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 1, 2024

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 1, 2024, the Company updated its corporate presentation, which is available on the "Investors" section of the Company's website at https://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 October 1, 2024
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/ Kyle Moran*
Kyle Moran
Chief Financial Officer

Date: October 1, 2024

Exhibit 99.1

Wave Life Sciences

Corporate Presentation

October 1, 2024

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.

Building a leading RNA medicines company

Novel RNA medicines platform (PRISM®)

- Multi-modal: RNA editing, RNAi, splicing, allele-selective silencing
- Best-in-class, clinically-validated oligonucleotide chemistry (PN, stereochemistry)

Differentiated RNA medicines pipeline

WVE-006 in AATD

WVE-007 in Obesity

WVE-N531 in DMD

WVE-003 in HD

Strategic collaborations (GSK and Takeda) | **In-house GMP manufacturing** | **Strong and broad IP** | **Well-capitalized with cash runway into 2027***

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

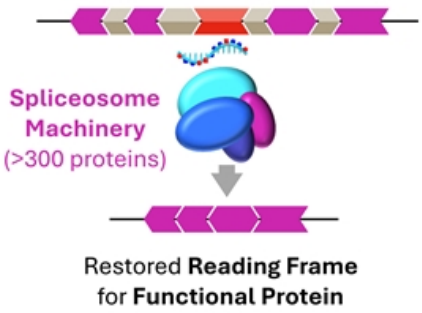
*Cash runway does not include potential future milestones or opt-in payments under GSK and Takeda collaborations

Wave's best-in-class multi-modal platform

Clinically-validated oligonucleotide chemistry (PN, stereochemistry)

Splicing

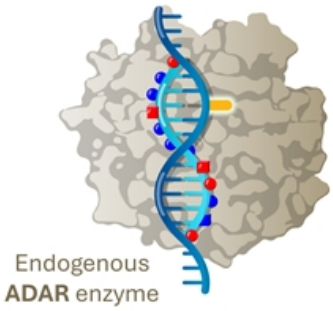
Restore RNA transcripts and **turn on** protein production



WVE-N531 (DMD)

Editing

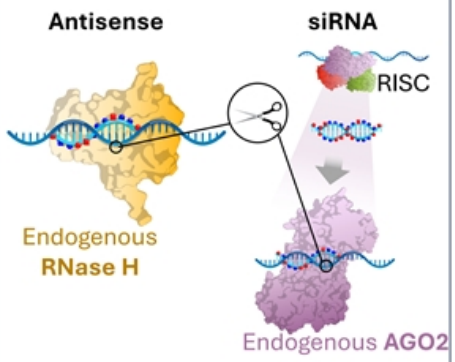
Efficient editing of RNA bases to **restore** or **modulate** protein production



WVE-006 (AATD)
Additional wholly owned editing programs

Silencing

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



WVE-003 (HD)

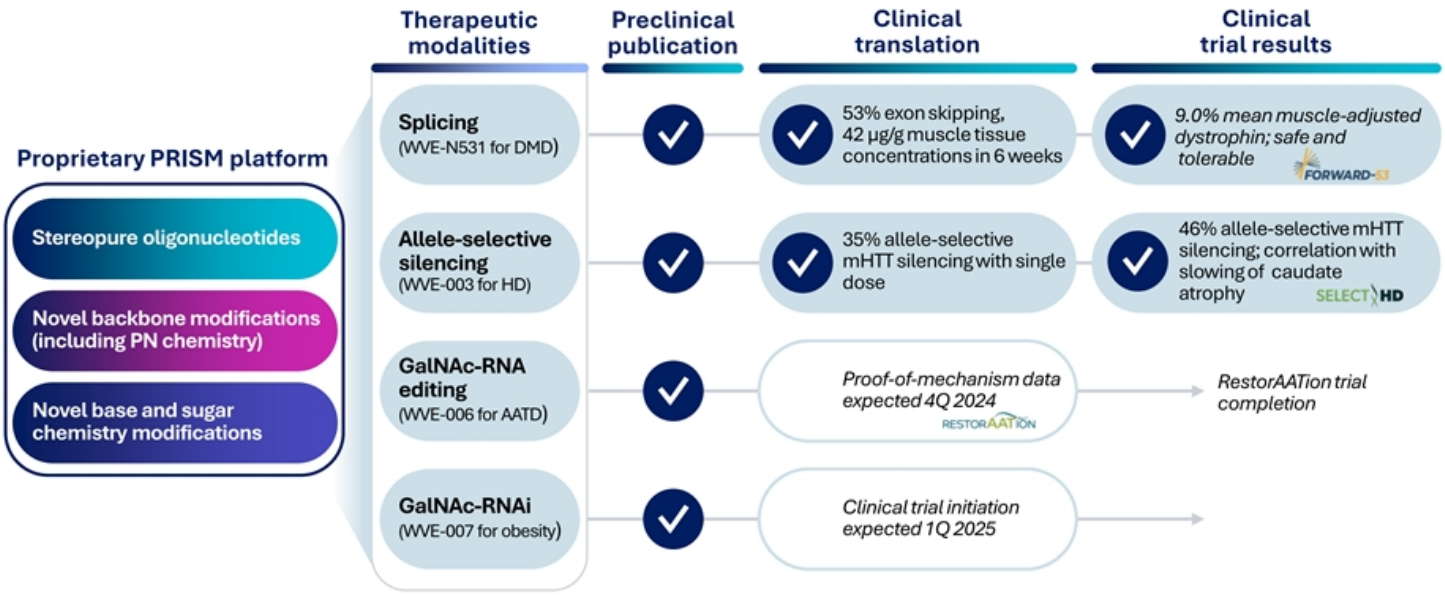
WVE-007 (obesity)

Wave has driven foundational advances in nucleic acid chemistry to expand platform technologies and develop next generation of RNA therapeutics

Further information can be found in recent platform publications

Silencing (RNase H and Ago2) | **Splicing** | **Editing**

Proprietary chemistry continues to translate in clinic across modalities, enabling first-in-class and best-in-class therapies



Full list of Wave publications: https://ir.wavelifesciences.com/events-publications/publications
*mHTT reductions compared to placebo

Robust, diversified RNA medicines pipeline including first-in-class RNA editing programs

Program	Discovery / Preclinical	IND / CTA Enabling Studies	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)
RNAi					
WVE-007 Obesity and other metabolic disorders				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
ALLELE-SELECTIVE SILENCING					
WVE-003 mHTT (HD)			SELECT-HD Trial (Phase 1b/2a) - *Trial Completed*	Takeda 50:50 Option	25K Symptomatic (SNP3) 60K Pre-Symptomatic (SNP3)

Editing for correction Editing for upregulation

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

WVE-006 + AIMers
RNA editing

Alpha-1 antitrypsin deficiency (AATD)

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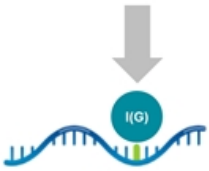
WVE-006: GalNAc-conjugated AIMer designed to correct mutant SERPINA1 transcript to address both liver and lung manifestations of AATD

WVE-006 for AATD

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



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

WVE-006 aims to address the large unmet need in AATD

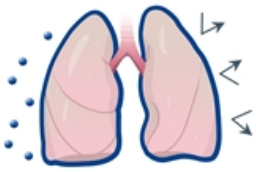
- 200,000 Pi*ZZ patients in US and Europe
- Current standard of care is weekly IV augmentation therapy
- No therapies address AATD liver disease

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

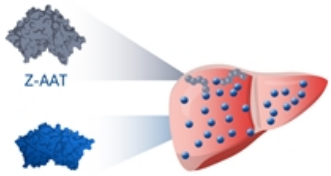
1) Restore circulating, functional wild-type M-AAT

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

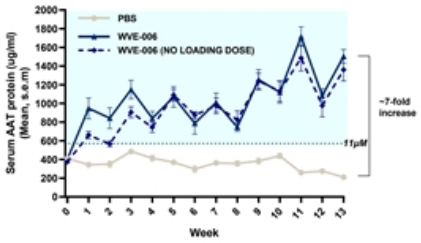
AAT: Alpha-1 antitrypsin Strnad et al., 2020 N Engl J Med 382:1443-55; Blanco et al., 2017 Int J Chron Obstruct Pulmon Dis 12:561-69; Remih et al., 2021 Curr Opin Pharmacol 59:149-56.

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

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

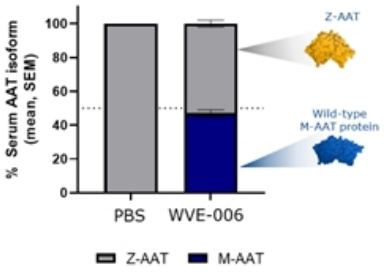
Increased AAT protein in NSG-PiZ mice

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



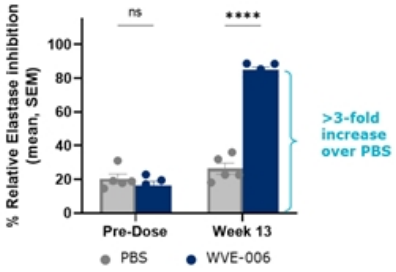
Confirmed restored wild-type M-AAT protein

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

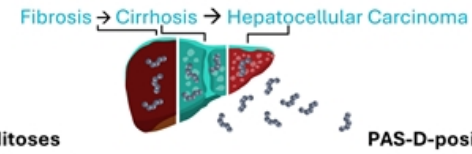


≥50% editing supports restoration of MZ phenotype

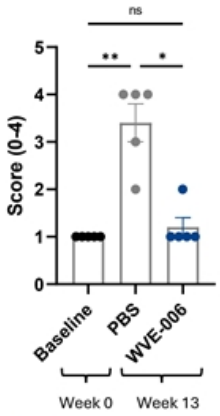
AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at wk 13 (1 wk after last dose) and SERPINA1 editing quantified 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

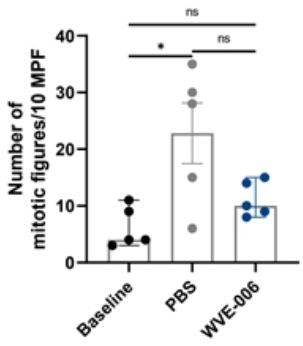
Correction of gain-of-function liver phenotypes



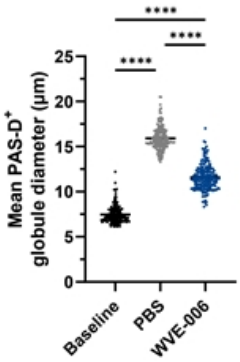
Lobular inflammation
(NSG PiZ mice, week 13)



Mitoses
(NSG PiZ mice, week 13)



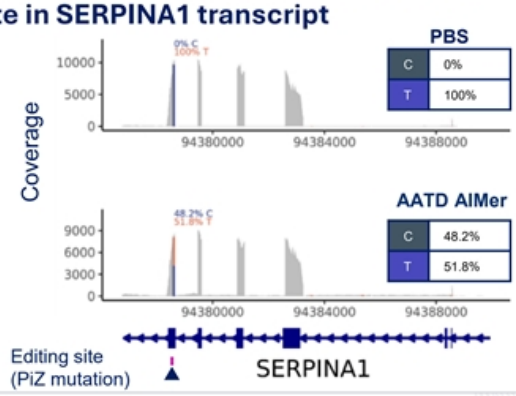
PAS-D-positive globule size
(NSG PiZ mice, week 13)



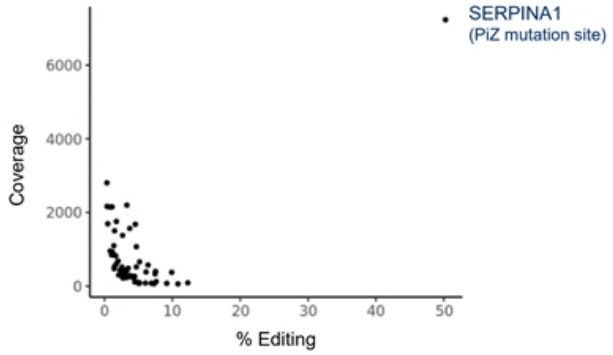
Left (Lobular inflammation) and Middle (Mitoses): Scatter plot showing inflammation grade or mitoses score. Each circle represents an individual mouse, (Mean ± SEM); Right (PAS-D Globule Size): 40 largest globules in each of 5 mice were measured. Each circle represents a single PAS-D globule, (Mean ±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

RNA editing only detected at PiZ mutation site in SERPINA1 transcript



RNA editing across transcriptome



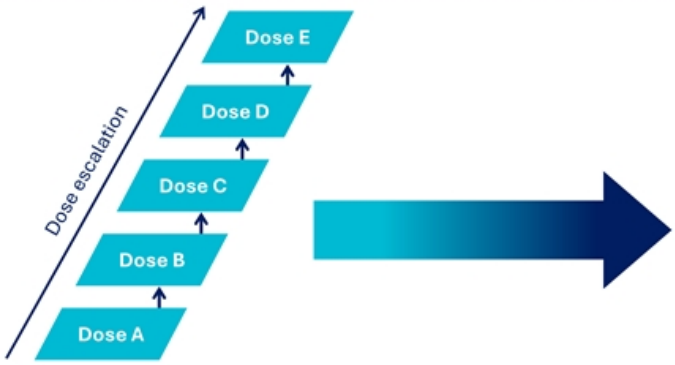
No bystander editing observed on SERPINA1 transcript

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

RestorAATion-2 underway, proof-of-mechanism data expected in 4Q 2024

RestorAATion-1: Healthy Volunteers → Informs dose & dose frequency → **RestorAATion-2: AATD Patients**

Single ascending dose (SAD) → Multiple-ascending dose (MAD) cohorts



Up to 7 doses

Cohort 3

Cohort 2

Cohort 1

Multiple assessments of serum AAT throughout cohort

Study key objectives

Safety and tolerability
Pharmacokinetics
Serum M-AAT levels

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

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

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

- Identifying new targets using proprietary "Edit-Verse", which is powered by genetic datasets and deep learning models
- Advancing work for a diverse set of undisclosed targets addressing areas of high unmet need, including both rare and prevalent diseases

Strategic collaboration with GSK to develop transformative RNA medicines

Collaboration Highlights

- $170 million upfront[1]
- Additional research funding
- Potential for up to $3.3 billion in milestones[2]
- Leverage GSK's expertise in genetics and genomics

	Maximize global potential for WVE-006 for AATD	Advance up to eight GSK collaboration programs	Expand Wave's pipeline
	Up to $525 million in total milestones and **tiered royalties on net sales**	**Up to $2.8 billion** in total milestones and **tiered royalties on net sales**	Wave to advance up to **three wholly owned collaboration programs** (or more with GSK's consent)[3]
Recent Highlights	✓ **$20 million milestone** with first individual dosing RestorAATion-2 trial underway (AATD patients)	✓ **$12 million aggregate initiation payment** for GSK's selection of two programs to advance	✓ **INHBE is Wave's first wholly owned program** emerging from GSK collaboration

1. $120 million in cash and $50 million equity investment; 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-007 (INHBE program)
GalNAc-siRNA silencing

Obesity and other metabolic disorders

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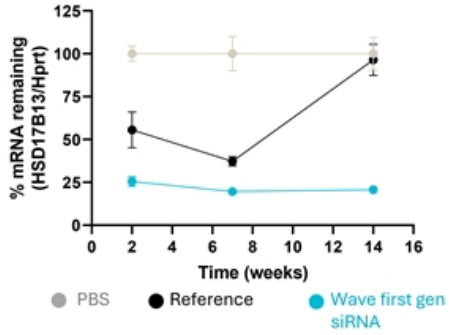
Potential for best-in-class siRNA enabled by Wave's PRISM® platform

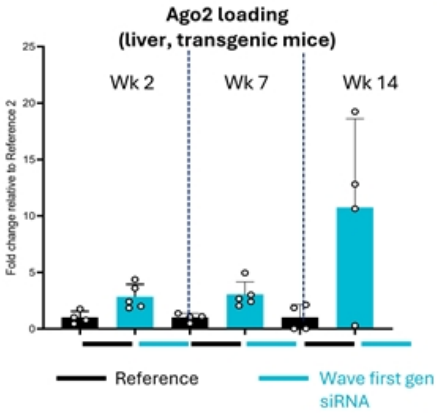
Nucleic Acids Research

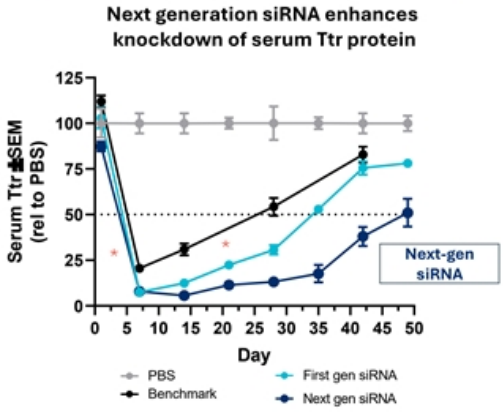
Impact of stereopure chimeric backbone chemistries on the potency and durability of gene silencing by RNA interference

- Unprecedented Ago2 loading increases potency and durability of silencing following administration of single subcutaneous dose

Next-generation siRNA results in more potent and durable silencing







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

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Left and Middle: 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; Right: Benchmark: Foster, DJ. et.al. Mol Ther. 2018, 26(3), 708. B6 mice administered PBS or 0.5 mg/kg of siRNA (subcutaneous). 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

Supported by human genetics, WVE-007 (INHBE GalNAc-siRNA) expected to drive healthy, sustainable weight loss

INHBE silencing expected to induce fat loss, while maintaining muscle mass

- Silencing INHBE gene by ≥ 50% is expected to recapitulate the healthy metabolic profile of INHBE loss of function (LoF) carriers, including:[1,2,3]

✓ Reduced waist-to-hip ratio
✓ Reduced odds ratio of type 2 diabetes and coronary artery disease by >25%
✓ Reduced serum triglycerides
✓ Elevated HDL-c

- INHBE (Inhibin βE) expressed primarily in liver and gene product (activin E) acts on its receptor in adipose tissue[4]
- Lowering of INHBE mRNA promotes fat burning (lipolysis) and decreases fat accumulation (adiposity)[5,6]

Distinct pathway as compared to GLP-1s

✓ Weight loss with no impact on muscle mass[1]
✓ Preferential reduction of visceral fat
✓ No suppression of general reward system[3]
✓ No loss of appetite
✓ GalNAc-siRNA enables infrequent dosing; 1 – 2x/year

Wave's INHBE siRNA program may address these limitations and / or work complementarily with GLP-1s

Obesity is estimated to impact 174M adults in the US and Europe

1. Sargeant, et al. 2019 Endocrinol Metab (Seoul) 34(3):247-262; 2. Prime Therapeutics Claims Analysis, July 2023; 3. Müller, et al. 2019 Molecular Metabolism 30: 72-130.

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. 5. Yogosawa et al. 2013 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3526038/ 6. Zhao et al. 2023 https://pubmed.ncbi.nlm.nih.gov/36626233/

WVE-007 has Wave's next generation siRNA format and best-in-class profile with infrequent dosing

INHBE program: Data from DIO mouse model supports best-in-class profile and potential use of WVE-007 in multiple treatment settings

- ✓ Highly potent (ED50 < 1mg/kg) and durable silencing following one, low-single-digit dose, supporting every-six-month or annual dosing
- ✓ **Monotherapy:** Weight loss similar to semaglutide with no loss of muscle mass and a reduction in fat mass, with preferential effect to the visceral fat (consistent with profile of INHBE LoF carriers in human genetics)
- ✓ **Add-on to GLP-1s:** When administered as an add-on with semaglutide, a single dose of Wave's INHBE GalNAc-siRNA doubled the weight loss observed with semaglutide alone and this effect was sustained throughout the duration of the study
- ✓ **Maintenance:** Curtailed rebound weight gain upon cessation of semaglutide

Expect to initiate clinical trial for WVE-007 in 1Q 2025

WVE-N531
Splicing

Duchenne muscular dystrophy

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Urgent need for improved therapeutic options for the treatment of DMD

Duchenne is a devastating and fatal disease

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Impacts ~1 / 5,000 newborn boys annually; ~20,000 new cases annually worldwide
  - ~8–10% are amenable to exon 53 skipping
  - Potential for Wave to address up to 40% of DMD with additional exon skipping therapeutics

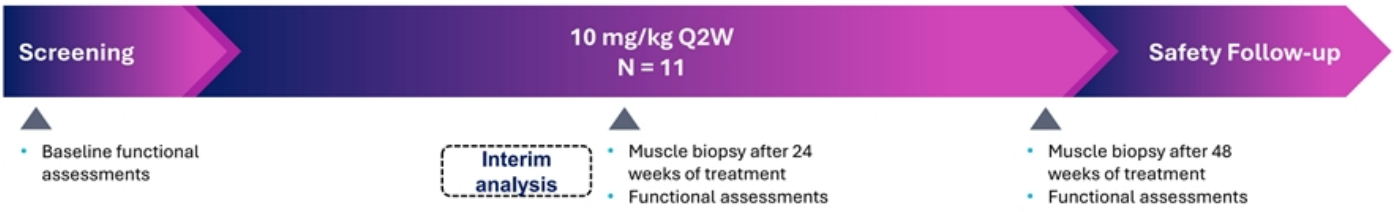
Multiple urgent unmet needs

- Need for therapies delivering **more consistent dystrophin expression,** as few patients today achieve dystrophin >5% of normal
- **Opportunity to extend dosing intervals** beyond weekly standard of care to alleviate burden for patients and caregivers
- **Need to reach stem cells and distribute broadly to muscle tissues** to potentially enable muscle regeneration and impact respiratory and cardiac function

Boy living with DMD

Duan, D. et al. 2021 Nat Rev Dis Primers 7, 13; Muscular Dystrophy Association; Aartsma-Rus, et al. 2009 Hum Mutat 30, 293.

FORWARD-53: An ongoing potentially registrational open-label Phase 2 clinical trial of WVE-N531 in boys with DMD amenable to exon 53 skipping



Key Assessments:

- Safety and tolerability
- Muscle biopsies after 24 and 48 weeks of treatment
  - PK: Drug tissue concentrations
  - PD: Exon-skipping, Dystrophin level (% of normal) as assessed by Western Blot
- Functional outcome measures
- 11 participants enrolled, including two from prior Part A clinical trial
  - Pre-specified analyses in ambulatory patients

IV: Intravenous; Q2W: Every 2 Weeks; PK: Pharmacokinetics; PD: Pharmacodynamics

Results of interim analysis: WVE-N531 has potential to be the best-in-class therapeutic for exon 53 DMD

Highly consistent dystrophin expression across patients

- 9.0% muscle-content adjusted dystrophin (5.5% unadjusted), quantified from two isoforms that are consistent with Becker patients who display milder disease
- 89% of patients over 5% of normal (muscle-content adjusted)

Muscle delivery and extended dosing intervals

- Skeletal muscle tissue concentrations of WVE-N531: ~41,000 ng/g
- WVE-N531 tissue half-life of 61 days supports monthly dosing
- Preclinical data suggests WVE-N531 is translating in heart and diaphragm

Evidence supporting improved muscle health

- Improvement in serum biomarkers for muscle health
- Localization of WVE-N531 in myogenic stem cells
- Improvement in myofiber regeneration

Safe and well tolerated

- No SAEs
- No discontinuations
- No oligonucleotide class effects

Expect to receive feedback from regulators on pathway to accelerated approval and deliver 48-week FORWARD-53 data in 1Q 2025

Dystrophin data from prespecified analysis of ambulatory boys; Muscle content adjustment was done using the formula: MHC-normalized dystrophin/(total myofiber area/total area of biopsy section). Interim analysis results announced September 24, 2024.

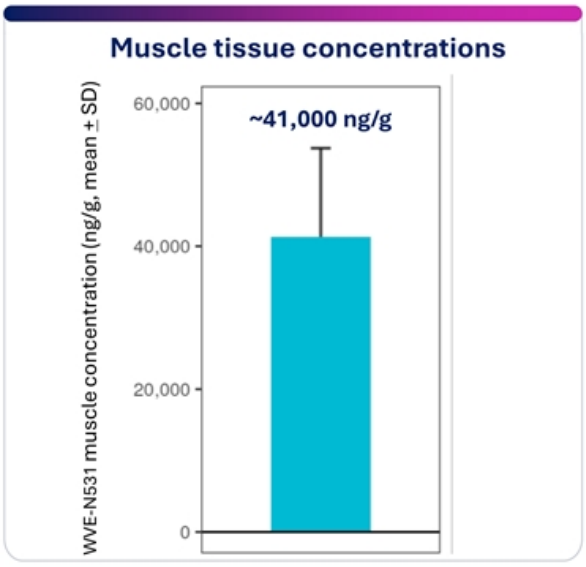
WVE-N531 was safe and well tolerated

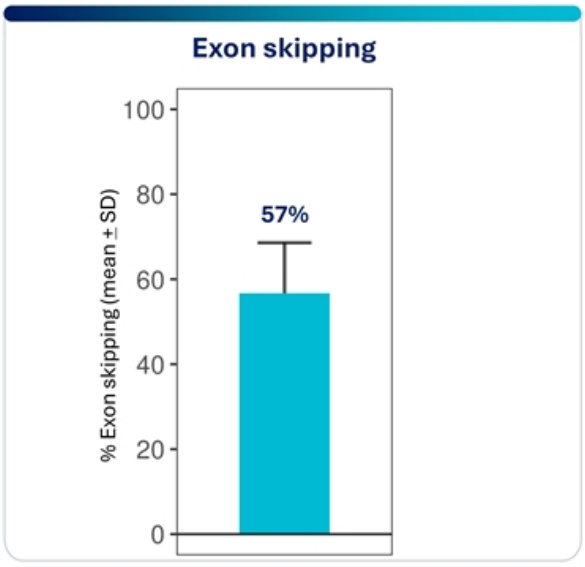
TEAE Category	WVE-N531 10 mg/kg n=11 Patients (%)
Any TEAE	10 (90.9)
Any drug-related TEAE	3 (27.3)
Mild	3 (27.3)
Moderate	0
Severe	0
Any serious TEAE	0
Any severe TEAE	0
Any TEAE leading to discontinuation	0
Any TEAE leading to death	0

No Serious Adverse Events and no oligonucleotide class-related events

TEAE: Treatment emergent adverse event; Data as of August 19, 2024

Industry-leading muscle tissue concentrations and exon skipping



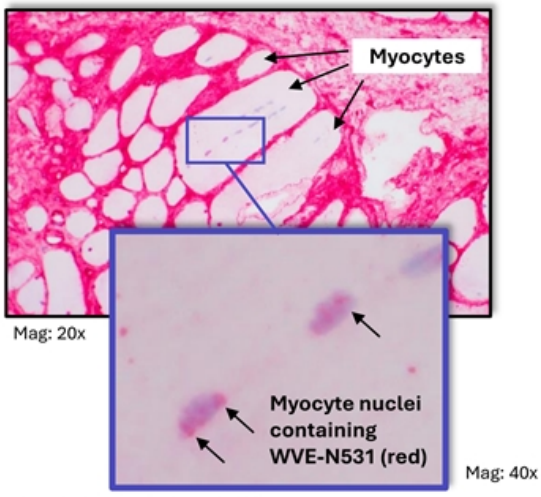


Tissue half-life of 61 days supports monthly dosing

Muscle tissue concentrations and exon skipping n=11; ~41,000 ng/g = ~5,900 nM

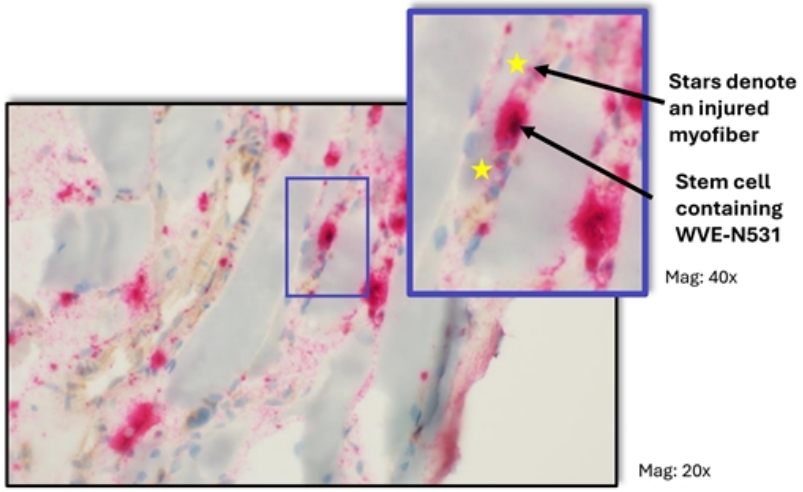
WVE-N531 was localized in myofiber nuclei and myogenic stem cells

WVE-N531 uptake in myofiber nuclei



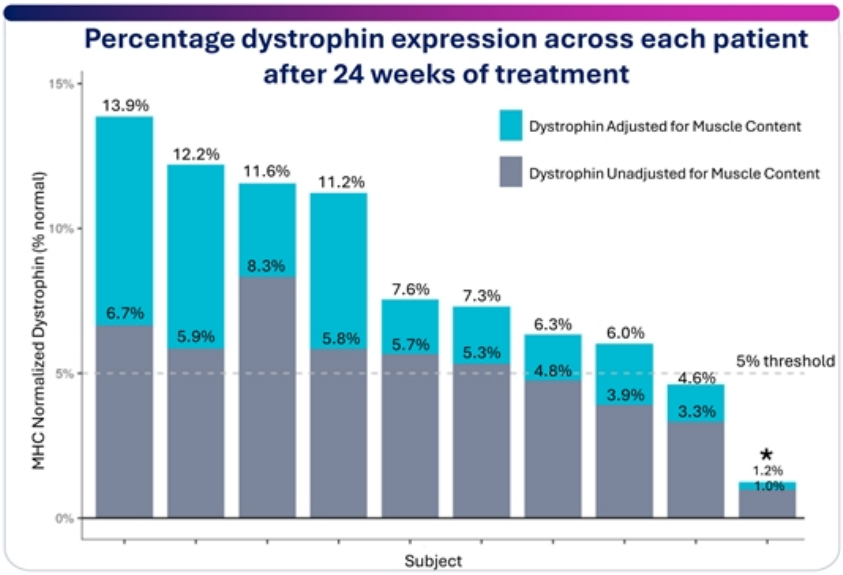
In-situ hybridization for WVE-N531

WVE-N531 uptake in myogenic stem cells



Dual staining utilizing in-situ hybridization for WVE-N531 and PAX7 immunohistochemistry for stem cells

Dystrophin expression of up to 14% with high consistency across participants



- Mean 9.0% absolute muscle content adjusted dystrophin
- Mean 5.5% absolute unadjusted dystrophin
- Dystrophin expression was quantified from two isoforms consistent with those observed in Becker patients who display milder disease

89% of ambulatory participants achieve muscle content-adjusted dystrophin levels of at least 5%

*Excluded from prespecified mean analysis of ambulatory patients; Muscle content adjustment was done using the formula: MHC-normalized dystrophin/(total myofiber area/total area of biopsy section); Graph shows all patients (including non-ambulatory) with appropriate biopsy sample; dystrophin measured by Western Blot (AB15277)

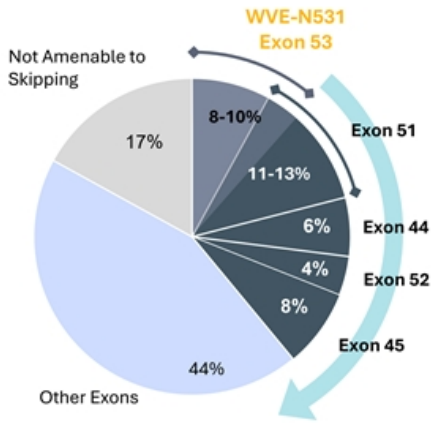
WVE-N531 in skeletal muscle likely to underrepresent activity in heart and diaphragm

Preclinical data:

dKO:	**Dystrophin restoration**	**~9%**	**~12%**	**~17%**	**→ Higher dystrophin in heart and diaphragm, survival benefit**
			cardiac and respiratory functional improvements		
NHP:	**WVE-N531 muscle tissue concentration (µg/g)**	**2.17**	**57.2**	**10.8**	**→ Greater exposure in heart and diaphragm**

Kandasamy et al., 2022 Nuc Acids Res doi: 10.1093/nar/gkac018

Unlocking Wave's best-in-class exon skipping portfolio



- Data for exons 51, 44, 52, 45 demonstrate potential for even greater dystrophin expression
- Opportunity to address up to 40% of population
- Expect to engage regulators on a platform trial design that incorporates multiple exons

Aartsma-Rus, et al. 2009 Hum Mut 30, 293

WVE-003
Allele-selective silencing

Huntington's Disease

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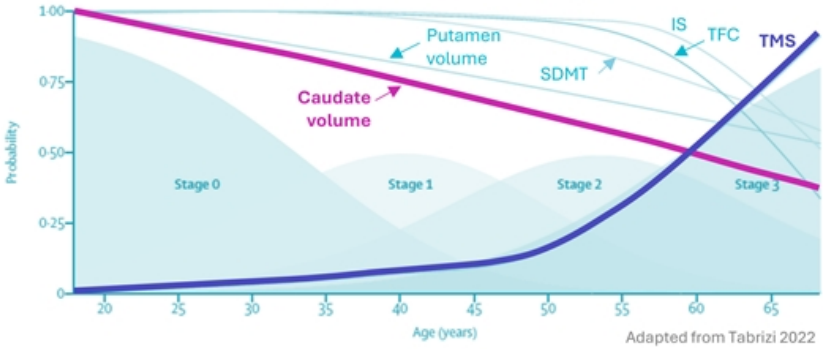
Huntington's disease is a devastating neurological disorder caused by a toxic gain of function and concurrent loss of function

- HD is a monogenic autosomal dominant genetic disease; fully penetrant and affects entire brain
- No current disease modifying therapies for HD
- Characterized by cognitive decline, psychiatric illness, and chorea; ultimately fatal
- Expanded CAG triplet repeat in *HTT* gene results in production of mutant huntingtin protein (mHTT) and loss of function in wild-type huntingtin protein (wtHTT)

HD-ISS stage probability and predicted clinical landmark changes as a function of age



Adapted from Tabrizi 2022

>200,000 patients with HD across all disease states

Pre-Symptomatic HD	Symptomatic HD
(~160K in US and Europe)	(~65K in US and Europe)

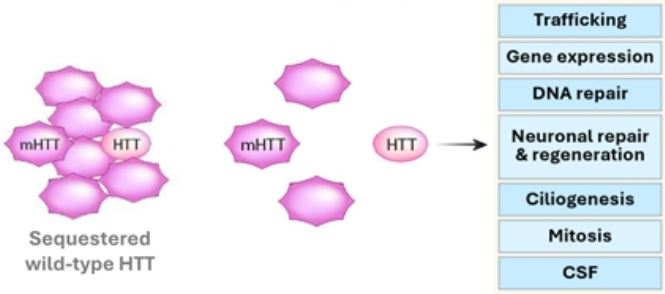
An allele-selective, wtHTT-sparing approach is uniquely suited to address HD across all stages of disease

Sources on wtHTT: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015; IS, Independence Scale; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Score

Wild-type HTT (wtHTT) is critical for normal neuronal function and loss of wtHTT contributes to cellular dysfunction

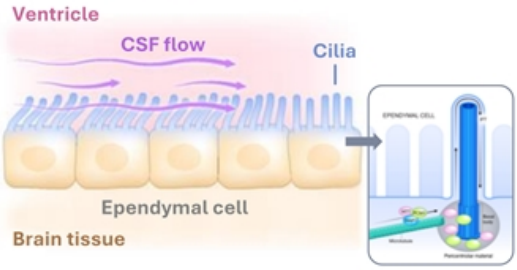
Mutant HTT has a detrimental effect on wild-type HTT function

- Lowering mHTT is expected to restore physiological control over HTT gene expression and relieve its detrimental effect on wtHTT function



Wild-type HTT is crucial for cilia health

- In the absence of wtHTT, ciliogenesis fails, disrupting CSF flow, causing hydrocephalus



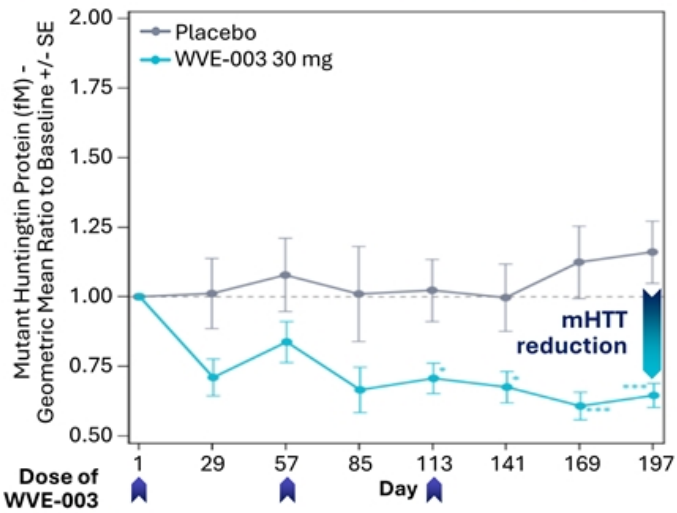
Only an allele-selective approach can ameliorate both loss-of-function and gain-of-function disruptions driven by mHTT

Saudou & Humbert 2016 Neuron; Cason et al., 2022 Nat Rev Cell Biol; Laundos et al., 2023 Front Cell Dev Biol; Kaliszewski et al., 2015 Cell Death Diff; Keryer et al., 2011 J Clin Invest Khoshnan & Patterson, 2011. Neurobiol Dis; Pogoda et al., 2021 Curr Med Chem; Hsiao et al., 2013 Hum Mol Genet

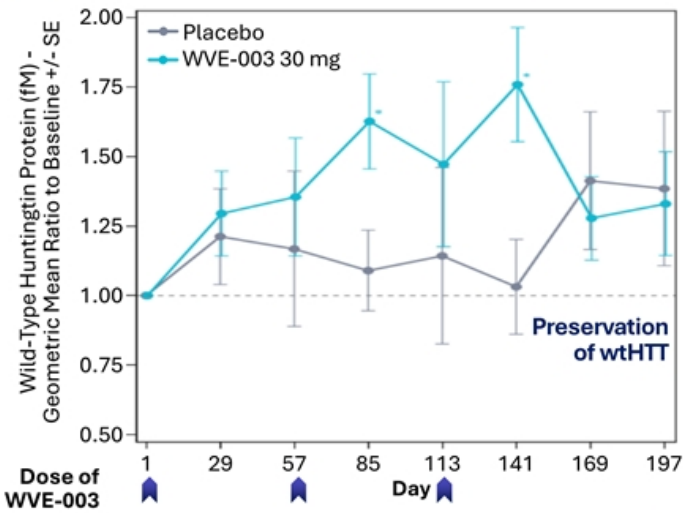
Allele-selective lowering of mutant HTT protein of up to 46% with three doses of WVE-003 and preservation of wild-type HTT

Durability of mHTT reductions supports potential for quarterly dosing intervals

Mutant HTT protein levels



Wild-type HTT protein levels



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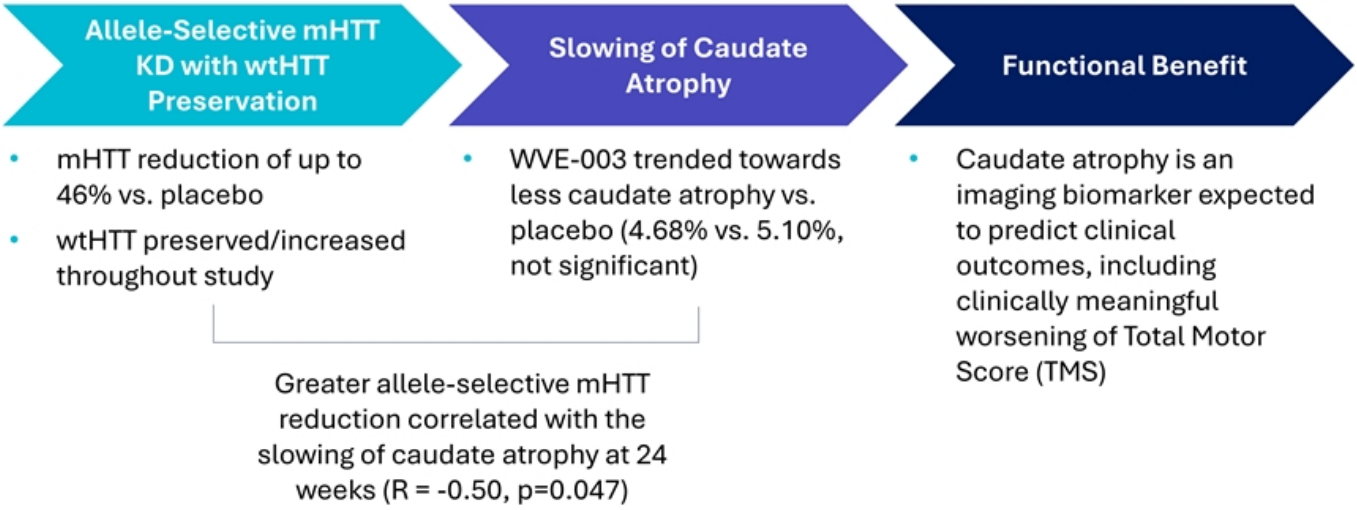
* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein

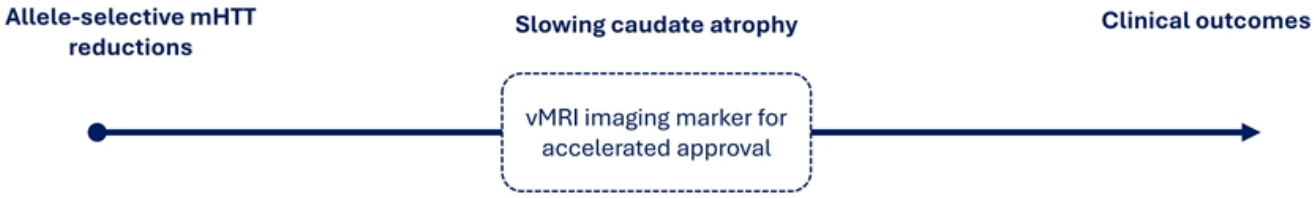
WVE-003 leads to allele-selective mHTT reduction, correlating with slowing of caudate atrophy



Liu et al., 2023 Brain Comm

Preservation of caudate volume offers an efficient pathway for potential accelerated approval for HD

Draft study design: Registrational study powered to show impact on caudate atrophy	• Randomized, placebo controlled clinical study Adults with SNP3 and HD Stage 1-2 • N = ~150 • 12-18 months duration

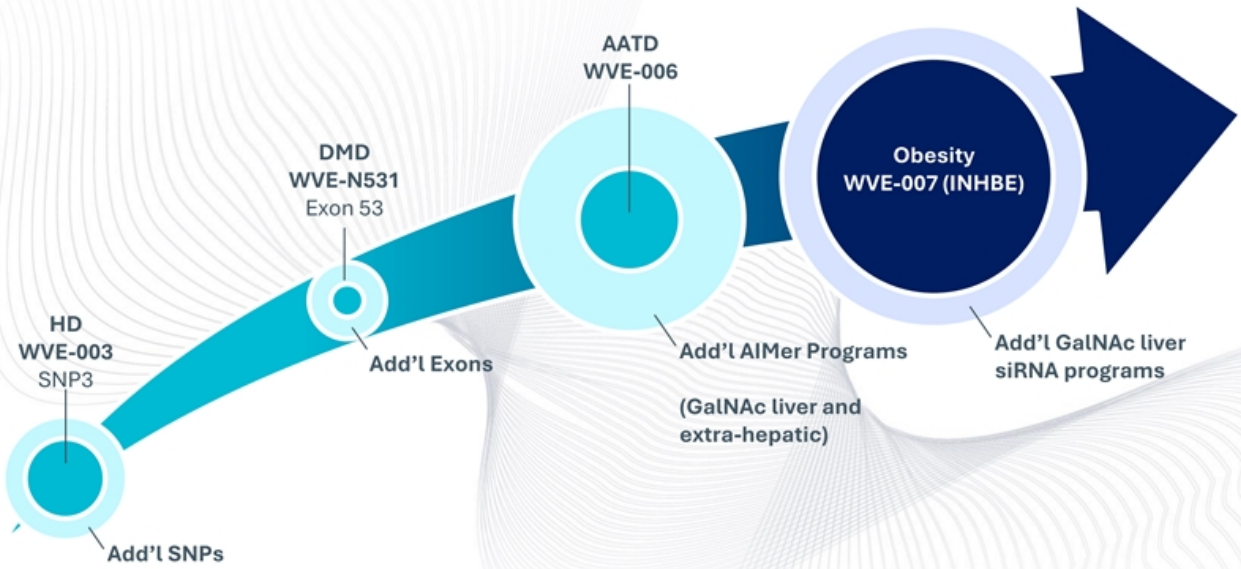


Expect feedback from regulators on path to accelerated approval by year-end 2024

vMRI: volumetric MRI

Anticipated upcoming milestones

Wave is poised for significant and sustained growth



Wave's platform is translating in the clinic; AATD proof-of-mechanism data expected in 4Q 2024 and initiation of clinical trial for WVE-007 (INHBE) expected in 1Q 2025

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