



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

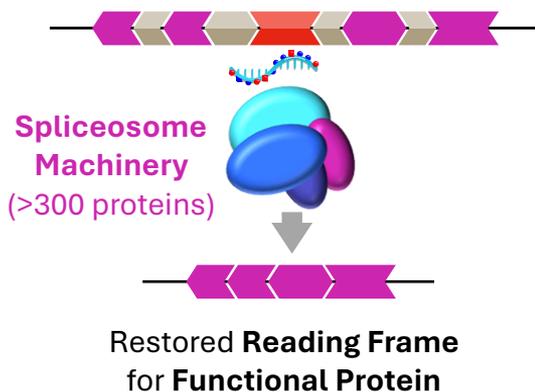
**Well-capitalized with cash
runway into 2027***

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

Clinically-validated oligonucleotide chemistry (PN, stereochemistry)

Splicing

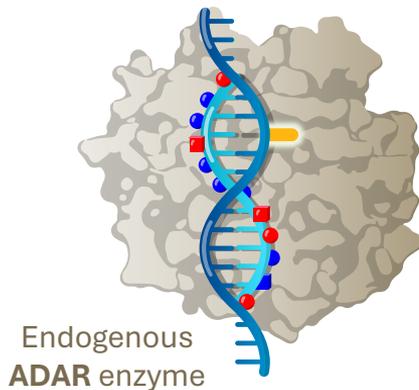
Restore RNA transcripts and **turn on** protein production



WVE-N531 (DMD)

Editing

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



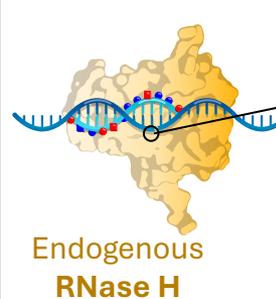
WVE-006 (AATD)

Additional wholly owned editing programs

Silencing

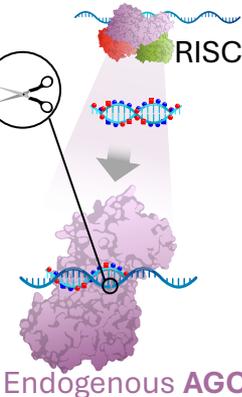
Degradation of RNA transcripts to **turn off** protein production

Antisense



WVE-003 (HD)

siRNA



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)



nature biotechnology
THE SCIENCE AND BUSINESS OF BIOTECHNOLOGY

VOLUME 35 NUMBER 9 SEPTEMBER 2017

Molecular Therapy Nucleic Acids Original Article

Preclinical evaluation of stereorep antisense oligonucleotides for allele-selective lowering of mutant HTT

Stereorep antisense oligonucleotides label neurons in vivo

Abstract

INTRODUCTION

RESULTS

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REFERENCES

NAR Breakthrough Article

Impact of guanidine-containing backbone linkages on stereorep antisense oligonucleotides in the CNS

Abstract

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Control of backbone chemistry and chirality boost oligonucleotide splice switching activity

Abstract

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

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REFERENCES



Full list of Wave publications: <https://ir.wavelifesciences.com/events-publications/publications>

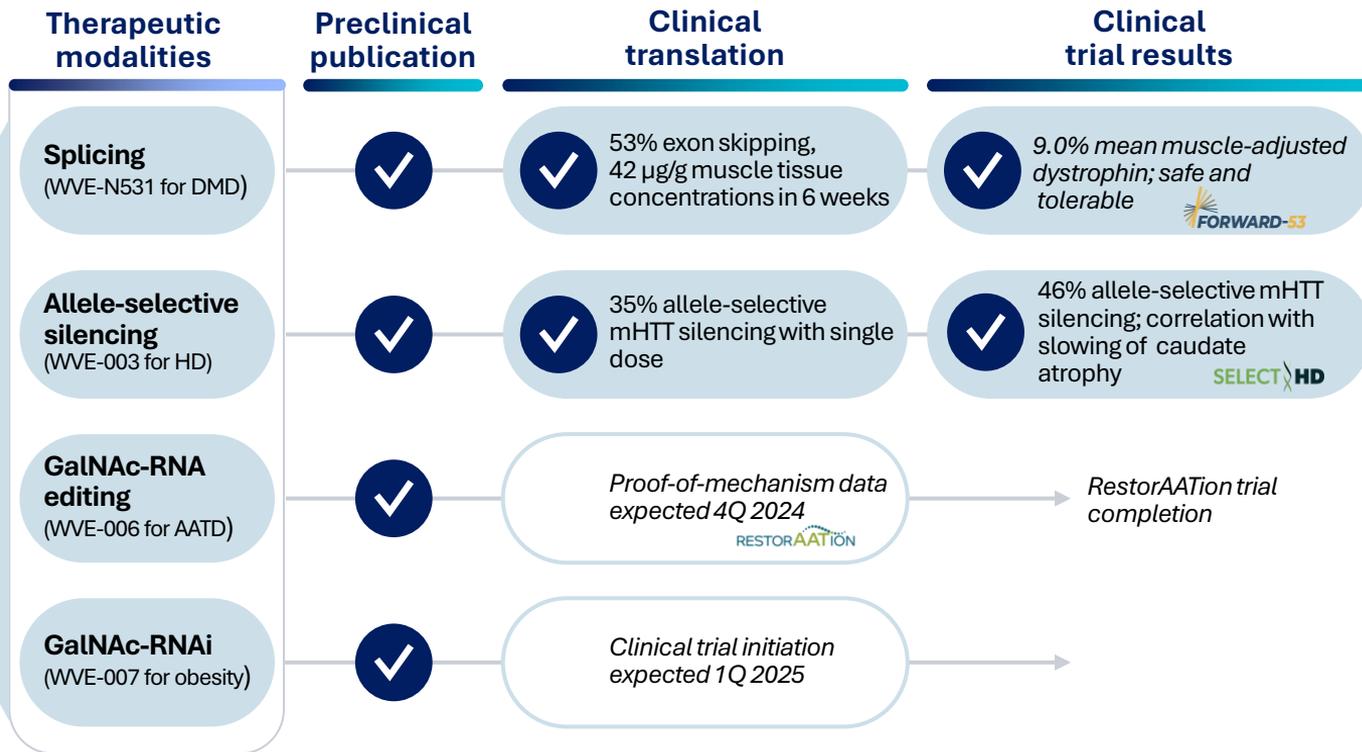
Proprietary chemistry continues to translate in clinic across modalities, enabling first-in-class and best-in-class therapies

Proprietary PRISM platform

Stereopure oligonucleotides

Novel backbone modifications
(including PN chemistry)

Novel base and sugar
chemistry modifications



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

WVE-006 + AIMers *RNA editing*

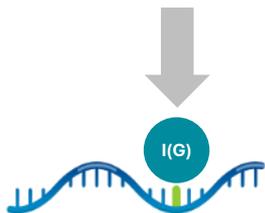
Alpha-1 antitrypsin deficiency (AATD)

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

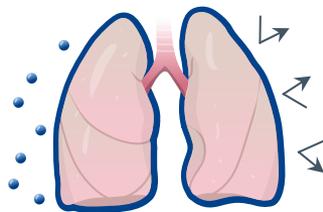
- 200,000 Pi*ZZ patients in US and Europe
- Current standard of care is weekly IV augmentation therapy
- No therapies address AATD liver disease

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

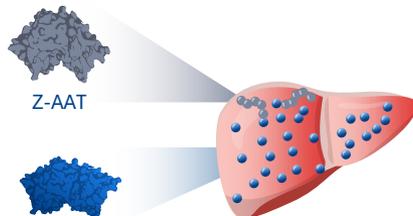
1) Restore circulating, functional wild-type M-AAT

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



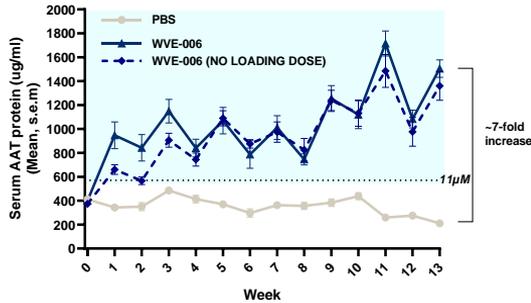
M-AAT secretion into bloodstream

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

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

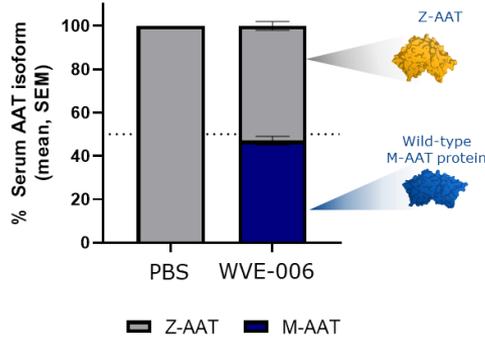
✓ Increased AAT protein in NSG-PiZ mice

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



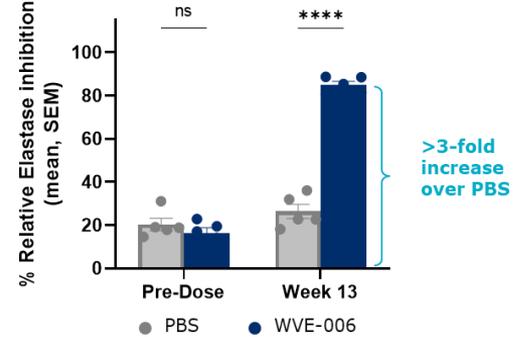
✓ Confirmed restored wild-type M-AAT protein

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

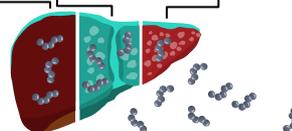


$\geq 50\%$ editing supports restoration of MZ phenotype

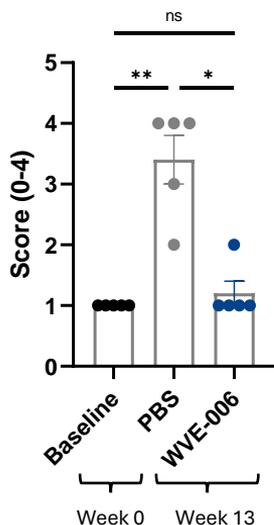
WVE-006 decreases lobular inflammation and PAS-D globule size, prevents increase in hepatocyte turnover

Correction of gain-of-function liver phenotypes

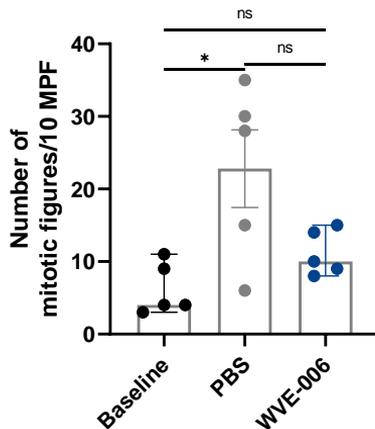
Fibrosis → Cirrhosis → Hepatocellular Carcinoma



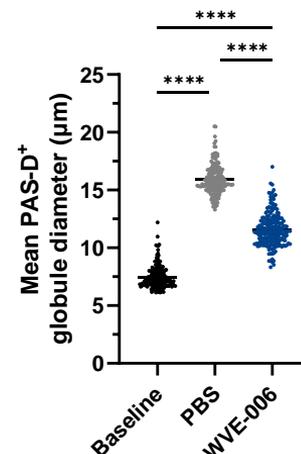
Lobular inflammation
(NSG PiZ mice, week 13)



Mitoses
(NSG PiZ mice, week 13)

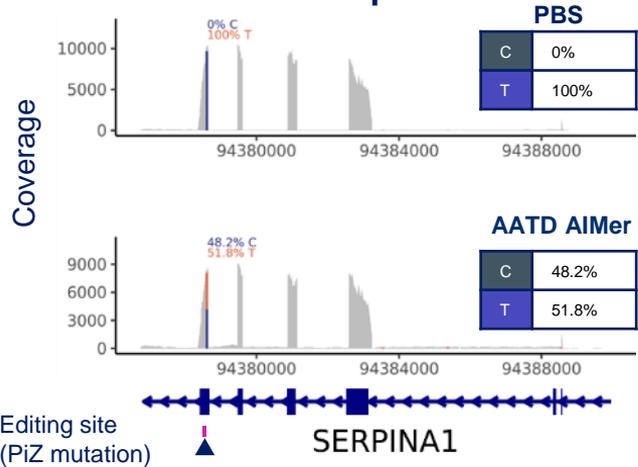


PAS-D-positive globule size
(NSG PiZ mice, week 13)

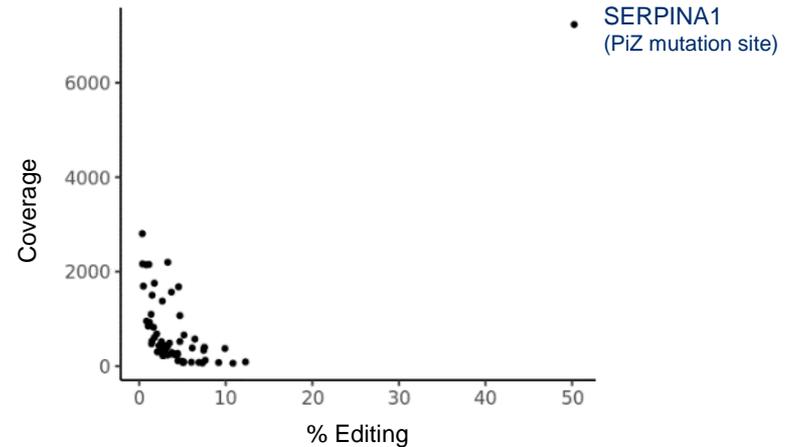


AIMer-directed editing is highly specific in mice

RNA editing only detected at PiZ mutation site in SERPINA1 transcript



RNA editing across transcriptome



No bystander editing observed on SERPINA1 transcript

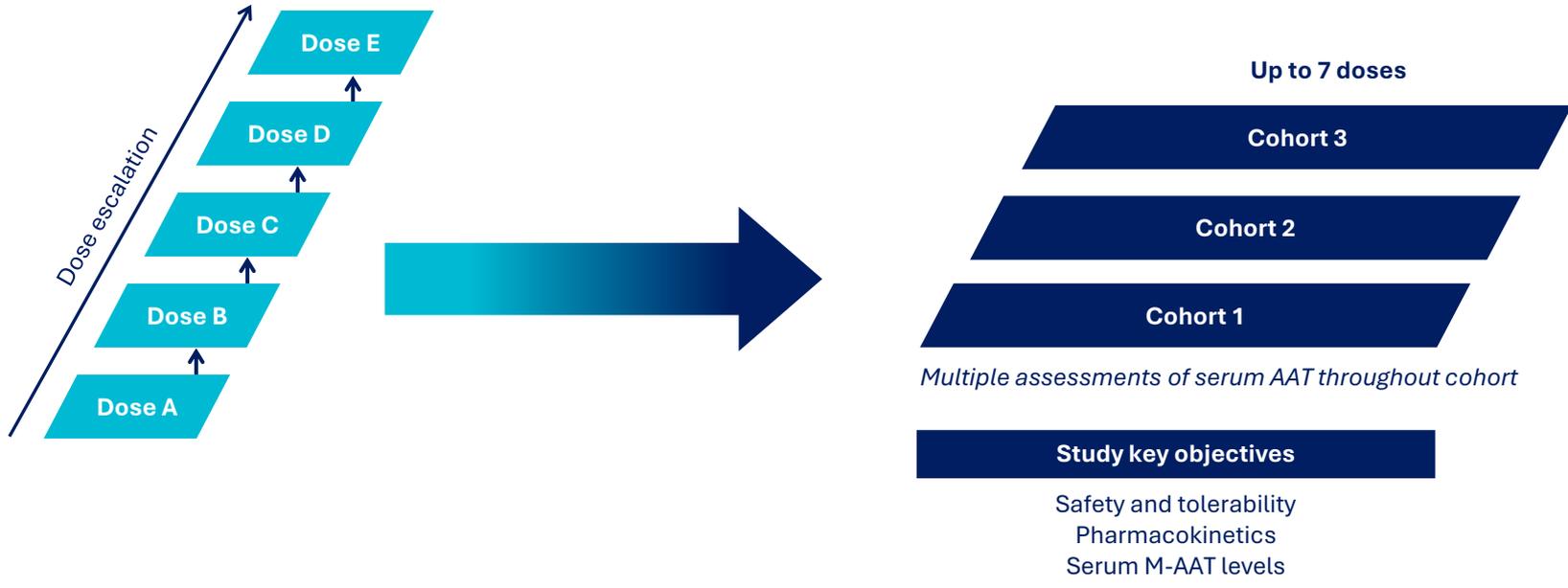
RestorAATion-2 underway, proof-of-mechanism data expected in 4Q 2024

RestorAATion-1: Healthy Volunteers

Informs dose & dose frequency

RestorAATion-2: AATD Patients

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



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 upfront¹
- Additional research funding
- Potential for up to \$3.3 billion in milestones²
- Leverage GSK's expertise in genetics and genomics

Maximize global potential for WVE-006 for AATD

Up to \$525 million in total milestones and tiered royalties on net sales



\$20 million milestone with first individual dosing
RestorAATion-2 trial underway (AATD patients)

Advance up to eight GSK collaboration programs

Up to \$2.8 billion in total milestones and tiered royalties on net sales



\$12 million aggregate initiation payment for GSK's selection of two programs to advance

Expand Wave's pipeline

Wave to advance up to **three wholly owned collaboration programs** (or more with GSK's consent)³



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

Recent Highlights

WVE-007 (INHBE program)
GalNAc-siRNA silencing

Obesity and other metabolic disorders

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

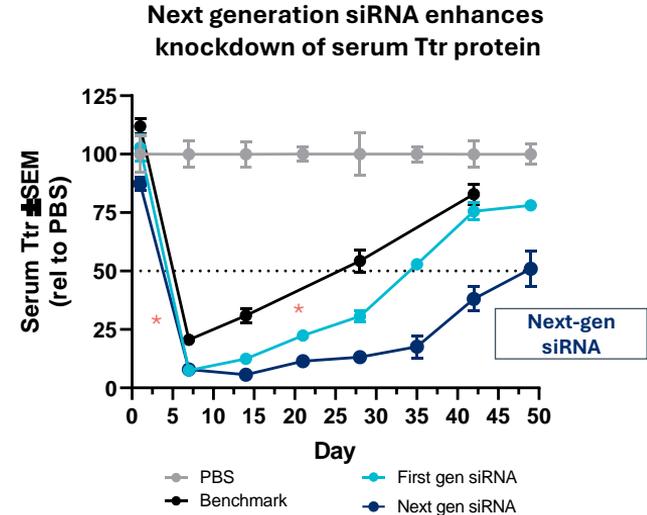
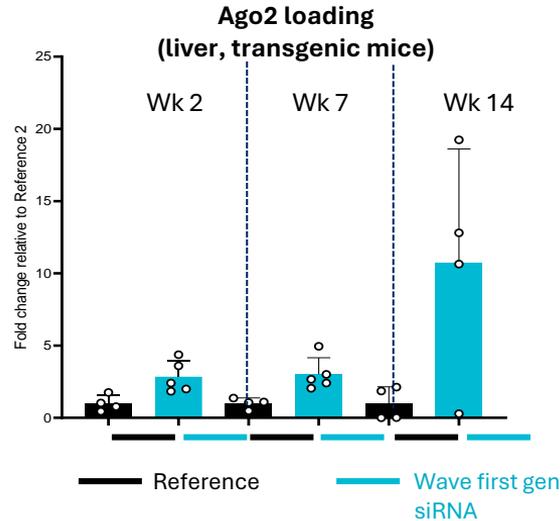
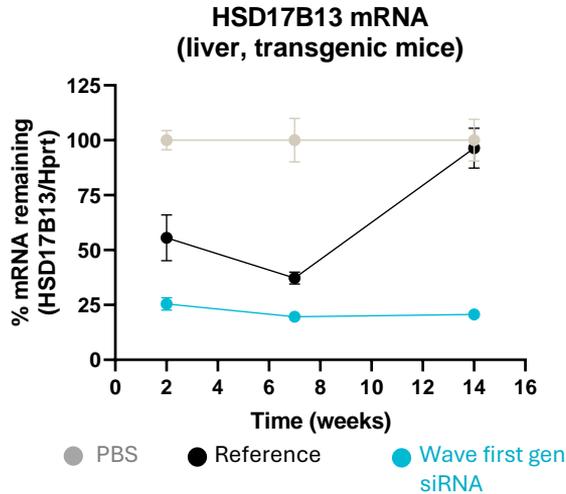


Nucleic Acids Research

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

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 $\geq 50\%$ 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 disease by $>25\%$
- INHBE (Inhibin β E) expressed primarily in liver and gene product (activin E) acts on its receptor in adipose tissue⁴
- 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 mass¹
- ✓ Preferential reduction of visceral fat
- ✓ No suppression of general reward system³
- ✓ 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

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

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

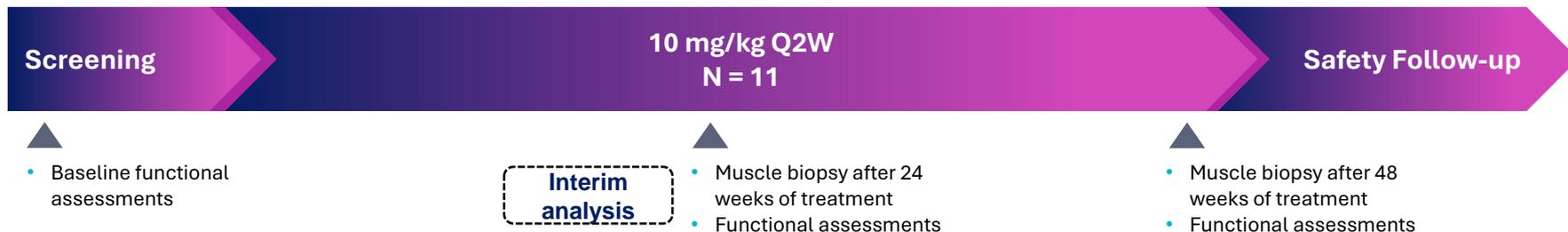
Multiple urgent unmet needs

- 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

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

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

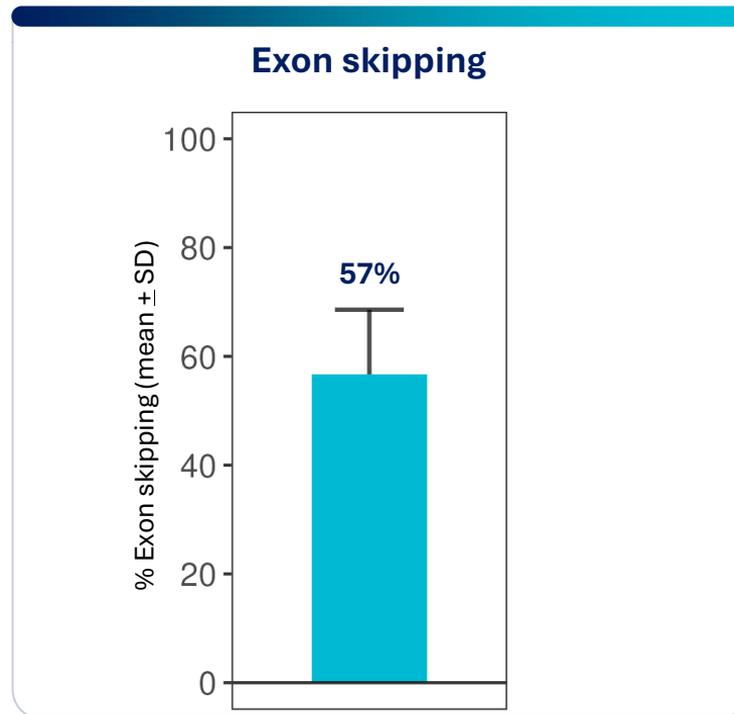
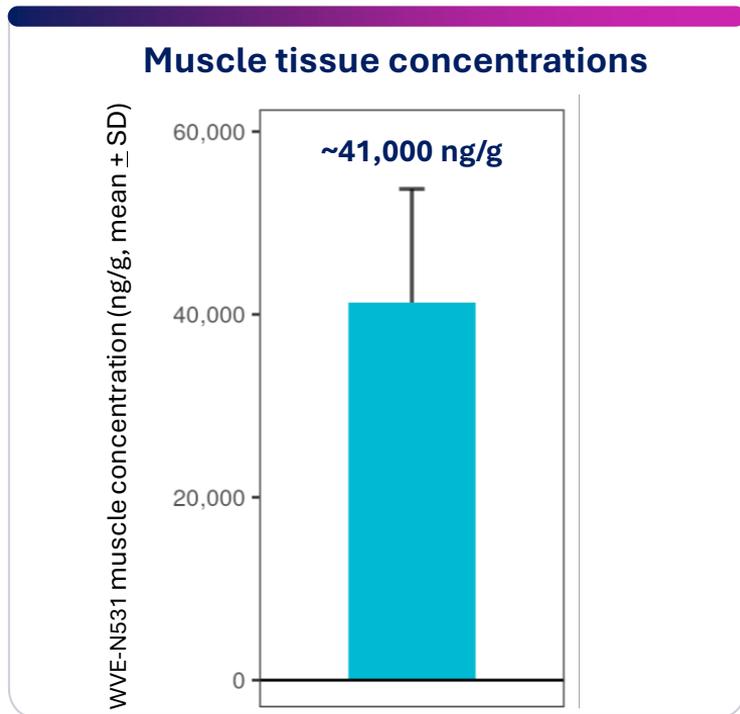
Expect to receive feedback from regulators on pathway to accelerated approval and deliver 48-week FORWARD-53 data in 1Q 2025

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

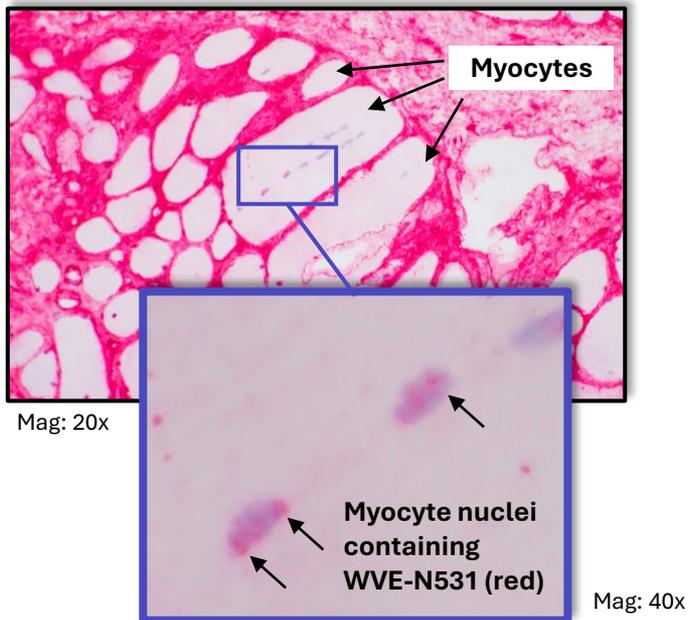
Industry-leading muscle tissue concentrations and exon skipping



Tissue half-life of 61 days supports monthly dosing

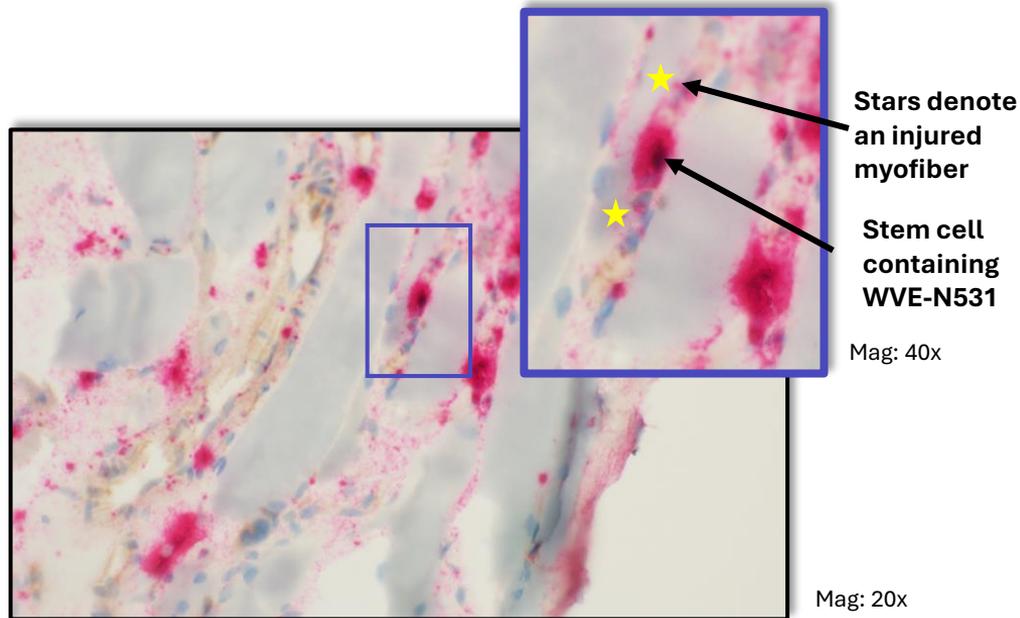
WVE-N531 was localized in myofiber nuclei and myogenic stem cells

WVE-N531 uptake in myofiber nuclei



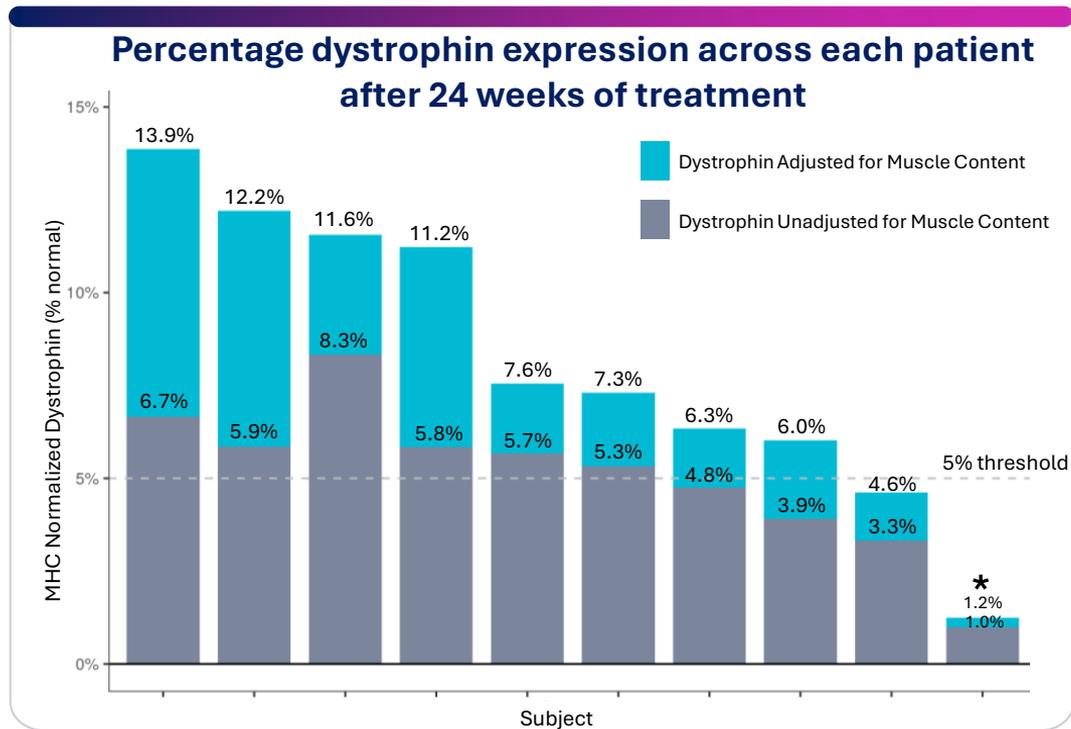
In-situ hybridization for WVE-N531

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%

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

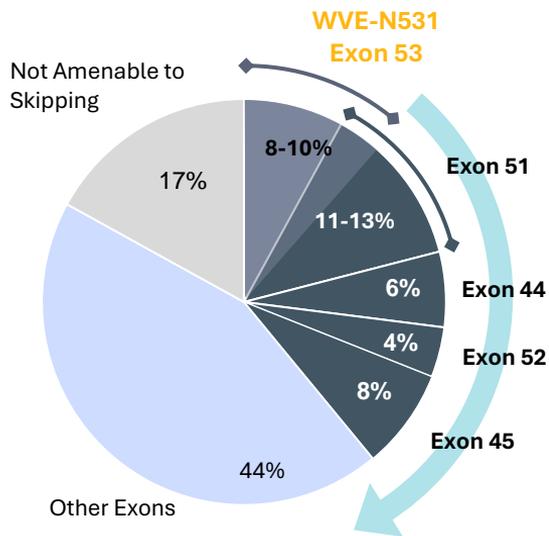


Preclinical data:

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

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

DMD Population



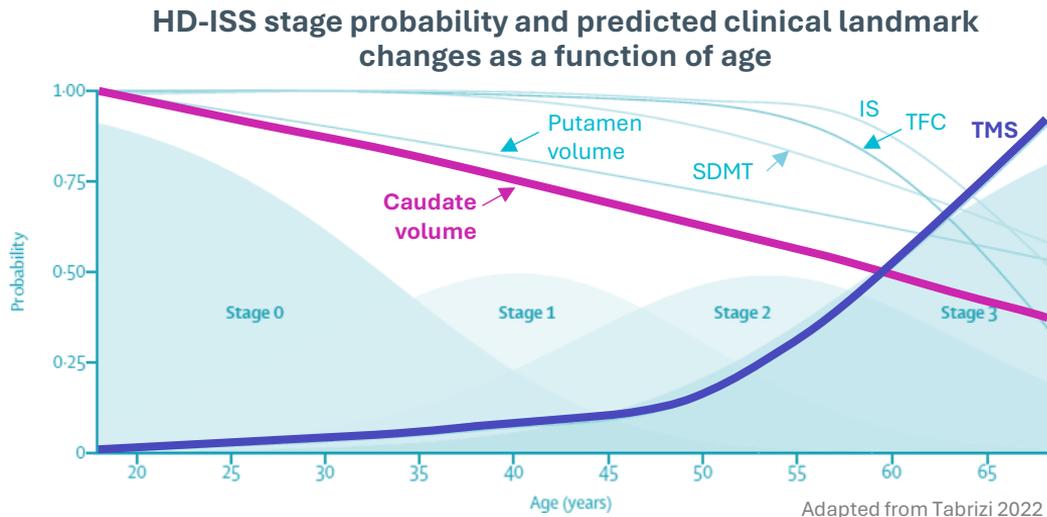
- Data for exons 51, 44, 52, 45 demonstrate potential for even greater dystrophin expression
- Opportunity to address up to 40% of population
- Expect to engage regulators on a platform trial design that incorporates multiple exons

WVE-003
Allele-selective silencing

Huntington's Disease

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)



>200,000 patients with HD across all disease states

Pre-Symptomatic HD

(~160K in US and Europe)

Symptomatic HD

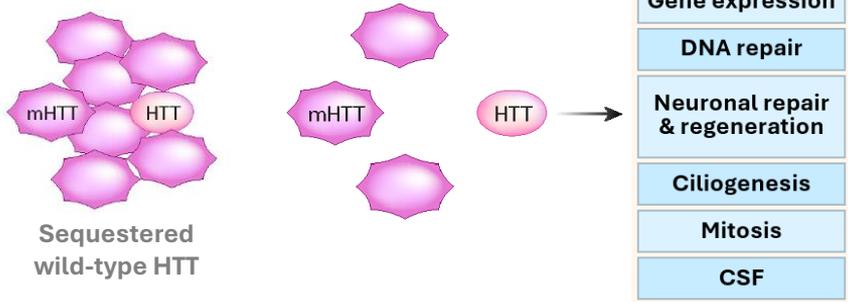
(~65K in US and Europe)

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

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

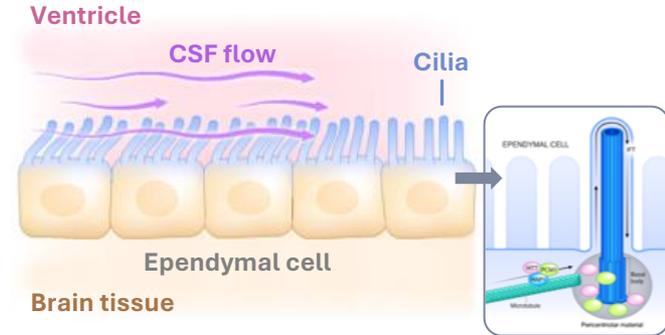
Mutant HTT has a detrimental effect on wild-type HTT function

- 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

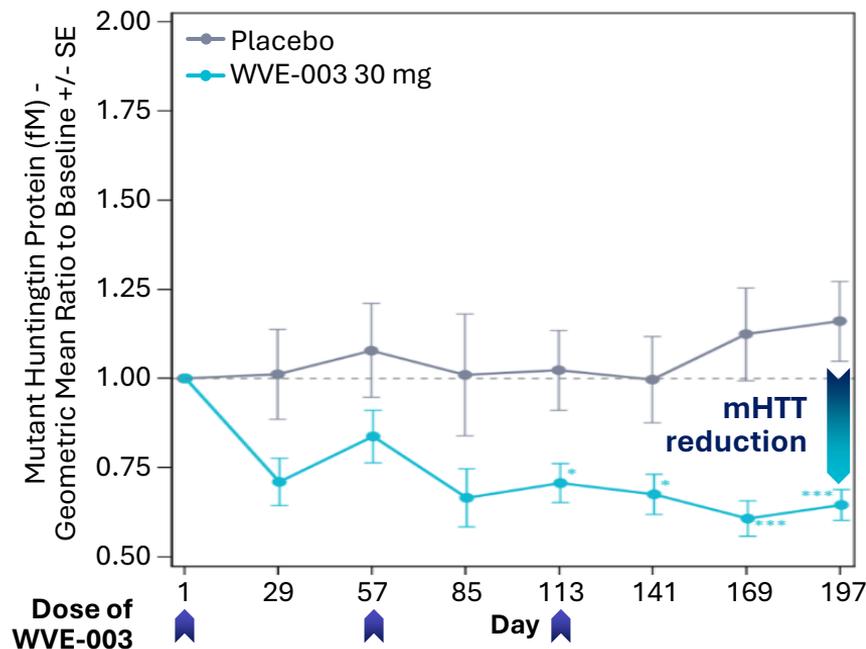


Only an allele-selective approach can ameliorate both loss-of-function and gain-of-function disruptions driven by mHTT

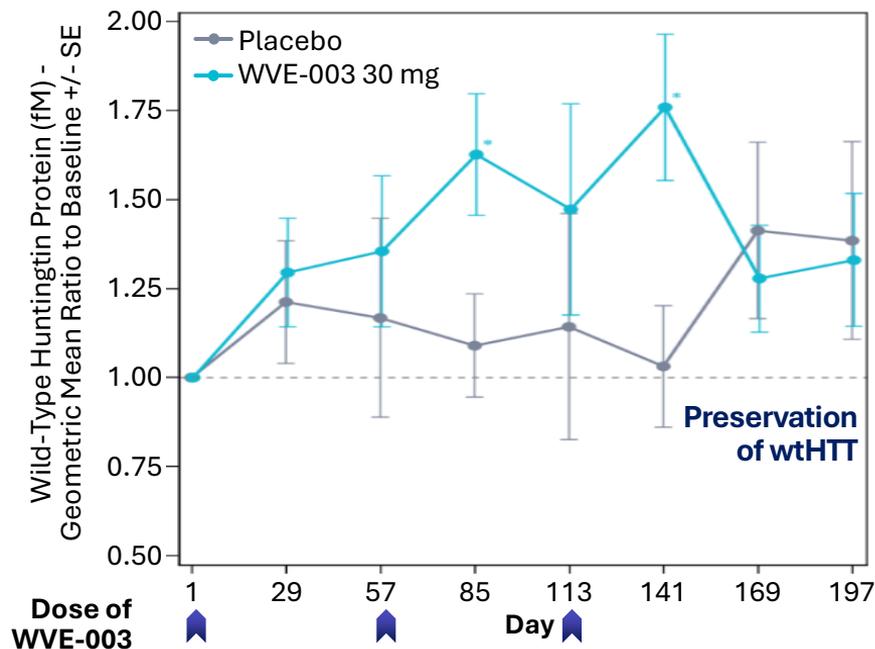
Allele-selective lowering of mutant HTT protein of up to 46% with three doses of WVE-003 and preservation of wild-type HTT

Durability of mHTT reductions supports potential for quarterly dosing intervals

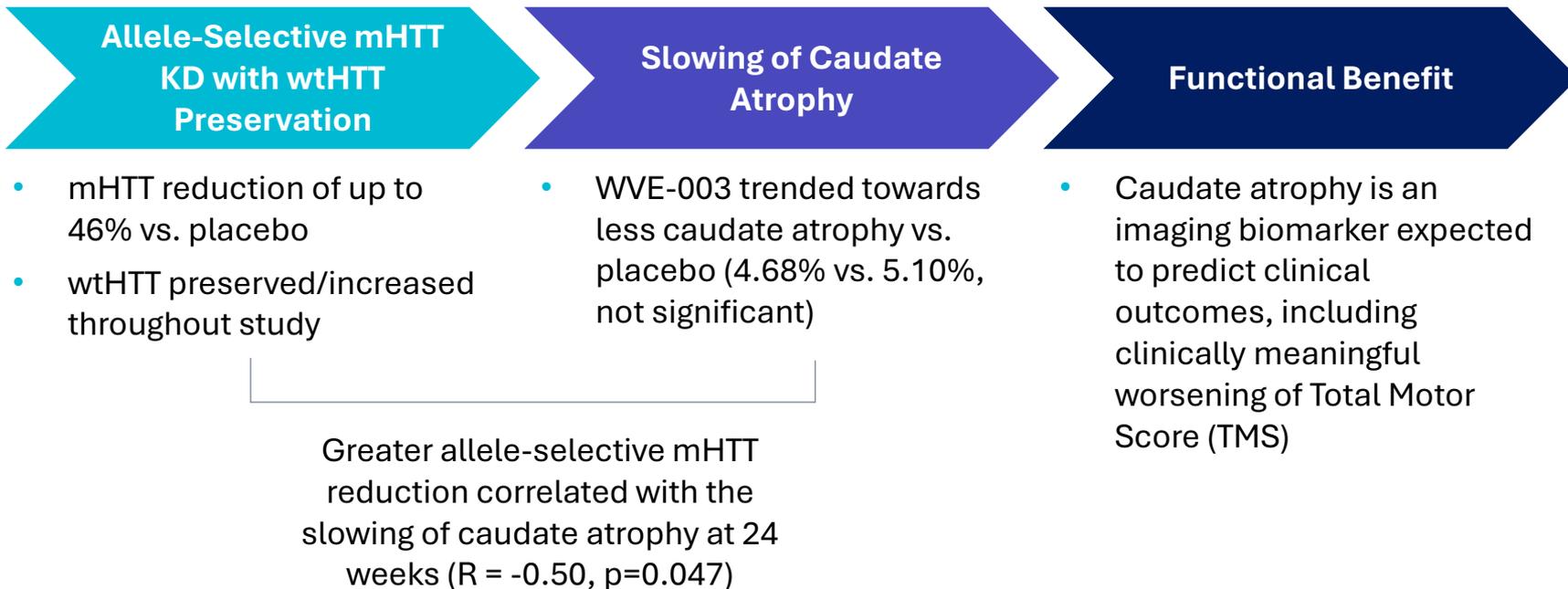
Mutant HTT protein levels



Wild-type HTT protein levels



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



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

Allele-selective mHTT
reductions

Slowing caudate atrophy

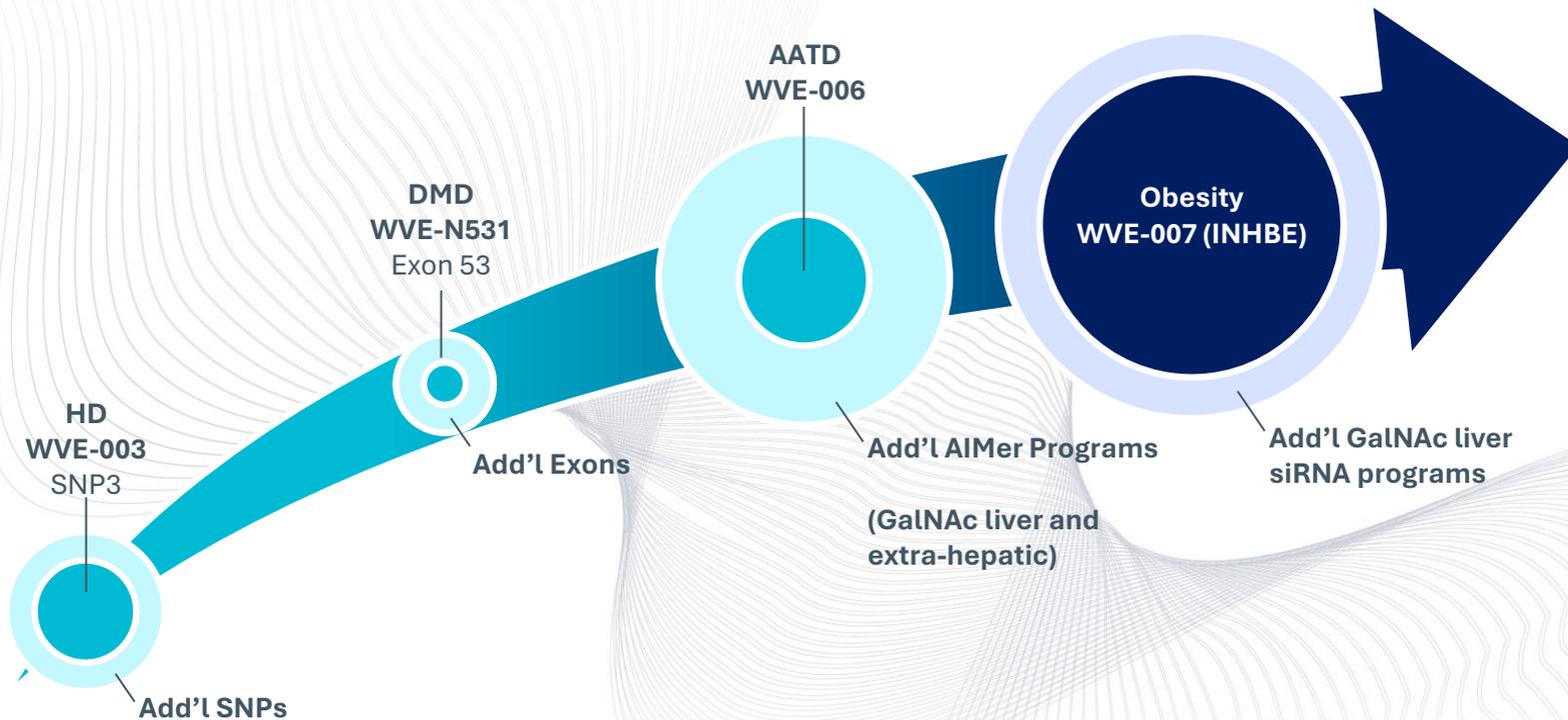
Clinical outcomes



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

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

WAVETM

LIFE SCIENCES

Reimagine possible.

For questions contact:
investorrelations@wavelifesci.com