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): May 23, 2023

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

Singapore	**001-37627**	**98-1356880**
(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 (see General Instruction A.2. below):

☐ 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))

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. ☐

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

Item 7.01 Regulation FD Disclosure.

On May 23, 2023, Wave Life Sciences Ltd. (the "Company" or "Wave") issued a press release announcing topline data from the Company's Phase 1b/2a FOCUS-C9 trial of WVE-004, the Company's clinical candidate for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD). In addition, the press release indicated that Wave will host an investor conference call at 8:30 a.m. ET on May 23, 2023 to review the FOCUS-C9 clinical trial results. A copy of the press release is attached hereto as Exhibit 99.1 and incorporated by reference herein.

In addition, from time to time, the Company presents and/or distributes slides and presentations to the investment community to provide updates and summaries of its business. On May 23, 2023, 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/. A copy of this presentation is also furnished as Exhibit 99.2 hereto and incorporated by reference herein.

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 they 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 8.01 Other Events.

The information set forth in the press release referred to in Item 7.01 above, other than the fourth and fifth paragraphs thereof, is incorporated by reference into this Item 8.01 of this Current Report on Form 8-K.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release issued by Wave Life Sciences Ltd. dated May 23, 2023
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated May 23, 2023
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: May 23, 2023

Wave Life Sciences Announces Topline Results from Phase 1b/2a FOCUS-C9 Study of WVE-004 for C9orf72-associated Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Potent and durable target engagement observed across cohorts, including with 10 mg doses administered every 12 weeks which were also generally safe and well-tolerated

WVE-004 did not show clinical benefit compared with placebo; additionally, poly(GP) reductions did not correlate with clinical outcomes — Wave to discontinue development of WVE-004

Wave to host investor conference call at 8:30 a.m. ET today

CAMBRIDGE, Mass., May 23, 2023 — Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced topline results from the Phase 1b/2a FOCUS-C9 study evaluating WVE-004 as an investigational treatment for C9orf72-associated amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (C9-ALS/FTD). The results include data from a planned analysis of the study, where participants received multiple 10 mg doses of WVE-004 or placebo every 12 weeks (Q12W) or every 4 weeks (Q4W), as well as an additional 20 mg single dose cohort.

WVE-004 was generally safe and well-tolerated across doses, with most adverse events presenting as mild in intensity. There were no clinically meaningful changes in cerebrospinal fluid (CSF) protein or white blood cell count and no new safety signals since the previous data update in April 2022.

Robust, sustained reductions in poly(GP) from baseline were observed, with a maximal mean reduction of 48% ($p<0.0001$) in the Q12W dose and 50% ($p=0.0001$) in the Q4W dose of WVE-004. Poly(GP) is a pharmacodynamic biomarker indicating WVE-004 is lowering C9orf72 hexanucleotide repeat expansion (G_4C_2) transcripts, which are hypothesized to contribute to pathogenesis in C9-ALS/FTD. However, no clinical benefit was observed at 24 weeks, and reductions in poly(GP) were not associated with stabilization or improvement in functional outcomes. Based on these data, and in the absence of biomarkers reasonably likely to predict clinical outcomes, Wave has decided to discontinue development of WVE-004.

“Following our initial positive single dose data last year, we advanced WVE-004 with the hope that its potency and differentiated pharmacology may deliver a better result than C9orf72-targeting oligonucleotides discontinued by others in the field. While we again saw substantial reductions of poly(GP) with multiple doses, we are deeply disappointed that we were not able to see any evidence of potential benefits that would be expected to drive meaningful outcomes for these patients,” said Paul Bolno, MD, MBA, President and CEO of Wave Life Sciences. “C9-ALS/FTD is complex and made all the more challenging by the absence of a clinically validated biomarker. Our hope is that these data can help advance future research, and we are committed to sharing results with the community at an upcoming medical congress. On behalf of everyone at Wave, I wish to sincerely thank the participants, their families, the clinical sites, and our study advisory committees for their participation and support.”

Continued Dr. Bolno: “These data do reinforce that our preclinical data on target engagement and pharmacology are translating in the clinic. Looking forward, our lead programs in Huntington’s disease, Duchenne muscular dystrophy and Alpha-1 antitrypsin deficiency are designed to leverage biomarkers correlated with functional outcomes, making us more confident in the future of these programs and our emerging preclinical pipeline.”

Wave remains on track to share data from its Phase 1b/2a SELECT-HD study in Huntington's disease investigating WVE-003 in the second half of 2023. The company is also rapidly advancing WVE-N531 for Duchenne muscular dystrophy amenable to exon 53 skipping into the potentially registrational Part B (Phase 2) clinical study, following its best-in-class exon skipping data observed in the Part A proof-of-concept study. Wave is also on track to bring the industry's first RNA editing compound, WVE-006, into a clinical trial in Alpha-1 antitrypsin deficiency in the second half of 2023. In addition, the company continues to advance preclinical research with its modalities that restore or repair endogenous proteins, including additional RNA editing programs, and expects to share an update on its preclinical pipeline highlighting new data in the third quarter of 2023.

Topline FOCUS-C9 Results

The FOCUS-C9 study initially evaluated single doses of 10, 30 or 60 mg of WVE-004 or placebo. Based on potency and durability observed in the single dose cohorts, Wave added a 20 mg single dose cohort (n=8) and advanced 10 mg as the dose for the repeat dose phase, administered every 12 weeks (Q12W; n=8) or every four weeks (Q4W; n=5) and compared with placebo (n=7).

Participants in the Q12W cohort receive two 10 mg doses and participants in the Q4W cohort receive four 10 mg doses; participants are followed for 24 weeks. Key observations from the planned analysis of the study include:

Safety/tolerability results

- WVE-004 was generally safe and well-tolerated across the single and multidose cohorts (n=26 unique WVE-004-treated participants) and the most common adverse events (AEs) in the study were related to disease progression and intrathecal administration.
- AEs were mostly mild in intensity across all treatment groups.
- Among WVE-004-treated participants, there was one SAE in the study reported by the investigator as related to study drug that occurred in the 60 mg single dose cohort, as previously reported in April 2022. There was also one SAE reported that was procedure related. All other SAEs were associated with disease progression.
- There were no AEs indicative of antisense oligonucleotide class effects, including no clinically meaningful changes in blood chemistry or hematology.
- There was no evidence of inflammation in the CSF as indicated by no clinically meaningful changes in CSF white blood cell count or protein.

Poly(GP) results

- In the multidose cohorts, the mean, maximal poly(GP) reduction from baseline was 48% (95% CI, 0.36, 0.58; $p<0.0001$) for the 10 mg Q12W cohort at week 16 and 50% (95% CI: 0.29, 0.64, $p=0.0001$) for the 10 mg Q4W cohort at week 24.
- In the 20 mg single dose cohort, the mean, maximal poly(GP) reduction from baseline was 51% (95% CI, 0.29, 0.67; $p=0.0006$) at week 24.

Exploratory biomarker results: CSF neurofilament light chain (NfL)

- NfL elevations were observed in the WVE-004 20 mg single dose cohort and the 10 mg Q4W cohort; the 10 mg Q12W cohort and placebo had overlapping confidence intervals.
- There was no correlation (absolute correlation coefficient <0.1) between CSF NfL increases and ALSFRS-R change.

Exploratory clinical outcomes

- There was no benefit observed for WVE-004-treated participants compared with placebo on any exploratory clinical outcome measure, including the Revised ALS Functional Rating Scale (ALSFRS-R).

- In the Q12W cohort, there was no statistically significant difference in ALSFRS-R mean change between WVE-004 and placebo at any timepoint.
- In the Q4W cohort, participants treated with WVE-004 showed greater reduction in ALSFRS-R mean change than placebo patients at week 24 ($p<0.0001$); however, ALSFRS-R scores were not statistically different from the decline seen in natural history (using a matched natural history control group from the PRO-ACT database).
- Additionally, there was no benefit observed for WVE-004 treated participants with FTD compared with placebo on the Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD) Behavior and Language Domains (CDR® plus NACC FTLD).
- Reductions in poly(GP) did not associate with improvement on ALSFRS-R and CDR plus NACC FTLD and as such, Wave determined it will discontinue development of WVE-004, including stopping the FOCUS-C9 study and the open label extension study.

Investor Conference Call

Wave will host an investor conference call today at 8:30 a.m. ET to review the FOCUS-C9 clinical trial results. A webcast of the conference call can be accessed by visiting "Investor Events" on the investor relations section of the Wave Life Sciences website: https://ir.wavelifesciences.com/events-and-presentations. Analysts planning to participate during the Q&A portion of the live call can join the conference call at the following audio conferencing link**:** available here. Once registered, participants will receive the dial-in information. Following the live event, an archived version of the webcast will be available on the Wave Life Sciences website.

About FOCUS-C9

The FOCUS-C9 trial is a global, multicenter, randomized, double-blind, placebo-controlled Phase 1b/2a clinical trial to assess the safety and tolerability of single- and multiple-ascending intrathecal doses of WVE-004 for people with C9-ALS and/or C9-FTD. Additional objectives include measurement of poly(GP) dipeptide repeat (DPR) proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics (PK), and exploratory biomarkers and clinical outcomes. The FOCUS-C9 trial is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee. Support for FOCUS-C9 was provided by the Alzheimer's Drug Discovery Foundation.

About WVE-004

WVE-004 is an antisense oligonucleotide (ASO) designed with Wave's proprietary and best-in-class chemistry, which selectively targets transcriptional variants containing the hexanucleotide repeat expansion (G_4C_2) associated with the C9orf72 gene, thereby sparing normal C9orf72 protein.

About Wave Life Sciences

Wave Life Sciences (Nasdaq: WVE) is a clinical-stage RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization, and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, our hope that our FOCUS-C9 data may be used to advance future research; our plans to share these results with the community at an upcoming medical congress; our expectations regarding the potential benefits and the anticipated timing of our upcoming milestones for our lead programs in Huntington's disease, Duchenne muscular dystrophy and Alpha-1 antitrypsin deficiency and our confidence in these programs because they leverage biomarkers correlated with functional outcomes; and our expectations regarding the timing and substance of upcoming datasets from our preclinical pipeline using modalities that restore or repair endogenous proteins, including our RNA editing capability. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and

similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release and actual results may differ materially from those indicated by these forward-looking statements as a result of these risks, uncertainties and important factors, including, without limitation, the risks and uncertainties described in the section entitled "Risk Factors" in Wave's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as amended, and in other filings Wave makes with the SEC from time to time. Wave undertakes no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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Exhibit 99.2

Wave Life Sciences
Corporate Presentation

May 23, 2023

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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.

Emerging leader in RNA medicines

Multi-modal drug discovery and development platform to address new areas of disease biology
RNA editing, splicing and silencing

Differentiated, clinical-stage RNA medicines pipeline with first-in-class RNA editing programs

Strategic collaborations to expand and advance pipeline (GSK and Takeda)

Multiple pipeline and platform catalysts expected in 2023 and beyond

Well-capitalized with expected cash runway into 2025

GMP manufacturing

Strong and broad IP position[1]

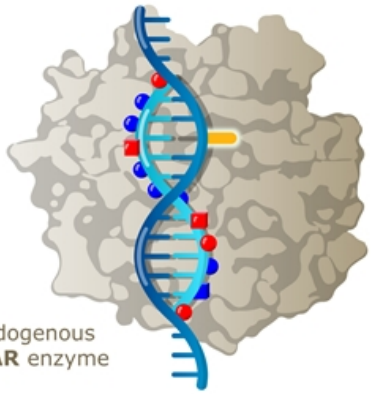
Wave Life Sciences is an RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases

[1]stereopure oligonucleotides and novel backbone chemistry modifications

RNA medicines allow matching disease target to therapeutic modality

RNA Base Editing

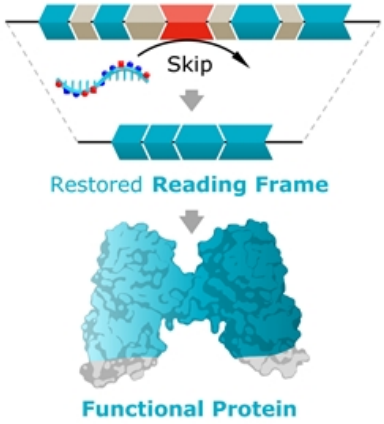
- Efficient editing of RNA bases to **restore** or **modulate** protein production



Endogenous **ADAR** enzyme

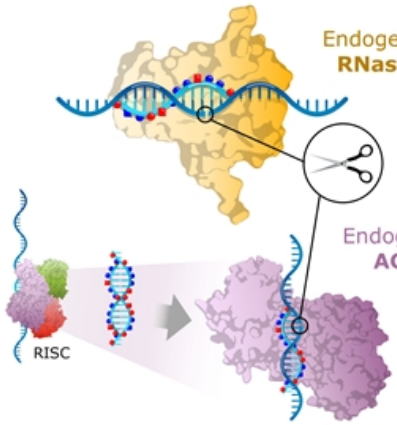
Splicing

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



Silencing

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



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Robust RNA medicines pipeline with first-in-class RNA editing programs

Program	Discovery	Preclinical	Clinical	Rights	Patient population (US & Europe)
RNA EDITING					
WVE-006 SERPINA1 (AATD)				GSK exclusive global license	200K
Multiple undisclosed				100% global	-
SPLICING					
WVE-N531 Exon 53 (DMD)			Phase 1/2	100% global	2.3K
Other exons (DMD)				100% global	Up to 18K
SILENCING: ANTISENSE					
WVE-003 mHTT (HD)			Phase 1/2	Takeda 50:50 Option	25K Manifest (SNP3) 60K Pre-Manifest (SNP3)
SCA3 (ATXN3)				Takeda 50:50 Option	8K
SILENCING: RNAi					
Undisclosed				100% global	-

Through GSK collaboration, Wave can advance up to three collaboration programs and GSK can advance up to eight collaboration programs

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AATD: Alpha-1 antitrypsin deficiency; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; SCA3: Spinocerebellar ataxia 3

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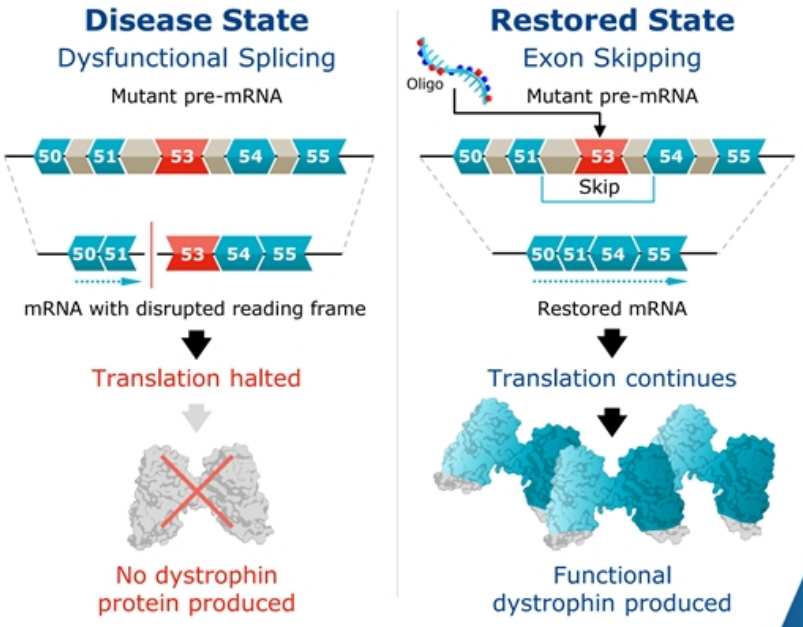
WVE-N531

Duchenne muscular dystrophy

Duchenne muscular dystrophy

- **Genetic mutation in dystrophin gene prevents the production of dystrophin protein**, a critical component of healthy muscle function
- **Impacts approx. 1 in every 5,000 newborn boys each year**; approx. 20,000 new cases annually worldwide
  - Approx. 8-10% are amenable to exon 53 skipping
- **Dystrophin protein established by FDA as surrogate endpoint** reasonably likely to predict benefit in boys[1] for accelerated approval in DMD
- Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for boys with DMD

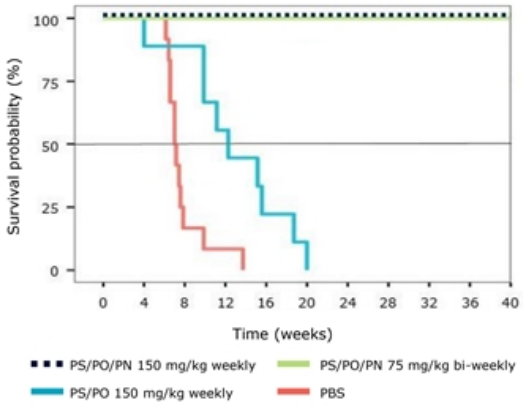


[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

Extended survival in dKO preclinical model supports potential of exon-skipping therapeutics for DMD

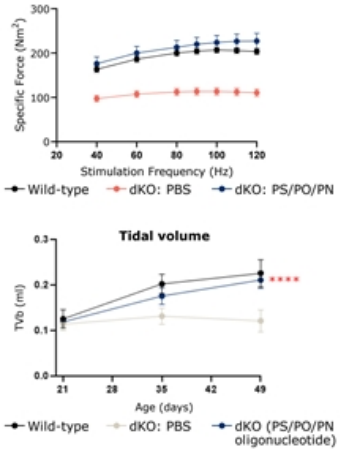
PN chemistry improved function and survival in dKO mice

100% survival at time of study termination

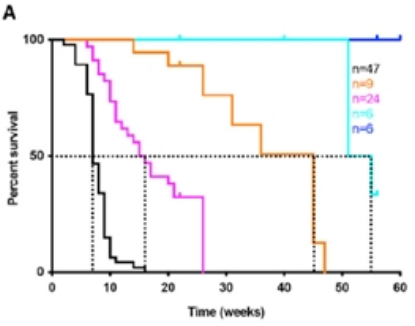


Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

Restored muscle and respiratory function to wild-type levels



dKO survival studies in literature



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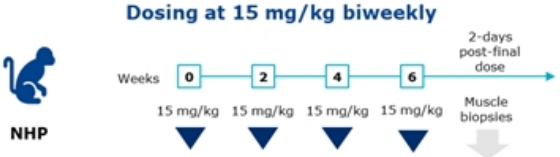
Left: Kandasamy et al., 2022; doi: 10.1093/nar/gkac018; Right: Forand et al., 2020; doi: https://doi.org/10.1016/j.omtm.2020.03.011.

Preclinical data supported advancing WVE-N531 to clinical development

WVE-N531 reached high concentrations in heart and diaphragm in NHP

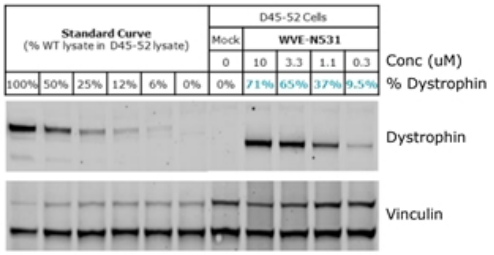


	Mean Tissue Concentration		
	Skeletal muscle	Diaphragm	Heart
15 mg/kg* IV dose	2.17 ug/g	10.8 ug/g	57.2 ug/g

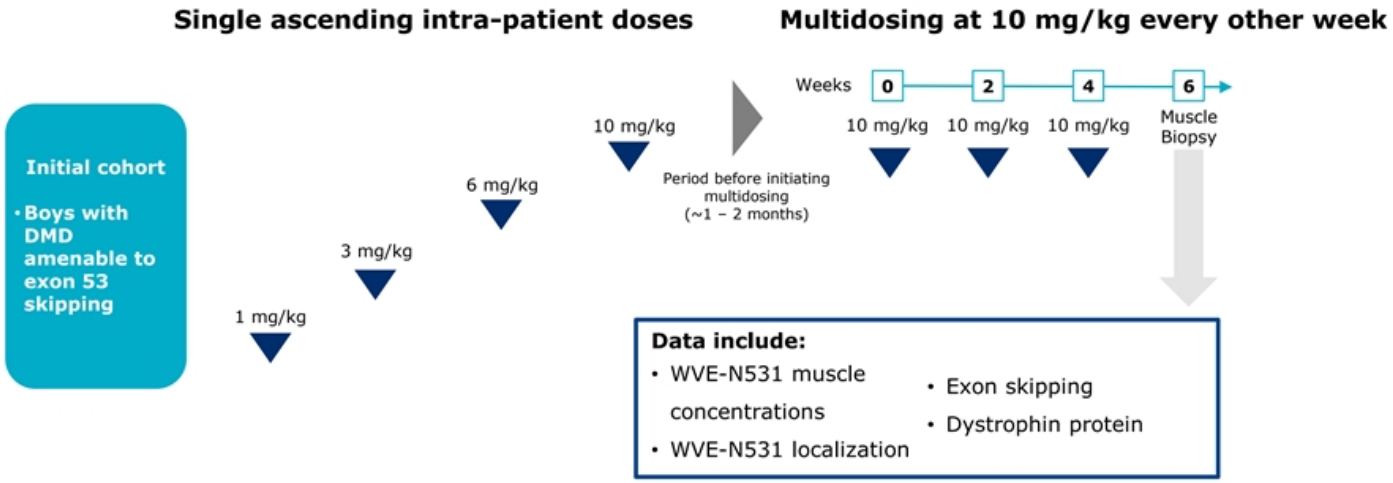
*approximately equivalent to 10 mg/kg in patients based on plasma AUC values

WVE-N531: Dystrophin restoration of up to 71% *in vitro*

Western Blot normalized to primary healthy human myoblast lysate



In multidose portion of study, patients received three biweekly 10 mg/kg doses



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▼ Dose WVE-N531

WVE-N531 in DMD: Delivered positive proof-of-concept data in 4Q 2022

- High exon skipping and muscle concentrations after three biweekly 10 mg/kg doses
- Similar exon skipping regardless of mutation
  - Patient 1: del48-52
  - Patient 2: del45-52
  - Patient 3: del51-52
- PK analysis indicated 25-day half-life in plasma
- WVE-N531 appeared safe and well-tolerated

Patient	Tissue Source	Tissue concentration (µg/g)	% Exon skipping by RT-PCR	Dystrophin by Western blot (% of normal)
1	Deltoid	85.5	61.5	0.24
2	Deltoid	33.5	49.8	0.23
3	Bicep	8.3	47.9	0.34

Mean muscle concentration: 42 µg/g

Mean exon skipping: 53%

Mean dystrophin: 0.27% of normal (BLQ)

Data presented March 22, 2023 at Muscular Dystrophy Association Clinical and Scientific Conference

Biopsies collected ~2 weeks post-last dose (3 biweekly doses of 10 mg/kg)
Data cut-off: December 6, 2022

42 µg/g = 6.1 µM

BLQ: Below level of quantification (1%)

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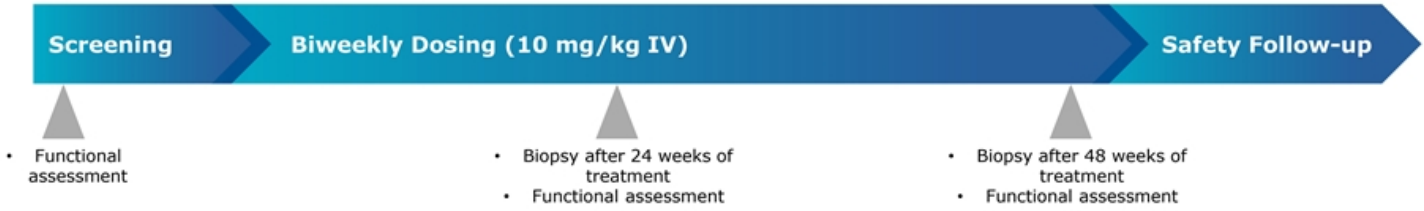
Initiating Part B, a potentially registrational Phase 2 clinical trial of WVE-N531



- **Design**: Phase 2, open-label, 10 mg/kg every other week, up to 10 patients
- **Endpoints**: Dystrophin (powered for >5% of normal), safety/tolerability, pharmacokinetics, functional assessments (incl. NSAA and others)
- **Biopsies**:
  - After 24 weeks of treatment
  - After 48 weeks of treatment
- **Data from Part B expected in 2024**

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IV: intravenous; NSAA: North star ambulatory assessment

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GSK Collaboration and WVE-006 for Alpha-1 antitrypsin deficiency (AATD)

Strategic collaboration with GSK to develop transformative RNA medicines for genetically defined diseases

- ✓ **$170 million upfront to Wave** (cash and equity[1])
- ✓ Additional research support funding
- ✓ Potential for **up to $3.3 billion in milestones**[2]
- ✓ Expands Wave's pipeline

Extends cash runway into 2025

PRISM

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Multiple value drivers to Wave

Milestone / royalties	Milestone / royalties	Genetic targets
GSK granted exclusive global license to WVE-006 for AATD	**GSK to advance up to eight collaboration programs**	**Wave to leverage GSK's genetic insights**
Up to $225 million in development and launch milestones	Up to $1.2 billion in aggregate in initiation, development and launch milestones	Wave to advance up to three wholly owned collaboration programs (or more pending agreement with GSK)[3]
Up to $300 million in sales-related milestones	Up to $1.6 billion in aggregate in sales-related milestones	
Double-digit tiered royalties as a percentage of net sales up to high-teens	Tiered royalties as a percentage of net sales up to low-teens	
Development and commercialization responsibilities transfer to GSK after completion of first-in-patient study	Development and commercialization responsibilities transfer to GSK at development candidate	
First-in-class RNA editing program	Collaboration leverages Wave's unique stereopure, PN-chemistry containing PRISM™ platform, including **editing**, **splicing**, **silencing** (RNAi and antisense)	

[1]$120 million in cash and $50 million equity investment received in January 2023, [2]Initiation, development, launch, and commercialization milestones for WVE-006 and programs progressed during initial 4-year research term (8 GSK collaboration programs) [3]GSK eligible to receive tiered royalty payments and commercial milestones from Wave

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)

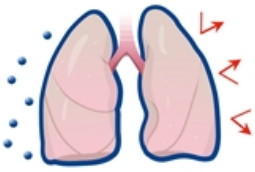
Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

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

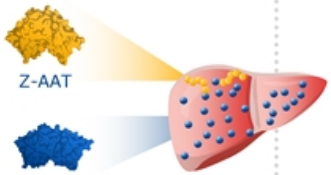
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

3) Retain M-AAT physiological regulation



M-AAT reaches lungs to protect from proteases



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

M-AAT secretion into bloodstream

WAVE LIFE SCIENCES

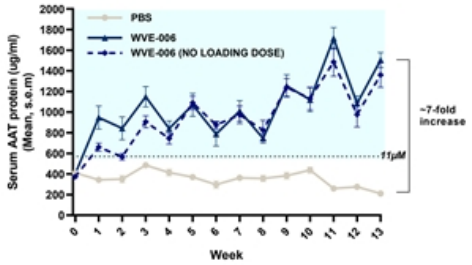
AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

WVE-006 in AATD: First-in-class RNA editing candidate approaching the clinic

Potentially comprehensive approach to address both lung and liver manifestations of AATD

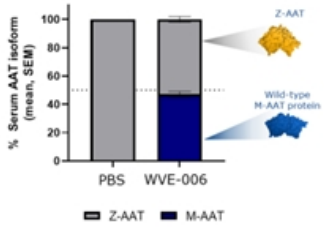
Increased AAT protein in NSG-PiZ mice

WVE-006 treatment results in serum AAT protein levels >11 uM in NSG-PiZ mice



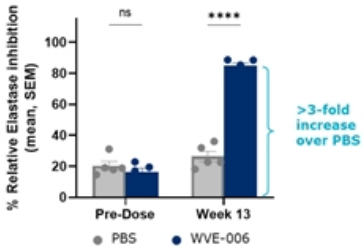
Confirmed restored wild-type M-AAT protein

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



Demonstrated functionality of M-AAT protein

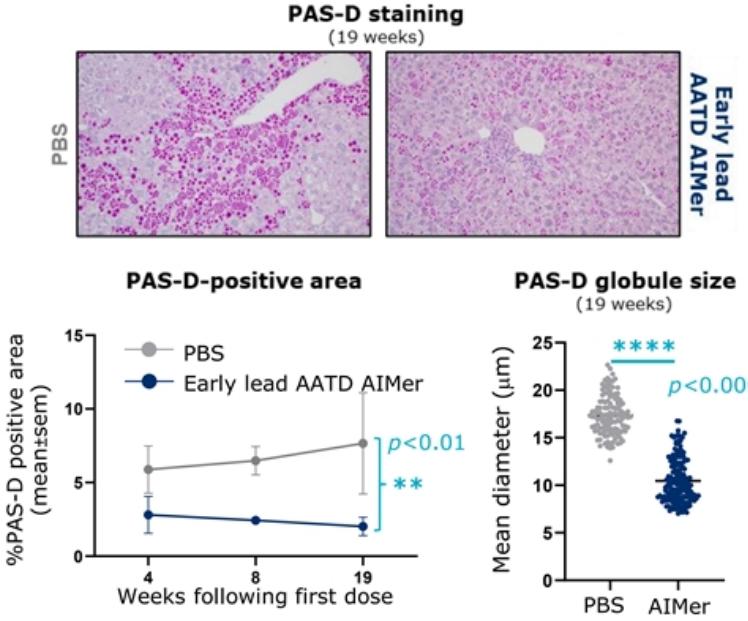
Serum neutrophil elastase inhibition activity in NSG-PiZ mice

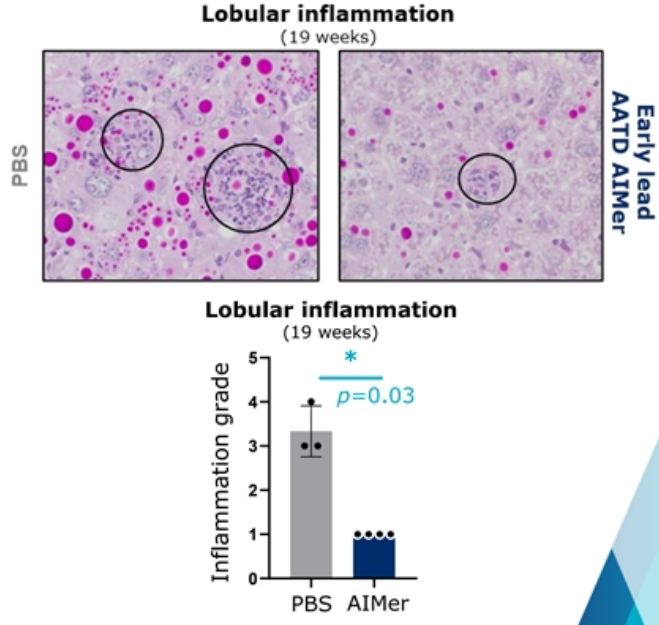


CTA submissions for first-in-human study expected in 2H 2023

AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; 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 wk 13 (1 wk after last dose) and SERPINA1 editing quantified by Sanger sequencing; Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

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





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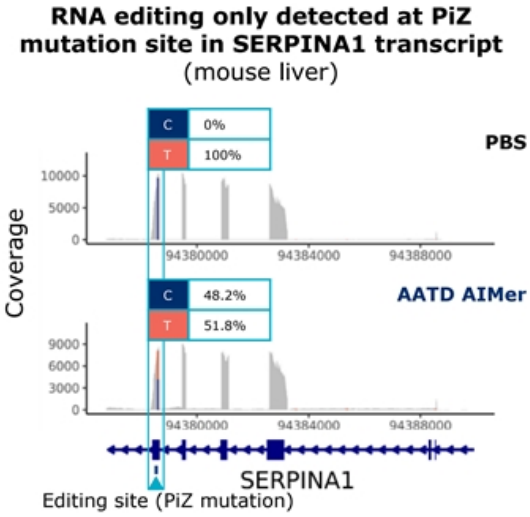
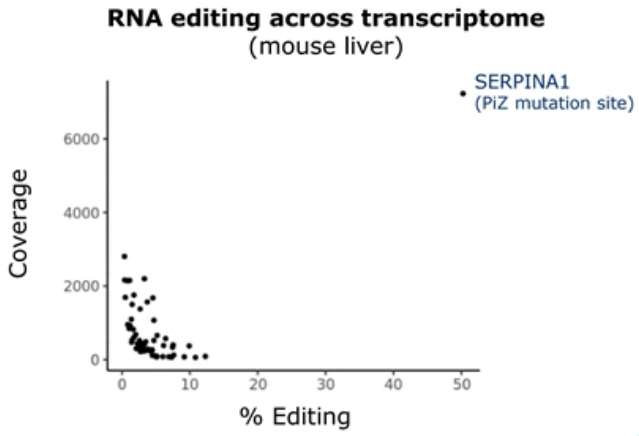
Early lead pre-optimization AATD AIMer (SA1-5) administered in hu*ADAR/SERPINA1* mice (8–10 wKs old); lower left: 20x liver images PAS-D stained, 19 weeks; Quantification of PAS-D positive staining, Stats 2-way ANOVA; Right: Quantification lobular inflammation grade (Grade based on # of inflammatory 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

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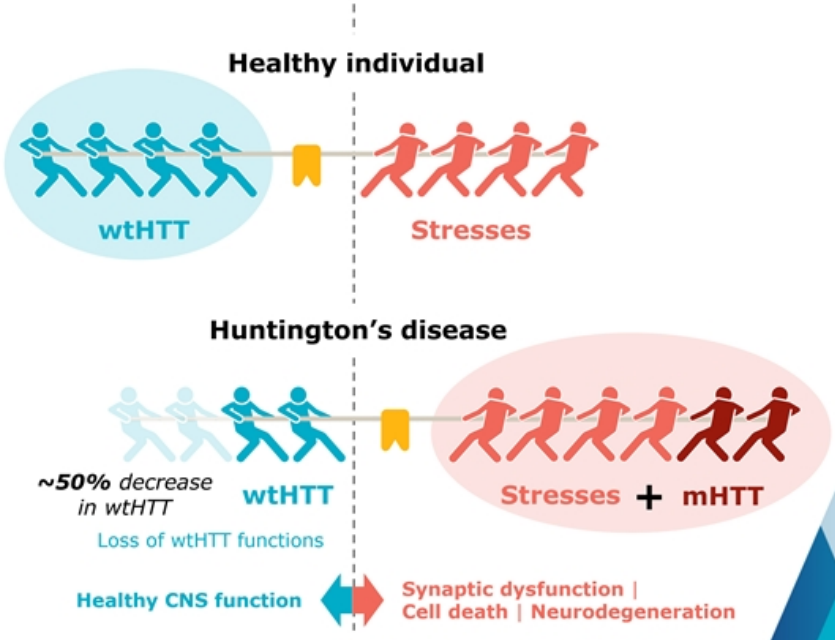
WVE-003

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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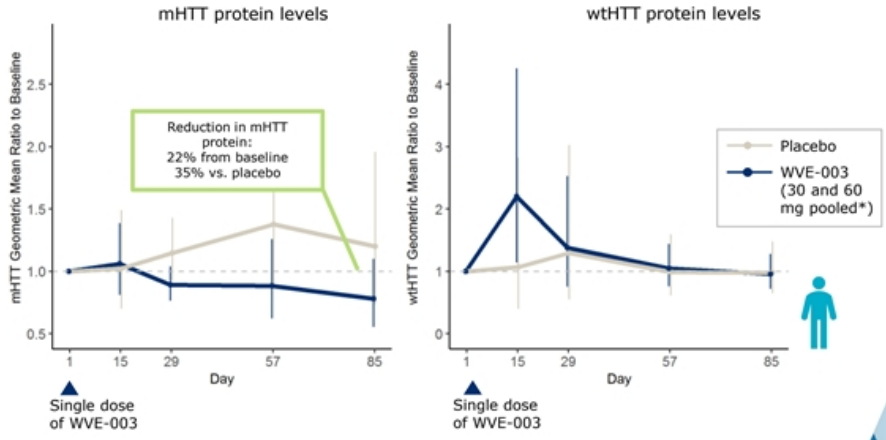
WVE-003: First-in-class allele-selective candidate for HD

- mHTT protein reductions observed in single dose cohorts (Sep. 2022)
- wtHTT protein levels appear consistent with allele-selectivity
- Generally safe and well-tolerated
- **Additional single-dose and multi-dose biomarker and safety clinical data expected in 2H 2023**

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



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mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein
*Pooled considering no apparent dose response between 2 cohorts; Data cut-off: August 29, 2022

AIMers

RNA base editing capability

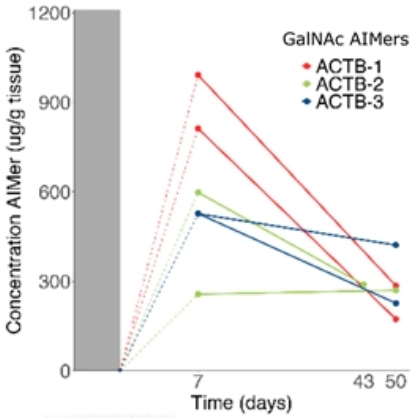
Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature biotechnology ARTICLES

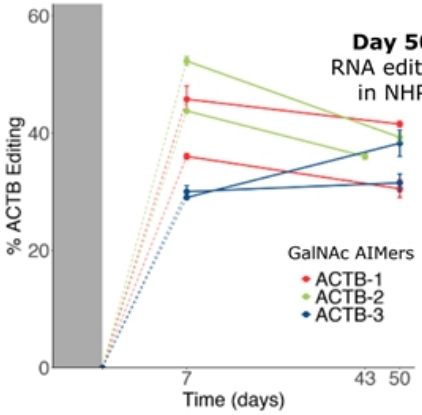
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- 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)

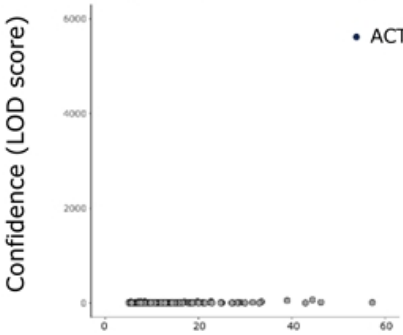


Substantial and durable editing in NHP liver *in vivo* (PD)



ADAR editing with ACTB AIMer is highly specific

RNA editing within full transcriptome (primary human hepatocytes)



RNA editing only detected at editing site in ACTB transcript

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

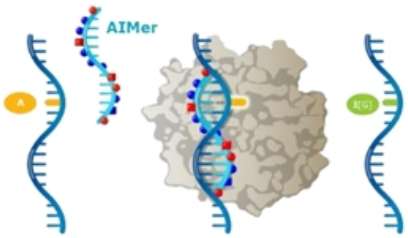
Expanding addressable disease target space using AIMers to activate pathways and upregulate expression

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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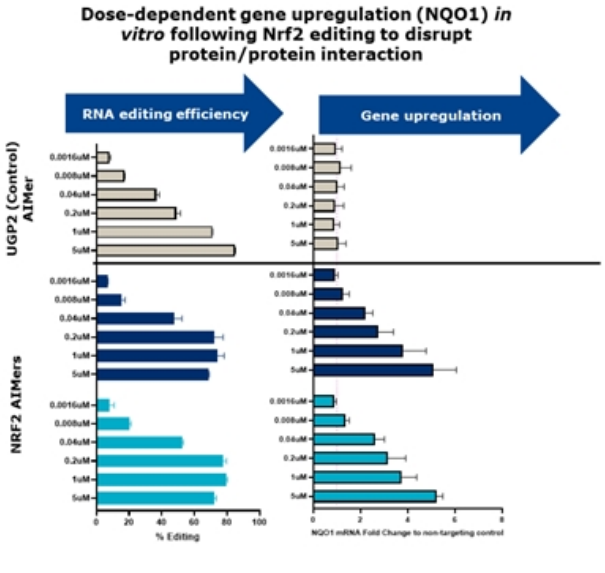
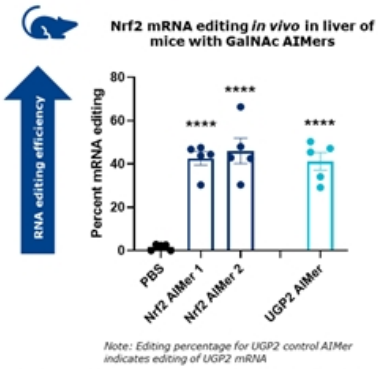
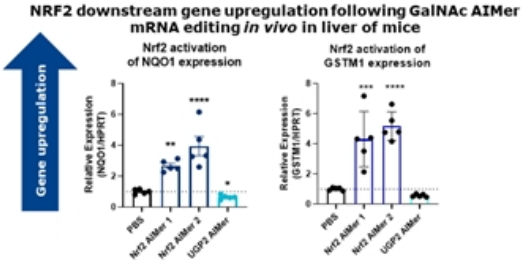
POC: proof of concept

Modulation of protein-protein interactions: AIMers enable activation of gene pathway *in vivo* with single edit







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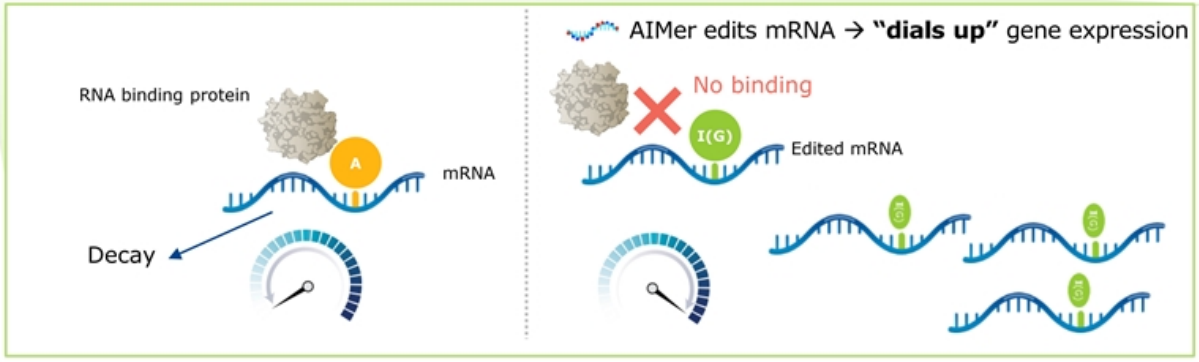
n=2; Primary hepatocytes 48h of treatment with the indicated dose concentration of AIMers

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

RNA binding proteins recognize sequence motifs to regulate various mRNA properties

Stability	Transport	Processing	Protein production
• Enhance or inhibit mRNA decay	• Intracellular localization	• Splicing • Capping • PolyA usage	• Translational efficiency



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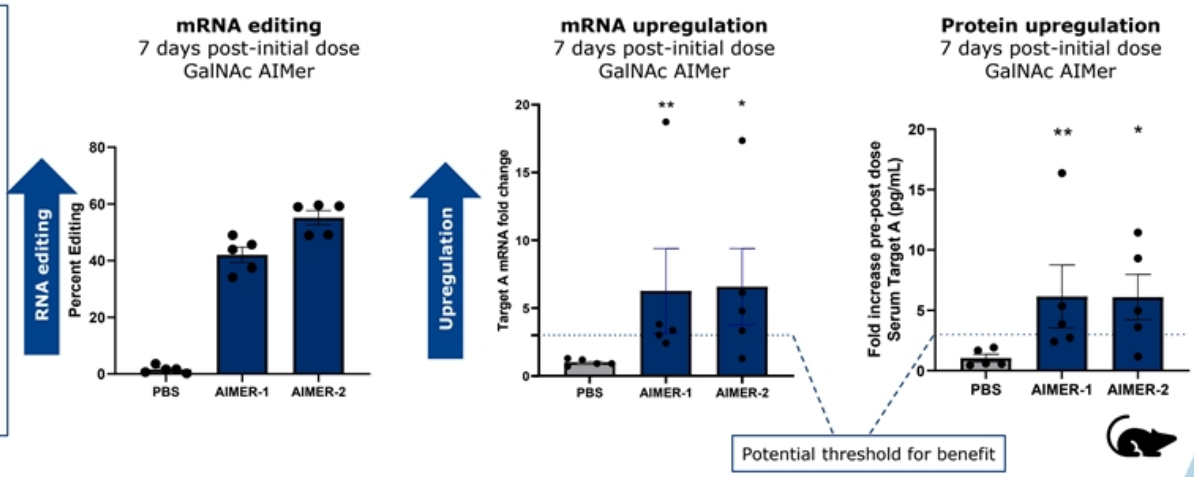
AIMers upregulate mRNA and downstream serum protein *in vivo* above anticipated threshold

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


WAVE
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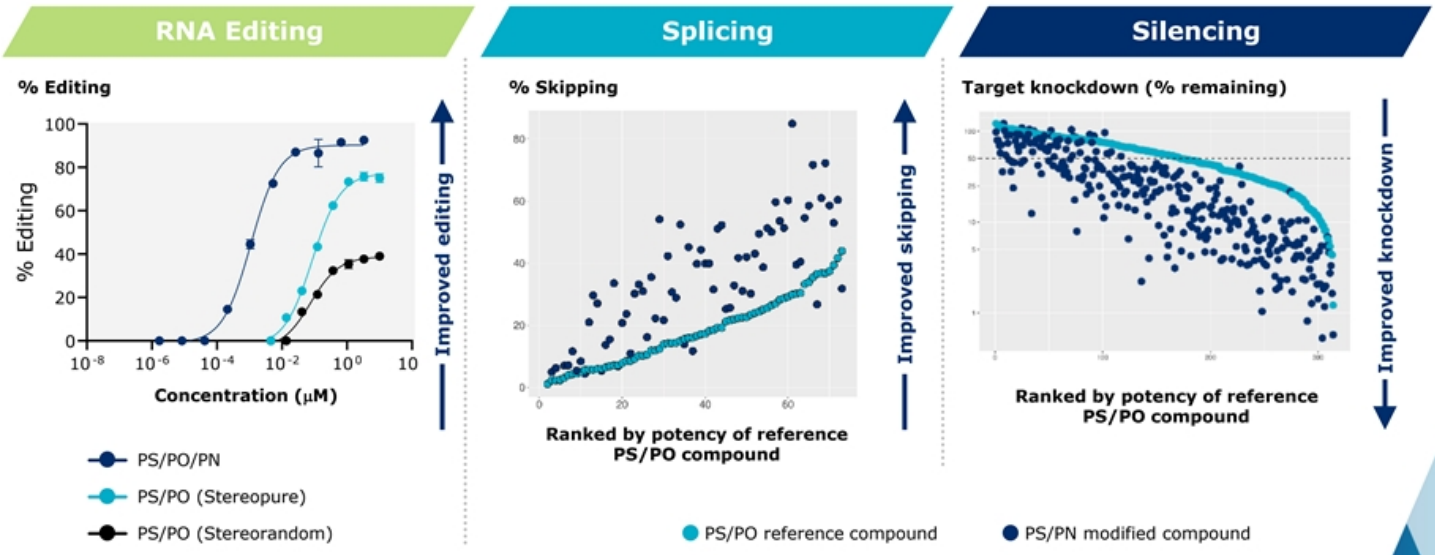
Wave's discovery and drug development platform
PRISM

Proprietary PN chemistry enhances potency across modalities



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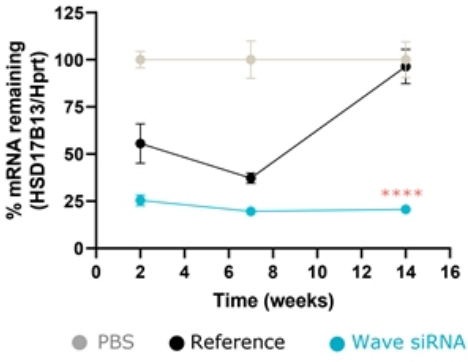
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake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

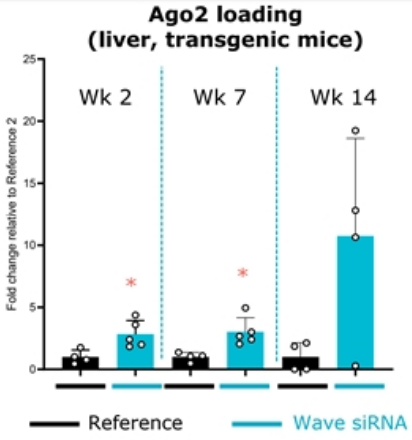
Potential for best-in-class RNAi enabled by Wave's PRISM platform

Nucleic Acids Research

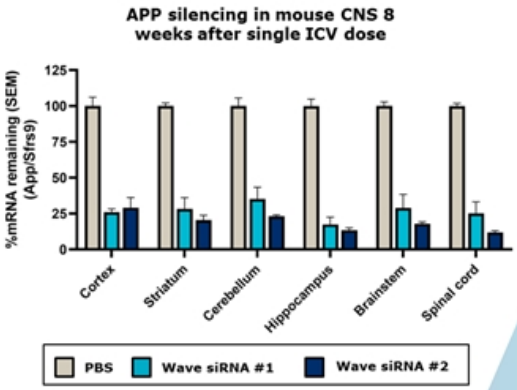
Impact of stereopure chimeric backbone chemistries on the potency and durability of gene silencing by RNA interference

- Unprecedented Ago2 loading following administration of single subcutaneous dose





- First in vivo study of unconjugated siRNAs demonstrated 70-90% APP silencing across six brain regions in mouse CNS at 8 weeks



RNAi is one of multiple Wave modalities being advanced in strategic research collaboration with GSK

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Left, Middle: Mice expressing human *HSD17B13* transgene treated (3 mg/kg)siRNA or PBS, liver mRNA, guide strand concentration, Ago2 loading quantified. Stats: Two-way ANOVA with post-hoc test * P<0.05, ****P<0.0001. Liu et al., 2023 *Nuc Acids Res* doi: 10.1093/nar/gkad268; Right: ICV: Intracerebroventricular; APP: Amyloid precursor protein ; CNS: central nervous system; B6 mice were administered PBS or 100 µg of APP siRNA by ICV injection on day 0 (n=7). Mice euthanized 8 weeks after administration. Taqman qPCR assays used for RNA PD, relative fold changes of *App* to *Sfrs9* mRNA normalized to percentage of PBS group. All treated group show *P*≤0.0001 compared to PBS group in 2way ANOVA.

Delivering on pipeline and platform catalysts

RNA EDITING	SPLICING	ANTISENSE SILENCING	RNAi
WVE-006 for AATD *Most advanced RNA editing candidate & potential best-in-class approach for AATD* **WVE-006 CTA submissions expected in 2H 2023** **Expansion opportunities in liver, CNS and kidney**	**WVE-N531 for DMD** *Potential best-in-class approach with highest exon skipping reported* **Dosing in potentially registrational clinical trial expected in 2023; data expected in 2024** **Expansion opportunities in other exons, as well as other muscle diseases and CNS**	**WVE-003 for HD** *First-in-class wild-type huntingtin protein (wtHTT)-sparing approach* **Data expected 2H 2023** **Enables discussion on next steps with Takeda**	**Newest modality in Wave platform** *Preclinical data suggest best-in-class potential for Wave RNAi capability* **Hepatic, CNS and beyond**

DISCOVERY PIPELINE & COLLABORATIONS

Anticipate investor event in 3Q 2023 during which Wave will demonstrate how it is continuing to extend its leadership in RNA editing and share preclinical data on new wholly-owned programs

Advance collaboration activities with GSK, with potential for additional cash inflows in 2023 and beyond

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Realizing a brighter future for people affected by genetic diseases

For more information:

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617.949.4827

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