Wave Life Sciences

43rd Annual J.P. Morgan Healthcare Conference

January 13, 2025

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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.

Our Mission

To unlock the broad potential of RNA medicines to transform human health

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2024 was a year of breakthroughs

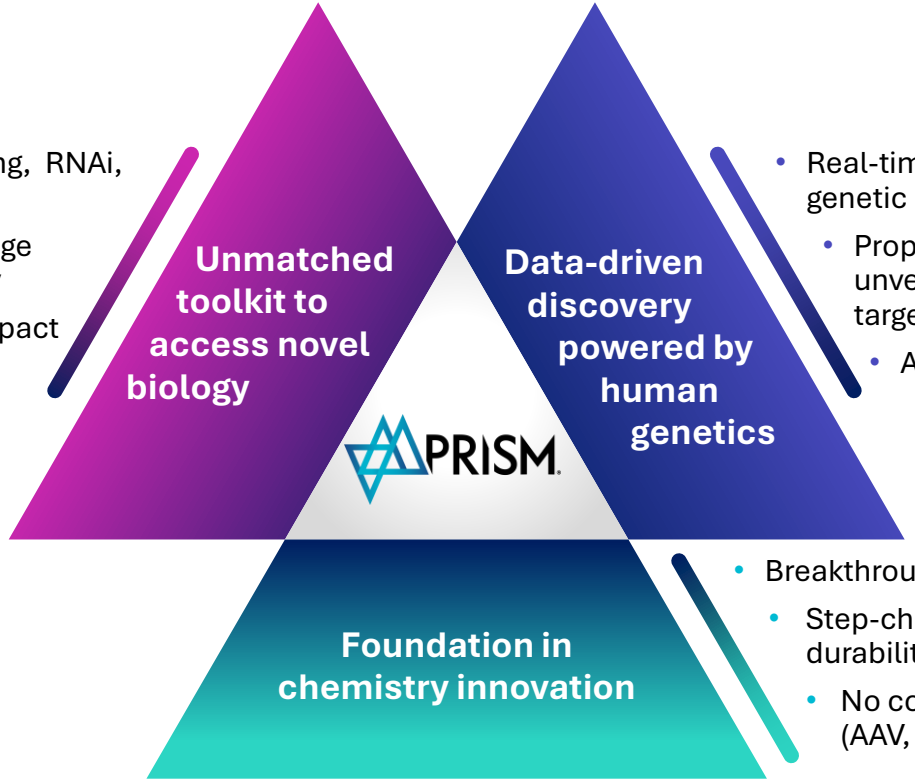
Pioneering RNA editing	✓ Achieved first-ever RNA editing in humans, advancing best-in-class treatment for AATD ✓ Expanded GalNAc-AIMer pipeline: unveiled three new wholly owned RNA editing programs targeting PNPLA3, LDLR, APOB
Innovating in obesity	✓ Selected and advanced INHBE GalNAc-siRNA clinical candidate, a novel, long acting, muscle sparing approach for obesity grounded in human genetics ✓ Submitted CTA for Phase 1 INLIGHT clinical trial of WVE-007
Advancing best-in-class treatments for HD and DMD	✓ Achieved first allele-selective mutant huntingtin silencing, wild-type sparing in clinic with WVE-003 for Huntington's disease ✓ Delivered positive interim DMD clinical data for WVE-N531 with highly consistent, mean muscle content-adjusted dystrophin expression of 9%
Unlocking potential of PRISM platform	✓ Demonstrated proprietary PN breakthroughs for intracellular delivery and ability to silence and edit preclinically in high priority extra-hepatic tissues, including CNS

Expect to continue momentum with multiple data updates in 2025 and beyond

AATD: Alpha-1 antitrypsin deficiency
CNS: Central nervous system
HD: Huntington's disease
DMD: Duchenne muscular dystrophy
CTA: clinical trial application

The powerful convergence of a validated, best-in-class platform with genetics

- Multi-modal: RNA editing, RNAi, antisense, splicing
- Best positioned to engage endogenous machinery
- Unlocking new, high-impact therapeutic targets



- Real-time integration of new human genetic insights into discovery
  - Proprietary deep learning models unveiling novel targets/ target sites
    - Accelerating time to clinic

- Breakthroughs in intracellular delivery
  - Step-change in potency, distribution, durability of effect
    - No complex delivery vehicles (AAV, LNP)

Differentiated RNA medicines clinical pipeline

WVE-007 in Obesity

GalNAc-siRNA targeting INHBE

Multiple CTAs submitted since mid-December 2024; proof-of-concept clinical data expected in 2025

~175M people living with obesity

WVE-006 in AATD

GalNAc-RNA editing oligonucleotide

RestorAATion-2 ongoing in Pi*ZZ AATD patients; multidose data expected in 2025

~200K patients with AATD

WVE-N531 in DMD

Exon 53 splicing oligonucleotide

FORWARD-53 trial ongoing; expect feedback from regulators and 48-week FORWARD-53 data in 1Q 2025

~2,300 boys with DMD amenable to exon 53 skipping

WVE-003 in HD

Allele-selective oligonucleotide

Planning underway for potentially registrational Phase 2/3 study; IND submission expected 2H 2025

~85K HD SNP3 patients across all disease stages

Patient populations represent US and Europe; WVE-006 is partnered with GSK
AATD: Alpha-1 antitrypsin deficiency DMD: Duchenne muscular dystrophy HD: Huntington's disease

Advancing WVE-007 as a novel, long acting, muscle sparing approach for obesity

WVE-007 is a GalNAc-conjugated small interfering RNA (GalNAc-siRNA) that targets INHBE to treat obesity

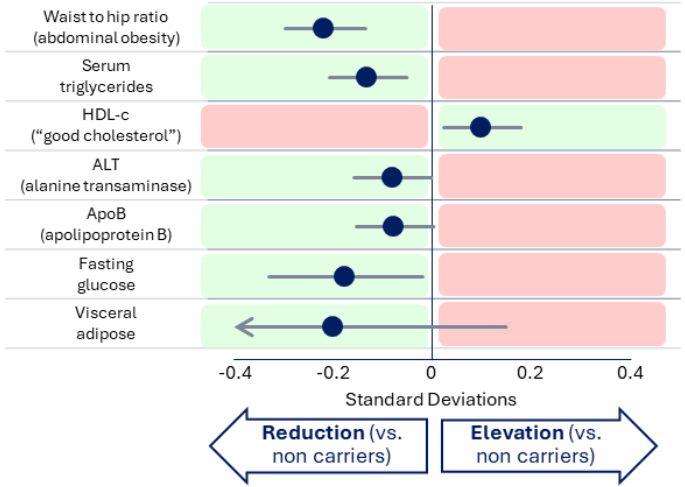
- Adults with obesity have higher risk for many serious health conditions, including heart disease, type 2 diabetes, and some forms of cancer[1]
- GLP-1s are current standard of care for weight loss, but impact is often limited by:
  - Loss of muscle mass[2]
  - Poor tolerability[3]
  - Frequent dosing[4]
  - High discontinuation rates[5,6]

~175 million adults with obesity in US and Europe

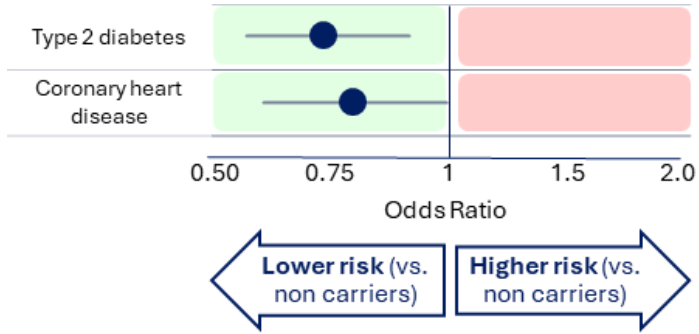
1. CDC.gov; 2. Sargeant, et al. 2019 Endocrinol Metab (Seoul) 34, 247; 3. Ghusn and Hurtado. 2024 Obesity Pillars 12, 100127; 4. Wegovy PI; 5. Leach, et al. 2023 Prime Therapeutics Claims Analysis; 6. Gasoyan, et al. 2024 *Obesity (Silver Spring)* 32, 486.

Human genetic data demonstrate that heterozygous INHBE LoF carriers have a healthy metabolic profile

Heterozygous INHBE LoF carriers have favorable traits: lower abdominal obesity, lower triglycerides, higher HDL-c



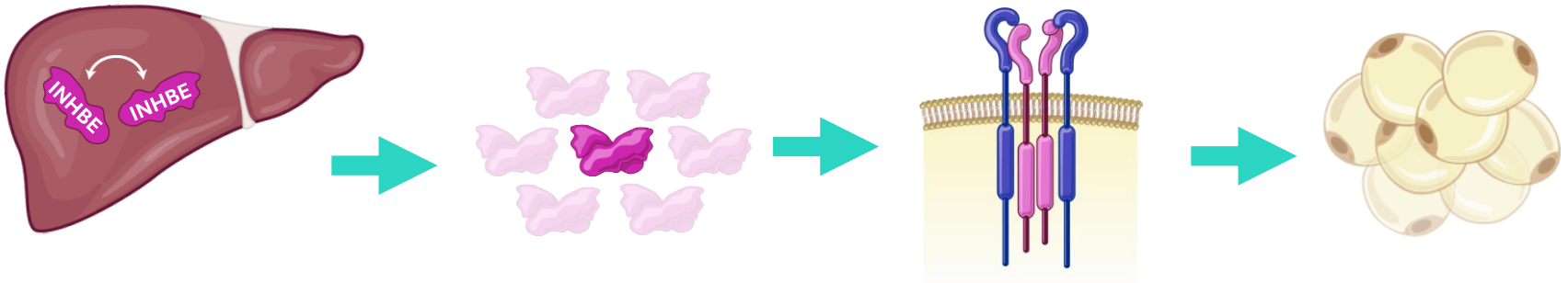
Heterozygous INHBE LoF carriers have lower risk of Type 2 diabetes and CHD



Silencing INHBE mRNA by ≥50% is expected to recapitulate the healthy metabolic profile of heterozygous INHBE loss of function (LoF) carriers

Akbari et al. Nat Commun. 2022 Aug 23;13(1):4844; Deaton et al. Nat Commun. 2022 Jul 27

INHBE GalNAc-RNA expected to address health issues associated with pathogenesis of obesity, associated metabolic disease



GalNAc-siRNA

Reduced release of hepatokine **Activin E**

Diminished activation of **ACVR1C** (ALK7) receptor in adipose tissue

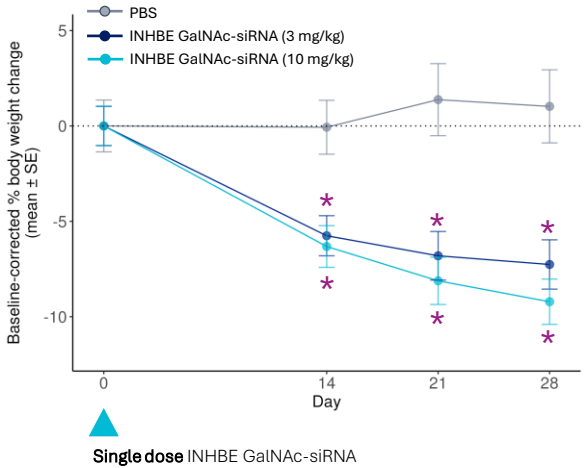
Increased adipose lipolysis and shrink adipocytes

Decreased abdominal adiposity leads to weight loss and reduced risk for CVD and T2D

1. Cell Reports (2018) 25, 1193–1203; 2. Biochemical Journal (2024) 481 547–564; 3. PNAS 2023 Vol. 120 No. 32 e2309967120; 4. Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 5. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8

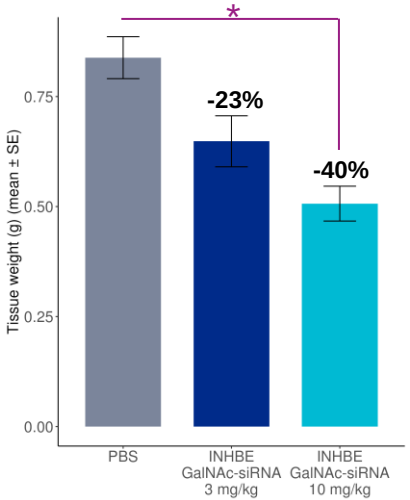
Single doses of INHBE GalNAc-siRNA result in dose-dependent weight loss and reduction of visceral fat, without affecting muscle mass

Reduction in body weight



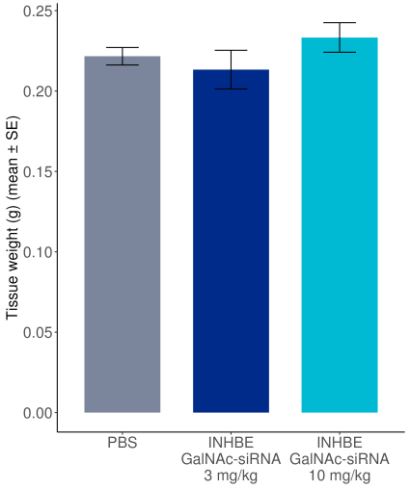
Reduction in visceral fat

Epididymal fat weight (Day 28)



No muscle loss

Quadricep weight (Day 28)

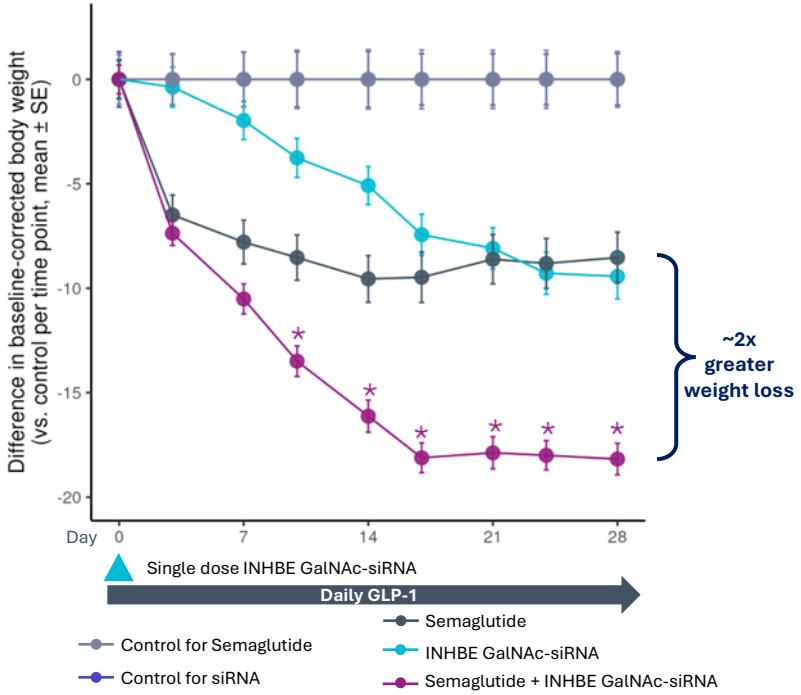


INHBE GalNAc-siRNA has potential as monotherapy weight loss therapeutic

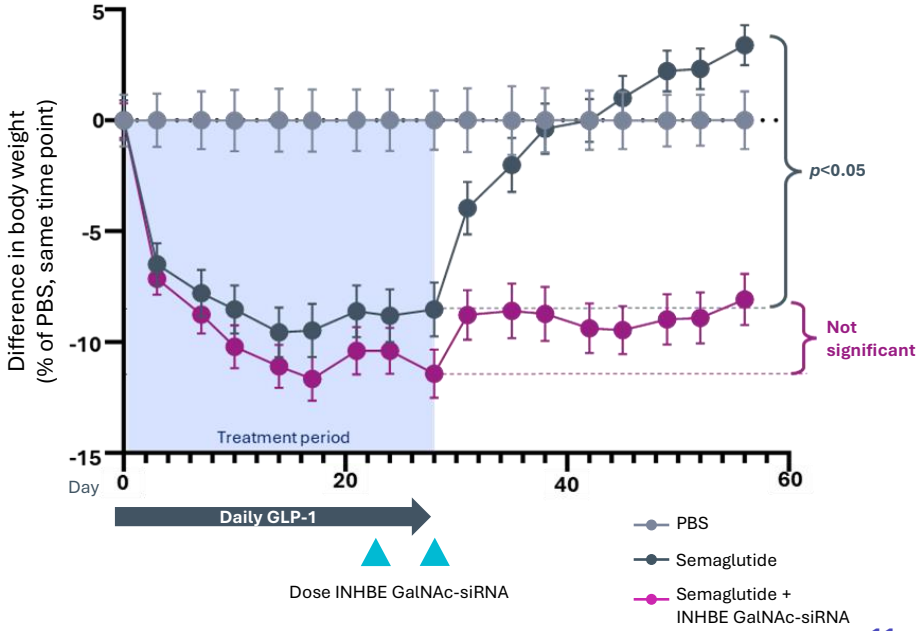
Stats: (left, middle, right) Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects vs. PBS per timepoint (left) or per tissue (middle, right) * $p < 0.05$

INHBE GalNAc-siRNA can be used synergistically with GLP-1s or to prevent weight regain after the cessation of treatment with GLP-1s

~2x greater overall weight loss when added to GLP-1s



Prevents weight regain after the cessation of GLP-1s



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Left: 10nmol/kg in mouse is equivalent to therapeutic dose of GLP-1s in human. Stats: Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects of Semaglutide vs. Semaglutide + INHBE GalNAc-siRNA per time point * $p < 0.05$; Right Stats: Linear Mixed Effects ANOVA with post hoc comparison of Day 28 vs. Day 56 marginal effects per treatment * $p < 0.05$

Preclinical data support best-in-class profile and potential to use WVE-007 across multiple treatment settings with 1-2x a year dosing

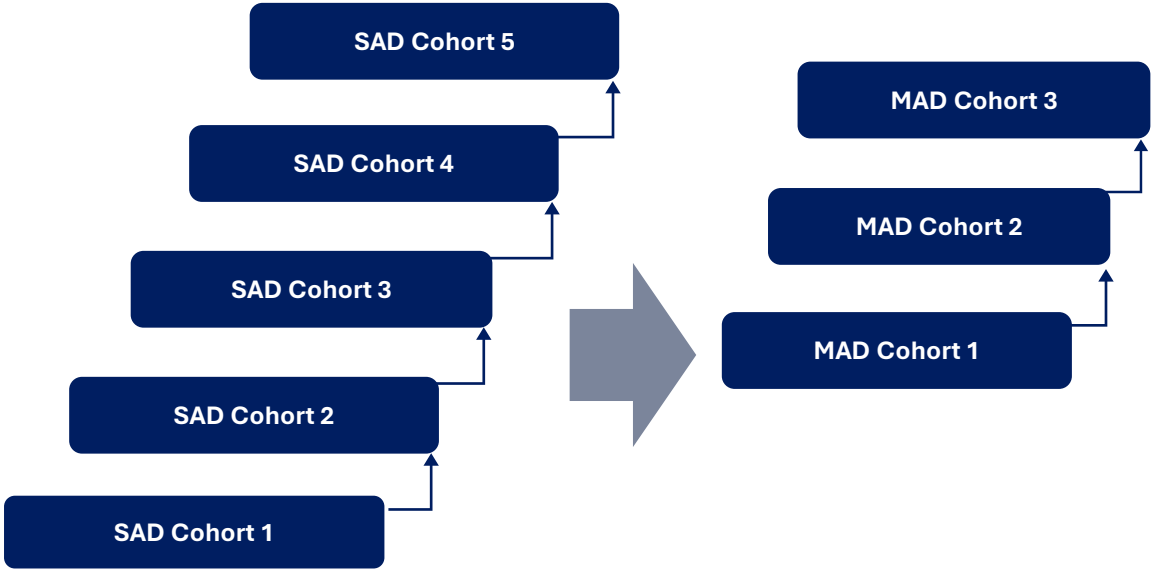
Monotherapy	*Add-on to GLP-1s*	*Maintenance*
WVE-007 as a single agent	**WVE-007 in addition to GLP-1 therapy**	**WVE-007 for patients who stop treatment with GLP-1 therapy**
✓ Weight loss similar to semaglutide with a single dose ✓ No loss of muscle mass ✓ Reduction in fat mass with preferential effect to the visceral fat ✓ Without suppressing food intake	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	✓ Curtailed rebound weight gain upon cessation of semaglutide ✓ Prevention of weight cycling, which worsens the outcomes of various metabolic diseases

INLIGHT: Phase 1 trial of WVE-007 in adults living with overweight or obesity, otherwise healthy

Randomized, double-blind, placebo-controlled study of ascending doses of WVE-007

Trial Design

- **Objective**: Assess dose safety, tolerability, PK and PD
- **Key measurements**
  - **Primary:** Safety and Tolerability
  - **Secondary:** PK, Activin E
  - **Exploratory PD:**
    - Body weight
    - Body composition
    - Metabolic health
    - Biochemical markers



Expect to initiate dosing in INLIGHT in 1Q 2025; proof-of-concept clinical data expected in 2025

Advancing WVE-006 (RNA editing) in AATD

WVE-006: GalNAc-conjugated, subcutaneously delivered, designed to address AATD-related lung disease, liver disease, or both

- AATD is a rare, inherited genetic disorder that is commonly caused by a G-to-A point mutation in the SERPINA1 gene
- Characterized by aggregation of mutant Z-AAT protein in hepatocytes and a lack of functional AAT in lungs
- People with AATD typically exhibit progressive lung damage, liver damage, or both
- Weekly intravenous augmentation therapy is the only treatment option for AATD in those with the lung pathology
- No approved therapies to address AATD liver disease

~200K people in the US and Europe are homozygous for the Z allele

Strnad et al., 2020 *N Engl J Med* 382:1443-55; Blanco et al. 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69

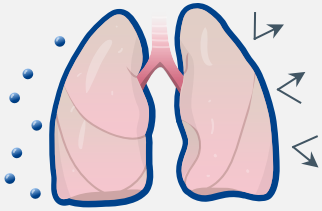
WVE-006 to address both liver and lung manifestations of AATD

WVE-006 RNA editing treatment

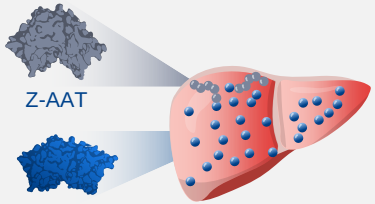
- **Subcutaneous injection (GalNAc)**
- **Infrequent dosing**
- **Highly specific (no bystanders)**

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

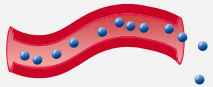
1. **Restore** circulating, functional wild-type M-AAT
2. **Reduce** Z-AAT protein aggregation in liver
3. **Retain** M-AAT physiological regulation



M-AAT reaches lungs to protect from proteases



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



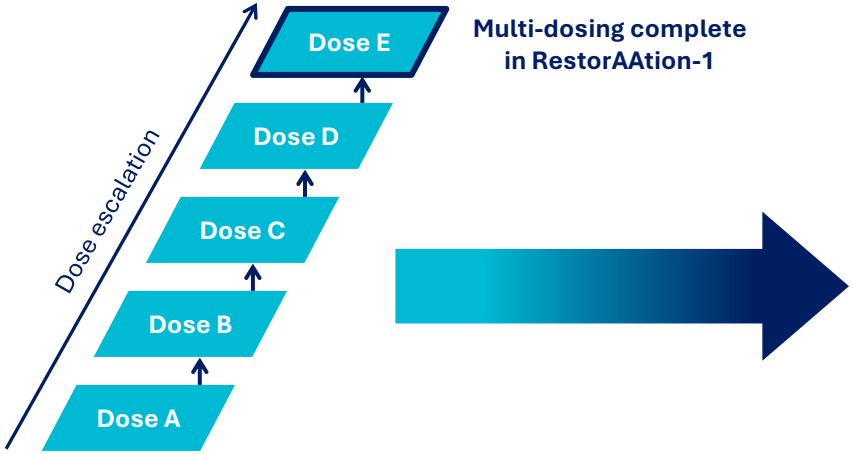
M-AAT secretion into bloodstream

Strnad et al., 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 Alpha-1 Antitrypsin Deficiency GeneReviews.

RestorAATion-2 clinical trial in Pi*ZZ AATD patients ongoing

RestorAATion-1: Healthy Volunteers → **RestorAATion-2: AATD Patients**

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



Multi-dosing complete in RestorAAtion-1

Up to 7 doses

Cohort 3

Cohort 2

Cohort 1
200 mg

Study key objectives

Safety and tolerability
Pharmacokinetics
Serum M-AAT levels

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

Achieved proof-of-mechanism for Wave's RNA editing platform

Proof-of-mechanism achieved after a single dose in RestorAATion-2

- ✓ Total AAT protein increased to a mean of 10.8 µM at day 15
  - ✓ Meets level that has been the basis for regulatory approval for AAT augmentation therapies
- ✓ Circulating wild-type M-AAT protein reached a mean of 6.9 µM at day 15; more than 60% of total AAT
- ✓ Increases in total AAT from baseline and M-AAT protein were observed as early as day 3 and through day 57
- ✓ Increases in neutrophil elastase inhibition from baseline were consistent with production of functional M-AAT
- ✓ WVE-006 well tolerated with a favorable safety profile; all AEs mild-to-moderate, no SAEs

Multidose data from RestorAATion-2 expected in 2025

Wholly owned GalNAc-AIMer programs

- **Strongly supported by human genetics**
- **Leverage unique platform capabilities; GalNAc-AIMers building on learnings of WVE-006**
- **Completely novel ways of treating diseases with high unmet need**
- **Readily accessible biomarkers and approaches to assess PD, defined regulatory paths**

Correction of PNPLA3
Genetically defined liver disease
Patient population: ~9 million

Upregulation of LDLR
HeFH
Patient population: ~900,000, with expansion to ~30 million in follow on indications

Correction of APOB
HeFH
Patient population: ~70,000

Expect to initiate clinical development of additional RNA editing programs, including PNPLA3, LDLR, and APOB programs in 2026

Patient populations are in US and Europe
HeFH: heterozygous familial hypercholesterolemia

Editing for correction Editing for upregulation

Advancing WVE-N531 in exon 53 amenable DMD

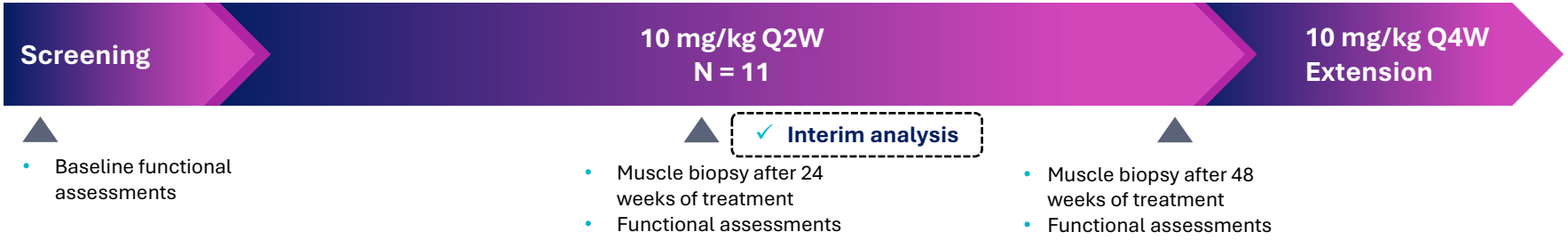
WVE-N531: exon skipping oligonucleotide designed to induce production of endogenous, functional dystrophin protein

- High unmet 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
- WVE-N531 has Rare Pediatric Disease Designation and Orphan Drug Designation from FDA

DMD impacts ~1 / 5,000 newborn boys annually; ~20,000 new cases annually worldwide

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



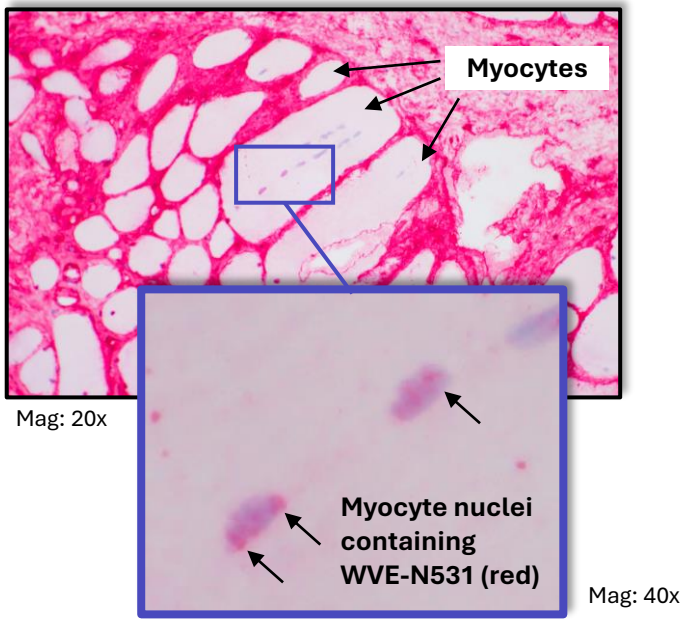
Key Assessments:

- 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

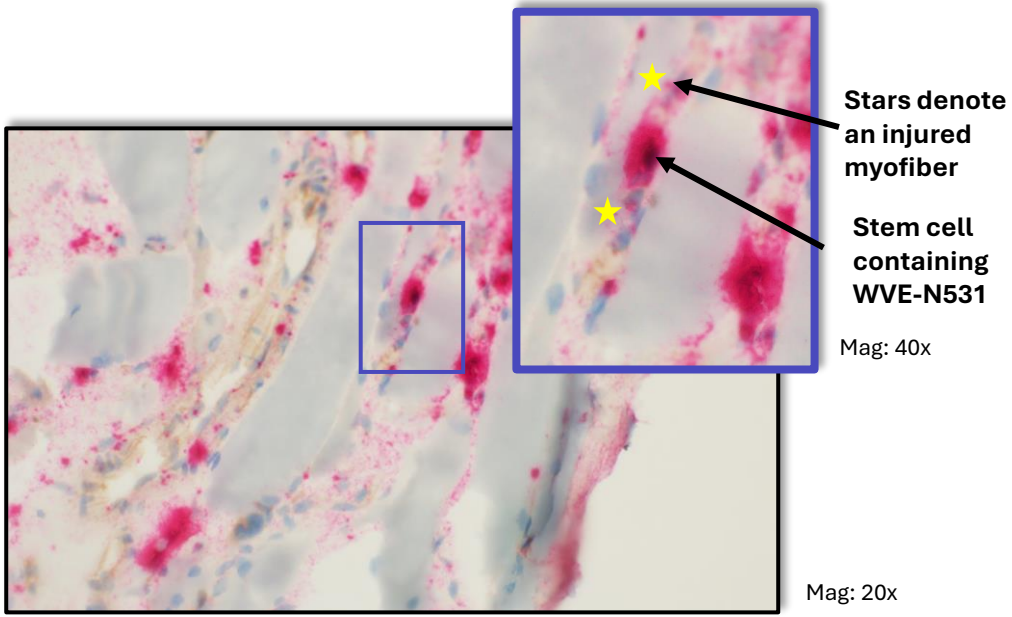
WVE-N531 is the only DMD therapeutic to show uptake in myogenic stem cells

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

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

Best-in-class dystrophin expression and muscle delivery

- Highly consistent, mean muscle content-adjusted dystrophin expression of 9%
- Muscle tissue concentrations of ~41,000 ng/g and tissue half-life of 61 days (supports monthly dosing)
- Preclinical data suggests higher levels of dystrophin protein expression in **heart** and **diaphragm** than skeletal muscle

Evidence supporting improved muscle health

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

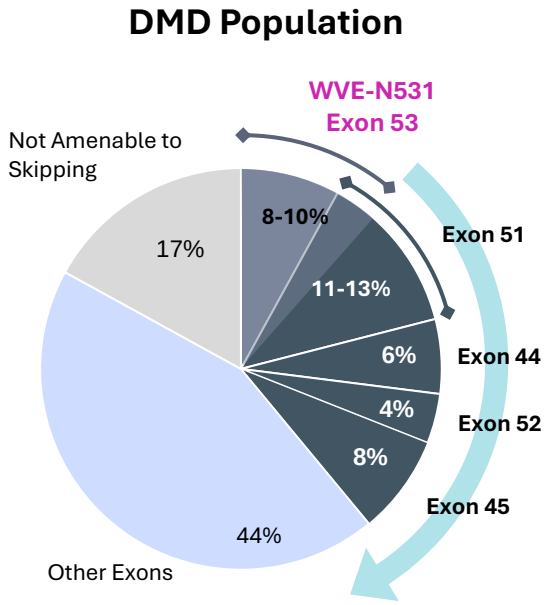
Safe and well tolerated

- No serious adverse events (SAEs)
- No discontinuations
- No oligonucleotide class effects

Expect feedback from regulators and the 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.

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 (~10,000 patients in US and Europe)
- Expect to engage regulators on a platform trial design that incorporates multiple exons

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

Advancing WVE-003 to address HD across all stages of disease

WVE-003 is a first-in-class, allele-selective oligonucleotide for the treatment of HD

- 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

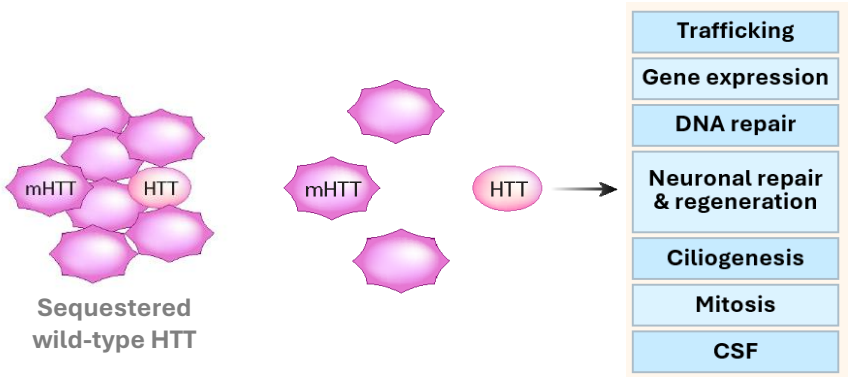
Pre-Symptomatic HD	Symptomatic HD
(~160K in US and Europe)	(~65K in US and Europe)

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

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

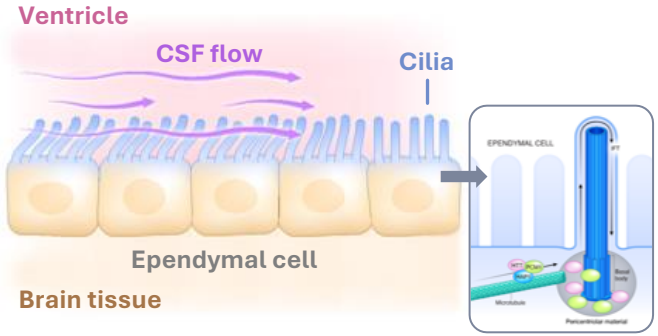
Mutant HTT has a detrimental effect on wild-type HTT function

- 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



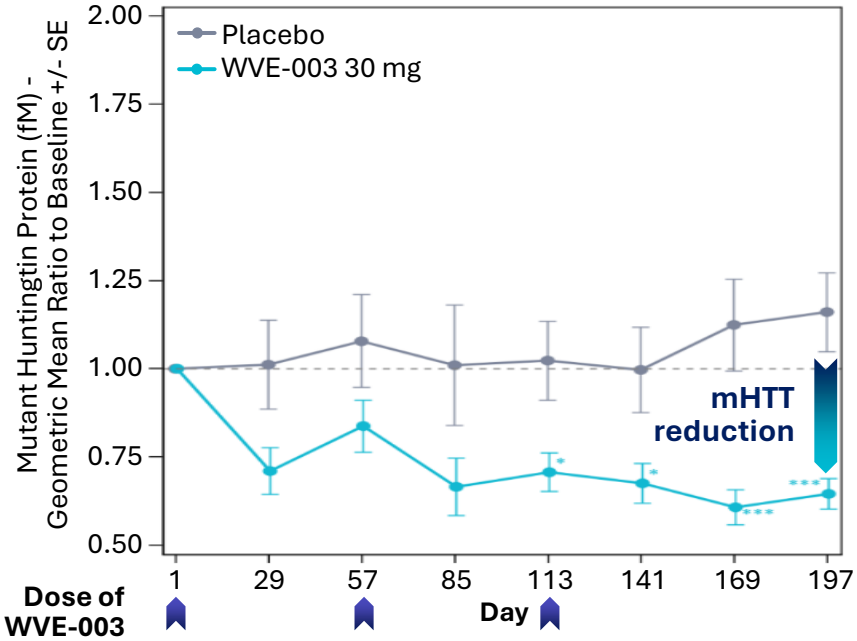
Only an allele-selective approach can ameliorate both loss-of-function and gain-of-function disruptions driven by mHTT

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

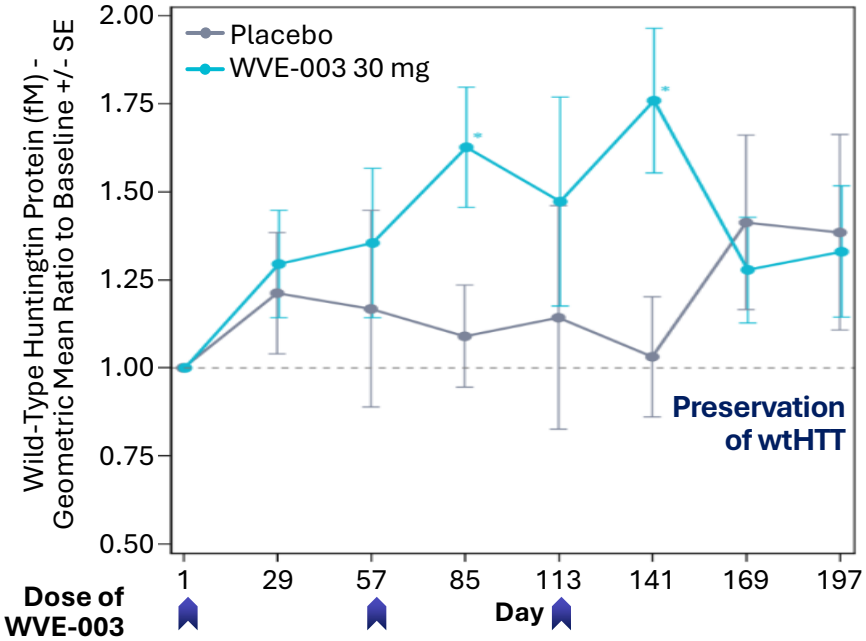
Allele-selective lowering of mutant HTT protein of up to 46% with three doses of WVE-003 and preservation of wild-type HTT

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
From June 25, 2024 SELECT-HD disclosure

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

Allele-selective mHTT Silencing with wtHTT Preservation

- mHTT reduction of up to 46% vs. placebo
- wtHTT preserved/increased throughout study

Slowing of Caudate Atrophy

- WVE-003 trended towards less caudate atrophy vs. placebo (4.68% vs. 5.10%, not significant)

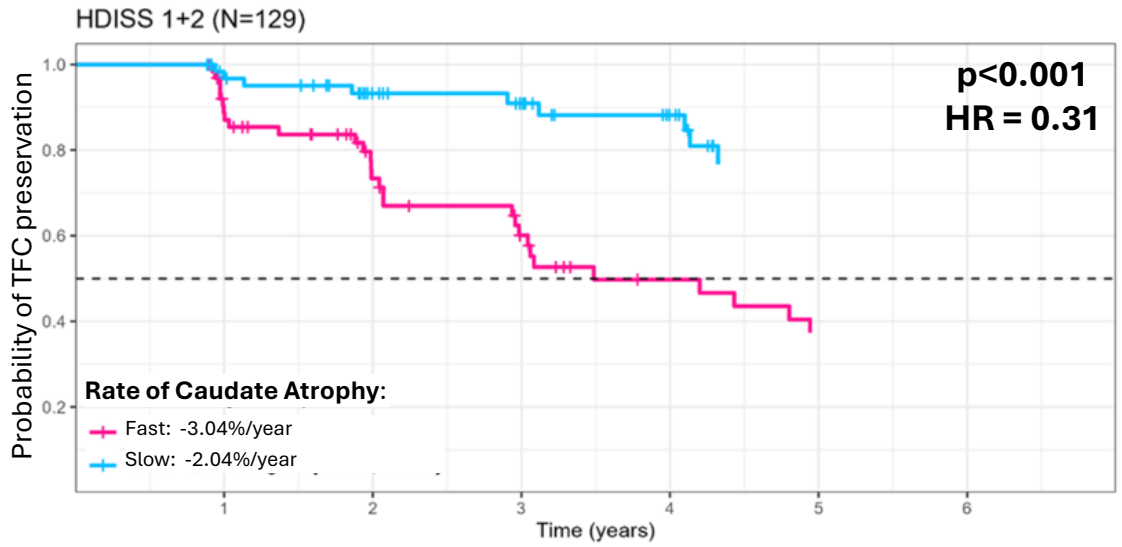
Functional Benefit

- Caudate atrophy is an imaging biomarker expected to predict clinical outcomes, including clinically meaningful worsening of Total Motor Score (TMS)

Greater allele-selective mHTT reduction correlated with the slowing of caudate atrophy at 24 weeks (R = -0.50, p=0.047)

Liu et al., 2023 Brain Comm

Internal analysis of natural history demonstrates 1% reduction in rate of caudate atrophy would delay onset of disability by ≥7.5-years



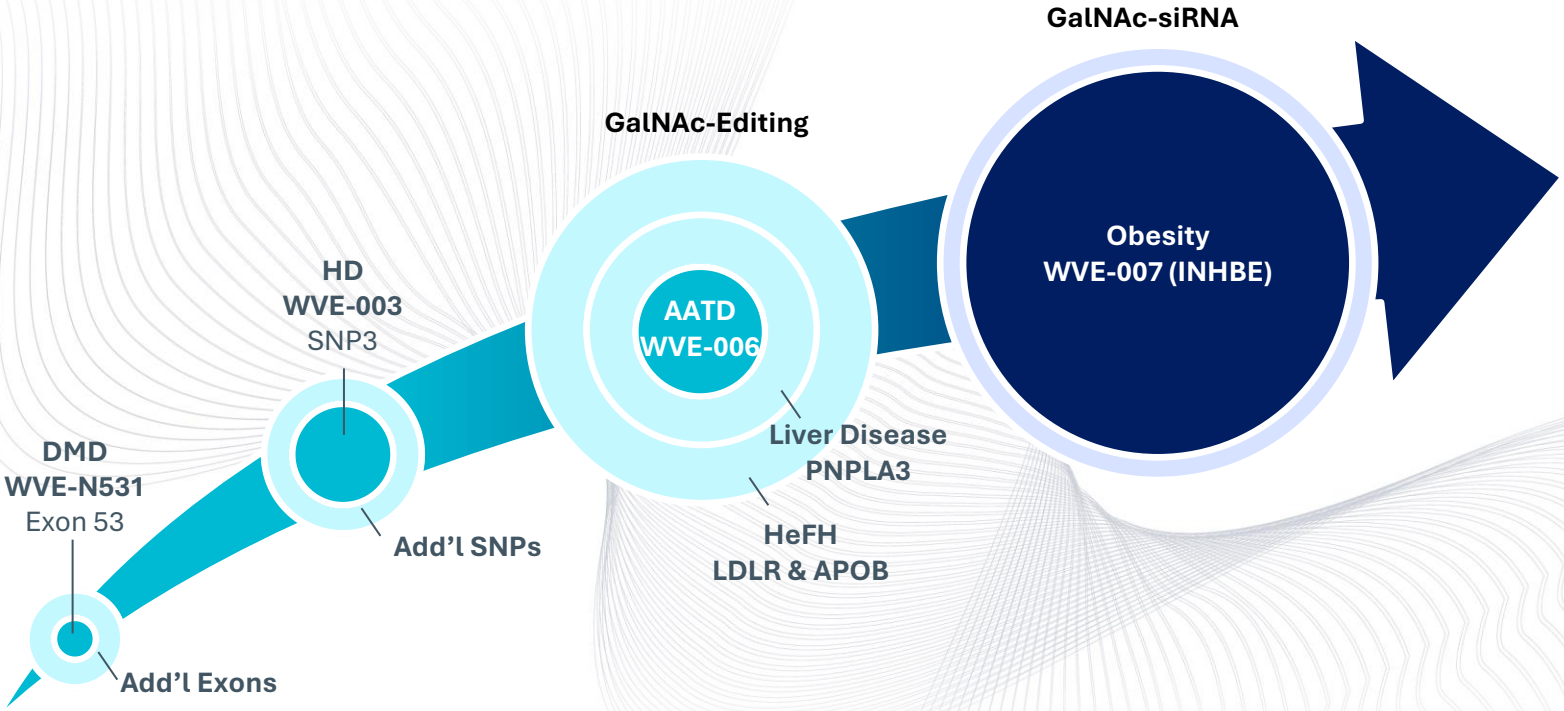
WVE-003 next steps

- Planning underway, including key aspects of study design, for a global, potentially registrational Phase 2/3 study in adults with SNP3 and HD
- Using caudate atrophy as a primary endpoint

Expect to submit IND application for potentially registrational Phase 2/3 study in 2H 2025

TRACK-HD (n=366) and PREDICT-HD (n=1,078) are longitudinal HD natural history studies that include MRI brain imaging, clinical outcome assessments. Paulson et al., Neurosci.2014, Tabrizi et al., Lancet Neurol 2009, Tabrizi et al., Lancet Neurol 2012, Tabrizi et al., Lancet Neurol. 2013
IND: Investigational New Drug TFC: Total Functional Capacity

Poised for significant and sustained growth driven by editing and siRNA



Current pipeline has potential to treat well over 100 million patients in US and Europe

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

Anticipated upcoming milestones

siRNA	*RNA editing*		*Splicing*	*Allele-selective silencing*
WVE-007 (INHBE) **Obesity**	**WVE-006** **AATD**	**PNPLA3, LDLR, APOB, additional wholly owned programs**	**WVE-N531 (Exon 53)** **DMD**	**WVE-003 (SNP3)** **HD**
1Q 2025: Initiate dosing in INLIGHT clinical trial **2025:** Deliver proof-of-concept clinical data	**2025:** Deliver multidose data from RestorAATion-2	**2025:** Deliver new preclinical data from hepatic and extra-hepatic RNA editing programs **2026:** Initiate clinical development of additional RNA editing programs	**1Q 2025:** Deliver 48-week FORWARD-53 data & receive feedback from regulators on pathway to accelerated approval	**2H 2025:** Submit IND application for potentially registrational Phase 2/3 using caudate atrophy as a primary endpoint

Well-capitalized with expected cash runway into 2027

AATD: Alpha-1 antitrypsin deficiency; LDLR and APOB programs for treatment of heterozygous familial hypercholesterolemia; PNPLA3 program for treatment of genetically defined liver disease; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; IND: Investigational New Drug

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