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): October 2, 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.

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 October 2, 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/. This presentation is also furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information in this Item 7.01 and exhibit 99.1attached hereto 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 October 2, 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: October 2, 2023

Exhibit 99.1

Wave Life Sciences
Corporate Presentation

October 2, 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.

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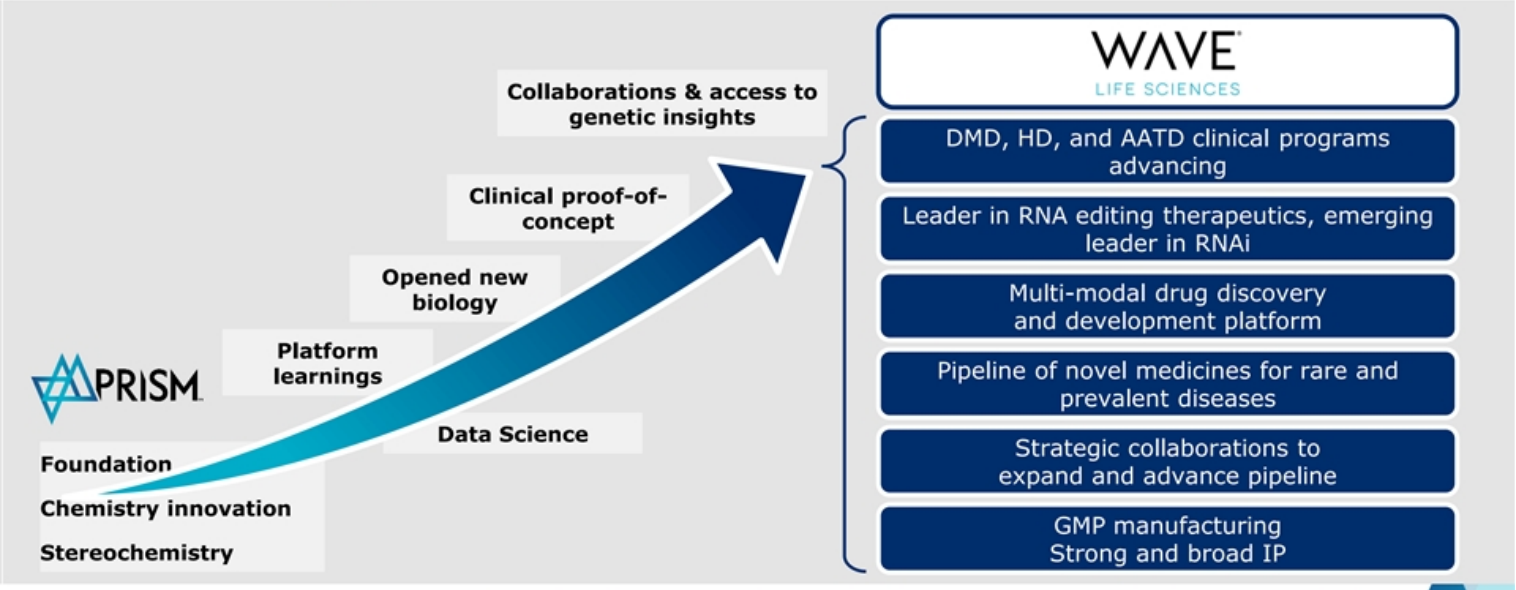
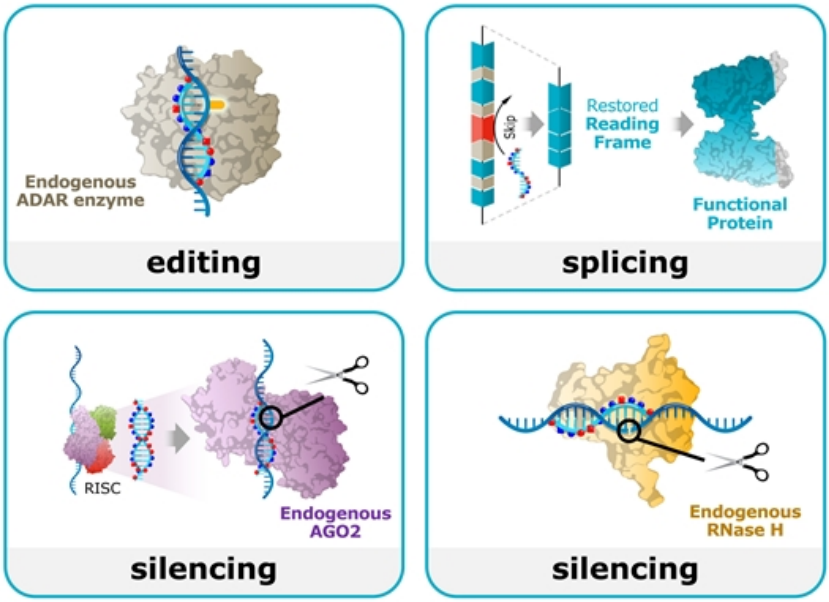
Wave today is well positioned for significant and sustained growth



RNA medicines allow matching disease target to therapeutic modality



- Most versatile RNA medicines platform (PRISM™) in the industry
- Best-in-class nucleic acid chemistry applicable across modalities
- Ability to access novel / untapped areas of disease biology
- Platform learnings and clinical validation continue to increase probability of success

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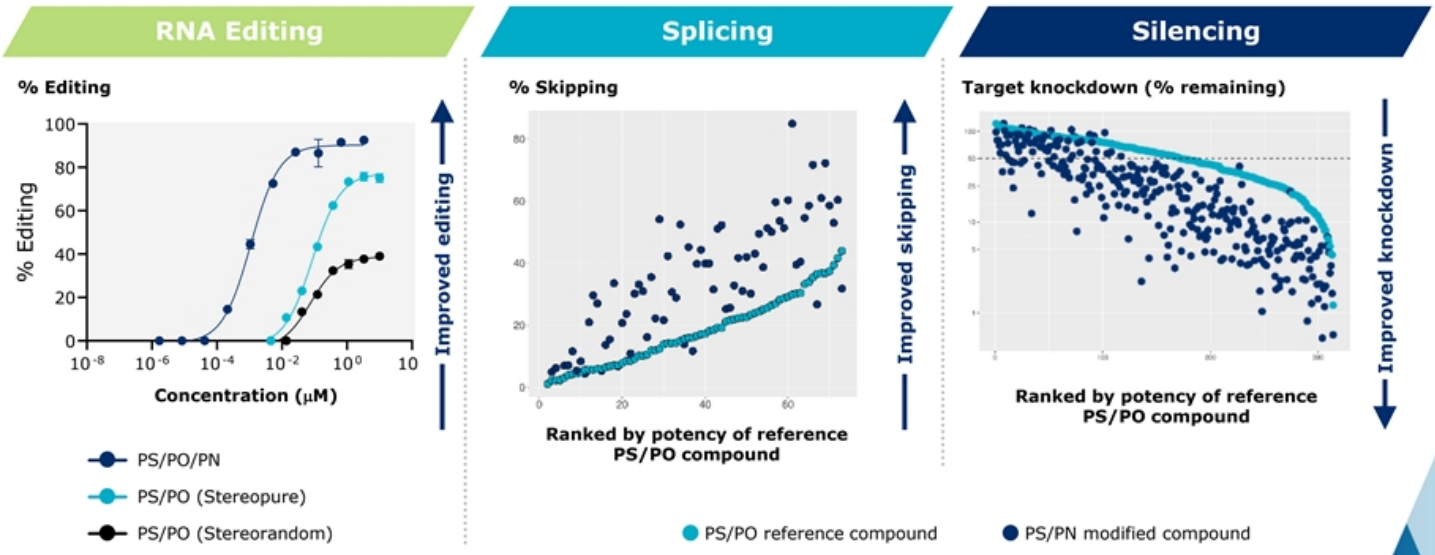
Proprietary PN chemistry enhances potency across modalities



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

Robust RNA medicines pipeline including 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 Correction				100% global	>20K (multiple)
Multiple undisclosed Upregulation				100% global	>3M (multiple)
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)
SILENCING: RNAi					
INHBE* (Metabolic disorders, including obesity)				100% global	47M

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*Through GSK collaboration, Wave can advance up to three collaboration programs (the first of which is INHBE) and GSK can advance up to eight collaboration programs.

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

Editing for correction

Editing for upregulation

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
- ✓ INHBE is Wave's first wholly-owned program emerging from GSK collaboration

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)	

PRISM

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[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


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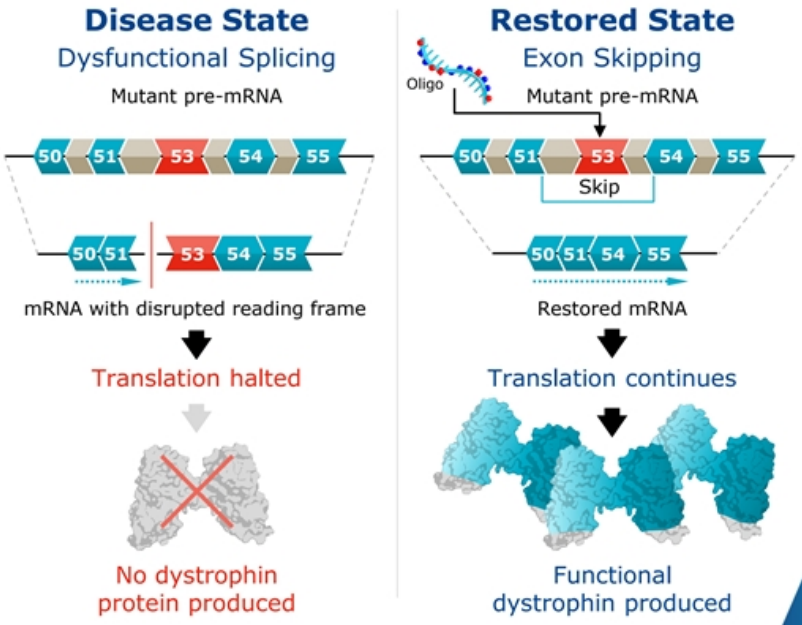
WVE-N531
Duchenne muscular dystrophy

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

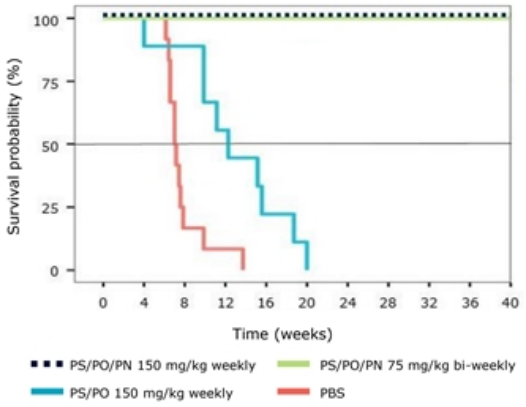


[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

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

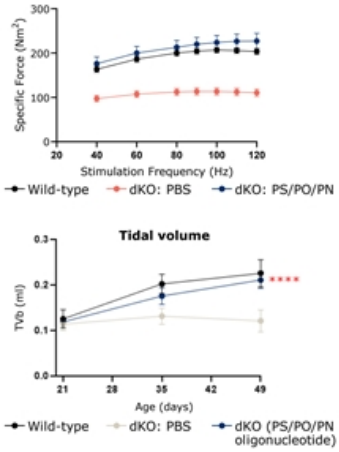
PN chemistry improved function and survival in dKO mice

100% survival at time of study termination

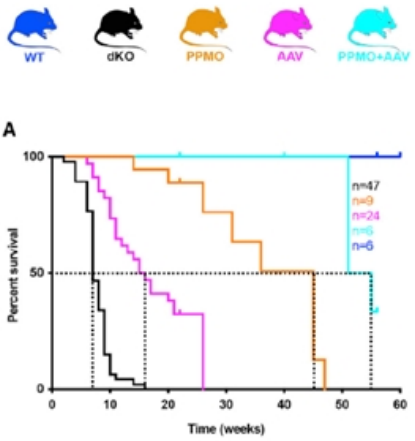


Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

Restored muscle and respiratory function to wild-type levels



dKO survival studies in literature



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

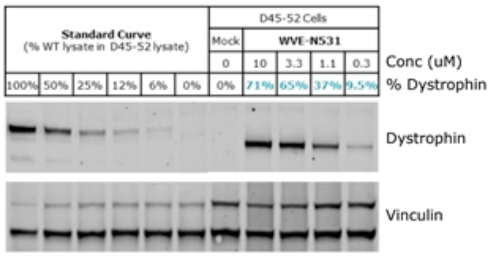
Dosing at 15 mg/kg biweekly

	Mean Tissue Concentration		
15 mg/kg* IV dose	Skeletal muscle	Diaphragm	Heart
	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*

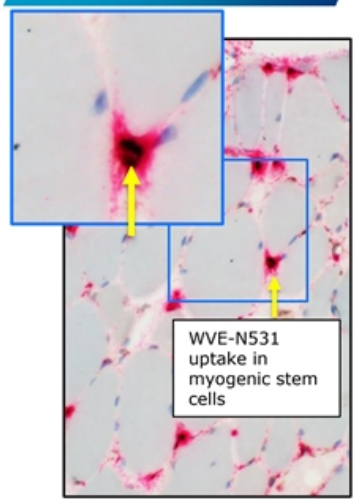
Western Blot normalized to primary healthy human myoblast lysate



WVE-N531 Part A clinical data: High exon-skipping & muscle concentrations after three bi-weekly doses

	suvodirsen	WVE-N531
Mean muscle concentration	0.7 µg/g	42 µg/g
Mean exon skipping	Not detectable	53%
Half-life in plasma	18 hours	25 days
Dose	22 weekly doses of 5 mg/kg	3 biweekly doses of 10 mg/kg

WVE-N531 uptake in myocyte stem cells



Important for potential muscle regeneration

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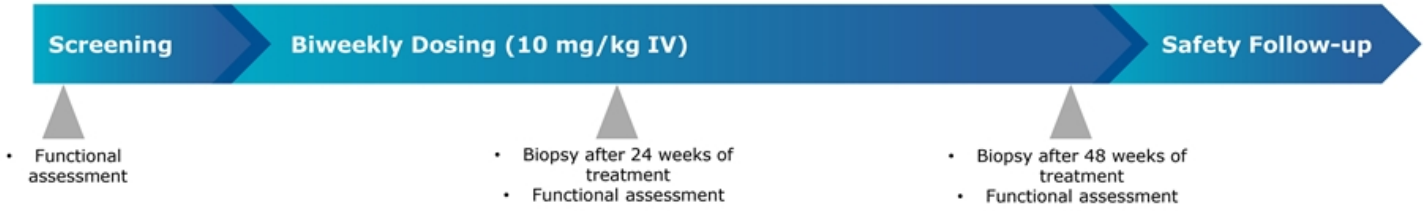
WVE-N531 data presented March 22, 2023 at Muscular Dystrophy Association Clinical and Scientific Conference; WVE-N531 biopsies collected ~2 weeks post-last dose (3 biweekly doses of 10 mg/kg) 42 µg/g = 6.1 µM; Suvodirsen biopsies collected post-last dose (weekly doses of 5 mg/kg) on week 22; Half-life as indicated by PK analysis; suvodirsen: discontinued first-generation non-PN chemistry compound; Right: Dual staining utilizing in-situ hybridization for WVE-N531 and PAX7 immunohistochemistry for stem cells

FORWARD-53, a potentially registrational Phase 2 clinical trial of WVE-N531 in DMD (Exon 53)



- **Design of FORWARD-53**: 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

FORWARD-53

Data from FORWARD-53 expected in 2024

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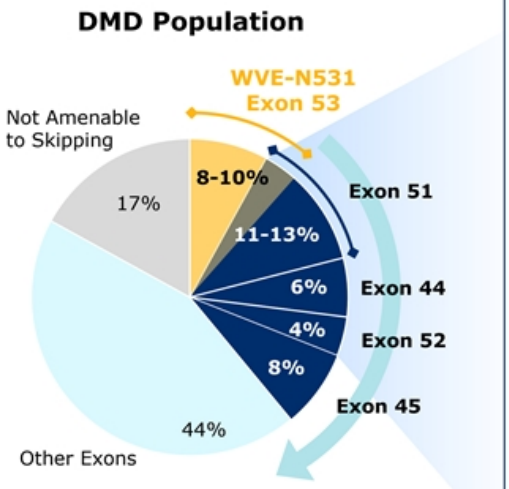
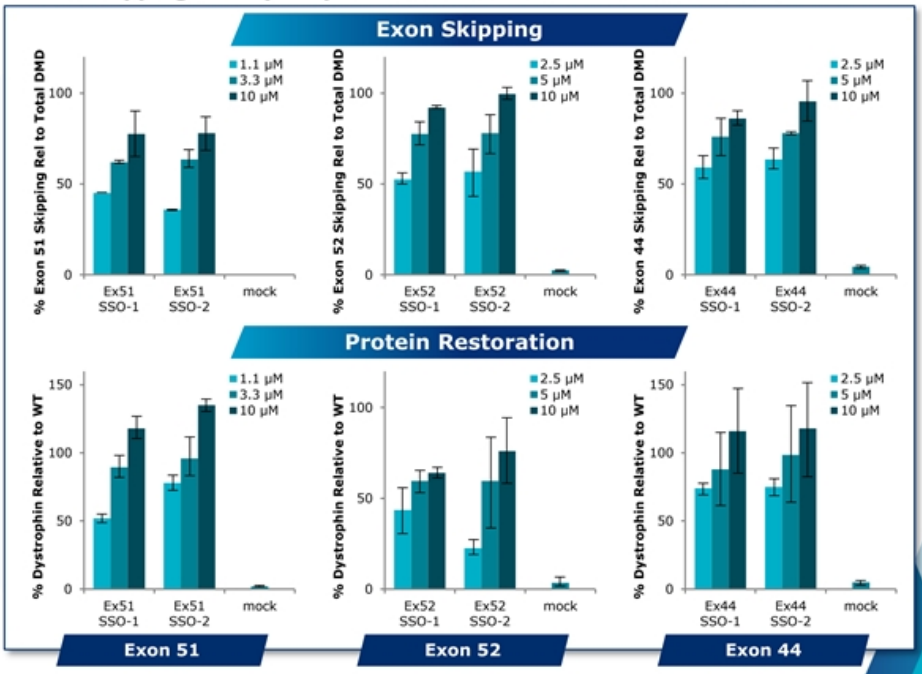
IV: intravenous; NSAA: North star ambulatory assessment

Potential for Wave to address up to ~40% of DMD population



Exon skipping and dystrophin restoration demonstrated *in vitro*



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Left: Aartsma-Rus, *et al.* 2009 *Hum Mutat* 30, 293.

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WVE-006 for 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)

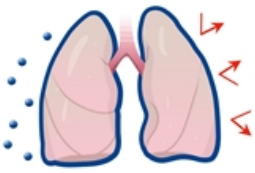
Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

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

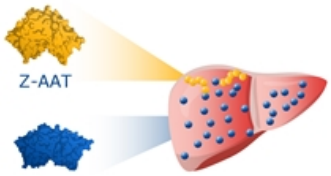
1) Restore circulating, functional wild-type M-AAT

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

200,000 Pi*ZZ patients in US and Europe

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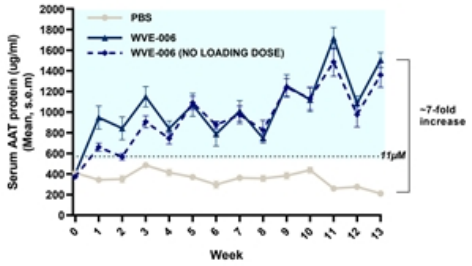
AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

WVE-006 in AATD: First-in-class RNA editing clinical candidate

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

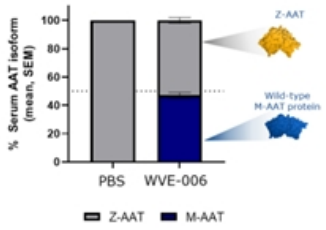
Increased AAT protein in NSG-PiZ mice

WVE-006 treatment results in serum AAT protein levels of up to 30 uM in NSG-PiZ mice



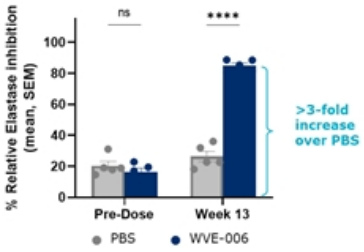
Confirmed restored wild-type M-AAT protein

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



~50% editing supports restoration of MZ phenotype

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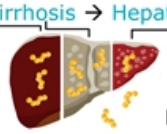
AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at wk 13 (1 wk after last dose) and SERPINA1 editing quantified by Sanger sequencing; Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

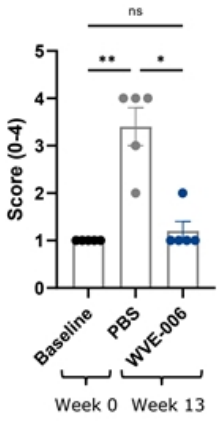
WVE-006 decreases lobular inflammation and PAS-D globule size, prevents increase in hepatocyte turnover

Correction of gain-of-function liver phenotypes

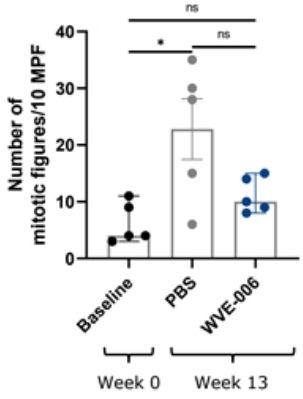
Fibrosis → Cirrhosis → Hepatocellular Carcinoma



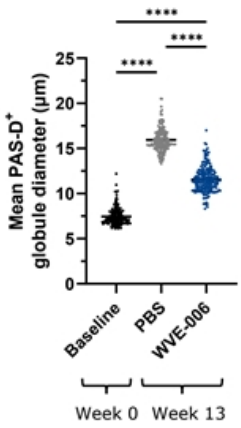
Lobular inflammation
(NSG PiZ mice, week 13)



Mitoses
(NSG PiZ mice, week 13)



PAS-D-positive globule size
(NSG PiZ mice, week 13)



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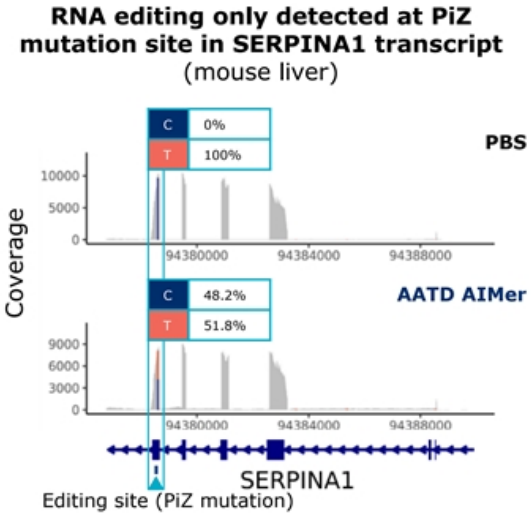
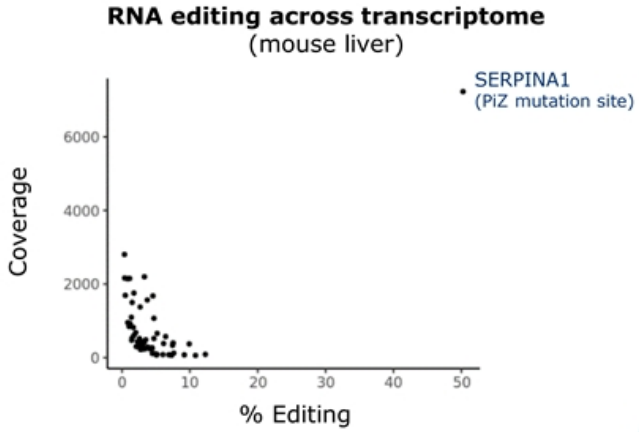
Left (Lobular inflammation) and Middle (Mitoses): Scatter plot showing inflammation grade or mitoses score. Each circle represents an individual mouse, (Mean ± SEM); Right (PAS-D Globule Size): 40 largest globules in each of 5 mice were measured. Each circle represents a single PAS-D globule, (Mean ± SEM). Baseline: week 0 (7 weeks old); Treated week 13 (20 weeks old); Stats: Kruskal-Wallis followed by Dunn's test

AIMer-directed editing is highly specific in mice

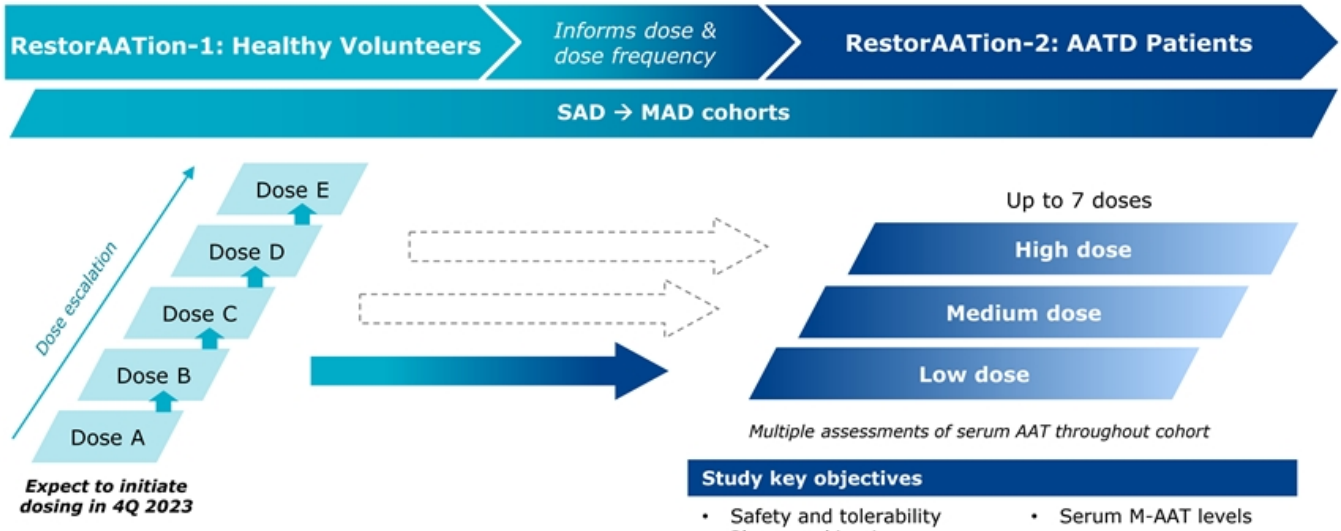
No bystander editing observed on SERPINA1 transcript





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

Proof of mechanism data in patients with AATD expected in 2024



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HV: healthy volunteer; SAD: single-ascending dose; MAD: multi-ascending dose

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AIMers

RNA base editing capability

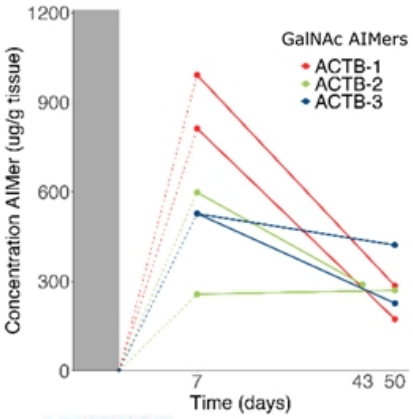
First-generation AIMer designs published in *Nature Biotechnology*

nature biotechnology ARTICLES

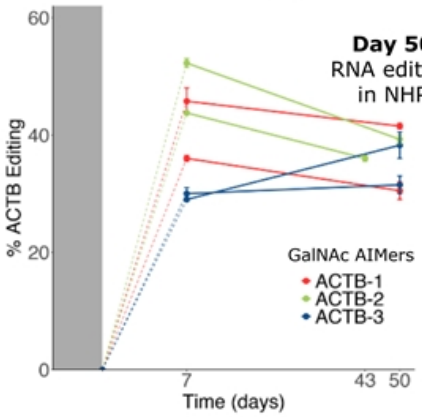
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

- 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)

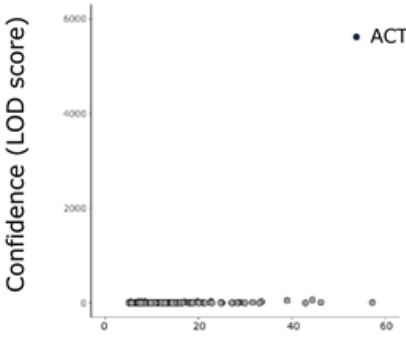


Substantial and durable editing in NHP liver *in vivo* (PD)



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

Innovating on applications of ADAR editing

Correct G-to-A driver mutations with AIMers

Restore or correct protein function

WVE-006
(GalNAc AIMer)
AATD

Modulate protein interactions with AIMers

Achieved POC

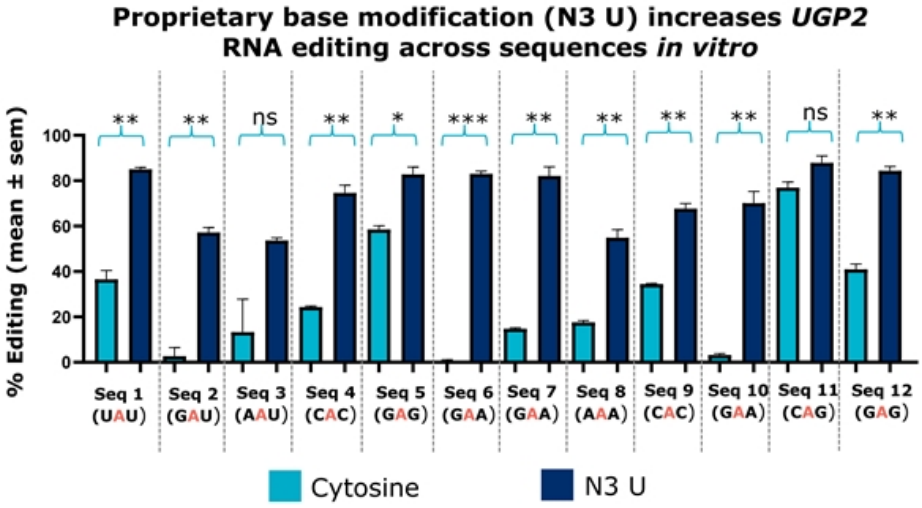
- **Modulate protein-protein interaction**
- **Upregulate expression**
- Modify function
- Post-translational modification
- Alter folding or processing

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

WAVE LIFE SCIENCES

POC: proof of concept

Proprietary base modifications increase editing across edit region sequences



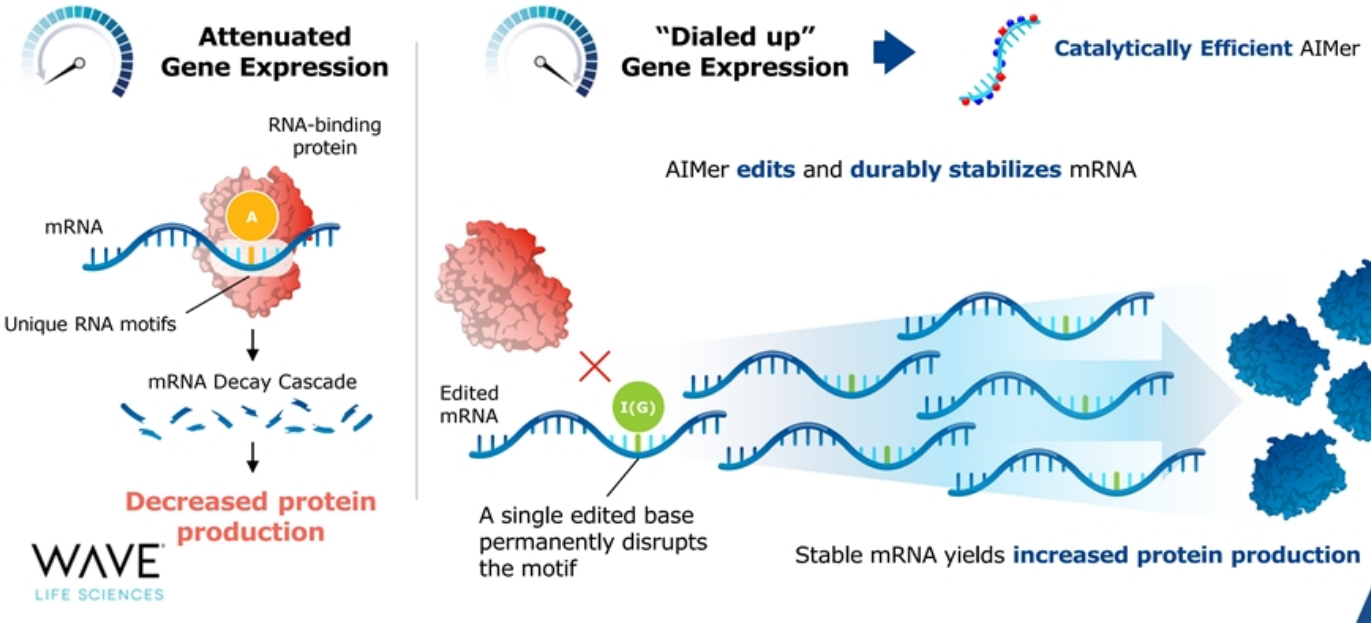
- N3 U: example of proprietary base modifications
- N3 U consistently improves RNA editing levels, including across sequences

WAVE LIFE SCIENCES

Presented at RNA Editing 2023 - Gordon Research Conference

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

RNA binding proteins recognize sequence motifs to regulate mRNA stability



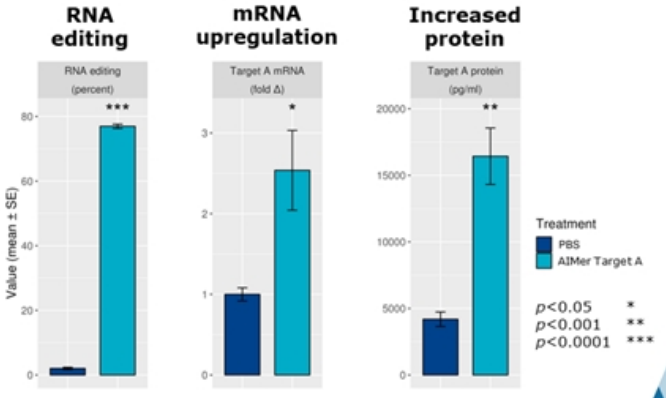
WAVE LIFE SCIENCES

Edit-verse subnetwork reveals "Target A": Metabolic syndrome target uniquely suited for AIMer upregulation

Target A

- Liver target for upregulation, non-incretin therapy
- Strongly implicated in metabolic disease, with indirect causation in familial disorders
- Few therapies today provide weight loss in this specific patient population
- Estimate 90 million potential patients in the US and Europe with metabolic syndrome and obesity
- Serum protein levels and biomarkers available to assess target engagement

>75% RNA editing led to >2-fold increase of mRNA, and similar degree of protein upregulation *in vivo* with GalNAc-AIMer in young DIO mice

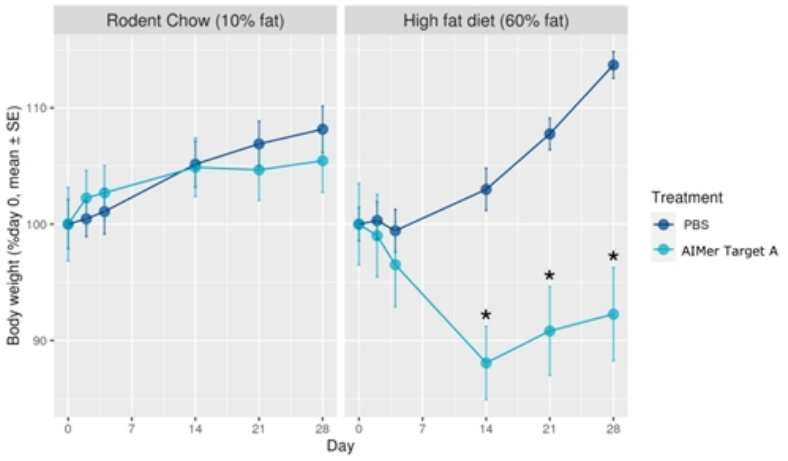


PoC: proof-of-concept Analysis of terminal endpoints (day 31) is shown. Each variable was analyzed using Welch's two-sided t-test. Significance was evaluated a $p<0.05$.

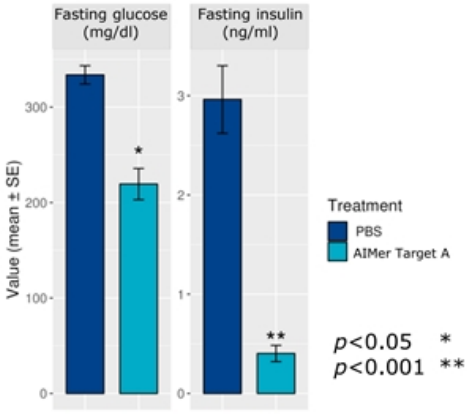
Substantial upregulation of protein induces weight loss and improves insulin sensitivity

- ~3-fold upregulation of Target A protein with GalNAc-AIMer led to weight reduction and improved insulin sensitivity in DIO mice

Significant Weight Loss



Improved Insulin Sensitivity



Body weight data were analyzed using a linear mixed effects model to assess the fix effects of diet, time and treatment, controlling for the initial day 0 body weight (continuous covariate) and subject (random effect). Fasted glucose and insulin data (from study termination, day 31) was analyzed using Welch's two-sided t-test. Significance was evaluated at $p<0.05$.

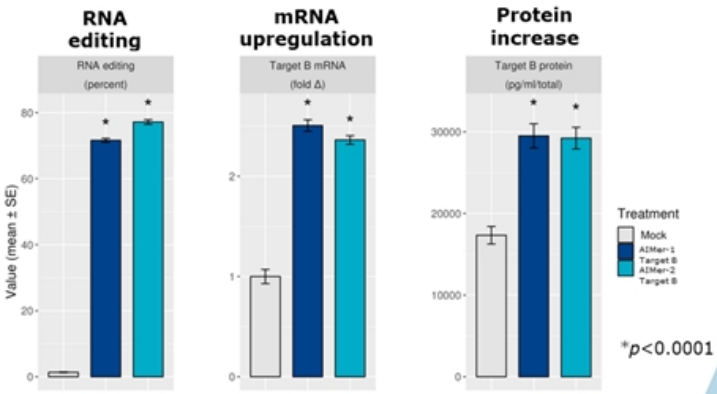
Target B upregulation offers a first-in-class therapeutic approach for hyperlipidemia

>70% editing achieves ~2-fold upregulation with corresponding increase in protein

Target B

- Liver target for upregulation
- Hyperlipidemia; first-in-class therapeutic approach
- Estimate ~3 million target patients in US and Europe
- Serum biomarkers available to assess target engagement and efficacy
- Potential clinically meaningful benefit of >2 fold upregulation of target mRNA

Primary human hepatocytes *in vitro*

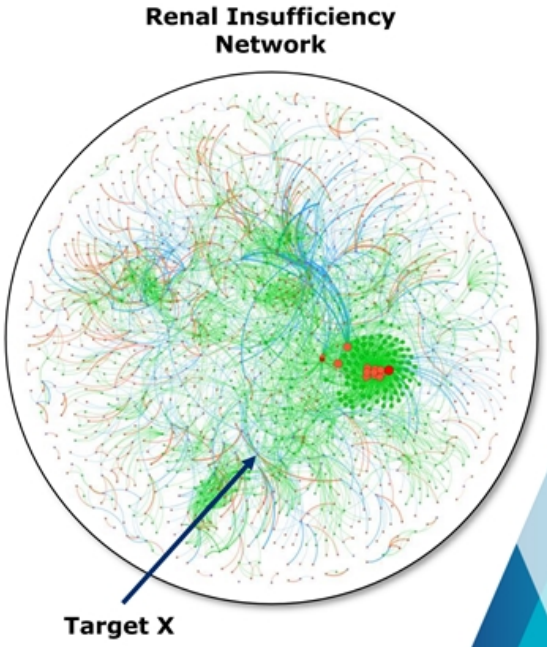


WAVE LIFE SCIENCES

Upregulation of liver Target X stops decline in kidney function

Target X

- Liver target for upregulation
- Target X produces a secreted protein to treat kidney disease
- Estimate ~170K target patients in US and Europe
- Therapeutic rationale supported by genetic insights, PheWAS, and observational data
- Plasma biomarkers available to assess target engagement
- ~2-fold upregulation in secreted protein expected to be clinically meaningful

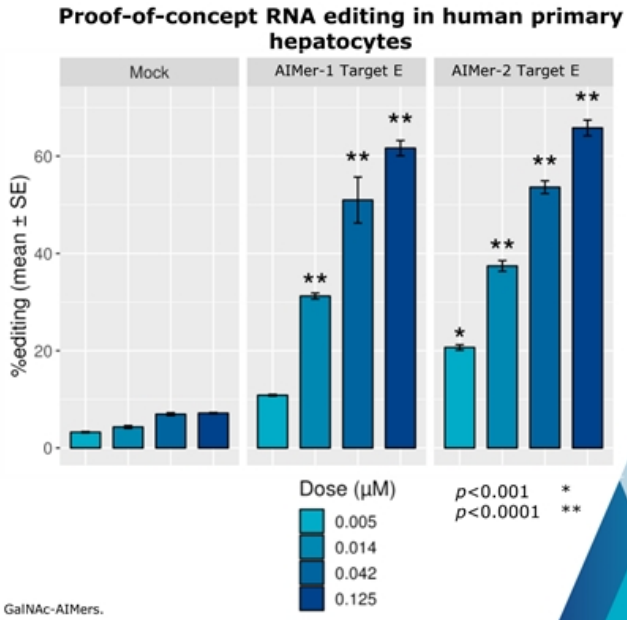


WAVE LIFE SCIENCES

Building on success of AATD: Target E correction restores normal metabolism in rare genetic disease

Target E

- Liver target for correction
- Rare genetic disease
- High unmet need population not addressed with current therapeutic options
- ~17,000 patients addressable with correction approaches in US and Europe
- Fully translatable serum biomarker
- ~15-30% editing expected to deliver clinically meaningful benefit



WAVE LIFE SCIENCES

Two-way ANOVA (Treatment, Dose) and Tukey's HSD. Significance was evaluated at $p<0.05$, GalNAc-AIMers.

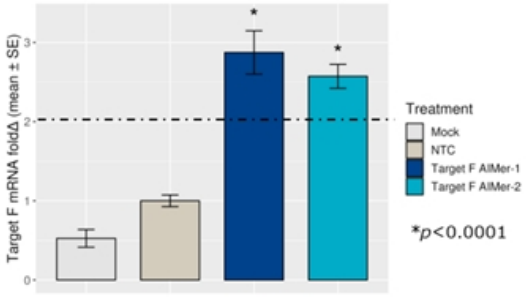
Upregulation of Target F restores kidney function in a rare genetic kidney disease

Achieved >2-fold upregulation of Target F mRNA *in vitro* with RNA editing

Target F

- Kidney target for upregulation
- Rare genetic kidney disease that leads to ESRD and need for dialysis / transplantation; High unmet need with few treatment options currently available
- ~85K patients in US and Europe addressable with upregulation approach
- Urinary biomarkers available to assess upregulation
- Clinically meaningful benefit may be achieved with 2-fold upregulation

Upregulation of Target F mRNA in Human kidney tubular epithelial cells



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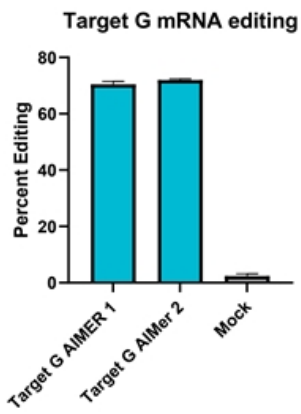
ESRD: End Stage Renal Disease; Right: One-Way Anova; samples compared to NTC with Tukey's HSD test. Significance evaluated at $p<0.0001$.

Correction of Target G mutation restores protein function in patients with a genetic lung disease

Target G

- Lung disease target for correction
- Genetic lung disease with target patient population not addressed with available therapies
- ~5K patients amenable to correction approaches in US and Europe
- Clinically meaningful benefit expected with 20% correction
- Established clinical regulatory pathway

In vitro



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Multiple RNA editing opportunities to build high-value pipeline beyond WVE-006

- The Edit-verse is substantial and still expanding
- Advancing work for a diverse set of undisclosed targets addressing areas of high unmet need, including both rare and prevalent diseases

Potential to advance any combination of targets into preclinical development

	Hepatic (GalNAc-AIMers)				Extra-Hepatic (AIMers)	
	Target A	**Target B**	**Target X**	**Target E**	**Target F**	**Target G**
Approach	Upregulation	Upregulation	Upregulation	Correction	Upregulation	Correction
Tissue	Liver	Liver	Liver	Liver	Kidney	Lung
Therapeutic Area	Metabolic	Metabolic	Renal	Rare	Renal	Rare
Estimated Patients (US and Europe)	~90M	~3M	~170K	~17K	~85K	~5K

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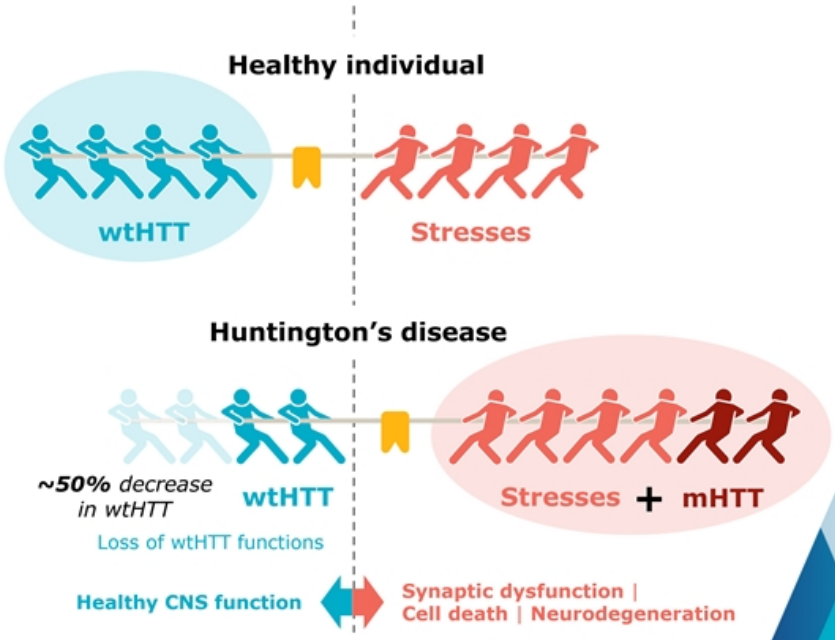
WVE-003

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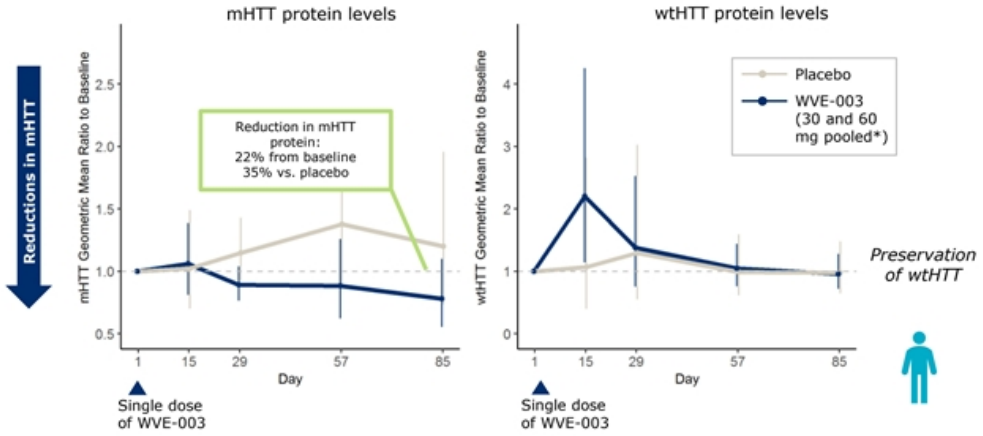
WVE-003: First-in-class allele-selective candidate for HD

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



Additional single-dose and available multi-dose data expected in 2H 2023
Complete multi-dose data from first cohort with extended follow-up expected 2Q 2024

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

WAVE
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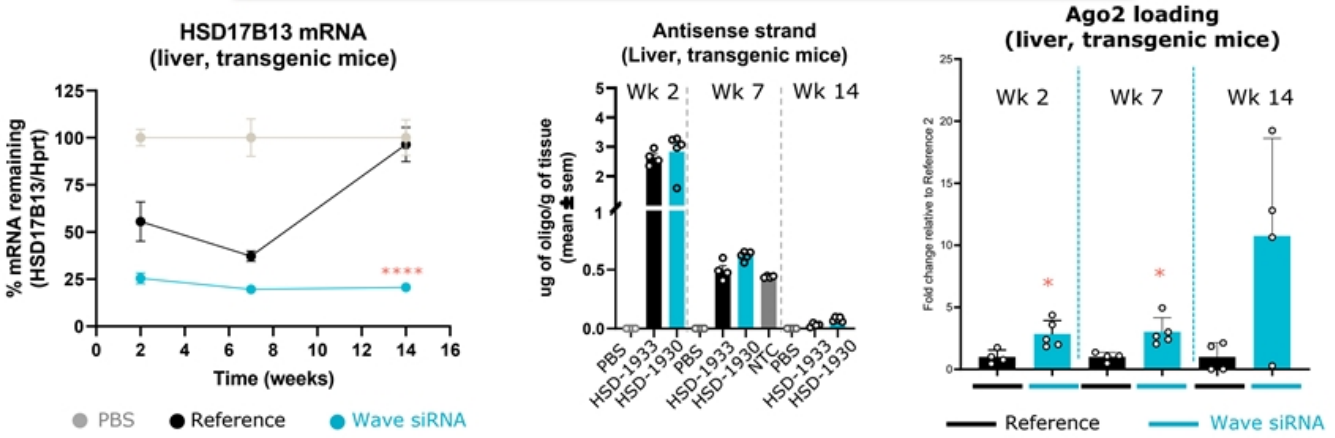
INHBE and siRNA

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 increases potency and durability of silencing following administration of single subcutaneous dose



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

WAVE LIFE SCIENCES

Left, Middle, and right: Mice expressing human *HSD17B13* transgene treated with siRNA (3 mg/kg) 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;

Driven by clinical genetics, Wave's first RNAi program addresses high unmet need in metabolic disorders, including obesity

INHBE program is Wave's first wholly owned program emerging from GSK collaboration

- Leverages novel genetic insights accessed through GSK collaboration
- INHBE loss-of-function heterozygous carriers exhibit healthy metabolic profile[1,2,3]:
  - ✓ Reduced waist-to-hip circumference
  - ✓ Reduced odds ratio of Type 2 diabetes by 28%, and coronary artery disease
  - ✓ Reduced serum triglycerides
  - ✓ Elevated HDL-c
  - ✓ Reduced HbA1c
  - ✓ Lowered ApoB
- INHBE expressed primarily in liver and gene product (subunit of activin E) acts on its receptor in adipose tissue[4]
- GalNAc-siRNA for targeted delivery to hepatocytes

≥50% reduction of INHBE with siRNA expected to restore a healthy metabolic profile

WAVE LIFE SCIENCES

1. *Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 2. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8; 3. PLOS ONE 2018. https://doi.org/10.1371/journal.pone.0194798; 4. Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120.*

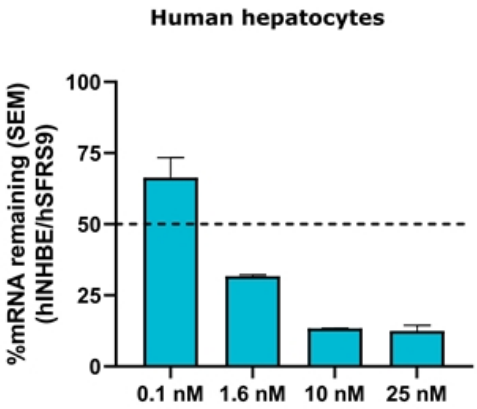
INHBE GalNAc-siRNA represents an evolution in treatment for metabolic diseases, including obesity

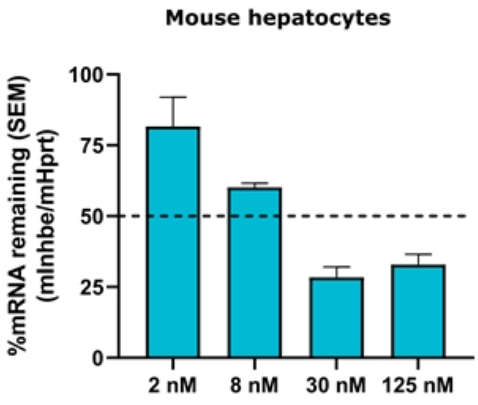
- Metabolic syndrome* is associated with type 2 diabetes, cardiovascular disease, hypertension, stroke, cancer, and increased mortality[1,2]
- Estimate ~47M people in US and Europe with metabolic disorders, including obesity
- Therapeutic options beyond GLP1s are needed
  - GLP1 receptor agonists lead to weight loss at the expense of muscle[4]
  - GLP1 receptor agonists suppress general reward system[7]
  - GLP1 receptor agonists associated with poor tolerability profile[5] with 68% drop-off after 1 year[6]
- Preferred approach would improve metabolism and increase fat loss while maintaining muscle mass
- Restoration of metabolic health via INHBE silencing can simultaneously address obesity and other drivers of metabolic syndrome

*Patients diagnosed with metabolic syndrome based on having 3 of the following: abdominal obesity, high bp, high blood glucose, high TG, or low HDL

1. Liang, et al. 2023 Postgraduate Medical Journal 99(1175):985; 2. Lakka, et al. 2002 JAMA 288(21):2709; 3. Ryan and Yockey 2017 Curr Obes Rep 6(2):187; 4. Sargeant, et al. 2019 Endocrinol Metab (Seoul) 34(3):247-262; 5. Liu, et al. 2022 Front. Endocrinol. 13:1043789; 6. Prime Therapeutics Claims Analysis, July 2023; 7. Müller, et al. 2019 Molecular Metabolism 30: 72-130.

INHBE knockdown of 90% demonstrated in human hepatocytes with GalNAc-siRNA



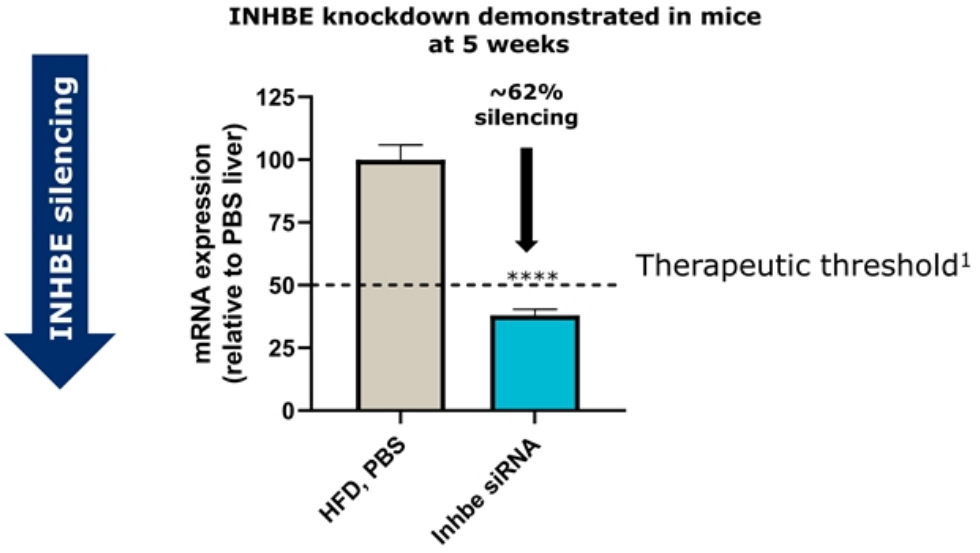


- This cross-reactive sequence demonstrates ~90% maximal knock-down in human hepatocytes and ~65% in mouse hepatocytes
- Additional human selective sequences are in development

WAVE LIFE SCIENCES

Primary hepatocytes were treated with a cross-reactive siRNA via free uptake. INHBE mRNA was quantified by RT-qPCR.

INHBE silencing achieved *in vivo* with GalNAc-siRNA exceeds therapeutic threshold

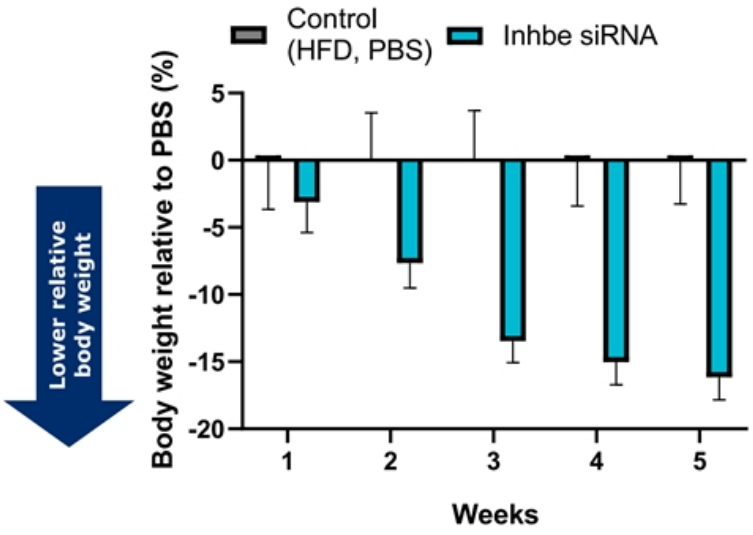


HFD: high-fat diet. Stats: two-sided Welch's T Test **** P < 0.0001

1. Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120.

INHBE knockdown led to 16% lower body weight

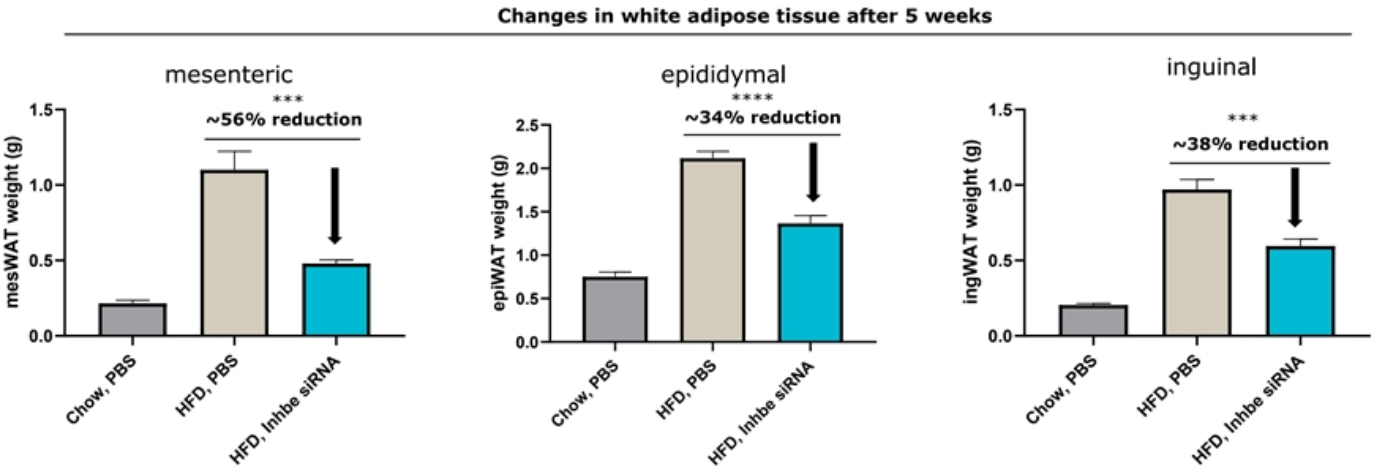
Similar effect seen in semaglutide preclinical studies



Data plotted by body weight difference as a percentage of PBS treated young DIO mice; *Coskun, T. et. al. Mol. Metab. 2018, 18, 3.* Stats: Repeated Measures ANOVA; Inhbe siRNA vs. Control significantly different at $P < 0.05$ level weeks 2 through 5

INHBE reduction leads to significant decrease in visceral fat at 5 weeks

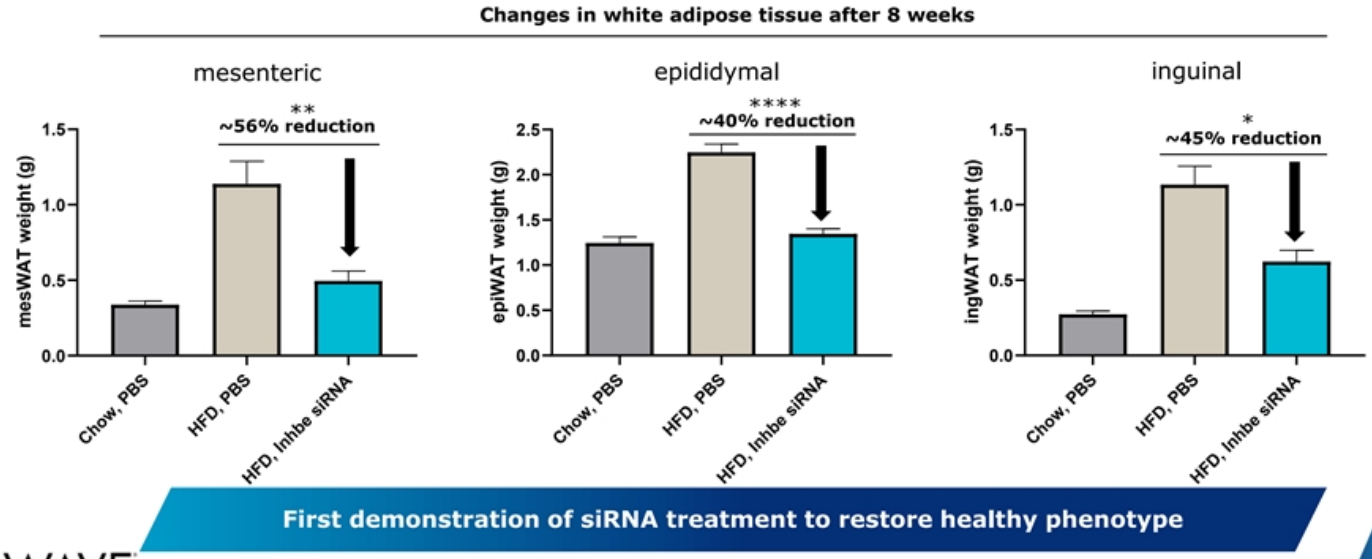
- INHBE knockdown in young DIO mice resulted in less fat mass across multiple types of white adipose tissue, without loss of brown fat



Stats: white-adjusted Two-way ANOVA with Bonferroni-adjusted post hoc comparisons per tissue type allowing heteroscedasticity (only HFD, Inhbe siRNA vs. HFD, PBS shown) *** P < 0.001, **** P < 0.0001

>50% reduction of INHBE mRNA recapitulates phenotype of heterozygous LoF carriers

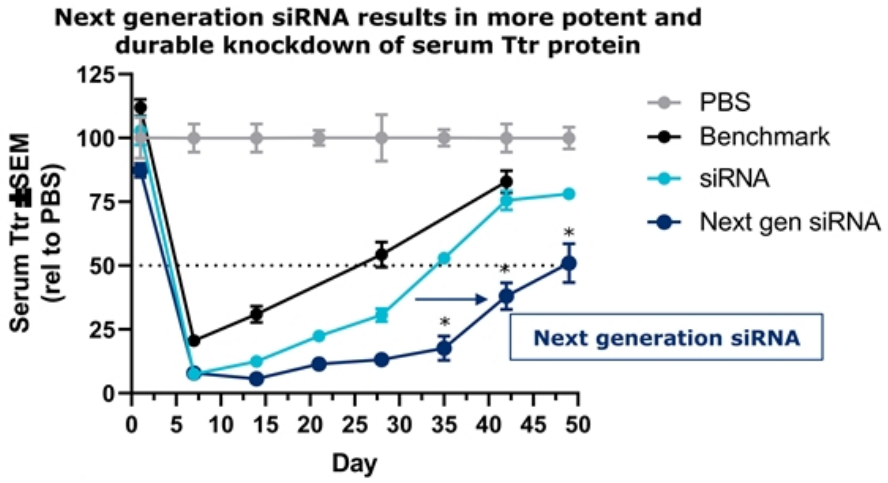
- Subsequent 8-week study demonstrates further reduction in excess visceral fat



First demonstration of siRNA treatment to restore healthy phenotype

Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120. HFD: high-fat diet. Stats: white-adjusted Two-way ANOVA with Bonferroni-adjusted post hoc comparisons per tissue type allowing heteroscedasticity (only HFD, INHBE siRNA vs. HFD, PBS shown) * P < 0.05, ** P < 0.01, **** P < 0.0001

Wave's next generation GalNAc-siRNA demonstrates best-in-class potential



- Applying next-generation siRNA chemistry to INHBE program
- Potential for infrequent administration

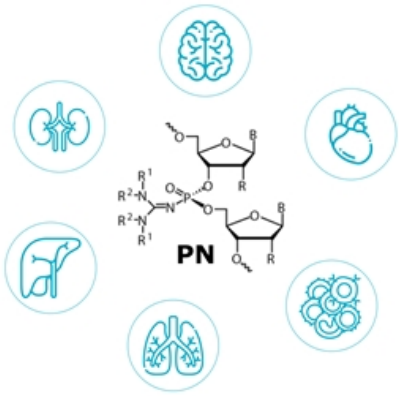
INHBE candidate for metabolic disorders, including obesity, expected in 4Q 2024

WAVE LIFE SCIENCES

Foster, DJ. et.al. Mol Ther. 2018, 26(3), 708. B6 mice administered PBS or 0.5 mg/kg of siRNA (subcutaneous). Benchmark: Stats: Mixed Two-way ANOVA followed by post hoc test comparing siRNA vs. Next gen siRNA per day derived from linear mixed effects model * P < 0.0001

Wave's platform chemistry enables siRNA extra-hepatic delivery

- Chemical impact
  - Introduction of neutral backbone
  - Unique structural feature of PN, specifically guanidine
  - Increased lipophilicity
  - Stereochemistry
- Extra-hepatic delivery
  - Titrating siRNA lipophilicity tunable PNs (PN variants)
  - Maintaining high Ago2 loading and intracellular trafficking
  - Titrating plasma protein binding
  - Altered delivery, enhanced potency and durability in various tissues



PN can tune extra-hepatic delivery of siRNA using rational design, including placement, number of modifications and PN variants

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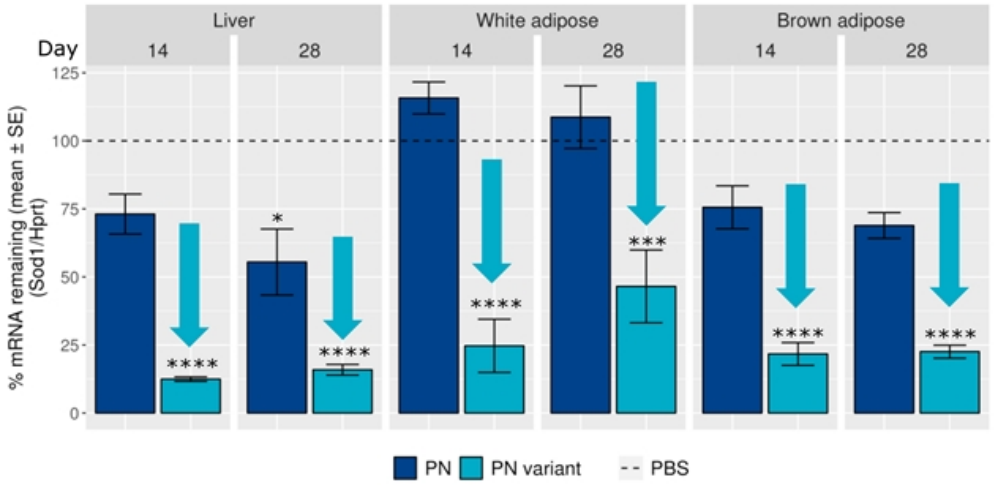
Tunable PN variants enhance potency and alter extra-hepatic delivery of non-GalNAc siRNAs

Non-GalNAc siRNA with PN variants improve silencing in liver and adipose tissue 14 and 28 days post single dose



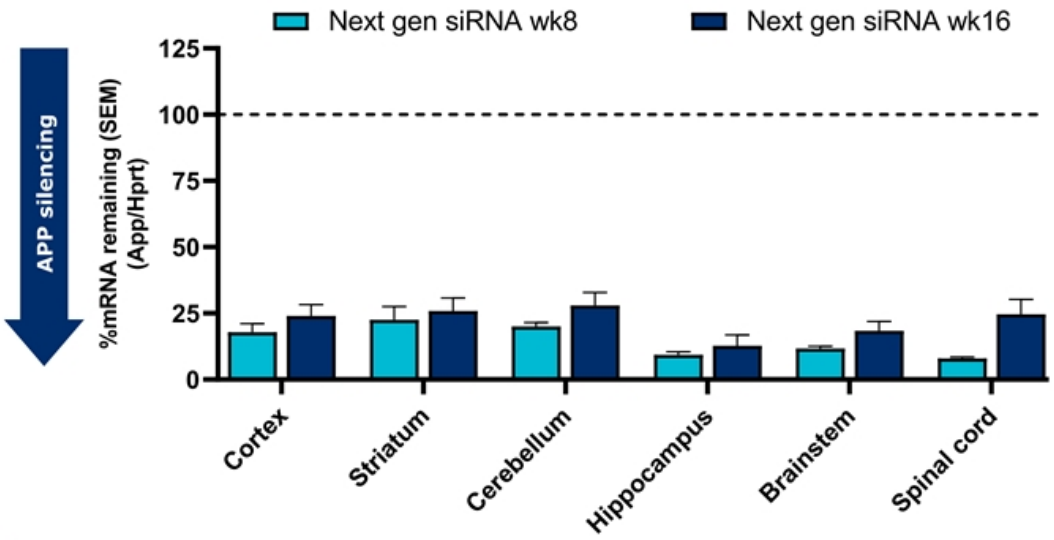
- Reaching adipose tissue in addition to liver with siRNA is important for certain metabolic disorders
- PN variants also enhanced siRNA silencing in muscle tissue, including heart and diaphragm

WAVE LIFE SCIENCES

Stats: Three-way ANOVA followed by Bonferroni-adjusted post hoc test comparing condition to PBS (data not shown) * P < 0.05, *** P < 0.001, **** P < 0.0001; B6 mice administered PBS or 5 mg/kg of Sod1 siRNA (no GalNAc conjugate) subcutaneous injection (n=7). Taqman qPCR assays used for RNA PD, relative fold changes of *Sod1* to *Hprt* mRNA normalized to % of PBS group.

Single dose of next generation siRNA delivers broad, potent and durable CNS target engagement

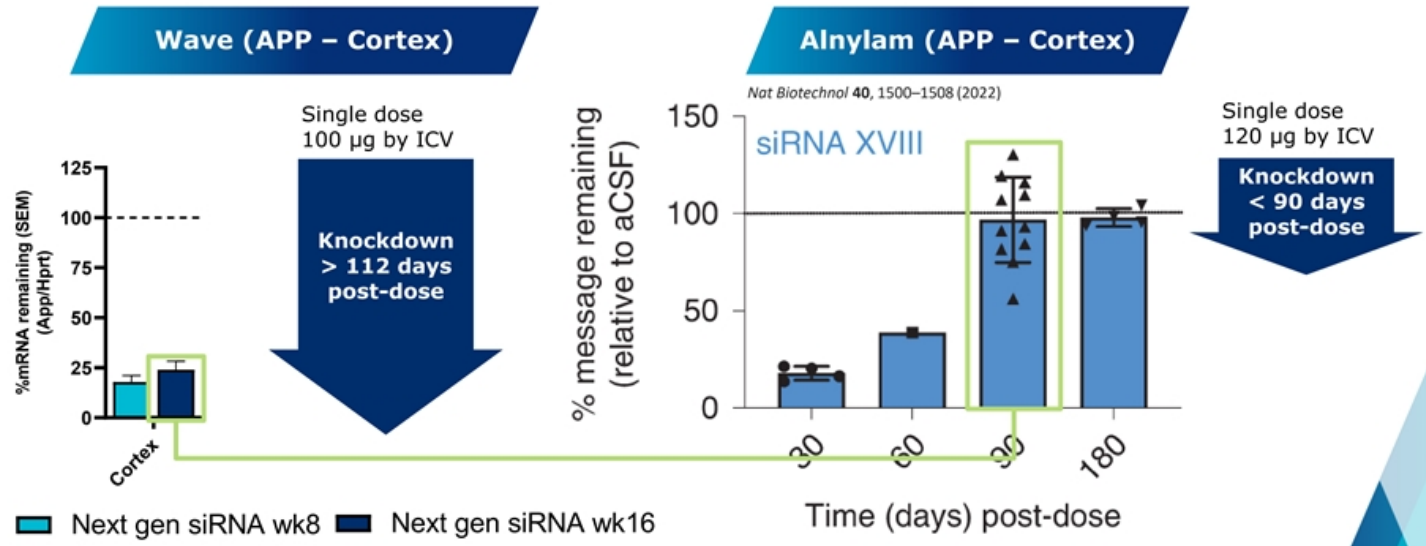
Sustained APP knockdown of at least 75% throughout the 16-week study *in vivo* in mice



WAVE LIFE SCIENCES

PBS (dotted line) or 100 µg of App siRNA administered ICV (n=7). PCR assays for RNA PD, relative fold changes of *App* to *Hprt* mRNA normalized to % of PBS; Stats: Three-way ANOVA followed by Bonferroni-adjusted post hoc test comparing condition to PBS (data not shown), Next gen siRNA significantly lower than PBS at both time points for all tissues at $P < 0.0001$ level

Wave siRNA demonstrates more potent and durable silencing as compared to published state-of-the-art

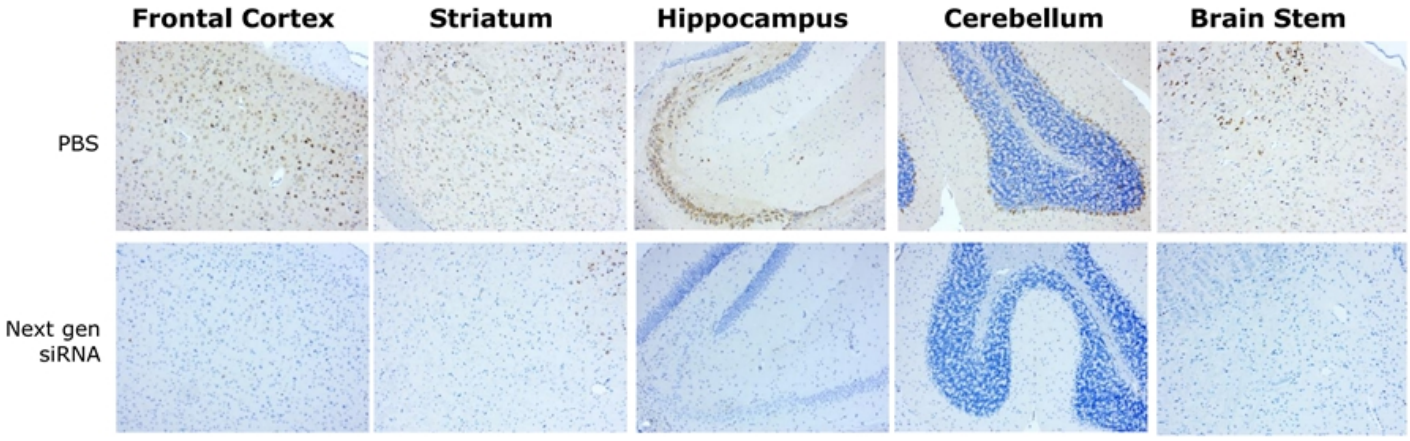


WAVE LIFE SCIENCES

PBS (dotted line) or 100 µg of App siRNA administered ICV (n=7). PCR assays for RNA PD, relative fold changes of *App* to *Hprt* mRNA normalized to % of PBS; Stats: Three-way ANOVA followed by Bonferroni-adjusted post hoc test comparing condition to PBS (data not shown), Next gen siRNA significantly lower than PBS at both time points for all tissues at P < 0.0001 level. Source: Brown, K.M., Nair, J.K., Janas, M.M. *et al.* Expanding RNAi therapeutics to extrahepatic tissues with lipophilic conjugates. *Nat Biotechnol* **40**, 1500–1508 (2022).

Robust target engagement translates to substantial App protein reduction across brain regions

Reductions observed 8-weeks post single-dose



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Immunohistochemical analysis of FFPE Mouse Brain tissue labeling App protein (**Color Brown**) with CS#19389 followed by a ready to use Polymer-HRP 2nd Detection antibody. Nuclei were counterstained with Hematoxylin (**Color Blue**). Single 100 ug ICV injection

First siRNA clinical candidate (INHBE) with proprietary chemistry expected in 4Q 2024

- **INHBE GalNAc-siRNA program is driven by clinical genetics, with potential to be next-generation therapeutic for obesity**
  - ≥50% silencing of INHBE is expected to improve metabolic health
  - INHBE siRNA silencing above therapeutic threshold restores healthy phenotype, with 16% lower body weight, as well as reduction of visceral fat to the level of lean-animals
- **Next generation GalNAc-siRNA formats are best-in-class and being applied to INHBE program**
- **Wave's platform chemistry enables extra-hepatic delivery for other non-hepatic targets**
  - PN-variants on non-GalNAc siRNA enhance silencing in multiple tissues, including liver, adipose tissue and muscle.
  - Single dose of next generation siRNA delivers broad, potent (>75%) and durable CNS target engagement

WAVE LIFE SCIENCES

WAVE LIFE SCIENCES

Anticipated upcoming milestones

Anticipated upcoming milestones

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 in 2H 2023** **Dosing in RestorAATion clinical program in 4Q 2023; AAT protein restoration data expected in 2024** **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 FORWARD-53 clinical trial expected in 2023; data expected in 2024** **Expansion opportunities in other exons, as well as other muscle and CNS diseases**	**WVE-003 for HD** *First-in-class wild-type huntingtin protein (wtHTT)-sparing approach* **Additional single dose and available multidose expected in 2H 2023** **Complete multi-dose data from first cohort of SELECT-HD trial with extended follow-up expected 2Q 2024** **Enables discussion on next steps with Takeda**	**INHBE program for metabolic disorders, including obesity** *Driven by clinical genetics, with potential to be next-generation therapeutic for obesity* **Selection of INHBE clinical candidate expected in 4Q 2024** **Wave's chemistry enables extra-hepatic delivery for CNS and beyond**

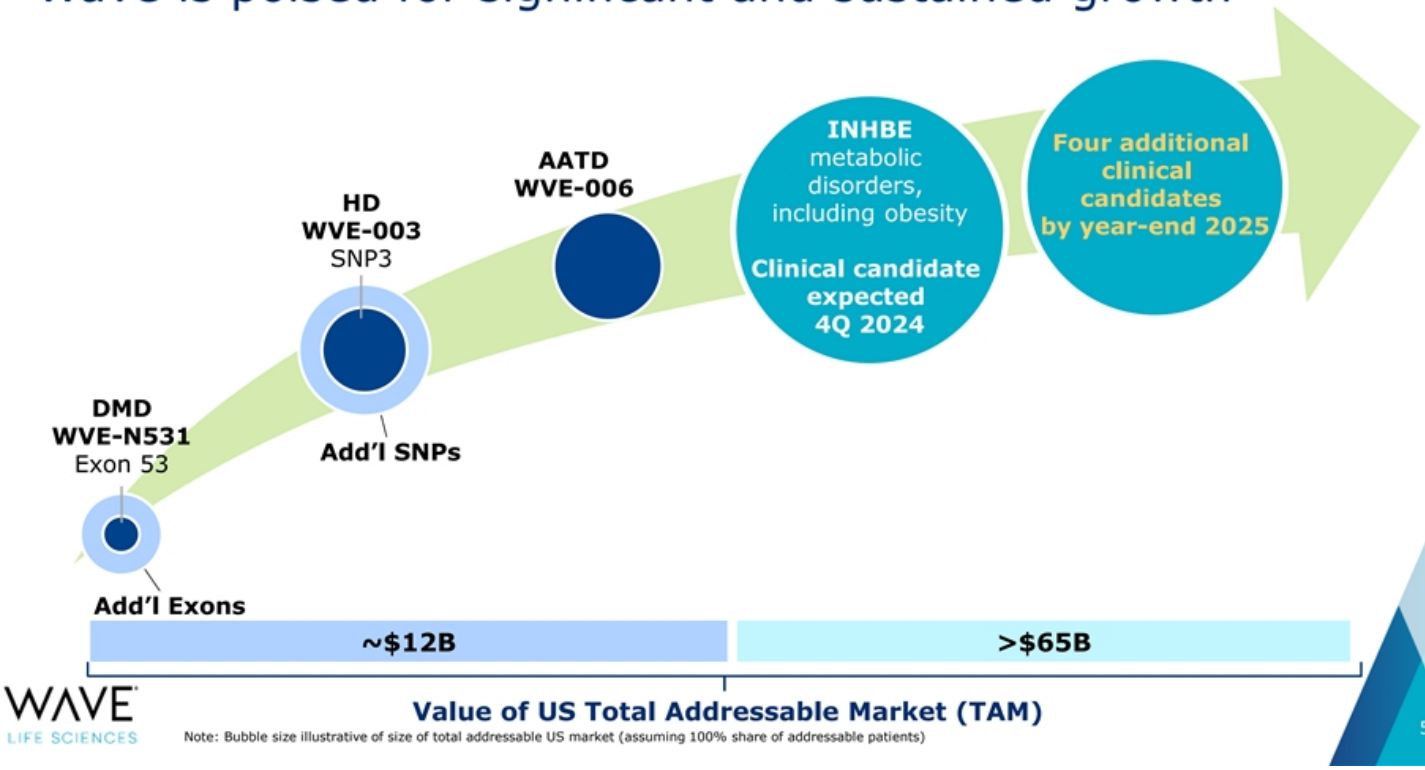
DISCOVERY PIPELINE & COLLABORATIONS

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

WAVE LIFE SCIENCES

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

Wave is poised for significant and sustained growth



Note: Bubble size illustrative of size of total addressable US market (assuming 100% share of addressable patients)

For more information:

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WAVE LIFE SCIENCES