# 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): December 15, 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 December 15, 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 99.1 attached 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 December 15, 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: December 15, 2023

Exhibit 99.1

# Wave Life Sciences
## Corporate Presentation

December 15, 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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# Building a leading RNA medicines company

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- DMD (splicing), HD (silencing), and AATD (RNA editing) clinical programs advancing
- INHBE, obesity (siRNA), muscle sparing, fat loss, improved metabolic profile
- Multi-modal drug discovery and development platform
- Leader in RNA editing with potential best-in-class oligonucleotide chemistry
- Strategic collaborations to expand and advance pipeline
- In-house GMP manufacturing; Strong and broad IP portfolio

**Upcoming Milestones:**

- Proof-of-mechanism data from RestorAATion clinical program of WVE-006 for AATD in 2024
- Select INHBE clinical candidate for metabolic disorders, including obesity, in 4Q 2024 and submit CTA in 2025
- Data from FORWARD-53 clinical trial of WVE-N531 for DMD in 2024
- Data from SELECT-HD clinical trial of WVE-003 for HD in 2Q 2024

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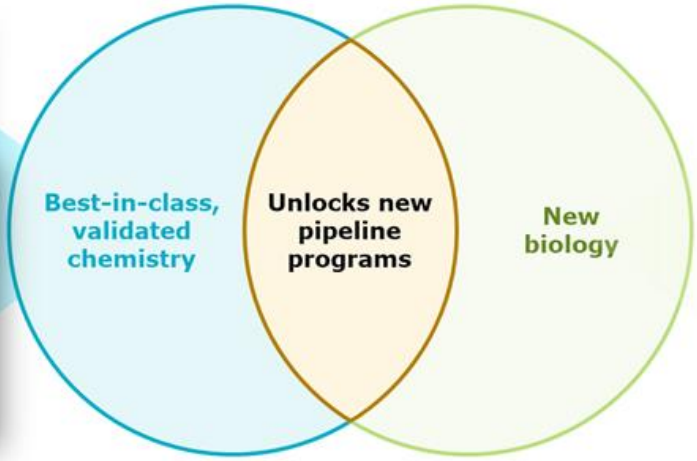
**$20 million milestone earned under GSK collaboration and $100 million offering in December 2023 extended cash runway into 4Q 2025***

*Cash runway does not include potential future milestones or opt-in payments under GSK and Takeda collaborations

# Combining potential best-in-class chemistry with novel biology and genetic insights: Opportunities for new high impact medicines


- Accessing new endogenous enzymes for novel modalities (RNA editing)
- Opening up new targets, including prevalent diseases

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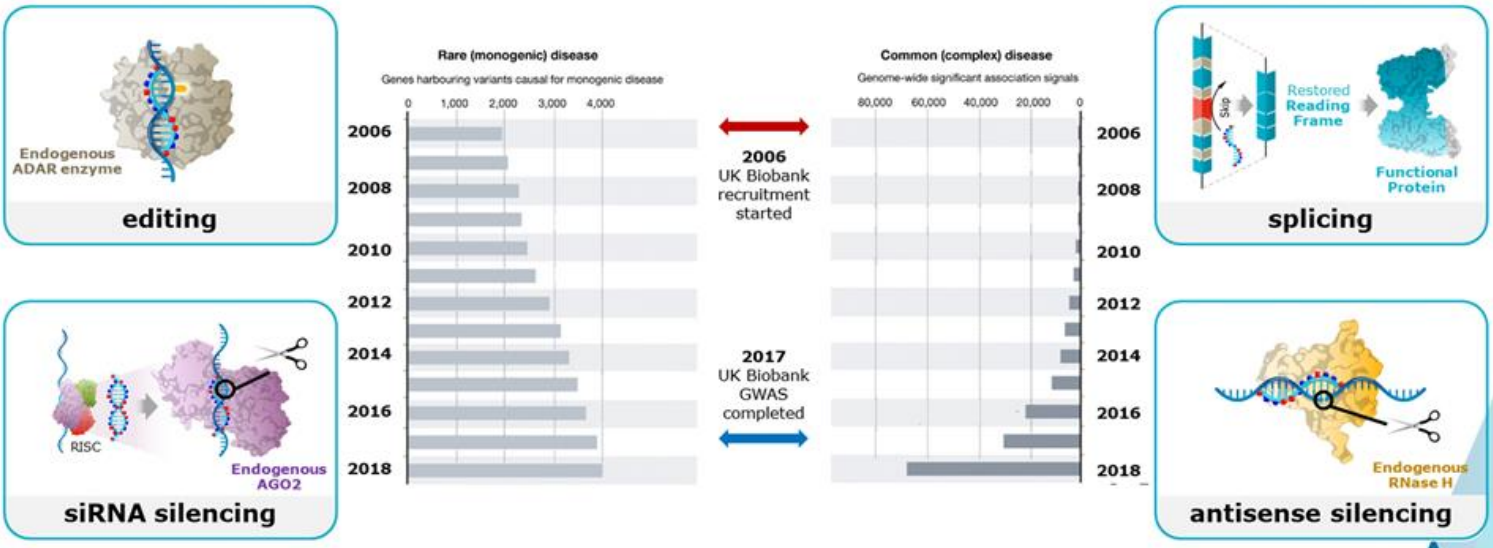
# Wave's versatile RNA medicines platform unlocks genetic insights for rare and common diseases opening up new target opportunities




**Accessing UK Biobank and building proprietary machine learning models to generate unique genetic insights**

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Claussnitzer, et al. Nature (2020) 577, 179; King et al. PLoS Genet (2019) 15, e1008489

# 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) | RestorAATion Clinical Program | | | GSK exclusive global license | 200K |
| Multiple undisclosed Correction | | | | 100% global | >20K (multiple) |
| Multiple undisclosed Upregulation | | | | 100% global | >3M (multiple) |
| **SILENCING: siRNA** | | | | | |
| INHBE* (Metabolic disorders, including obesity) | | | | 100% global | 47M |
| **SPLICING** | | | | | |
| **WVE-N531** Exon 53 (DMD) | FORWARD-53 Trial (Phase 2) | | | 100% global | 2.3K |
| Other exons (DMD) | | | | 100% global | Up to 18K |
| **SILENCING: ANTISENSE** | | | | | |
| **WVE-003** mHTT (HD) | SELECT-HD Trial (Phase 1b/2a) | | | Takeda 50:50 Option | 25K Manifest (SNP3) 60K Pre-Manifest (SNP3) |

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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


# WVE-006 (RNA editing)

## 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)

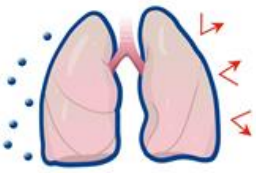

Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

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

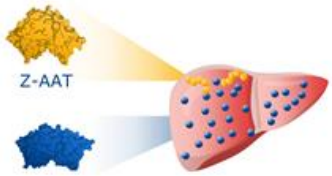
**1) Restore** circulating, functional wild-type M-AAT

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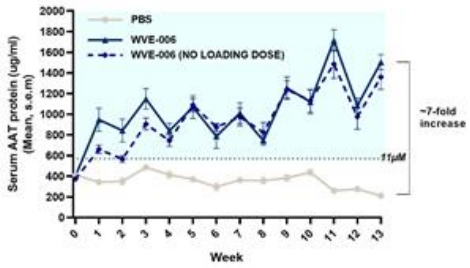
AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

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

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

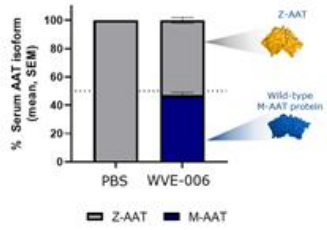
### Increased AAT protein in NSG-PiZ mice

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



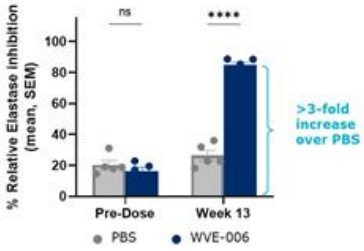

### Confirmed restored wild-type M-AAT protein

**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**




**Potent and durable editing yields functional AAT protein**

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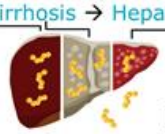
AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at wk 13 (1 wk after last dose) and SERPINA1 editing quantified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

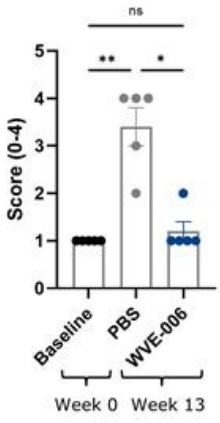
# WVE-006 decreases lobular inflammation and PAS-D globule size, prevents increase in hepatocyte turnover

**Correction of gain-of-function liver phenotypes**

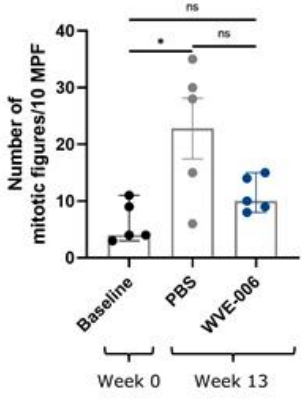
Fibrosis → Cirrhosis → Hepatocellular Carcinoma



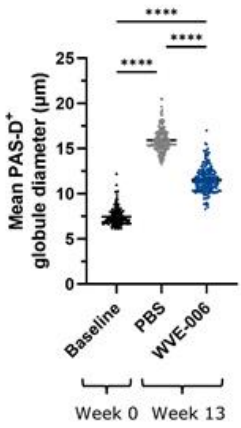
**Lobular inflammation**
(NSG PiZ mice, week 13)




**Mitoses**
(NSG PiZ mice, week 13)




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

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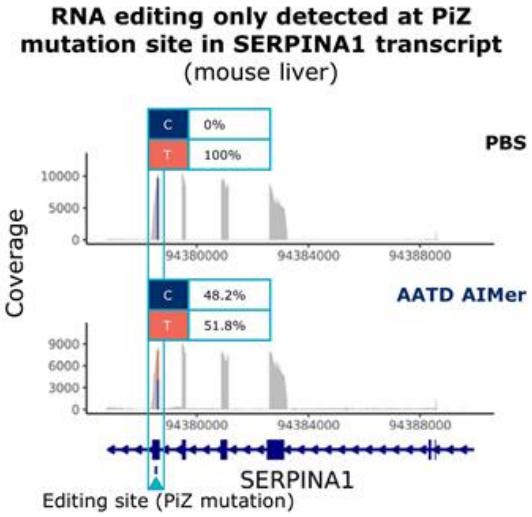
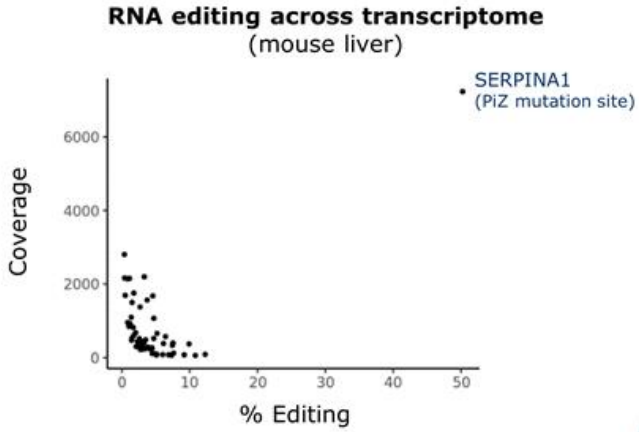
Left (Lobular inflammation) and Middle (Mitoses): Scatter plot showing inflammation grade or mitoses score. Each circle represents an individual mouse, (Mean ± SEM); Right (PAS-D Globule Size): 40 largest globules in each of 5 mice were measured. Each circle represents a single PAS-D globule, (Mean ± 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

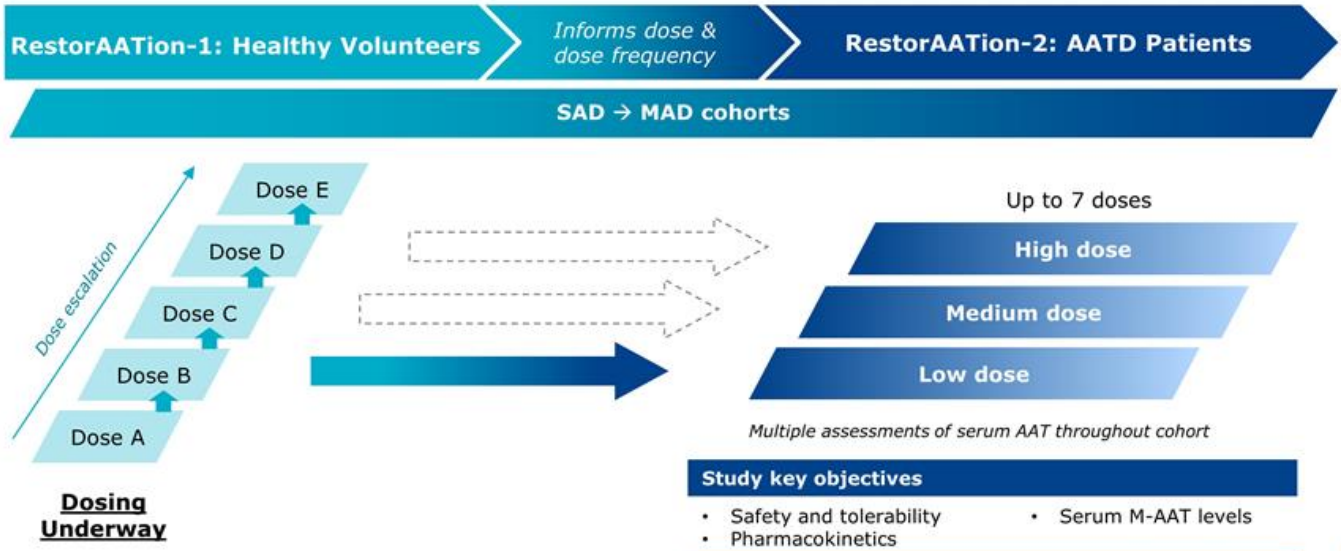
## No bystander editing observed on SERPINA1 transcript




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

# Dosing underway in RestorAATion clinical program; 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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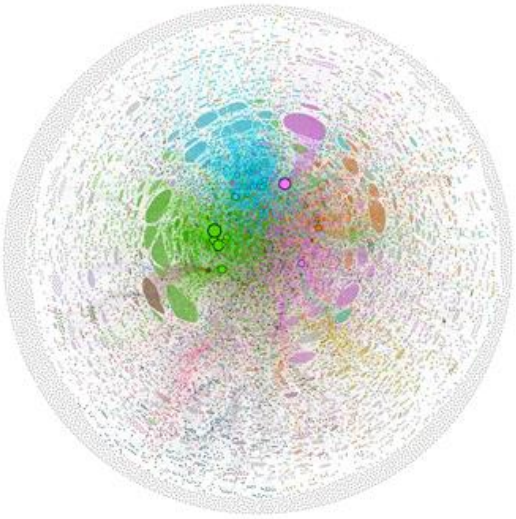
# AIMers

## RNA editing capability

# The AIMer-targetable 'Edit-Verse' is substantial

- **The Edit-verse is the editable gene-disease universe, including upregulation**
- **>13,000 genes** with a high-probability[1] of being amenable to transcriptional regulation with A-to-G editing
- Model development ongoing to expand access to **more protein-coding genes** and expand the Edit-verse
- AIMers are expected to be able to target ~50% of the transcriptome

**Gene-Disease Network**



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[1](score >95th p-tile)

# 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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# INHBE program (siRNA silencing)

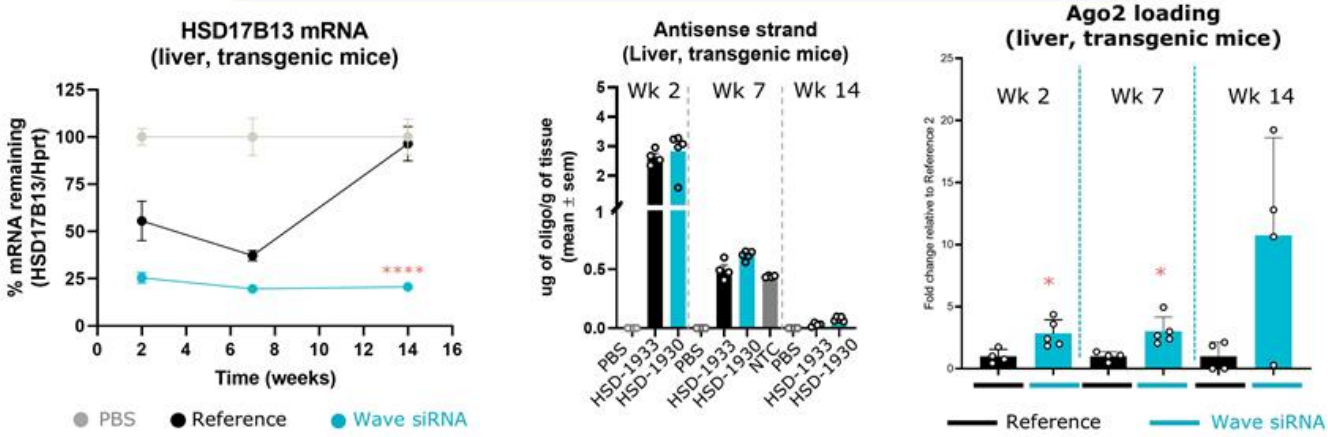
## Metabolic disorders, including obesity

# Potential for best-in-class siRNA 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




**siRNA silencing is one of multiple Wave modalities being advanced in strategic research collaboration with GSK**

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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;

# INHBE: Evolution in treatment for obesity; muscle sparing, sustained fat loss, improved metabolic profile

- 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 GLP-1s are needed
  - GLP-1 receptor agonists lead to weight loss at the expense of muscle mass[3]
  - GLP-1 receptor agonists suppress general reward system[6]
  - GLP-1 receptor agonists associated with poor tolerability profile[4] with 68% drop-off after 1 year[5]
- Preferred approach would improve metabolism and increase fat loss while maintaining muscle mass
- Restoration of metabolic health via INHBE silencing expected to 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. Sargeant, et al. 2019 Endocrinol Metab (Seoul) 34(3):247-262; 4. Liu, et al. 2022 Front. Endocrinol. 13:1043789; 5. Prime Therapeutics Claims Analysis, July 2023; 6. Müller, et al. 2019 Molecular Metabolism 30: 72-130.

# Driven by clinical genetics, GalNac-siRNA 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 ratio
  - ✓ 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**

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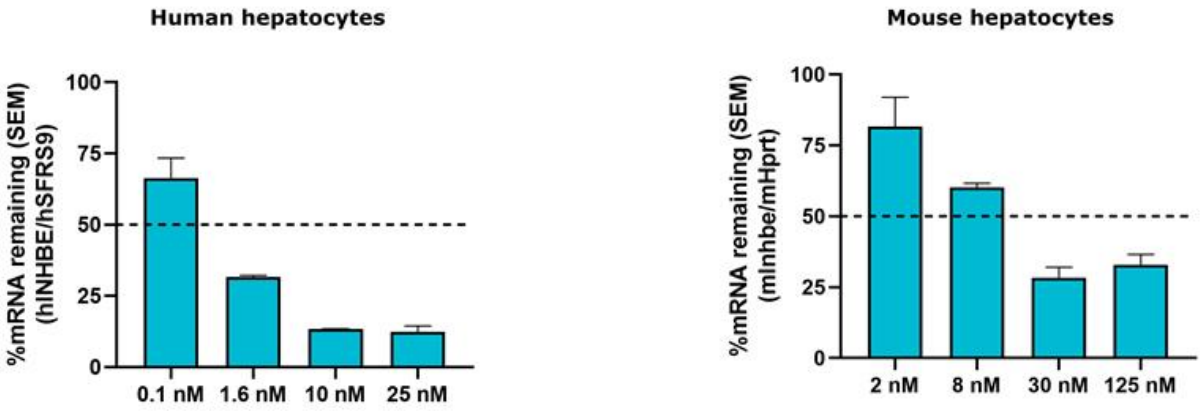
1. *Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 2. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8; 3. PLOS ONE 2018. https://doi.org/10.1371/journal.pone.0194798; 4. Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120.*

# INHBE 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

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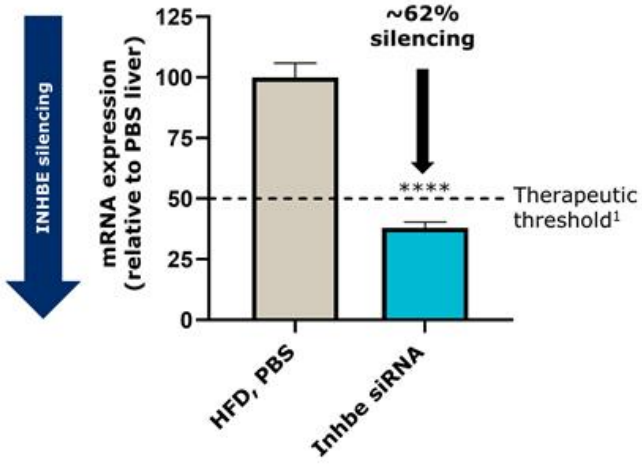
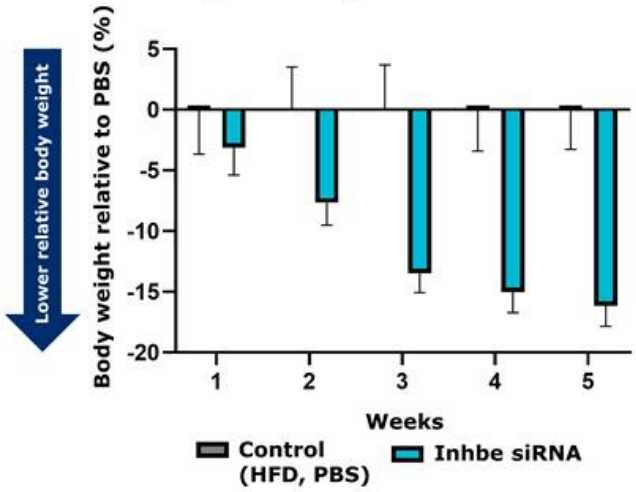
Primary hepatocytes were treated with a cross-reactive siRNA via free uptake. INHBE mRNA was quantified by RT-qPCR.

# INHBE silencing achieved *in vivo* with GalNAc-siRNA exceeds therapeutic threshold and led to lower body weight

**INHBE knockdown demonstrated in mice at 5 weeks**




**INHBE knockdown led to 16% lower body weight as compared to control**




*Similar effect seen in semaglutide preclinical studies*

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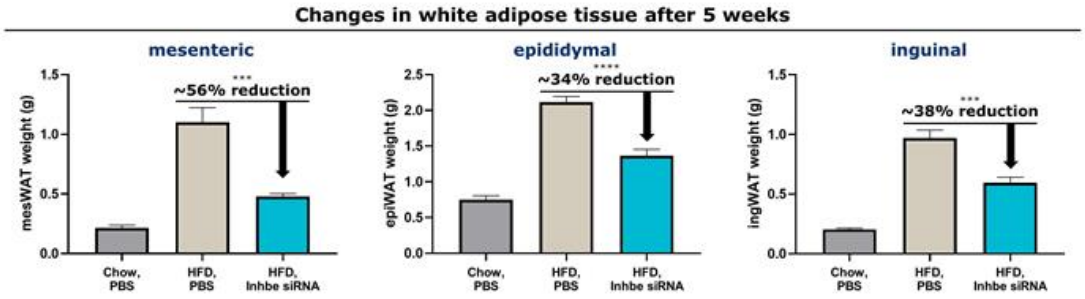
HFD: high-fat diet. Stats: two-sided Welch's T Test **** P < 0.0001

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

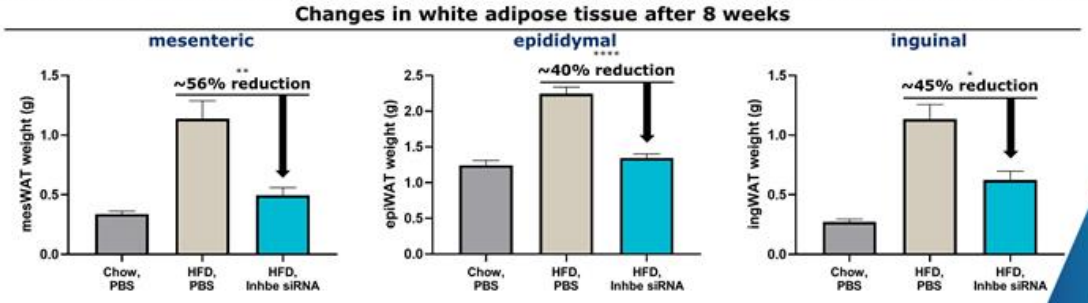
Data plotted by body weight difference as a percentage of PBS treated young DIO mice; Coskun, T. et. al. *Mol. Metab. 2018, 18, 3.* Stats: Repeated Measures ANOVA; Inhbe siRNA vs. Control significantly different at P < 0.05 level weeks 2 through 5

# INHBE silencing leads to significant decrease in visceral fat, consistent with UK Biobank human data on loss-of-function carriers

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




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

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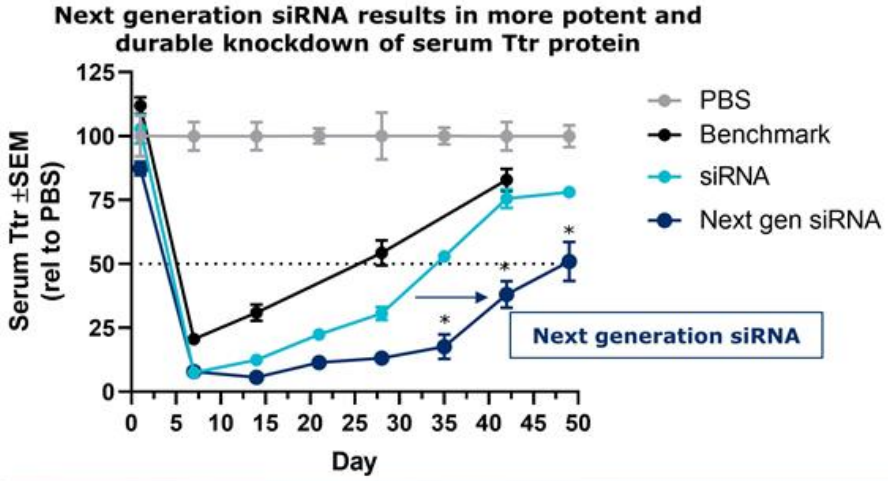
Adam, RC. et.al. Proc Natl Acad Sci USA. 2023, 120(32): e2309967120. HFD: high-fat diet. Stats: white-adjusted Two-way ANOVA with Bonferroni-adjusted post hoc comparisons per tissue type allowing heteroscedasticity (only HFD, Inhbe siRNA vs. HFD, PBS shown) *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001

# INHBE candidate for metabolic disorders, including obesity, expected in 4Q 2024; CTA expected in 2025




**INHBE program**

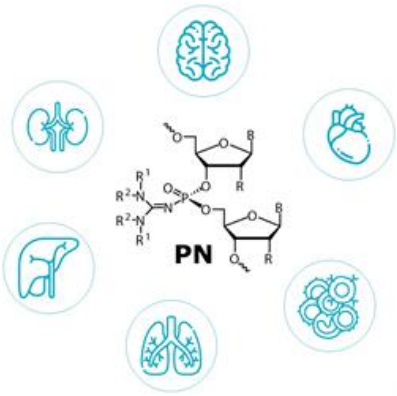
- Applying next-generation siRNA chemistry to INHBE program
- Potent and highly specific leads identified
- Potential for infrequent administration

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

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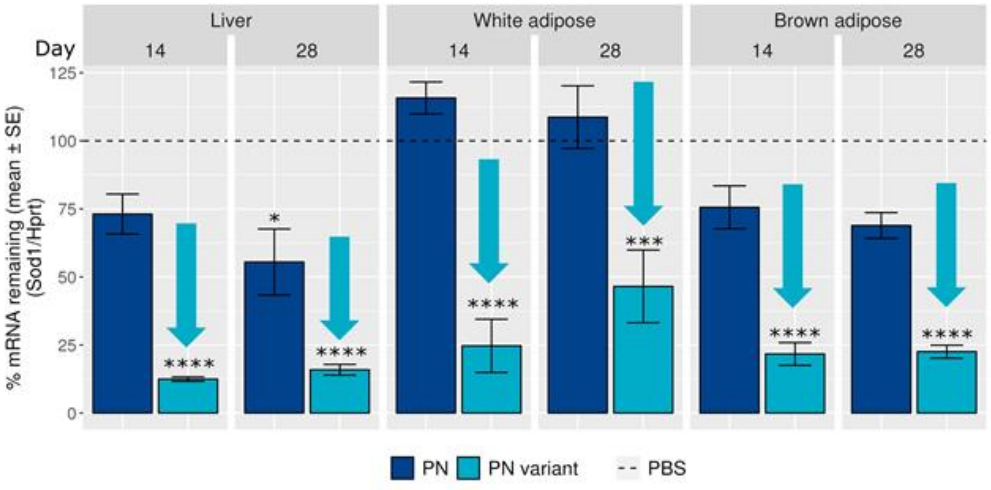
# Tunable PN variants enhance potency and alter extra-hepatic delivery of non-GalNAc siRNAs

**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

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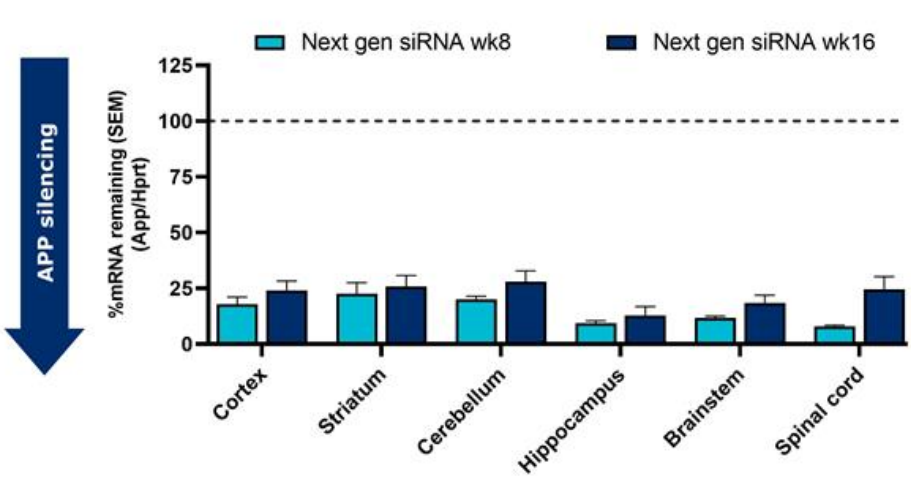
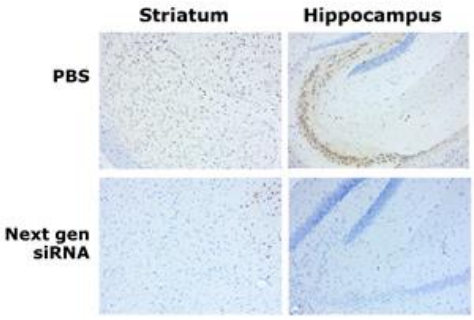
Stats: Three-way ANOVA followed by Bonferroni-adjusted post hoc test comparing condition to PBS (data not shown) * P < 0.05, *** P < 0.001, **** P < 0.0001; B6 mice administered PBS or 5 mg/kg of Sod1 siRNA (no GalNAc conjugate) subcutaneous injection (n=7). Taqman qPCR assays used for RNA PD, relative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

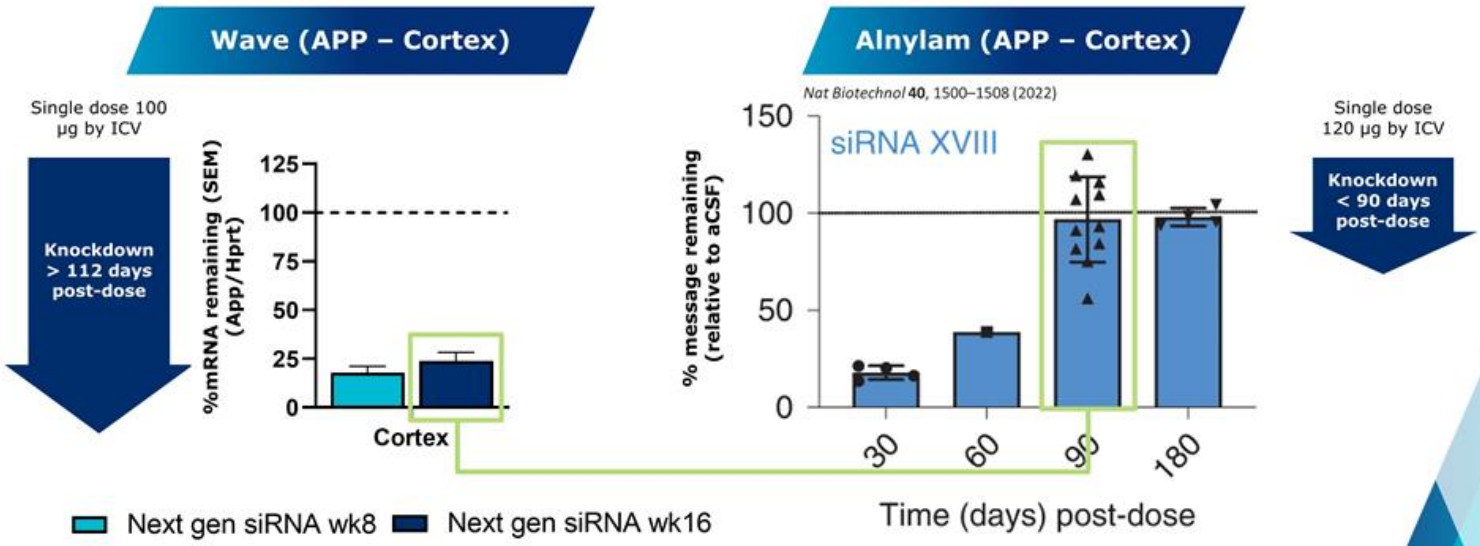



**Robust target engagement translates to substantial App protein reduction across brain regions 8-weeks post single dose**




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; 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

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




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).

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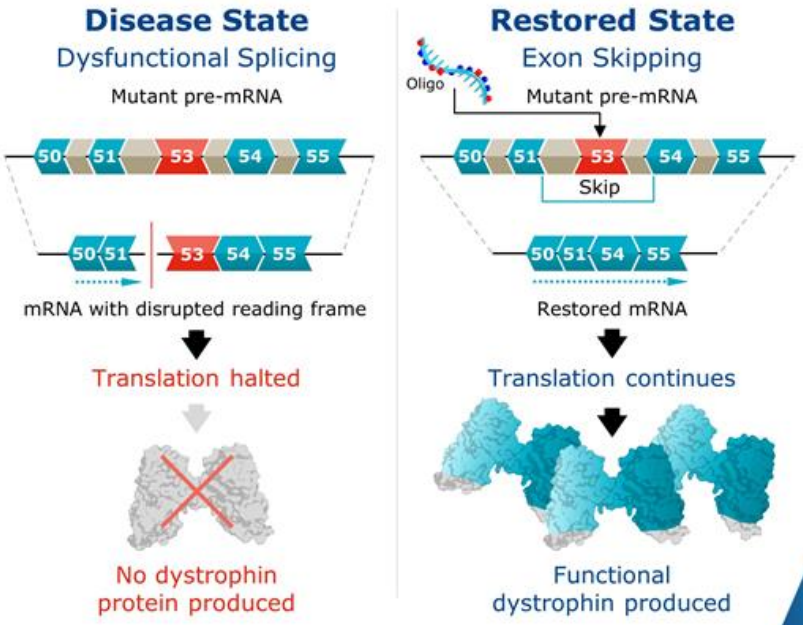
# WVE-N531 (splicing)

## 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

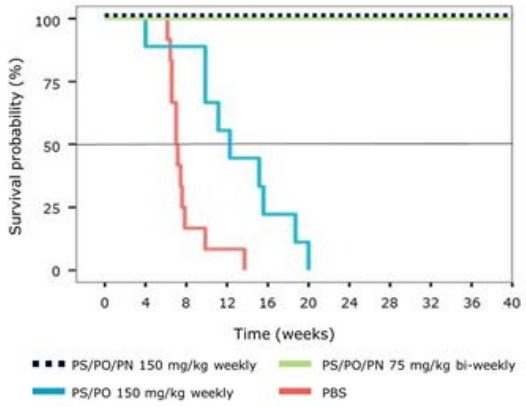



[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

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

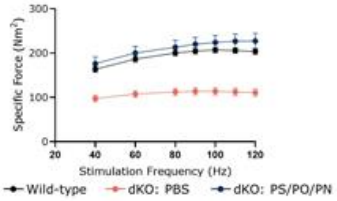
**PN chemistry improved function and survival in dKO mice**

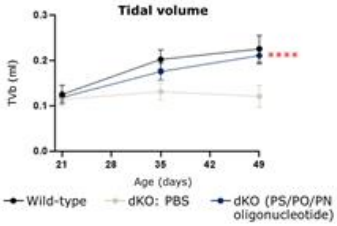
**100% survival at time of study termination**




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

**Restored muscle and respiratory function to wild-type levels**

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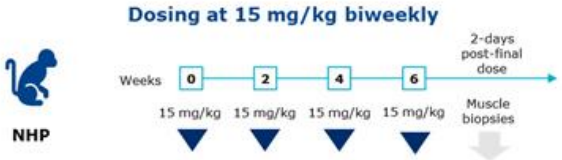
Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

# Preclinical data supported advancing WVE-N531 to clinical development: enhanced delivery and high levels of dystrophin

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

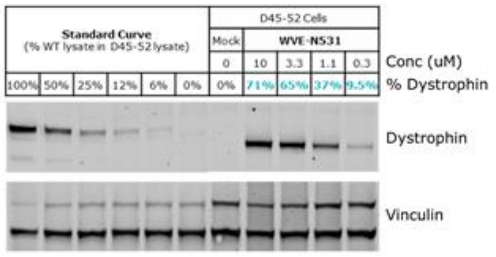



| | Mean Tissue Concentration | | |
|---|---|---|---|
| | Skeletal muscle | Diaphragm | Heart |
| 15 mg/kg* IV dose | 2.17 ug/g | 10.8 ug/g | 57.2 ug/g |

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

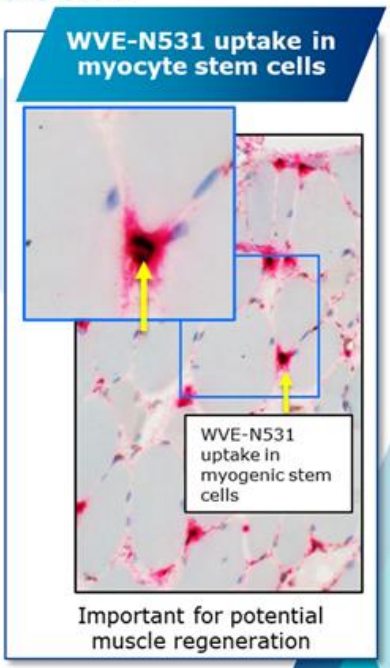
## WVE-N531: Dystrophin restoration of up to 71% *in vitro*

**Western Blot normalized to primary healthy human myoblast lysate**



# Clinical data from WVE-N531 Part A: 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 |

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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

# Dosing underway in 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, 10 patients enrolled
- **Endpoints**: Dystrophin (powered for >5% of normal), safety/tolerability, pharmacokinetics, digital and functional assessments (incl. NSAA and others)
- Muscle biopsies to assess dystrophin expression
- Fully enrolled and dosing underway

FORWARD-53

**Potentially registrational dystrophin expression data are expected in 2024**

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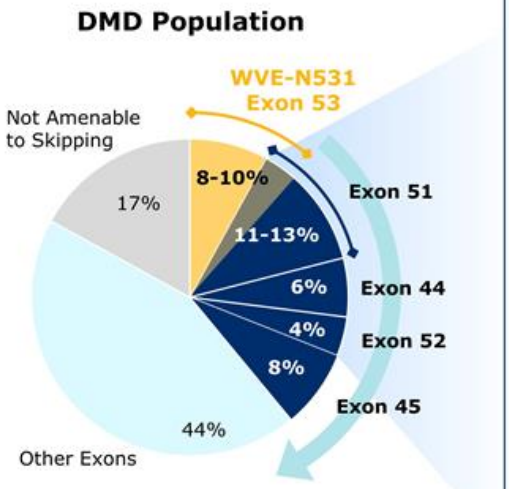
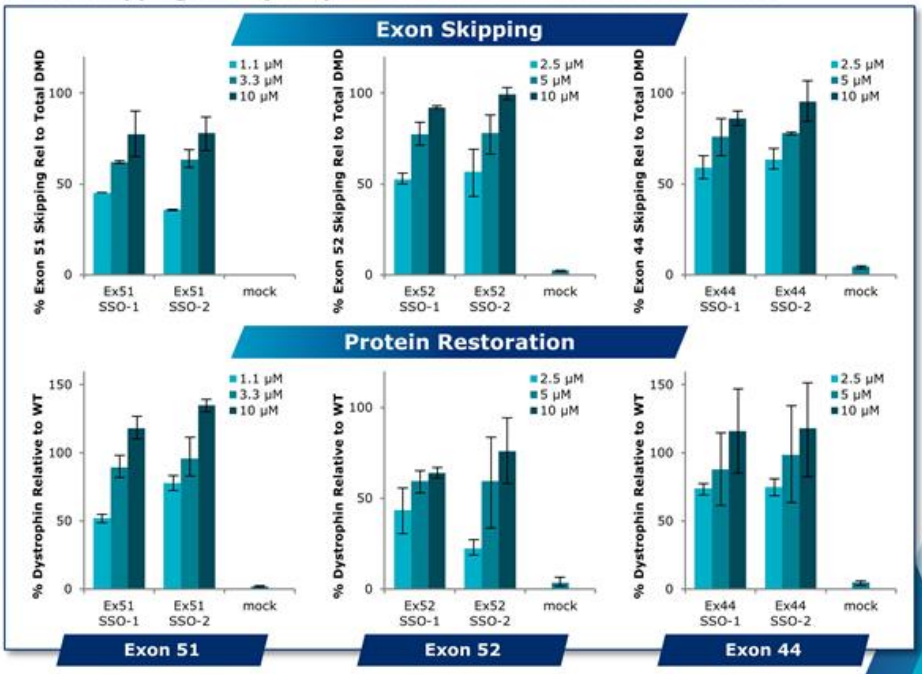
IV: intravenous; NSAA: North star ambulatory assessment

# 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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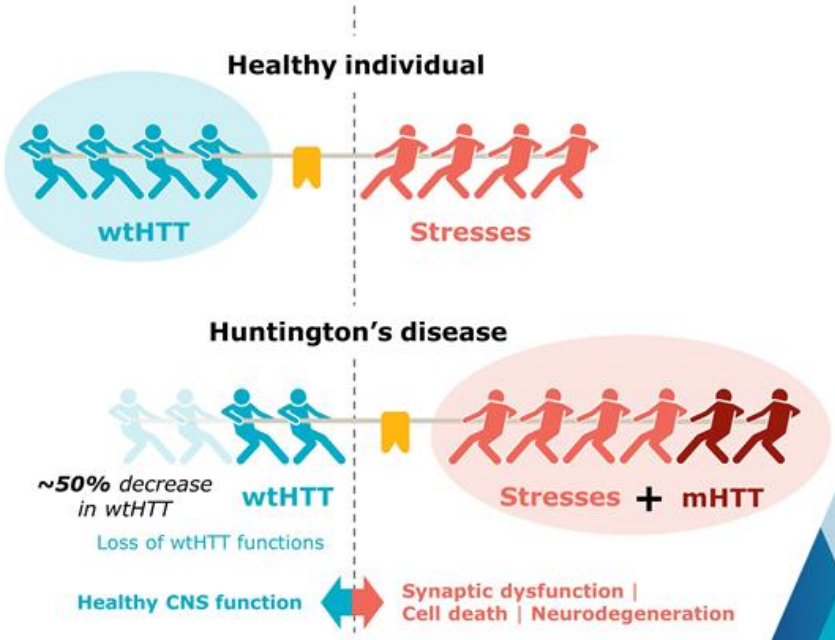
# WVE-003 (Allele-selective antisense silencing)

## 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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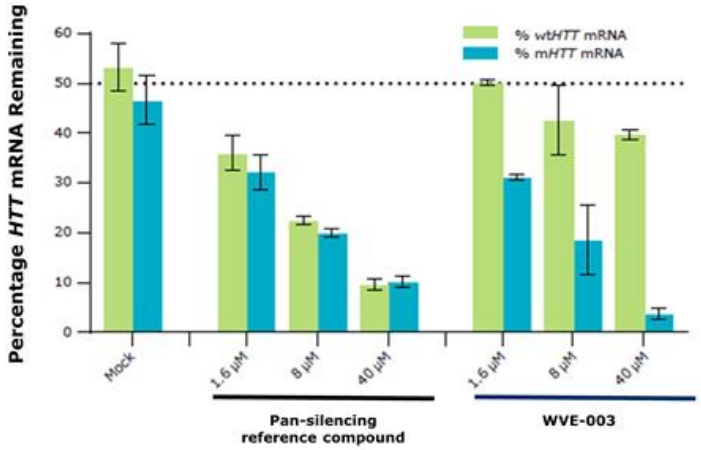
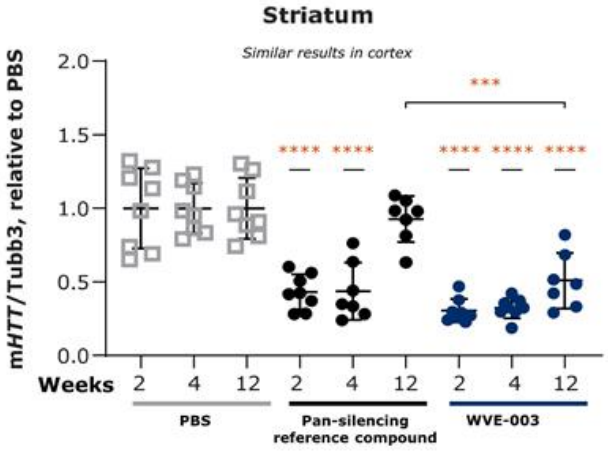
# WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

**Selectively reduces mHTT mRNA in HD iPSC neurons *in vitro***




**Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model**

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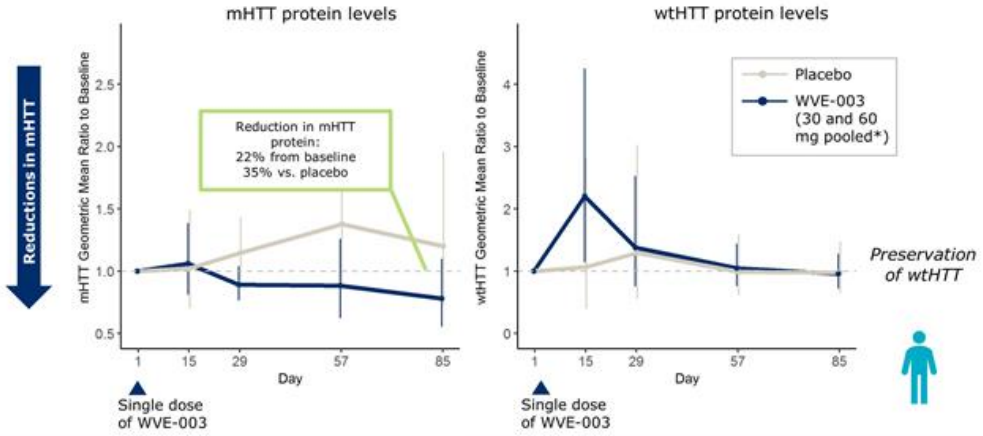
Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1. Oligonucleotide or PBS [100 µg ICV injections through cannula on days 1, 3, 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS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

# 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**




**Data from 30 mg multi-dose cohort with extended follow-up, along with all single-dose data 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

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# Anticipated upcoming milestones

# Anticipated upcoming milestones

| | |
|---|---|
| **WVE-006 (AATD)**<br>Most advanced RNA editing candidate & potential best-in-class approach for AATD | **2024:** Deliver proof-of-mechanism data from RestorAATion clinical program |
| **INHBE Program (Metabolic disorders, including obesity)**<br>Driven by clinical genetics, with potential to be next-generation therapeutic for obesity | **4Q 2024:** Select INHBE clinical candidate<br>**2025:** Submit a clinical trial application (CTA) |
| **WVE-N531 (DMD)**<br>Potential best-in-class approach with highest exon skipping reported | **2024:** Deliver potentially registrational dystrophin expression data from FORWARD-53 |
| **WVE-003 (HD)**<br>First-in-class mHTT lowering, wtHTT-sparing approach | **2Q 2024:** Deliver data from 30 mg multi-dose cohort with extended follow up, along with all single-dose data |

**Discovery Pipeline & Collaborations**

Advance collaboration activities with GSK, with potential for additional cash inflows in 2024 and beyond

Select five new clinical candidates by year-end 2025, including INHBE

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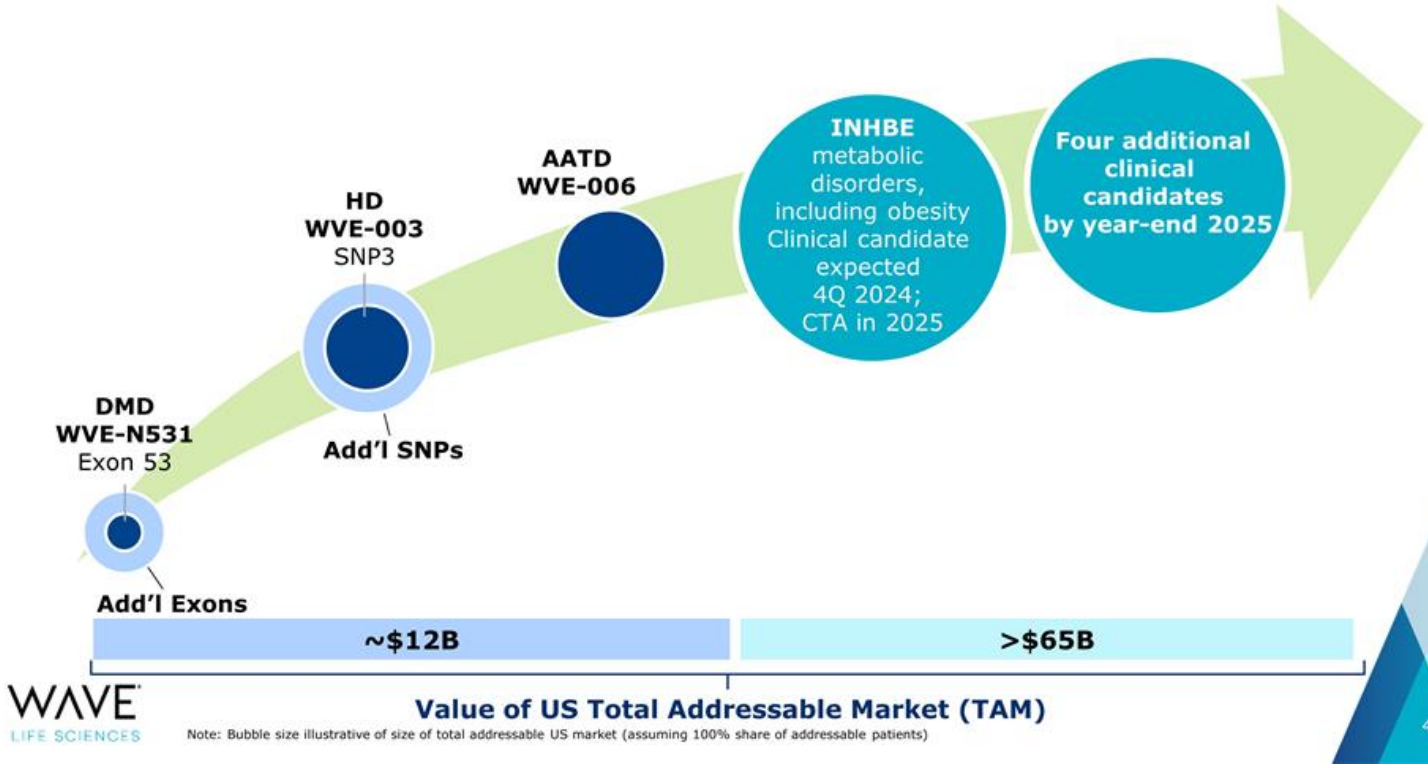
AATD: Alpha-1 antitrypsin deficiency; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; mHTT: Mutant huntingtin; wtHTT: Wild-type huntingtin

# 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)

# Thank you!

For more information:

InvestorRelations@wavelifesci.com

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