** = p<0.001; **** = p<0.0001

Upregulation: AIMers can edit RNA motifs to restore or upregulate gene expression



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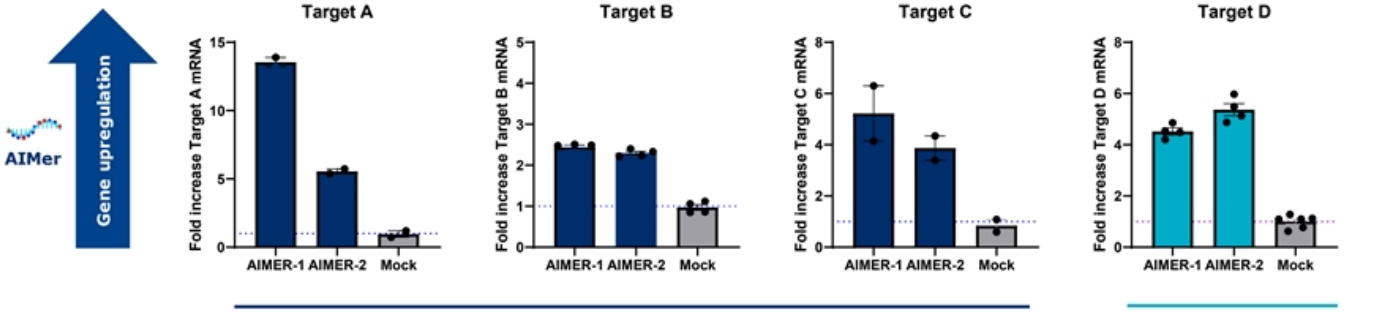
AIMers can edit RNA motifs to upregulate gene expression in hepatocytes and T-cells *in vitro*

Editing RNA Motifs to regulate RNA half-life to upregulate RNA expression is possible for clinically-relevant targets, including both metabolic and immune targets



Primary human hepatocytes (*in vitro*) | **Primary human T-cells (*in vitro*)**

Achieving >2-fold mRNA upregulation *in vitro* across multiple different targets with AIMer editing

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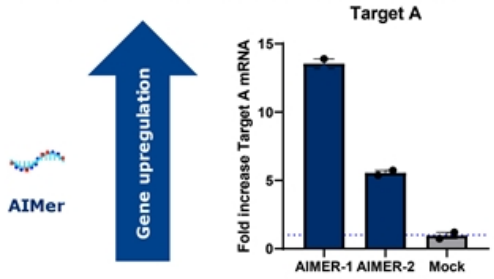
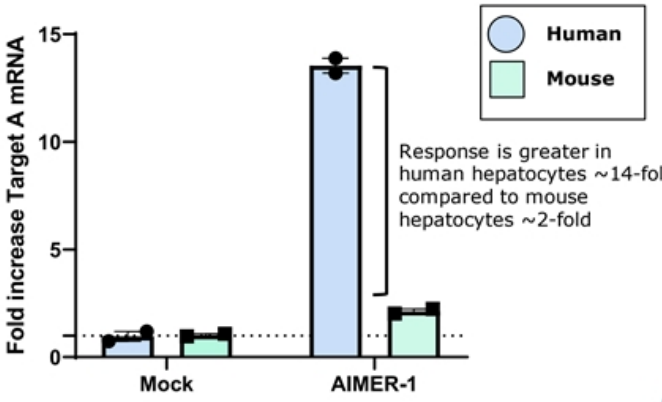
Proof-of-concept: Considerations to translate Target A upregulation results *in vivo*

Target A (undisclosed liver target)

- High unmet need with potential for multiple large indications
- Preserves endogenous protein function
- Serum protein with biomarkers of pathway activation
- Potential benefit 3-fold+ upregulation in mouse models



Mouse model may underpredict potential translation of Target A upregulation



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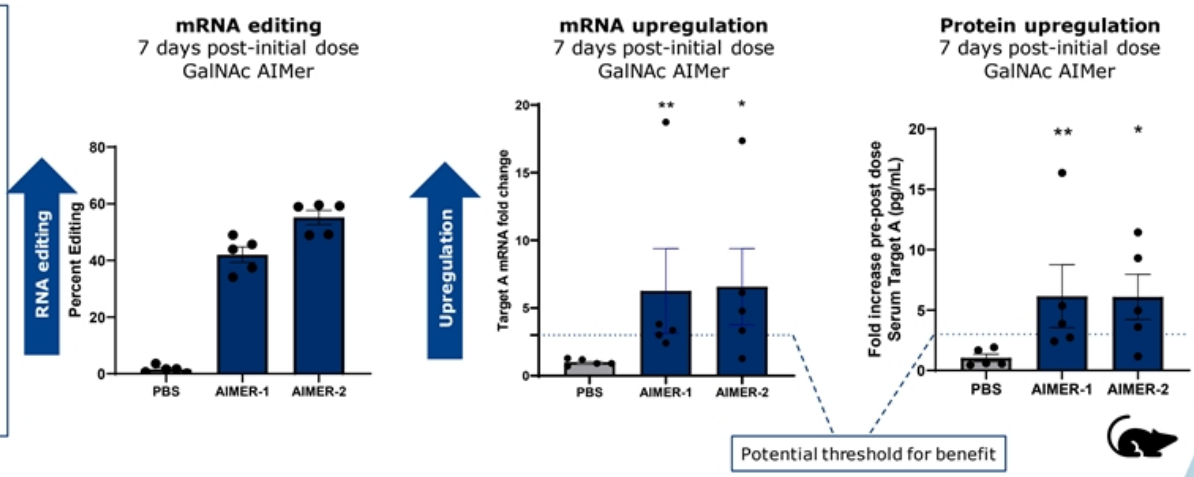
In vitro Target A mRNA fold upregulation (gymnotic 10uM, ~48h)

AIMers upregulate mRNA and downstream serum protein *in vivo* above anticipated threshold

Target A (undisclosed liver target)

- High unmet need with potential for multiple large indications
- Preserves endogenous protein function
- Serum protein with biomarkers of pathway activation
- Potential benefit 3-fold+ upregulation in mouse



- ✓ *In vitro* to *in vivo* translation of mouse Target A mRNA upregulation
- ✓ *In vivo* mRNA upregulation corresponds to an upregulation of Target A protein in serum at Day 7 demonstrating proof-of-concept

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hADAR mouse dosed subcutaneously 3 x 10 mg/kg GalNAc-conjugated AIMer or PBS days (0, 2, 4), taken down at day 7

RNA editing of nonsense mutation found in MECP2 (Rett Syndrome) restores functional protein

Normal: ... CGA... wild type protein
Rett Syndrome: ... TGA... premature stop codon
ADAR editing: ... TGG... restored protein

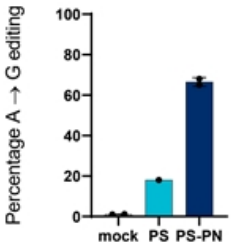
Variant base

ADAR editing site

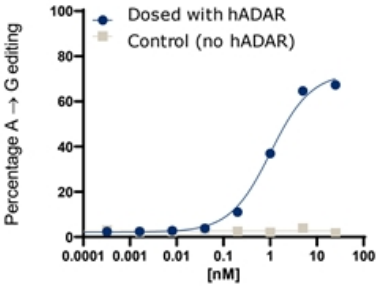
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

in vitro ADAR editing of over 60% targeting MECP2 disease transcript

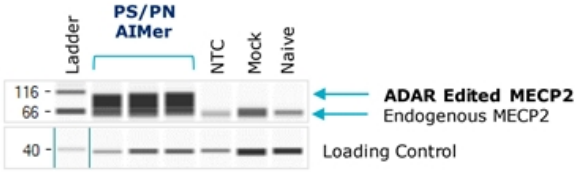
PN chemistry improved editing efficiency *in vitro*



Dose-dependent RNA editing of MECP2 mutation with PS/PN AIMer



Full length MECP2 protein is expressed following ADAR editing



293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold dilution, 48h treatment) in presence or absence of hADAR Right: Western blot for MECP2 protein. Three biological replicates, NTC AIMer, mock and naive 293T cells probed for fusion protein.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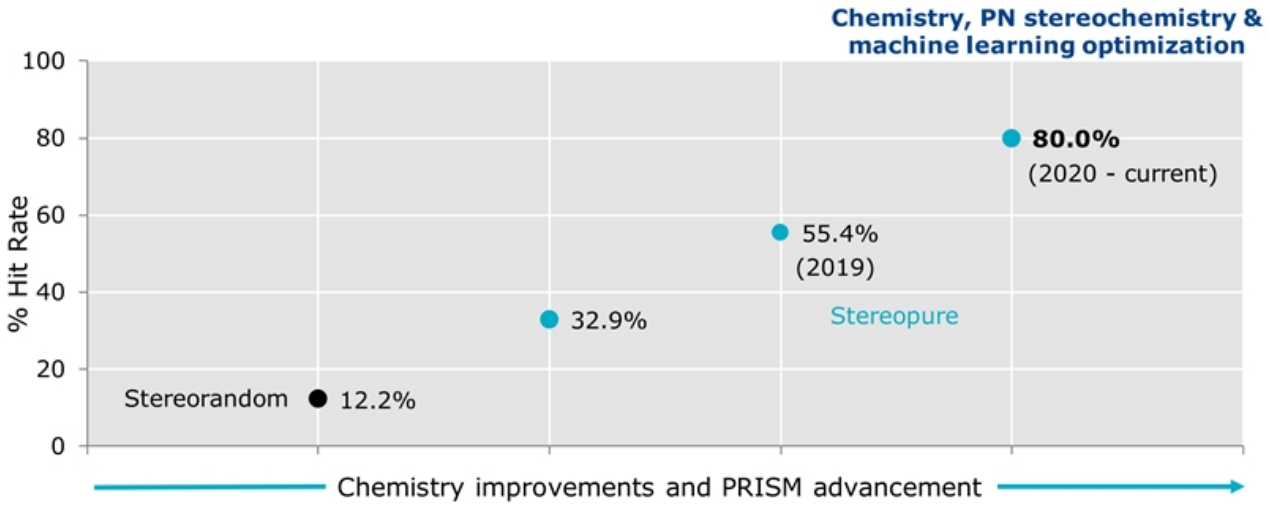
PRISM
Wave's discovery and drug development platform

Improvements in PRISM primary screen hit rates accelerate drug discovery over time

Primary screen hit rates with silencing far above industry standard hit rates



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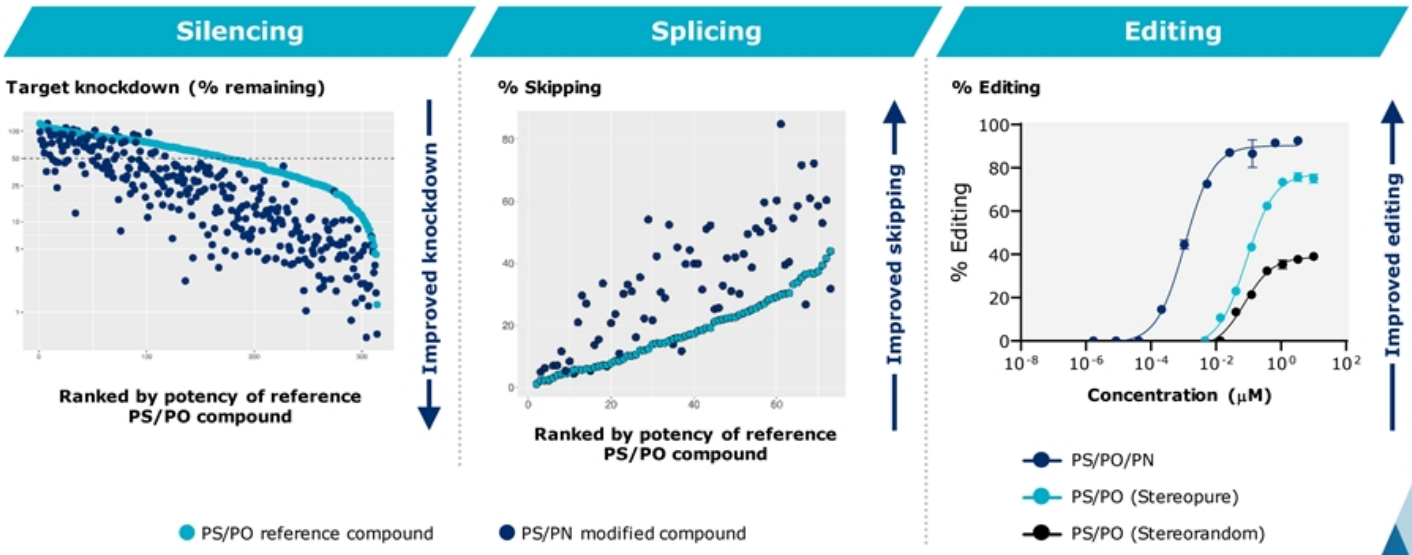
All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning

Potency is enhanced with addition of PN modifications across modalities



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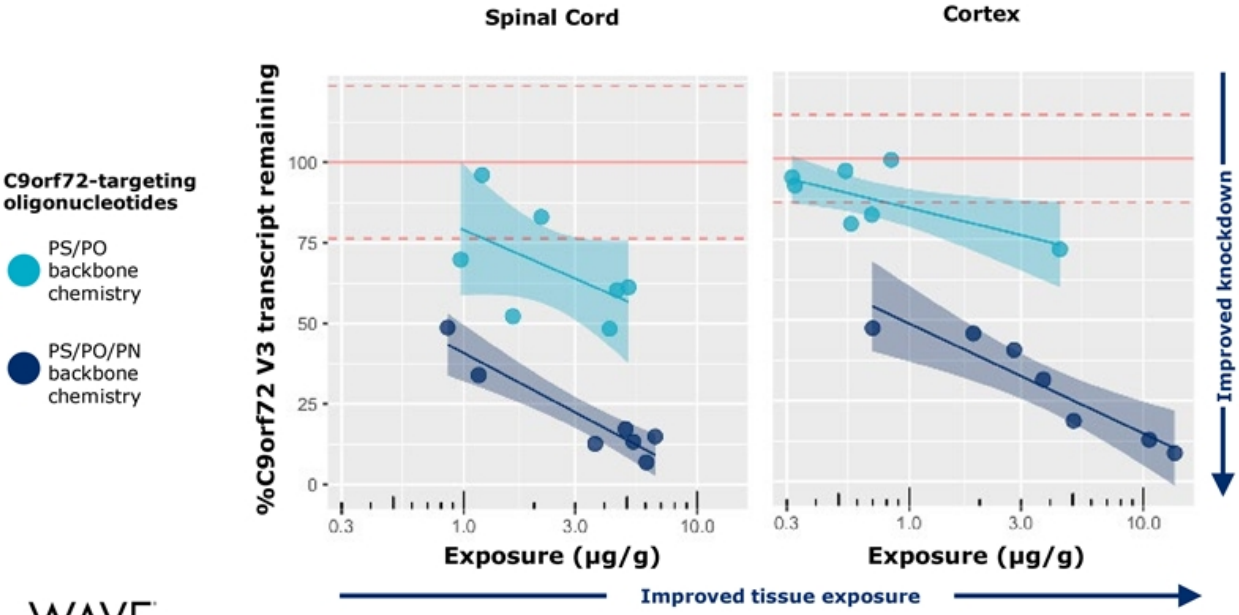
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. Right: Data from independent experiments

Adding PN chemistry modifications to C9orf72-targeting oligonucleotides improved potency *in vivo*



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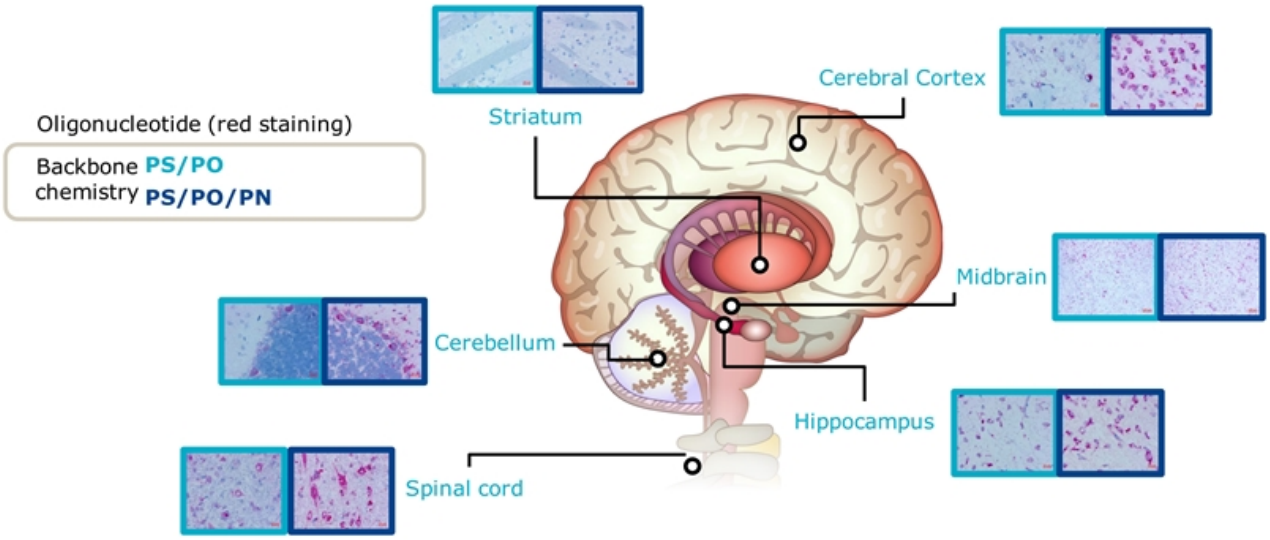
Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis; Liu et al. Molecular Therapy Nucleic Acids 2022; Kandasamy et al., Nucleic Acids Research, 2022, doi: 10.1093/nar/gkac037

PN chemistry improves distribution to CNS

Distribution of oligonucleotides in non-human primate CNS 1-month post single IT dose



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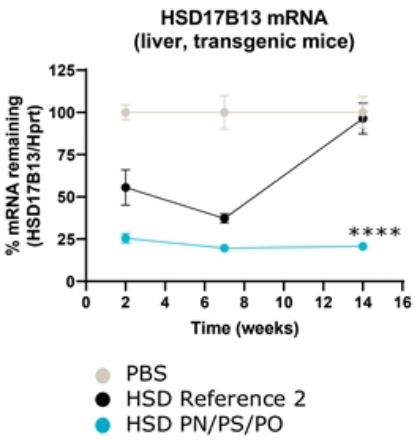
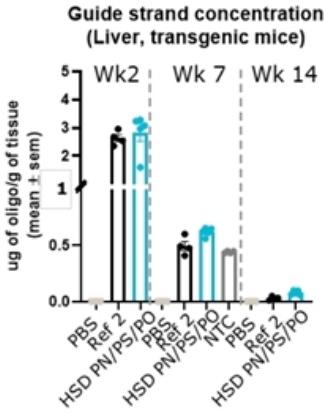
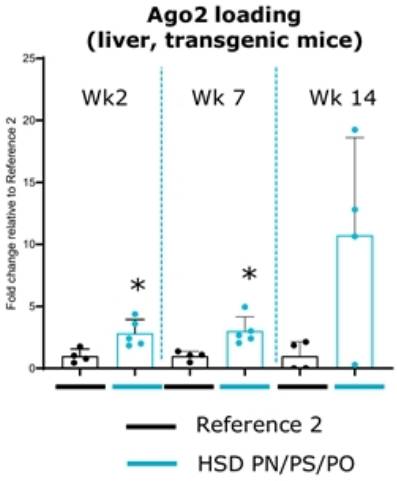
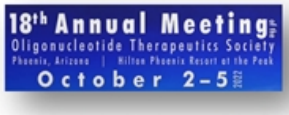
NHPs administered 1x12 mg oligonucleotide or PBS by intrathecal injection/lumbar puncture (IT). CNS tissue evaluated 11 or 29 days after injection (n=6 per group). Oligonucleotide was visualized by ViewRNA (red), and nuclei are counterstained with hematoxylin. Images from day 29.

PRISM PN siRNA led to unprecedented silencing >3 months after single dose









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Mice expressing a human *HSD17B13* transgene were treated with 3 mg/kg of the indicated siRNA or PBS, and liver mRNA, guide strand concentration, and Ago2 loading were quantified at the indicated times post-dose. Stats: Two-way ANOVA with post-hoc test * P<0.05, ****P<0.0001. Reference 2 is based on Foster, et al., 2018. Mol. Ther. 26, 708-717

Established internal GMP manufacturing for multiple oligonucleotide modalities

Strong technical knowhow and operating expertise

- Experienced team led by Sridhar Vaddeboina, PhD (SVP Chemistry, Manufacturing, Controls)
- Experts in oligonucleotide synthesis (ASOs, DNAs, RNAs, siRNAs)
- Proven track record scaling complex chemistries; delivered clinical supply for six programs at Wave

Established infrastructure

- State of the art facilities (90,000 sq ft) and expansion space
- Process and analytical development labs
- GMP oligonucleotide (API) manufacturing
- Established Quality and GMP systems (QA, supply chain, logistics, QC testing)

Scalable to support Wave's GMP manufacturing needs, as well as potential new partners

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Upcoming milestones

Steady flow of data updates expected to further inform future opportunities and unlock value

WVE-004 C9orf72 ALS & FTD	✓ Delivered clinical target engagement data with single doses ✓ Initiated OLE clinical trial in 4Q 2022 • Data from all cohorts in FOCUS-C9 trial expected in 1H 2023	**Silencing**	**CNS** *(Intrathecal)*
WVE-003 HD SNP3	✓ Delivered single-dose clinical data indicating reduction in mHTT with wtHTT preserved, appearing consistent with allele-selectivity • Additional single-dose biomarker and safety data in 1H 2023		
WVE-N531 DMD Exon 53	• Clinical data, including muscle biopsies, to enable decision making in 4Q 2022	**Splicing**	**Muscle** *(IV)*
WVE-006 AATD	✓ Selected an AATD AIMer development candidate and initiated IND-enabling activities • Submit clinical trial applications in 2023	**ADAR editing**	**Targeted delivery liver** *(Subcutaneous)*

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WVE-004 FOCUS-C9 clinical trial (NCT04931862); WVE-003 SELECT-HD clinical trial (NCT05032196); WVE-N531 open-label clinical trial (NCT04906460)

Realizing a brighter future for people affected by genetic diseases

For more information:

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