RNA Editing for the Treatment of Alpha-1 Antitrypsin Deficiency (AATD)

Kenneth R. Chapman, MD, MSc, FRCPC, FACP, FCCP, FERS

Director, Asthma & Airway Centre, University Health Network, Professor of Medicine, University of Toronto

May 18th, 2026

Presented at ATS, 2026

Disclosures

Kenneth R Chapman

Consultations

Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Grifols, InhibRx, Kamada, Merck Frosst, Novartis, Regeneron, Roche, Sanofi, Takeda

Research Grants/Contracts

Amgen, AstraZeneca, Bellus, BMS, CSL Behring, Genentech, GlaxoSmithKline, Grifols, Kamada, Lilly, Novartis, Regeneron, Roche, Sanofi, Takeda

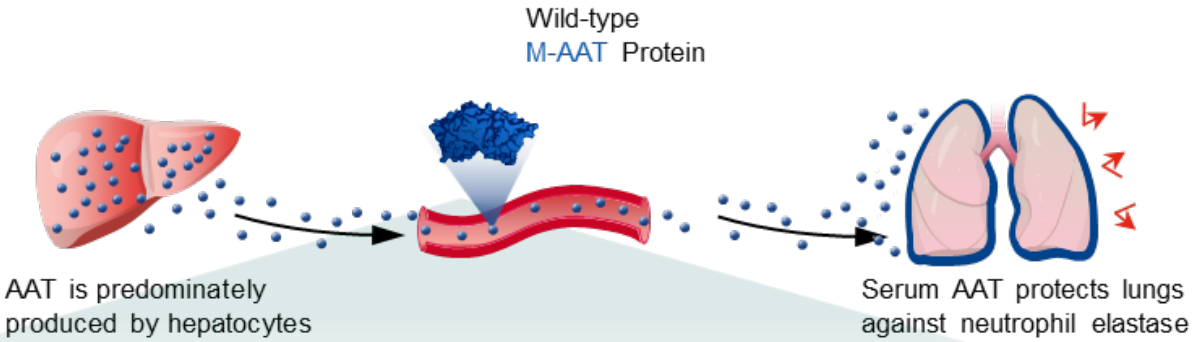
Lectures

AstraZeneca, Boehringer-Ingelheim, Grifols, GlaxoSmithKline, Merck Frosst, Novartis, Regeneron, Sanofi

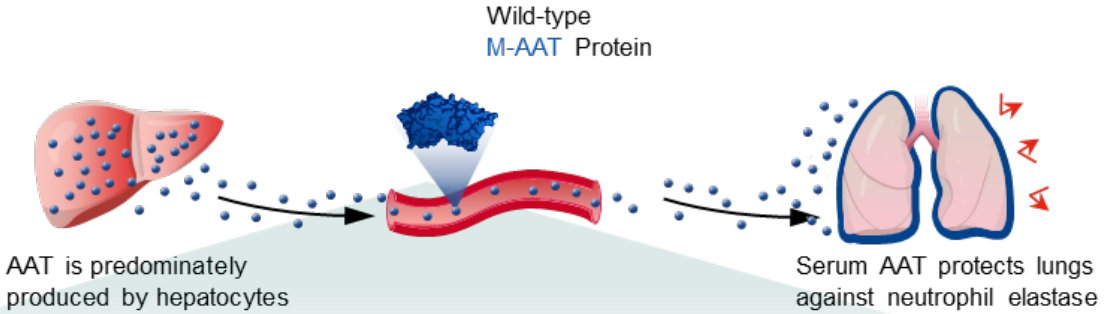
Disclosures

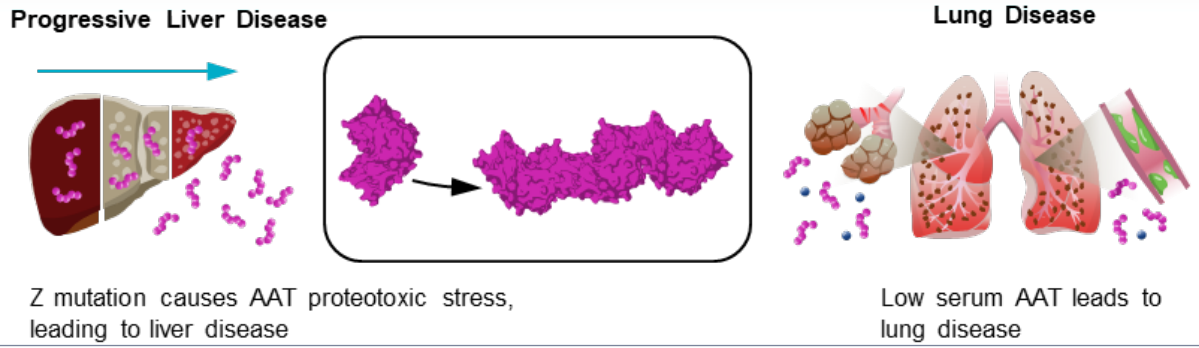
- **Alice M Turner** has received grants and/or honoraria from GSK, Takeda, Vertex, CSL Behring, Grifols, Sanofi, Beam, Tessera, Korrobio, AiRNA
- **Pavel Strnad** has received grants and honoraria from Arrowhead Pharmaceuticals, CSL Behring, Grifols Inc, consulting fees or honoraria from AiRNA Pharmaceuticals, Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, Beam Pharmaceuticals, BioMarin Pharmaceuticals, Dicerna Pharmaceuticals, GSK, Korro Bio, Intellia Pharmaceuticals, Takeda Pharmaceuticals, Tessera Pharmaceuticals, Novo Nordisk and Ono Pharmaceuticals, participating in leadership or fiduciary roles in Alpha1-Deutschland, Alpha1 Global, and material transfer support for AiRNA Pharmaceuticals, BioMarin Pharmaceuticals, Vertex Pharmaceuticals and Dicerna Pharmaceuticals.
- **Matthew Conron** provided no disclosures
- **William Griffiths** has done advisory work for AiRNA
- **Paul Hernandez** has conducted clinical research at his institution funded by: Wave Life Sciences, Grifols, Boehringer Ingelheim, Roche, and Canadian Institutes Health Research; and has participated on advisory boards and/or presented continuing education events funded by AstraZeneca, GSK, Janssen, Merck, Roche, Sanofi, and Takeda.
- **John R Hurst** has received support to attend meetings, research grants, and payment for educational and advisory work (personally and to his institution) from pharmaceutical companies that make medicines to treat respiratory disease including AstraZeneca, Boehringer Ingelheim, Chiesi, GlasxoSmithKline, Regeneron and Sanofi.
- **Heli Yla-Outinen** has received support to attend educational meetings, has been an investigator in clinical trials (SI, PI) and has received payment for advisory work from Grifols; CSI, AstraZeneca, Boehringer-Ingelheim, BMS, Chiesi, GSK, and MDS
- **Employees of Wave Life Sciences** - Varun Goel, Joseph Haegele, Ken Longo, Melinda Louie-Gao, Mark McLaughlin, Prashant Monian, Michael Monine, Padma Naryanan, Shushma Patel, Abu Siddiqui, Andrew Strahs, Chikdu Shivalila, Lanyie Xie, Christopher I Wright, and Cynthia F Caracta

AAT protein which is predominately produced by the liver protects the lung against neutrophil elastase



Pi*ZZ genotype is leading cause of severe AATD, predisposing to progressive lung damage, liver damage or both

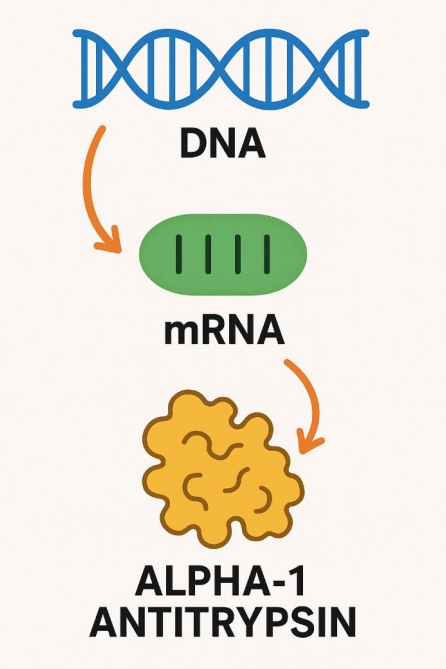




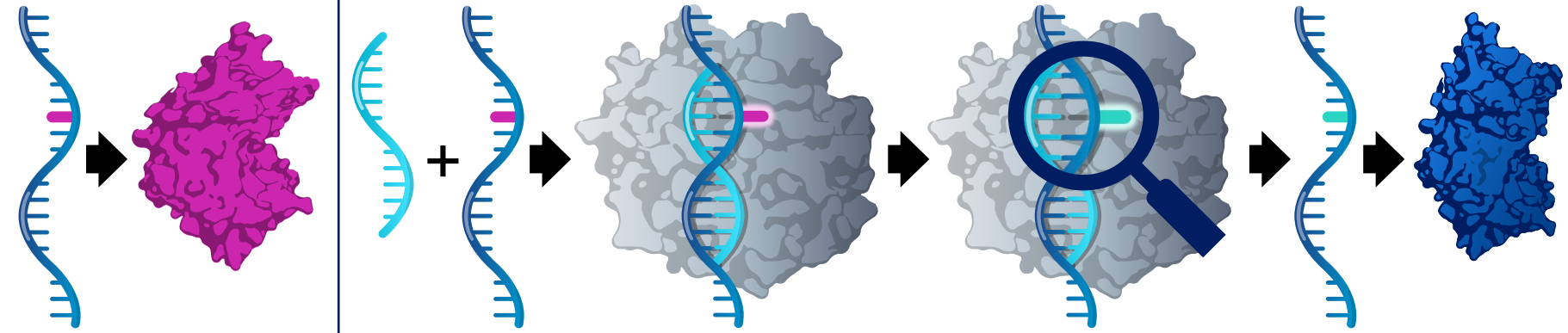
Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 *Alpha-1 Antitrypsin Deficiency* GeneReviews

DNA is transcribed into RNA, which is then translated into the alpha-1 antitrypsin protein

In patients with AATD, correcting the mutant Z-AAT RNA transcript in the liver can restore the normal protein and address both lung and liver manifestations of the disease



Wave Life Sciences has developed RNA editing oligonucleotides that direct efficient and specific editing of mRNA by endogenous ADAR* enzymes



RNA with Z Mutation

Disease-causing Mutant Z-AAT Protein

Wave Compound & RNA with Z Mutation

Wave compound joins with RNA; recognized by ADAR enzyme

ADAR makes single letter change

RNA is edited

Functional, Healthy M-AAT Protein

* Adenosine Deaminase Acting on RNA

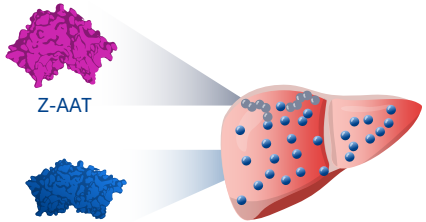
WVE-006 is designed to replace Z-AAT with M-AAT, addressing both lung and liver manifestations of AATD

RNA editing approach is designed to release M-AAT in the blood, potentially protecting the lungs and reducing the risk of disease in humans

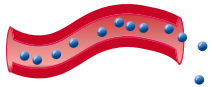
1) Reduce Z-AAT protein trapped in the liver

2) Release M-AAT in blood

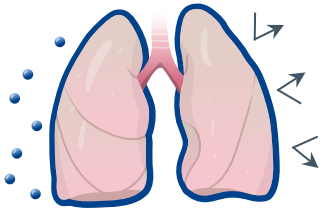
3) Restore functional, healthy M-AAT in lungs



Wild-type M-AAT protein replaces misfolded Z-AAT



M-AAT in bloodstream



M-AAT reaches lungs to protect against enzymes that breakdown tissue

First ever RNA editing therapeutic in humans

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.

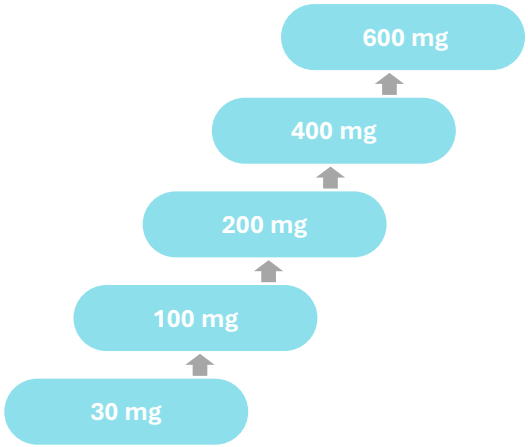
RestorAATion-2

RestorAATion-2 clinical trial in Pi*ZZ patients ongoing

RESTORAATION

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

SAD → MAD Multi-dosing complete



SAD Cohort 3
600 mg → **MAD Cohort 3**
600 mg; Q4W

SAD Cohort 2
400 mg → **MAD Cohort 2**
400 mg; Q4W

SAD Cohort 1
200 mg → **MAD Cohort 1**
200 mg Q2W

Study key objectives		
Safety and tolerability	Pharmacokinetics	Serum M-AAT levels

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

Baseline participant characteristics were similar across first two cohorts

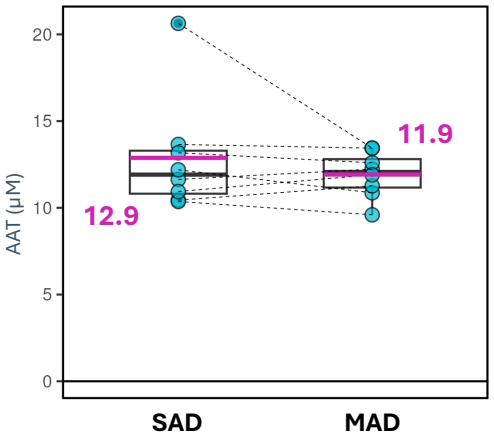
Key Inclusion Criteria

- 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

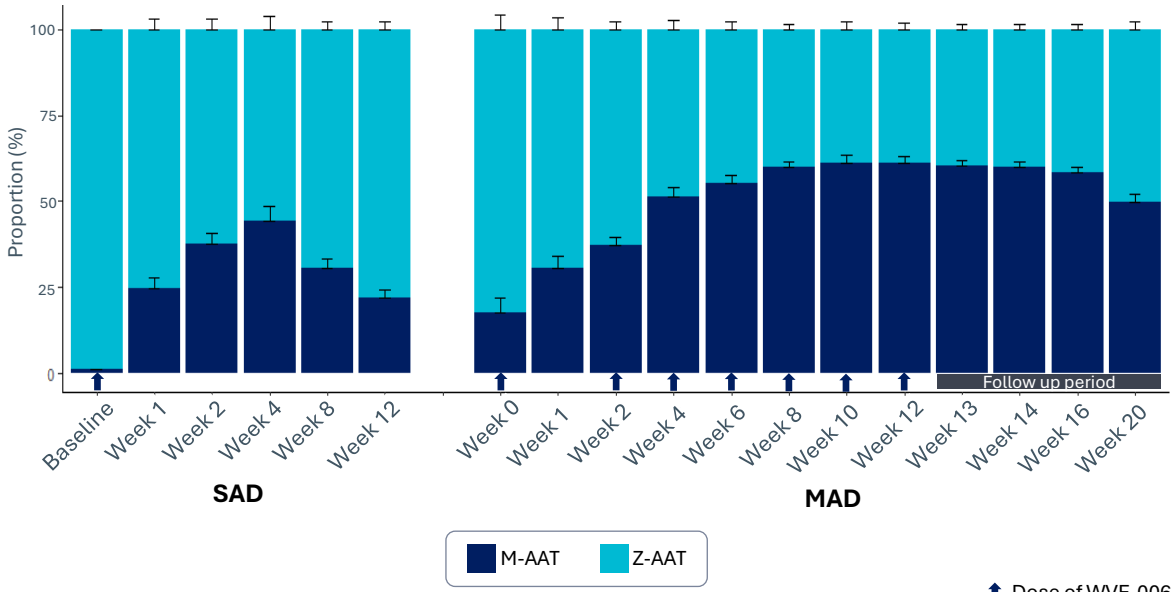
RestorAATion-2 Baseline Participant Characteristics	WVE-006 200 mg N=8	WVE-006 400 mg N=8
Age at consent (years) (mean (SD))	51.4 (12.0)	49.4 (18.1)
Gender, N Male Female	8 2 (25.0) 6 (75.0)	8 4 (50.0) 4 (50.0)
Weight (kg), Median (min, max)	79.7 (64.8,100.0)	82.0 (65.6, 97.5)
Years since AATD diagnosis (mean)	15.9	16.2
Baseline Day 1 FEV1 (mean (L) (min, max)) Baseline Day 1 ppFEV1 (mean (%) (min, max))	3.2 (2.2, 5.8) 94.3 (78, 120)	2.9 (1.3, 5.1) 79.9 (51, 104)
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)

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



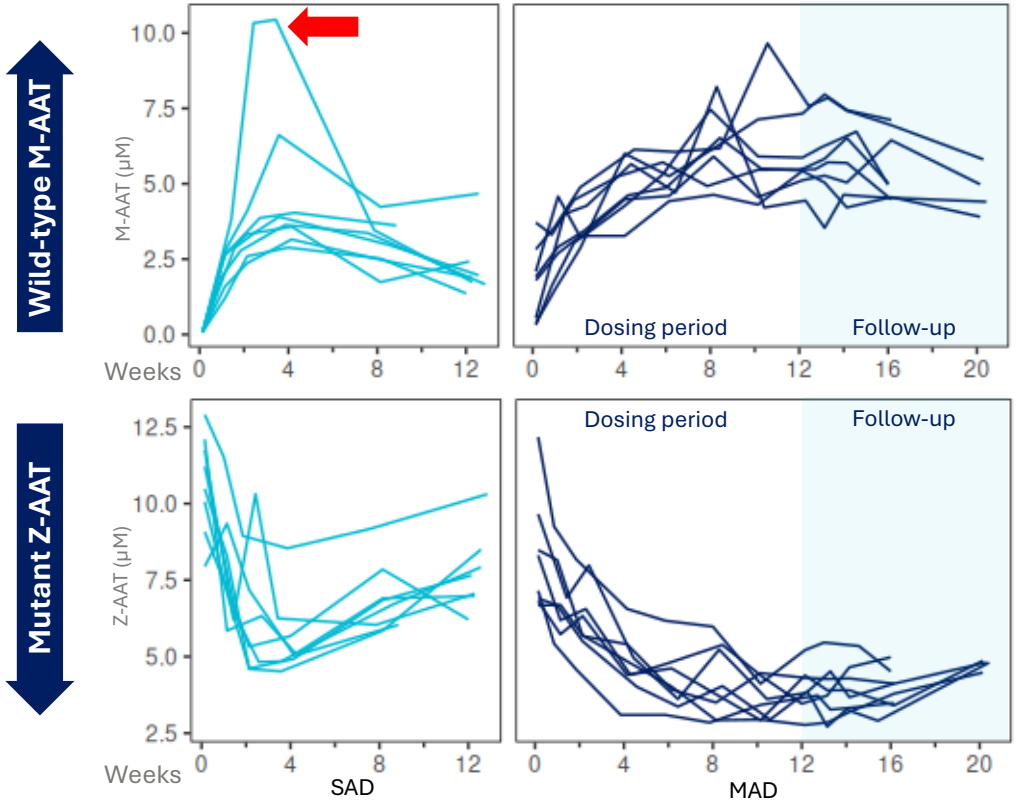
Proportion of circulating serum wild-type M-AAT and mutant Z-AAT protein

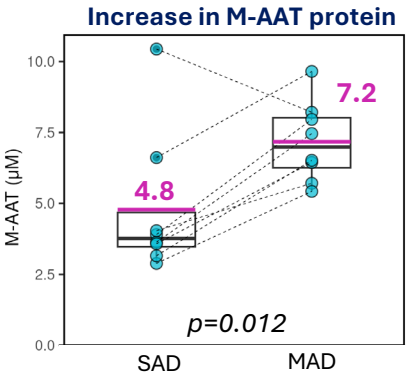


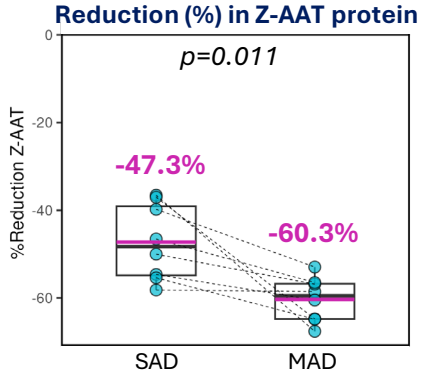
Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums

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





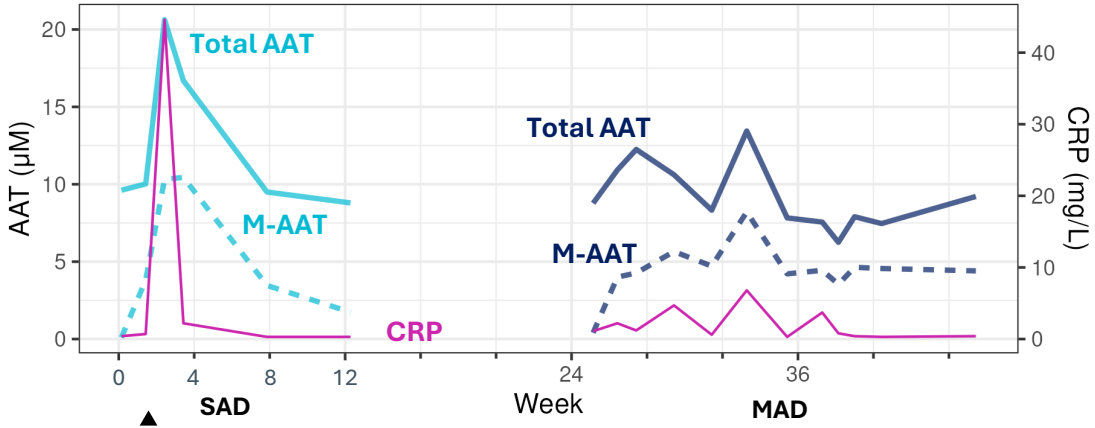


Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean participant SAD and MAD maximums
Right: black line represents median

Restoration of 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



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

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

400 mg monthly dosing complete with potential for an infrequent dosing regimen

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 monthly dosing complete

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

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

Summary: Ongoing RestorAATion-2 clinical trial of WVE-006 for alpha-1 antitrypsin deficiency (AATD)

Achieved durable production of serum AAT at levels 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 — **Therapeutically restored physiological serum AAT production in a Pi*ZZ individual during a non-drug related acute phase response**

400 mg monthly dosing complete with potential for an infrequent dosing regimen

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

Pi*ZZ genotype is leading cause of severe AATD, predisposing to progressive lung damage, liver damage or both

Correcting the mutant Z-AAT RNA transcript in the liver restores and addresses the normal protein and which will address both lung and liver manifestations of the disease

WVE-006, the first-ever RNA editing therapeutic in humans, is designed to be a durable and convenient therapy for AATD, which reduces Z-AAT aggregation in the liver, restores functional M-AAT in the lungs and restores endogenous production of AAT during an acute phase response

Interim data from ongoing **RestorAATion-2** study support the continued development of WVE-006 in the treatment of AATD

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

Thank you