WVE-006: RNA editing for AATD

Positive RestorAATion-2 clinical data update

Investor presentation

September 3, 2025

Forward-looking statements

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Today's agenda

WVE-006: first-in-class RNA editing therapeutic for AATD
Paul Bolno, MD, MBA
President and CEO

RestorAATion-2 clinical data update
Chris Wright MD, PhD
Chief Medical Officer

Closing remarks
Paul Bolno, MD, MBA
President and CEO

Q&A

WVE-006

Paul Bolno, MD, MBA

President & CEO

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Today's update: Positive clinical data update from RestorAATion-2 clinical trial of WVE-006 for alpha-1 antitrypsin deficiency (AATD)

Achieved durable production of serum AAT at levels associated with lower risk of AATD liver and lung disease following repeat 200 mg doses of WVE-006

- **11.9 µM** Total AAT
- **7.2 µM** M-AAT
- **64.4%** Circulating M-AAT
- **60.3%** Decrease in Z-AAT

20.6 µM Total AAT — **First-ever demonstration of therapeutically restored physiological serum AAT production in a Pi*ZZ individual during a non-drug related acute phase response**

400 mg single dose

12.8 µM Total AAT

400 mg monthly multidose cohort ongoing with potential to deliver further increases in serum AAT; Data expected in 1Q 2026

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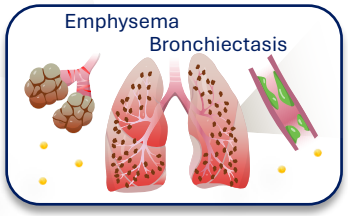
Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums

AATD impacts multiple organ systems and has limited treatment options

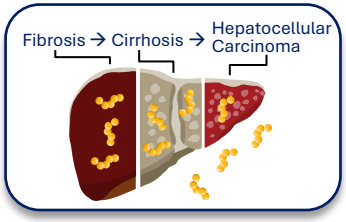
- AATD is a rare, inherited genetic disorder that is commonly caused by a G-to-A point mutation in the SERPINA1 gene
- Pi*ZZ genotype is leading cause of severe AATD, predisposing to progressive lung damage, liver damage or both
- Aggregation of mutant Z-AAT protein in hepatocytes and a lack of functional, wild-type M-AAT drives liver and lung disease, respectively

AATD Lung Disease



- **Treatment goal:** Minimize episodic exacerbations and associated damage
- Lung damage occurs during exacerbations that induce an inflammatory acute phase response, when more AAT protein is needed for protection
- **Weekly IV augmentation therapy is only treatment option**
  - No protective increase in AAT protein levels during acute phase response without additional IV infusions

AATD Liver Disease



- **Treatment goal:** Decrease Z-AAT protein
- Progressive liver disease results from Z-AAT-induced proteotoxic stress
- **No approved therapies**

~200K people in the US and Europe are homozygous for the Z allele (Pi*ZZ genotype)

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

RNA editing aims to increase M-AAT and restore physiological AAT production during acute phase response

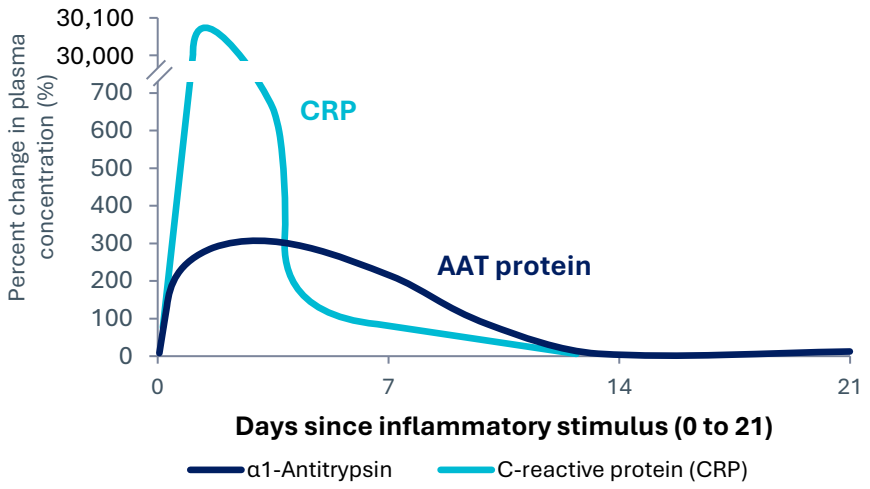
Genotype	Null	Pi*ZZ	Pi*MZ	Pi*MM
	No AAT protein	100% Z-AAT	Z-AAT and M-AAT	100% M-AAT
AAT levels increase during acute phase response	No	No	Yes	Yes
Risk of lung disease	Very high	High	Low	Normal
Risk of liver disease	None	High	Low	Normal

>50% RNA editing
> 11 µM AAT

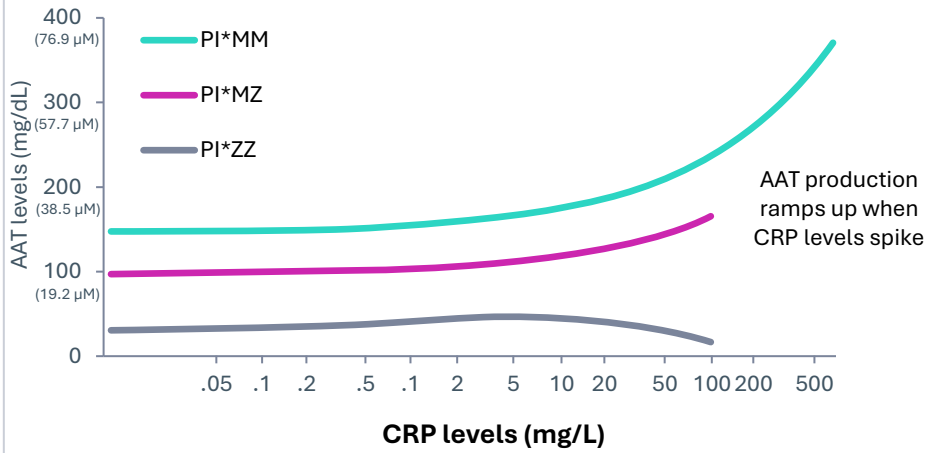
Goal: Shift Pi*ZZ individuals to AAT biomarker profile consistent with Pi*MZ genotype

RNA editing aims to restore production of dynamic and therapeutically relevant levels of AAT protein in Pi*ZZ patients during acute phase response

AAT protein has protective functions and is produced during acute phase response



AAT levels in healthy individuals increase during acute phase response, but not in Pi*ZZ patients



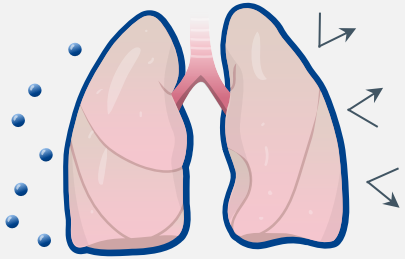
Left: Mantovani A, Garlanda C. N Engl J Med2023;388:439-452 Right: Sanders et al., J COPD, 2018

WVE-006: Potential first-in-class, convenient therapy for AATD that addresses both liver and lung manifestations of disease

WVE-006
(RNA editing)

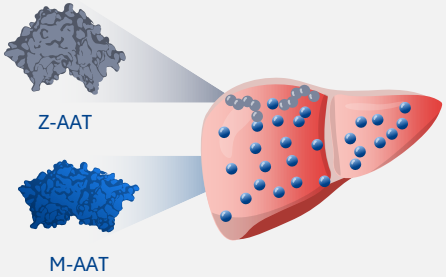
- **Proprietary chemistry**
- **Subcutaneous injection (GalNAc)**
- **Highly specific (no bystanders)**
- **Infrequent dosing**

Restore circulating M-AAT and physiological AAT protein production



M-AAT reaches lungs to protect from proteases and **reduce risk of lung disease**

Reduce Z-AAT protein aggregation in liver



RNA correction replaces mutant Z-AAT protein with wild-type M-AAT protein to **reduce risk of liver disease**

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

RestorAATion-2 clinical data update

Chris Wright, MD, PhD

Chief Medical Officer

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RestorAATion-1 clinical trial in healthy volunteers complete, RestorAATion-2 clinical trial in Pi*ZZ patients ongoing

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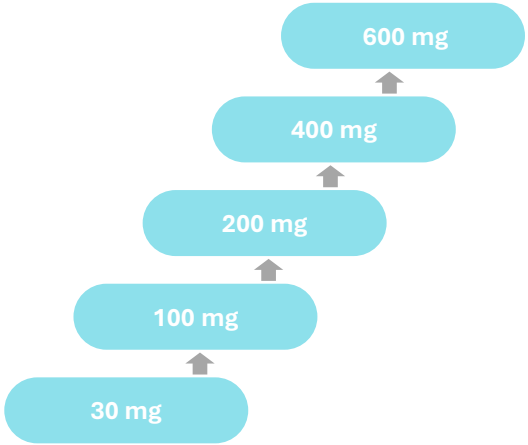
RestorAATion-1: Healthy Volunteers

SAD → MAD Multi-dosing complete



RestorAATion-2: AATD Patients

Up to seven doses in multi-dose portion

SAD Cohort 3	MAD Cohort 3
SAD Cohort 2 400 mg	MAD Cohort 2 400 mg; 1x/month
SAD Cohort 1 200 mg	MAD Cohort 1 200 mg Q2W

Study key objectives

Safety and tolerability | Pharmacokinetics | Serum M-AAT levels

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

WVE-006 was safe and well-tolerated in RestorAATion-1 healthy volunteer study

TEAE Category	WVE-006 30 mg SAD N=6 n (%)	WVE-006 100 mg SAD N=5 n (%)	WVE-006 200 mg SAD N=6 n (%)	WVE-006 400 mg SAD N=6 n (%)	Pooled Placebo SAD N=10 n (%)	WVE-006 600 mg Q2wk x 3 N=6 n (%)	Placebo MAD N=2 n(%)
Any TEAE	5 (83.3)	4 (80.0)	3 (50.0)	3 (50.0)	8 (80.0)	2 (33.3)	1 (50.0)
Mild	3 (50.0)	0	2 (33.3)	1 (16.7)	2 (20.0)	0	0
Moderate	2 (33.3)	4 (80.0)	1 (16.7)	2 (33.3)	6 (60.0)	2 (33.3)	1 (50.0)
Severe	0	0	0	0	0	0	0
Any drug-related TEAE	0	0	1 (16.7)	0	0	0	0
Mild	0	0	1 (16.7)	0	0	0	0
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0	0
Any TEAE leading to discontinuation	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0

SAD: single ascending dose MAD: multi-ascending dose

Baseline participant characteristics were similar across first two cohorts

Key Inclusion Criteria

- Pi*ZZ genotype
- 18 to 70 years of age
- Healthy or mild to moderate AATD-induced lung disease and/or stable mild AATD-induced liver disease
- Non-smoker for at least 1 year prior to screening

RestorAATion-2 Baseline Participant Characteristics	WVE-006 200 mg N=8	WVE-006 400 mg N=8
Age at consent (years) (mean (SD))	51.4 (12.0)	49.4 (18.1)
Gender, N Male Female	8 2 (25.0) 6 (75.0)	8 4 (50.0) 4 (50.0)
Weight (kg), Median (min, max)	79.7 (64.8,100.0)	82.0 (65.6, 97.5)
Years since AATD diagnosis (mean)	15.9	16.2
Baseline Day 1 FEV1 (mean (L) (min, max))	3.2 (2.2, 5.8)	2.9 (1.3, 5.1)
Baseline Liver Elastography (n participants with F0-2 score; % of participants)	F0 (7; 87.5) F1 (1; 12.5) F2 (0; 0)	F0 (5; 62.5) F1 (2; 25.0) F2 (1; 12.5)

RestorAATion-2: WVE-006 continues to be safe and well tolerated

TEAE Category	200 mg SAD N=8 n (%)	200 mg MAD N=8 n (%)	400 mg SAD N=8 n (%)
Any TEAE	6 (75.0)	5 (62.5)	5 (62.5)
Mild	2 (25.0)	0	1 (12.5)
Moderate	4 (50.0)	5 (62.5)	4 (50.0)
Severe	0	0	0
Any drug-related TEAE	1 (12.5)	2 (25.0)	3 (37.5)
Mild	1 (12.5)	1 (12.5)	1 (12.5)
Moderate	0	1 (12.5)	2 (25.0)
Severe	0	0	0
Any serious TEAE	0	0	0
Any TEAE leading to discontinuation	0	0	0
Any TEAE leading to death	0	0	0

- No SAEs, discontinuations or withdrawals due to TEAEs
- All TEAEs were mild to moderate in severity
- No treatment-related, clinically relevant changes in labs, ECG, or vital signs

Data as of August 26, 2025
SAD: single ascending dose MAD: multi-ascending dose

RestorAATion-2 clinical update: Biomarker results

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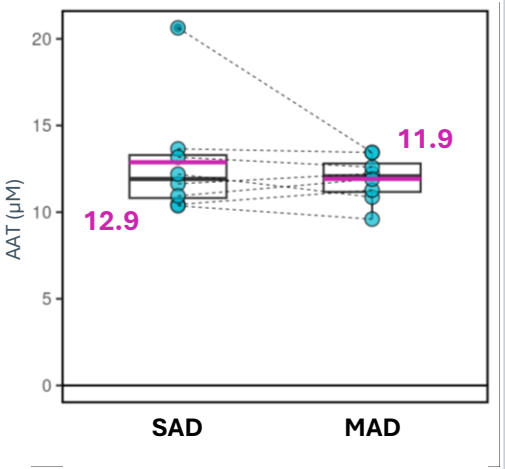
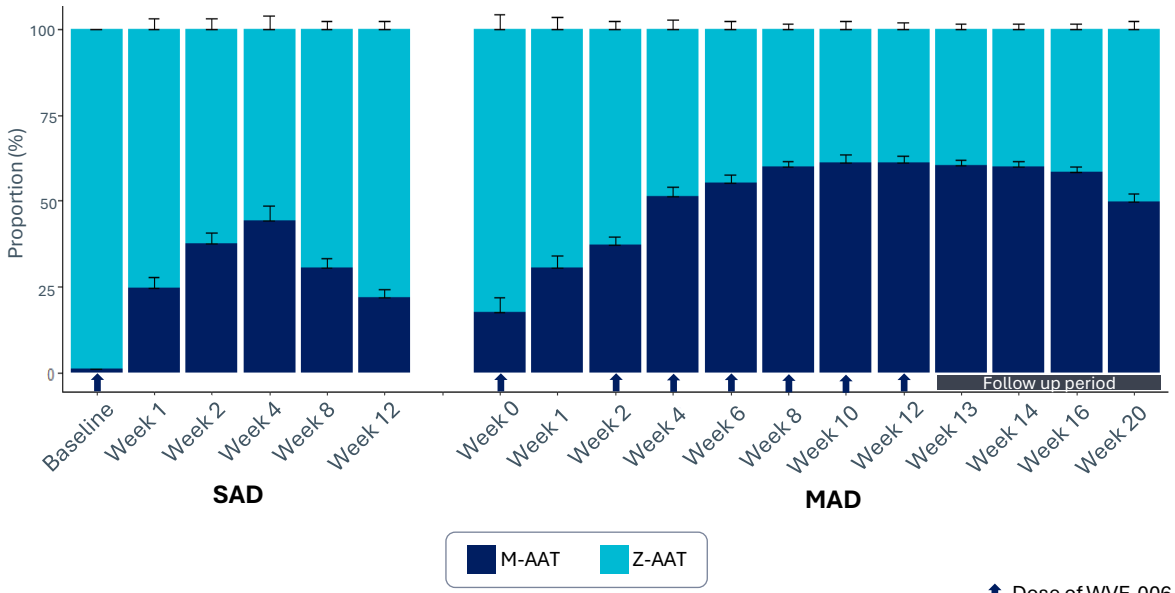
Therapeutically relevant levels of total AAT protein with durable editing and M-AAT reaching 64% of total protein in 200 mg cohort

Circulating serum total AAT protein



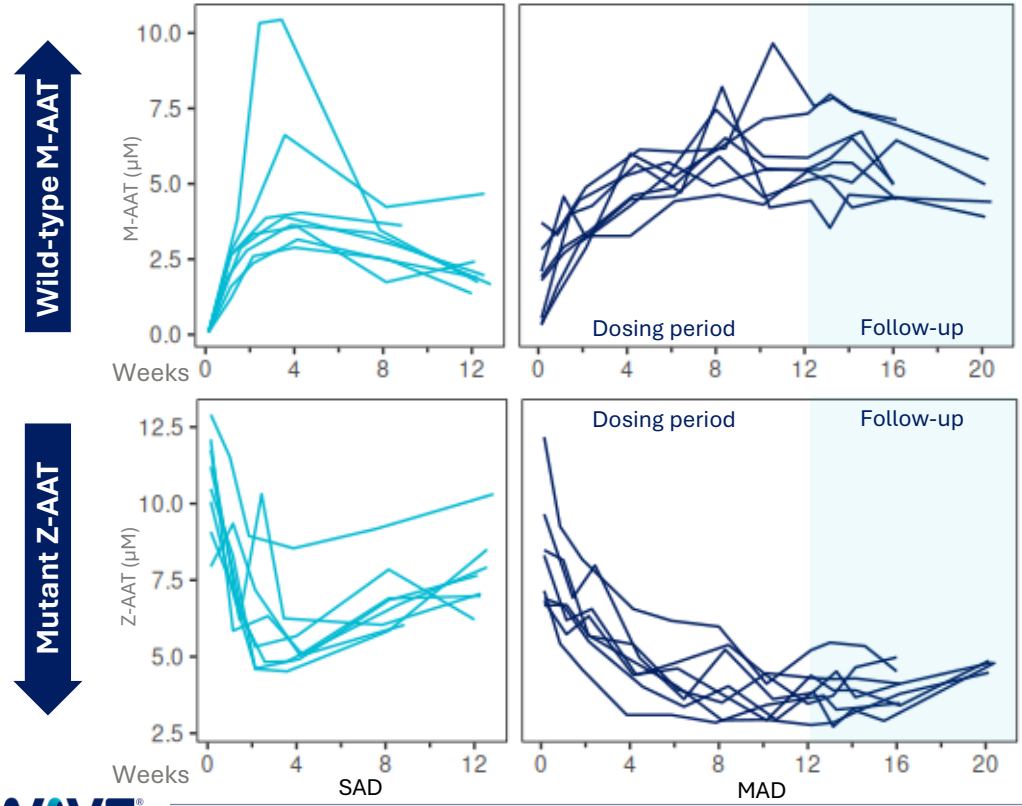
Proportion of circulating serum wild-type M-AAT and mutant Z-AAT protein

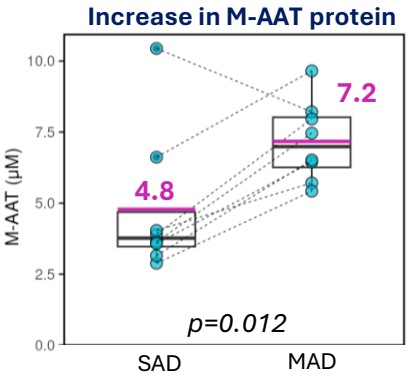


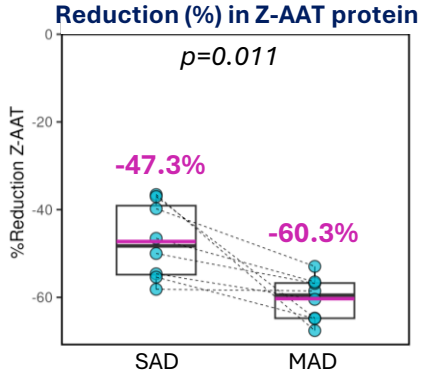
Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 μM (M), 0.029 μM (Z)) and reported as mean participant SAD and MAD maximums

200 mg cohort: Consistent M-AAT increase and Z-AAT decrease observed, MAD significantly enhances effects versus SAD

Increases in neutrophil elastase inhibition from baseline confirmed production of functional M-AAT





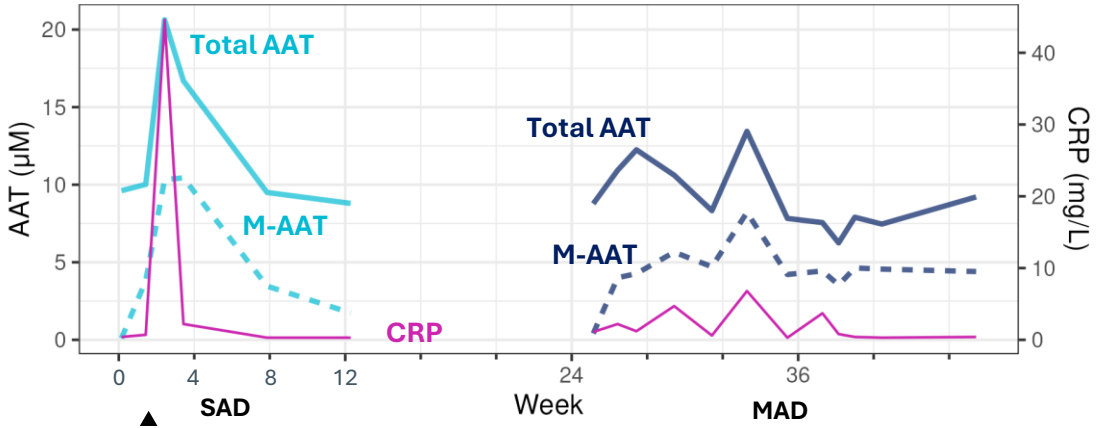


Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums
Right: black line represents median

First-ever demonstration of ability to restore physiological serum AAT production; total AAT reached 20.6 µM during acute phase response

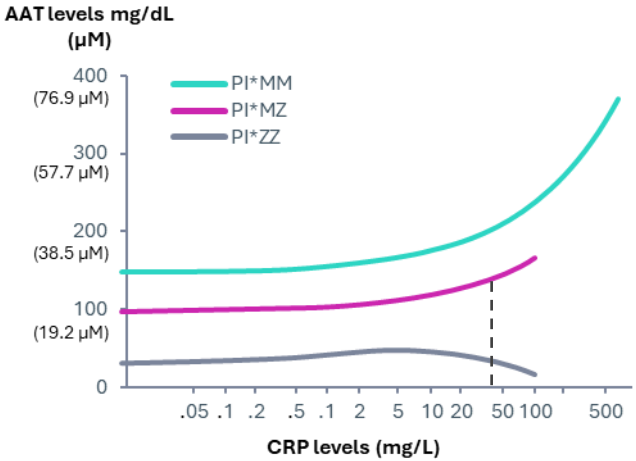
Pi*ZZ patients have a reduced capacity to produce AAT protein during an acute phase response

Following WVE-006 200 mg single dose, total AAT and M-AAT increased significantly in one patient during an acute phase response



▲ Acute phase response due to a kidney stone

Published data[1] on CRP levels and AAT levels across different genotypes



AAT response in Pi*ZZ participant treated with WVE-006 mirrors Pi*MZ phenotype

1 - Sanders et al., J COPD, 2018 CRP: C-reactive protein

Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums

Data from single dose cohorts support potential to further increase serum AAT levels with 400 mg multidose cohort and monthly dosing

400 mg SAD Cohort

12.8 µM
Total AAT

5.3 µM
M-AAT

47.2%
Circulating M-AAT

49.0%
Decrease in Z-AAT

As compared to 200 mg SAD Cohort

- **Increases in M-AAT protein**
- **Greater % of M-AAT protein**
- **Greater reductions in Z-AAT protein**

400 mg multidose cohort ongoing with monthly dosing; clinical data expected in 1Q 2026

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Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums

Closing remarks

Paul Bolno, MD, MBA

President & CEO

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WVE-006: A potentially transformative therapeutic for AATD

Achieving profile consistent with MZ phenotype	**Durable RNA editing to restore circulating wild-type, M-AAT**	✓ Total AAT levels of up to ~13 µM ✓ M-AAT of >60% of circulating total AAT ✓ No bystander edits
Preventing lung damage	**Restoring physiological AAT protein production**	✓ Total AAT level of ~21 µM observed during acute phase response
Preventing liver damage	**Reducing aggregated Z-AAT in liver**	✓ >60% decrease in circulating Z-AAT ✓ No LNP delivery ✓ No liver enzyme adverse events
Reducing treatment burden	**Convenient, subcutaneous monthly or less frequent dosing**	✓ RNA editing effects sustained at least two months post last dose ✓ Safe and well tolerated

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Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums

WVE-006 is part of strategic collaboration with GSK to develop transformative RNA medicines

Collaboration Highlights

- $170 million upfront
- Additional research funding
- Potential for up to $3.3 billion in milestones
- Leverages 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**
Continuing to advance RestorAATion-2 trial for AATD	GSK has selected **three programs** to advance to development candidates following achievement of target validation	**INHBE (WVE-007) is Wave's first wholly owned** program that emerged from GSK collaboration

Anticipate milestone payments in 2025 and beyond

Unlocking wholly-owned RNA editing pipeline

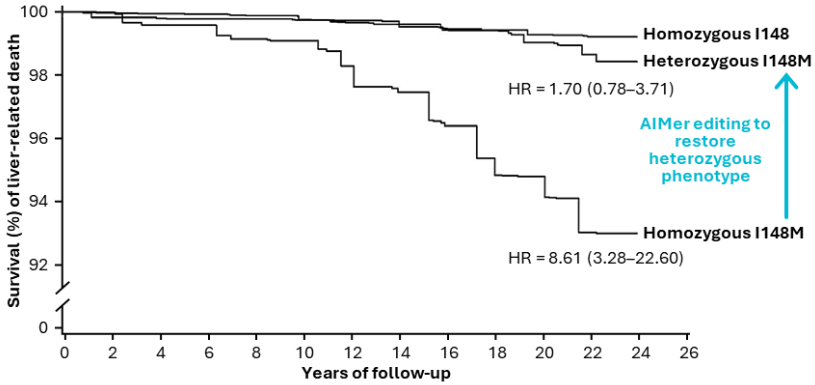
WVE-006: RNA editing capability translating in clinic

- Efficient and consistent RNA editing
- Restore dynamic physiological response
- Durability of effect supporting monthly or less frequent dosing
- Safe and well-tolerated at top dose tested

GalNAc-RNA Editing: PNPLA3

Genetically defined liver disease

Patient population: ~9 million



Expect to share updates from emerging pipeline at Research Day in fall 2025

Unalp-Arida and Ruhl 2020 Hepatology

Anticipated upcoming milestones

siRNA	*RNA editing*		*Splicing*	*Allele-selective silencing*
WVE-007 (INHBE) Obesity	**WVE-006 AATD**	**Wholly owned programs**	**WVE-N531 (Exon 53) DMD**	**WVE-003 (SNP3) HD**
4Q 2025: Deliver data from the expanded Cohort 2 (240 mg) as well as data from Cohort 1 (75mg) **1Q 2026** Deliver data from Cohort 3 (400 mg)	**1Q 2026:** Deliver data from the 400 mg multidose cohort	**2025:** Deliver new preclinical data from hepatic and extra-hepatic RNA editing programs **2026:** Initiate clinical development of additional RNA editing programs	**2026:** Submit NDA to support accelerated approval of WVE-N531 with monthly dosing Submit CTAs for other exon skipping candidates	**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; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; IND: Investigational New Drug

Thank you to the participants, families, clinicians and study site staff who are participating in this study

RESTORAATION

Q&A

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For questions contact:
investorrelations@wavelifesci.com