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

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KEY TAKEAWAYS

- Administration of WVE-006, an investigational *N*-Acetylgalactosamine (GalNAc)-conjugated RNA editing oligonucleotide, in individuals with AATD (Pi*ZZ genotype), resulted in production of wild-type M-AAT protein, lowering of Z-AAT protein, and dynamic endogenous upregulation of AAT protein in individuals during stress (acute phase response).
- WVE-006 was generally well tolerated; all adverse events were mild to moderate, with no serious adverse events.
- These data support the ability of WVE-006 to provide robust, durable RNA editing therapy to potentially treat the root cause of both clinical lung and liver manifestations of AATD.

INTRODUCTION

- Wave Life Sciences has developed RNA editing oligonucleotides that direct efficient and specific A-to-I RNA editing of mRNA by endogenous ADAR (adenosine deaminase acting on RNA) enzymes (**Figure 1**).[2]

Figure 1. Introduction to RNA editing

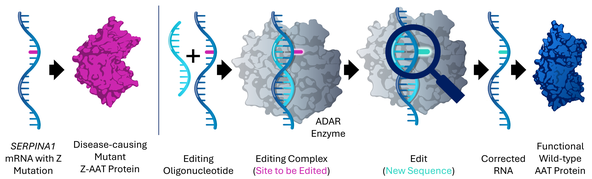
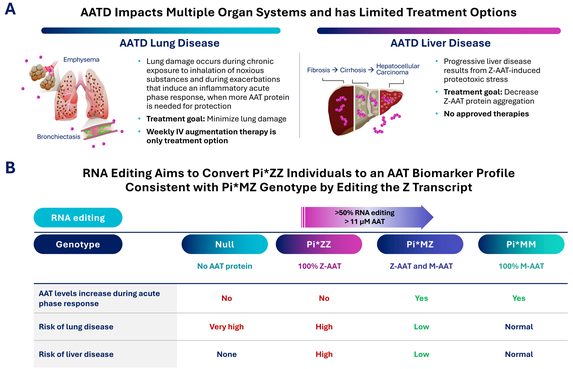
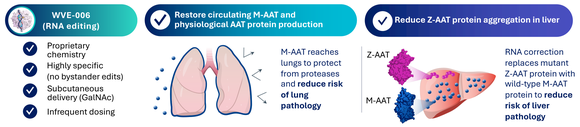


Figure 2. RNA editing is uniquely suited to address both lung and liver disease in AATD and restore dynamic regulation of AAT protein



- AATD, commonly caused by homozygous mutations in the SERPINA1 gene (Pi*ZZ), causes both lung and liver disease. The Z mutation leads to misfolding and aggregation of mutant Z-AAT protein in the liver, which may lead to progressive liver injury and culminate in end-stage liver disease.[2] The Z mutation also results in decreased circulating functional M-ATT and serum AAT levels, leaving lung tissue vulnerable to protease-induced damage (e.g., by neutrophil elastase) (**Figure 2A**).[2]
- There are no approved approaches to address AATD-associated liver disease. Current standard of care, weekly IV augmentation, addresses lung manifestations only (**Figure 2A**).
- Because AAT is an acute-phase response protein that is dynamically regulated,[2] retaining endogenous control over its expression may be an advantage. Heterozygous Pi*MZ individuals retain dynamic regulation of AAT lowering risk of lung and liver disease.

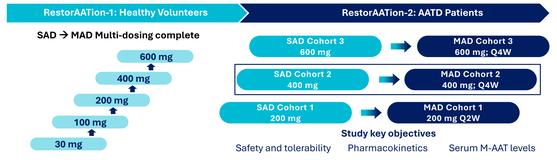
Figure 3. WVE-006: Potential first-in-class, convenient therapy for AATD that addresses both lung and liver manifestations of the disease



- RNA editing is uniquely suited to address unmet need in AATD. After correction of the Z mutation at the RNA level in hepatocytes, M-AAT protein is expected to replace Z-AAT protein, alleviating protein aggregation in the liver and its associated pathology. Secretion of M-AAT protein in serum will help protect the lungs from protease-induced damage (**Figure 3**).

RESULTS

Figure 4. The RestorAATion-1 (NCT06186492) and RestorAATion-2 clinical trials (NCT06405633)



HV: healthy volunteer; SAD: single-ascending dose; MAD: multiple ascending dose.

- In December 2023, Wave initiated the RestorAATion clinical program, which includes a healthy volunteer study (RestorAATion-1) and a phase 1b/2a study in individuals with a ZZ genotype (**Figure 4**).[3]
- RestorAATion-1 (NCT06186492) is complete.
- RestorAATion-2 (NCT06405633) is an ongoing phase 1b/2a clinical trial evaluating the safety, tolerability, pharmacodynamics, and pharmacokinetics of single- and multiple-ascending doses of WVE-006 (200, 400, 600 mg; n=8-9 per cohort) in individuals with a ZZ genotype.
- Participants receive a single subcutaneous dose of WVE-006 with a 12-week observation period, followed by biweekly (200 mg) or monthly doses (400, 600 mg) for 12 weeks, with a subsequent 12-week observation period.
- Serum levels of M-AAT, Z-AAT and total (M + Z) AAT were measured by LC-MS/MS assays, while functional AAT levels were assessed by a neutrophil elastase inhibition assay.

Table 1. RestorAATion-2 key inclusion criteria and baseline participant characteristics

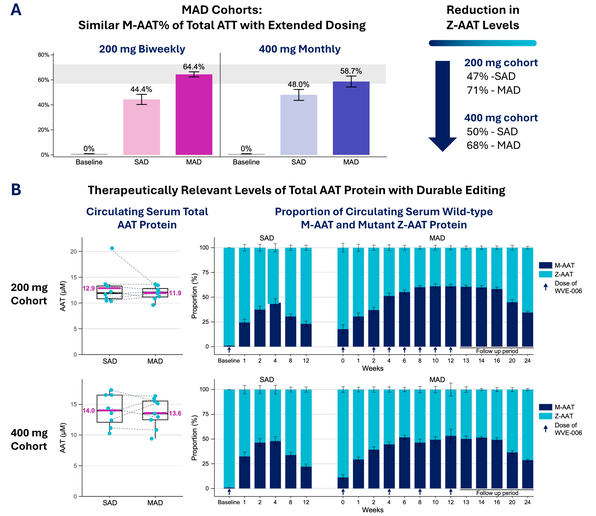
Key Inclusion Criteria

- Pi*ZZ genotype
- 18 to 70 years of age
- Healthy or mild to moderate AATD-associated 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)	84.1 (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)

- Baseline participant characteristics were similar across the first two cohorts of RestorAATion-2 (**Table 1**).

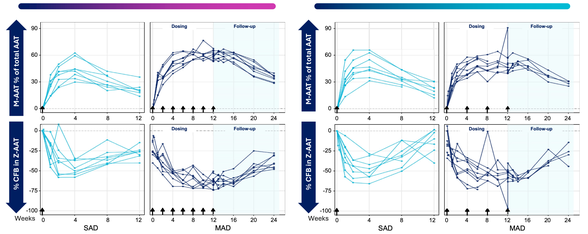
Figure 5. WVE-006 generated circulating wild-type M-AAT up to 64% of total AAT and decreased Z-AAT



A. Circulating M-AAT protein in the serum was measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM) Error bars represent the standard error of the mean (SE). B. 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.

- Single doses of 200 and 400 mg produced serum M-AAT levels of 44% and 48% of total serum AAT (**Figure 5A**).
- In the 200 and 400 mg multiple dose cohorts, editing was durable with serum M-AAT reaching 64% and 59% of total serum AAT (12 µM and 14 µM), respectively (**Figures 5A, B**).
- Therapeutically relevant reductions in Z-AAT protein were also seen in both 200 and 400 mg cohorts, 47% and 50% (SAD) and 71% and 68% (MAD), respectively.

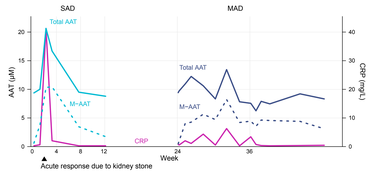
Figure 6. Consistent and durable generation of M-AAT and reductions of Z-AAT



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. %CFB: percent change from baseline. Arrows indicate scheduled dose administration times of WVE-006.

- RNA editing sustained out to at least three months post last dose supports monthly dosing (**Figure 6**).

Figure 7. WVE-006 demonstrated dynamic increases of AAT during acute phase responses



CRP Levels are Correlated with AAT Elevations Across RestorAATion-2

- Two additional acute phase responses (URI-common cold) accompanied by 57.8% and 59.8% increases in AAT from pre-event*
- CRP increases are strongly correlated with AAT increases ($r=0.73$, $p<0.001$, $n=19$) †,‡

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. CRP: C-reactive protein; URI: upper respiratory infection. *The most recent non-missing assessment obtained prior to the first observation where CRP exceeded the upper limit of normal (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.

- Following WVE-006 200 mg single dose, total AAT and M-AAT increased significantly in one patient during an acute phase response, with total AAT reaching 20.6 µM (**Figure 7**).
- Two additional acute phase responses (URI-common cold) in the 400 mg MAD cohort resulted in 58% and 60% increases in AAT from pre-event.
- Based on published data[4] on CRP levels and AAT levels across different *SERPINA1* genotypes, the AAT response in the Pi*ZZ participant treated with WVE-006 mirrors the Pi*MZ phenotype.

Table 2. WVE-006 has been generally safe and well-tolerated to date

TEAE Category	200 mg SAD N=8 | n (%)	200 mg MAD N=8 | n (%)	400 mg SAD N=8 | n (%)	400 mg MAD N=9 | 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

TEAE data as of April 3rd, 2026. SAD: single ascending dose; MAD: multiple ascending dose.

- WVE-006 continues to be generally safe and well tolerated (**Table 2**). There were no SAEs, discontinuations or withdrawals due to TEAEs. All TEAEs were mild to moderate in severity. There were no treatment-related, clinically relevant changes in labs, ECG, or vital signs.

CONCLUSION

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 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.

References: 1.Monian, et al., 2022. *Nat Biotechnol* doi: 10.1038/s41587-022-01225-14; 2. Strnad, et al., 2020 *New Engl J Med* doi: 10.1056/ NEJMra1910234; 3. https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-initiation-dosing-restoration; 4. Sanders, et al., 2018. *J COPD* doi: 10.1080/15412555.2017.1401600. **Acknowledgments:** Dr. Chapman is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Grifols, InhibRx, Kamada, Merck Frosst, Novartis, Regeneron, Roche, Sanofi, and Takeda, has research grants/contracts with Amgen, AstraZeneca, Bellus, BMS, CSL Behring, Genentech, GlaxoSmithKline, Grifols, Kamada, Lilly, Novartis, Regeneron, Roche, Sanofi, and Takeda, and has lectured for AstraZeneca, Boehringer-Ingelheim, Grifols, GlaxoSmithKline, Merck Frosst, Novartis, and Regene. The authors are grateful to Jill Slater (Wave Life Sciences) for editorial support and Eric Smith for graphical support. This work was funded by Wave Life Sciences.