RNA Editing for the Treatment of Alpha-1 Antitrypsin Deficiency (AATD): Interim Results From RestorAATion-2

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Disclosures

Prof. Dr. Pavel Strnad has received grants and honoraria from Arrowhead Pharmaceuticals, CSL Behring, and Grifols Inc; has received consulting fees and honoraria from AiRNA Pharmaceuticals, Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, Beam Therapeutics Inc., BioMarin Pharmaceutical Inc., Dicerna Pharmaceuticals, GSK, Korro Bio, Intellia Pharmaceuticals, Takeda Pharmaceuticals, Tessera Pharmaceuticals, Novo Nordisk, and Ono Pharmaceuticals; reports leadership or fiduciary roles with Alpha1-Deutschland and Alpha1 Global; and has received material transfer support from AiRNA Pharmaceuticals, BioMarin Pharmaceutical Inc., Vertex Pharmaceuticals, and Dicerna Pharmaceuticals.

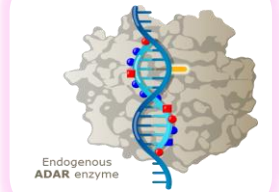
From Silencing to Repair, RNA Editing Uses the Proven GalNAc-Based Specific Delivery Into Hepatocytes

Translating genetic insights into potentially best-in-class medicines

RNA editing – New treatment modality in humans

- Industry-leading A-to-I RNA-editing oligonucleotides (AIMers) enable access to areas of disease biology that are inaccessible for other therapeutic modalities
- There is no risk of permanent bystander edits, indels, and off-target edits (including cancer-associated genes), which have been connected to DNA editing

RNA base editing



WAVE clinical development programs

WVE-006 (AATD liver and lung disease)
WVE-008 (PNPLA3 liver disease)

- Address root cause of mutant protein production and restore functional protein production

1. Packer M, et al. (2024) Available from: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024259364. Last accessed 21 October 2026.

AATD, alpha-1 antitrypsin deficiency; ADAR, adenosine deaminase acting on RNA; DNA, deoxyribonucleic acid; GalNAc, N-acetylgalactosamine; PNPLA3, patatin-like phospholipase domain-containing protein 3; RNA, ribonucleic acid.

Alpha-1 Antitrypsin Deficiency: Two Pathologies, One Disease

The Pi*ZZ genotype is the leading cause of severe AATD, predisposing individuals to progressive liver disease, lung disease, or both[1,2]

The liver

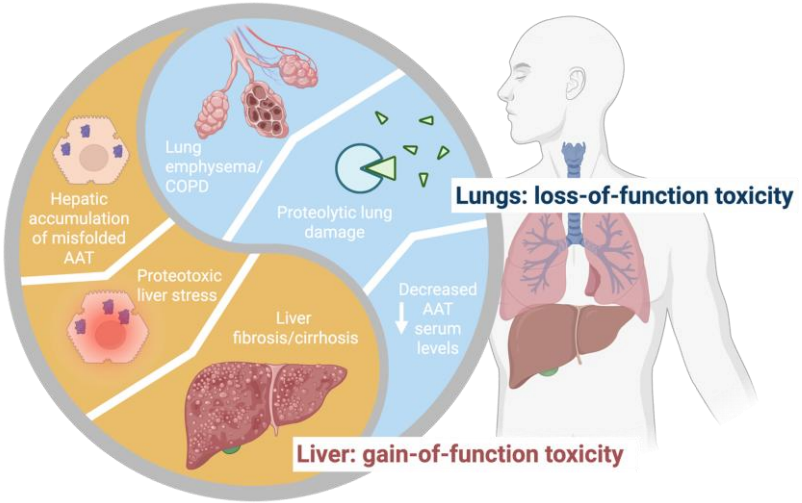
- Z mutation leads to misfolding and aggregation of the mutant Z-AAT protein in the liver, creating proteotoxic stress, which may lead to progressive liver injury and culminate in end-stage liver disease.

The serum

- Z mutation also results in a decreased release of protective AAT, leading to a diminished serum AAT level and inability to upregulate AAT production in response to stress.

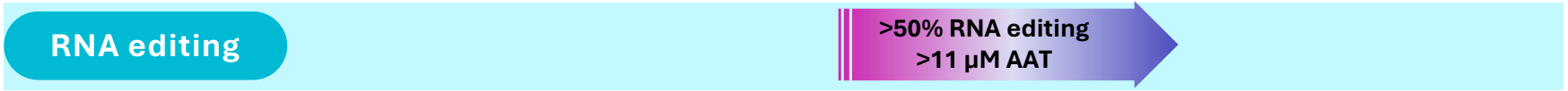
The lungs

- Decreased Z-AAT function and serum AAT levels leave the lung tissue vulnerable to protease-induced damage (e.g., by neutrophil elastase).



1. Strnad P, et al. *N Engl J Med*. 2020;382:1443-1455; 2. Stoller JK, et al. Alpha-1 antitrypsin deficiency. GeneReviews.1993. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK1519/.
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; Pi*ZZ, protease inhibitor ZZ.

RNA Editing Aims to Increase M-AAT and Restore Physiological AAT Production

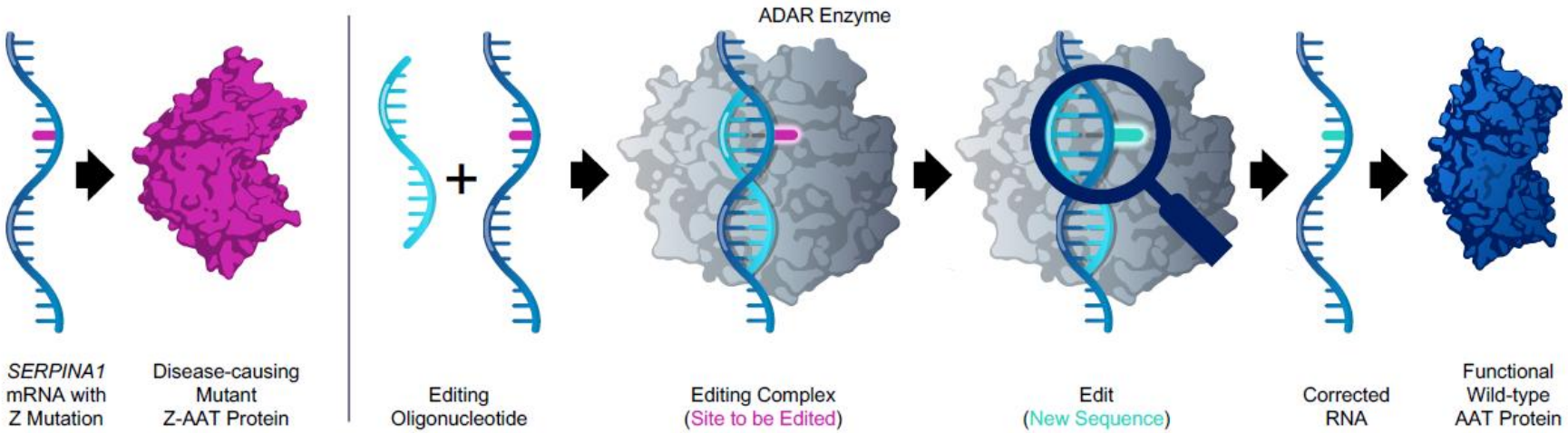


Genotype	Null	Pi*ZZ	Pi*MZ	Pi*MM
	No AAT protein	100% Z-AAT	Z-AAT and M-AAT	100% M-AAT
AAT level increases during acute phase response	No	No	Yes	Yes
Risk of liver disease	None	High	Low	Normal
Risk of lung disease	Very high	High	Low	Normal

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

AAT, alpha-1 antitrypsin; Pi*MM, protease inhibitor MM; Pi*MZ, protease inhibitor MZ; Pi*ZZ, protease inhibitor ZZ; RNA, ribonucleic acid.

Wave Life Sciences has Developed RNA-Editing Oligonucleotides that Direct Efficient and Specific Editing of mRNA by Endogenous ADAR Enzymes[1,2]



WVE-006, the first RNA-editing therapeutic in humans, is designed to replace Z-AAT with M-AAT, addressing both lung and liver manifestations of AATD

1. Strnad P, et al. *N Engl J Med*. 2020;382:1443-1455; 2. Monian P, et al. *Nat Biotechnol*. 2022;40:1093-1102.
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ADAR, adenosine deaminase acting on RNA; mRNA, messenger RNA; RNA, ribonucleic acid.

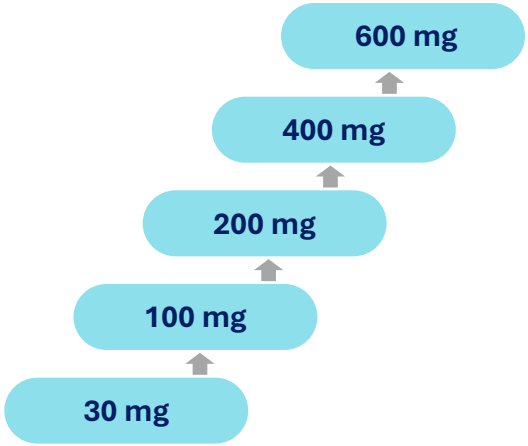
RestorAATion-2

RestorAATion-2: Ongoing Clinical Trial in Individuals with the Pi*ZZ Genotype

RESTORAATION

RestorAATion-1: Healthy volunteers → **RestorAATion-2: Individuals with AATD**

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

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; MAD, multiple-ascending dose; Pi*ZZ, protease inhibitor ZZ; Q2W, every 2 weeks; Q4W, every 4 weeks; SAD, single-ascending dose.

RestorAATion-2: Baseline Participant Characteristics were Similar Across all Cohorts

Key inclusion criteria

- Pi*ZZ genotype
- 18 to 70 years of age
- Stable mild AATD-induced liver disease and/or healthy or mild-to-moderate AATD-associated lung 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	WVE-006 600 mg N=8
Age at consent (years), mean (SD)	51.4 (12.0)	49.4 (18.1)	51.3 (15.5)
Gender, n (%) Male Female	 2 (25.0) 6 (75.0)	 4 (50.0) 4 (50.0)	 6 (75.0) 2 (25.0)
Weight (kg), median (min, max)	79.6 (64.8, 100.0)	84.0 (65.6, 97.5)	78.5 (64.4, 96.5)
Years since AATD diagnosis, mean	15.9	16.2	10.9
Baseline day 1 FEV_1 (L), mean (min, max)	3.2 (2.2, 5.8)	2.9 (1.3, 5.1)	3.6 (2.4, 5.0)
Baseline liver elastography (F0-2 score; N (%) of participants)	F0: 8 (100.0)	F0: 5 (62.5) F1: 2 (25.0) F2: 1 (12.5)	F0: 5 (62.5) F1: 2 (25.0) F2: 1 (12.5)

AATD, alpha-1 antitrypsin deficiency; FEV_1, forced expiratory volume in 1 second; Pi*ZZ, protease inhibitor ZZ; SD, standard deviation.

RestorAATion-2: WVE-006 Continues to be Safe and Well Tolerated

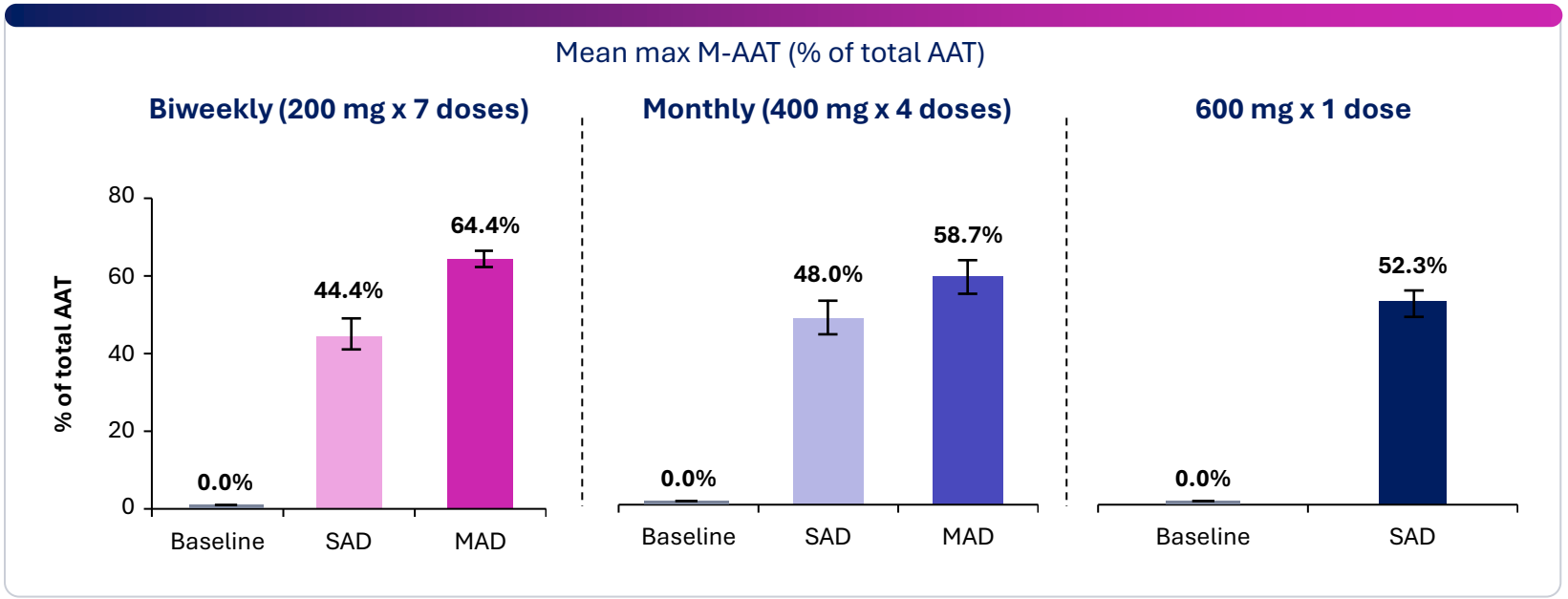
TEAE Category	200 mg SAD N=8 n (%)	200 mg MAD N=8 n (%)	400 mg SAD N=8 n (%)	400 mg MAD N=8 n (%)	600 mg SAD N=8 n (%)
Any TEAE	6 (75.0)	6 (75.0)	7 (87.5)	7 (77.8)	8 (100.0)
Mild	2 (25.0)	0	1 (12.5)	3 (33.3)	6 (75.0)
Moderate	4 (50.0)	6 (75.0)	6 (75.0)	4 (44.4)	2 (25.0)
Severe	0	0	0	0	0
Any drug-related TEAE	1 (12.5)	3 (37.5)	2 (25.0)	5 (55.6)	5 (62.5)
Mild	1 (12.5)	3 (37.5)	0	2 (22.2)	4 (50.0)
Moderate	0	0	2 (25.0)	3 (33.3)	1 (12.5)
Severe	0	0	0	0	0
Any serious TEAE	0	0	0	0	0
Any TEAE leading to discontinuation	0	0	1 (12.5)	0	0
Any TEAE leading to death	0	0	0	0	0

- No SAEs; all TEAEs were mild to moderate in severity
- No treatment-related, clinically relevant changes in labs[†], ECG, or vital signs

[†]Including liver function tests; TEAE data as of April 3, 2026.
ECG, electrocardiogram; MAD, multiple-ascending dose; SAD, single-ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Restored Wild-Type M-AAT Protein (Up to 64% of Total Circulating AAT) Consistent with Target Engagement and Hepatocyte RNA Editing

SAD and MAD cohorts:
M-AAT restoration (SAD) and similar M-AAT% with an extended dosing interval (MAD)

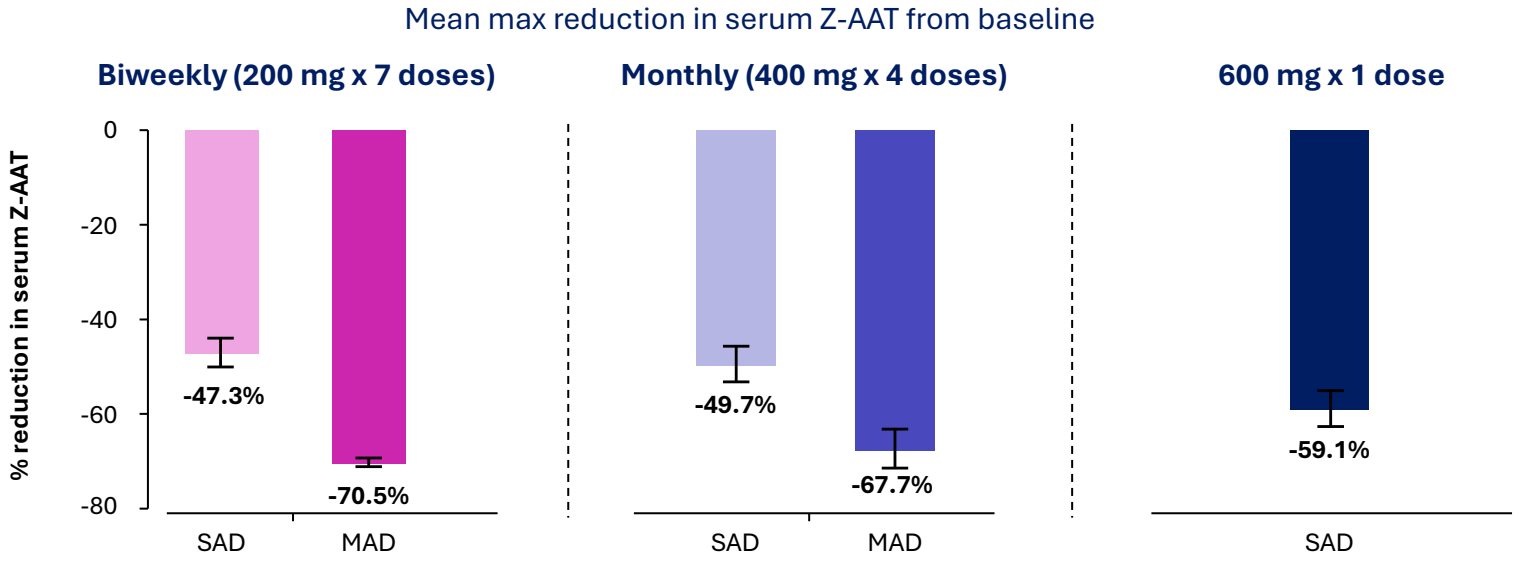


At baseline, serum M-AAT values were below the LLOQ (0.096 µM); the LLOQ value was used for baseline calculations. Error bars represent the standard error of the mean.
AAT, alpha-1 antitrypsin; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; SAD, single-ascending dose.

Up to 71% Reduction in Circulating Mutant Z-AAT, Supporting Potential Improvement in Liver Health

SAD and MAD cohorts:

Z-AAT reductions (SAD) and similar reductions with an extended dosing interval (MAD)

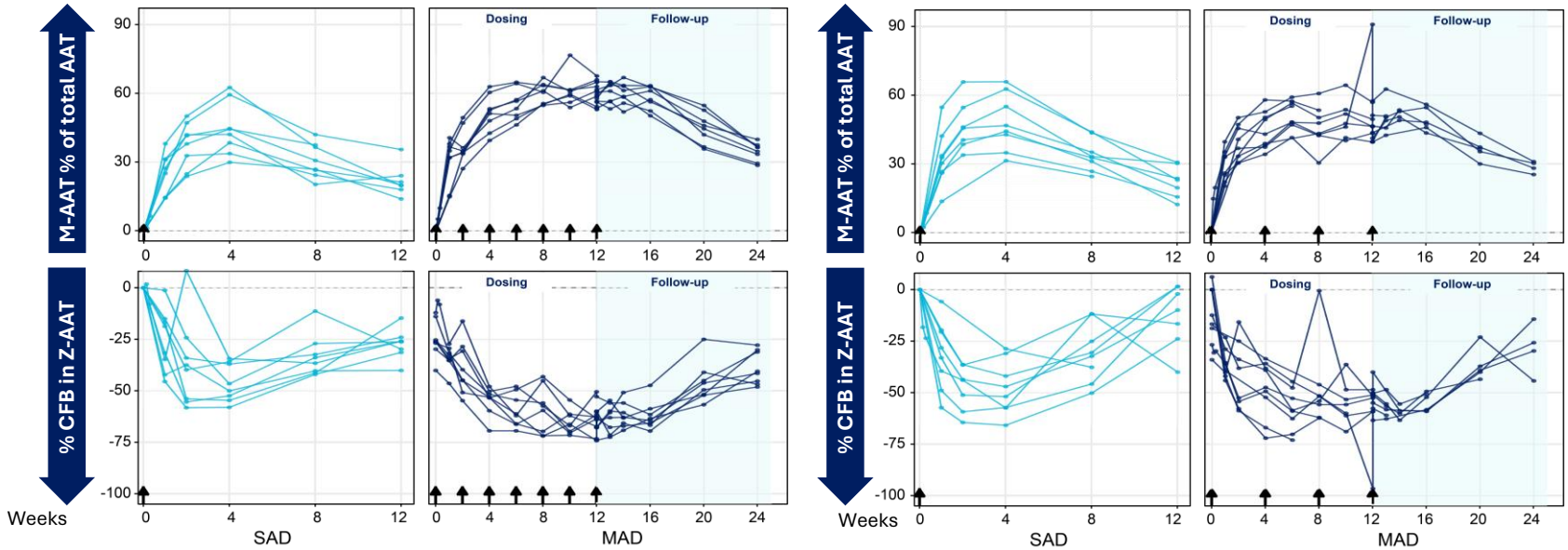


Error bars represent the standard error of the mean.
AAT, alpha-1 antitrypsin; MAD, multiple-ascending dose; SAD, single-ascending dose.

Therapeutically Relevant Levels of Total AAT Protein with Durable Editing - Sustained RNA Editing for at least 3 months post last dose

200 mg Cohort: Single and Biweekly Doses

400 mg Cohort: Single and Monthly Doses



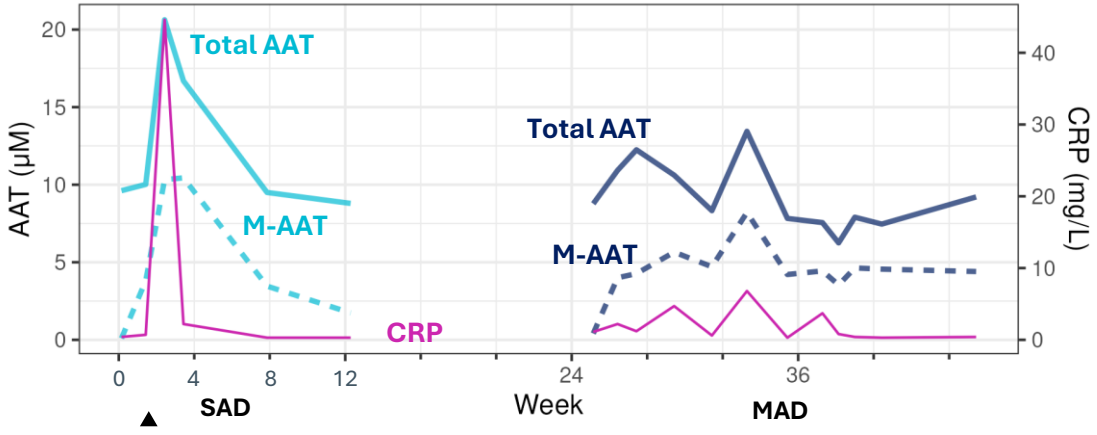
Total ATT levels of 12µM and 14µM in the 200 mg and 400 mg MAD cohorts, respectively

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. %CFB: percent change from baseline.
Arrows indicate scheduled dose administration times of WVE-006; Circulating serum total AAT reported as mean (maximum)
AAT, alpha-1 antitrypsin; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MAD, multiple-ascending dose; RNA, ribonucleic acid; SAD, single-ascending dose.

Dynamic Restoration of Physiological AAT Production During the Acute Phase Response

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

Total AAT reached 20.6 µM at 2 weeks after a single 200 mg dose during acute phase response



▲ Acute phase response due to a kidney stone

CRP levels are correlated with AAT elevations across RestorAATion-2

- Two additional acute phase responses (URTI: common cold), accompanied by a 57.8% and 59.8% increase in AAT from pre-event[†]
- CRP increases are strongly correlated with AAT increases (r=0.73; $p<0.001$; n=19)[‡,#]

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

[†]The most recent non-missing assessment obtained prior to the first observation where CRP exceeded the ULN; [‡] Pearson correlation of log-transformed fold changes from pre-event ($p<0.001$); [#]N=19; defined as transitions from normal (≤ULN) to elevated (>ULN) CRP. Circulating M-AAT, Z-AAT, and total (M + Z) AAT serum protein levels were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: M, 0.096 µM; Z, 0.029 µM) and are reported as mean (maximum) values across participants in the SAD and MAD cohorts. AAT, alpha-1 antitrypsin; CRP, C-reactive protein; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; Pi*MZ, protease inhibitor MZ; Pi*ZZ, protease inhibitor ZZ; SAD, single-ascending dose; ULN, upper limit of normal; URTI, upper respiratory tract infection.

WVE-006 is a Potential First-in-Class, Convenient Therapy for AATD that Addresses Both Liver and Lung Manifestations of the Disease

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

Correcting the mutant Z-AAT RNA transcript in the liver restores normal protein production, addressing **both liver AND lung 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 AAT production** during an acute phase response

WVE-006 was generally **well tolerated**; all adverse events were **mild to moderate**, with **no serious adverse events** or **liver toxicities** reported to date

Interim data from the ongoing **RestorAATion-2** study support the continued development of WVE-006 as a **robust, durable RNA-editing therapy** for individuals with AATD

1. Strnad P, et al. *N Engl J Med*. 2020;382:1443-1455; 2. Blanco I, et al. *Int J Chron Obstruct Pulmon Dis*. 2017;12:561-569.
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; Pi*ZZ, protease inhibitor ZZ; RNA, ribonucleic acid.

Thank you