First-in-human in vivo gene editing for severe alpha-1 antitrypsin deficiency (AATD): initial data from the Phase 1/2 study of BEAM-302

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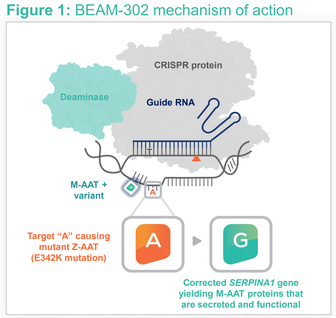
Introduction

- Alpha-1 antitrypsin deficiency (AATD) is a genetic disease caused by *SERPINA1* mutations, leading to lung and liver disease[1,2]
- Genotype is the primary determinant of AATD disease risk and manifestations; individuals with the PiZZ genotype are at the highest risk[2,3]
- There remains an unmet need due to a lack of disease-modifying therapies[4]
- BEAM-302: potential first-in-class and first-in-human investigational in vivo base-editing therapy that corrects an AATD disease-causing mutation (**Figure 1**)[5]
  - Targets liver via a lipid nanoparticle (LNP) to correct PiZ mutation, restoring AAT function by producing M-AAT while reducing mutant Z-AAT
  - Designed to treat the root cause of disease, impacting both lung and liver disease manifestations

Figure 1: BEAM-302 mechanism of action



A, adenine; CRISPR, clustered regularly interspaced short palindromic repeats; G, guanine; RNA, ribonucleic acid

Methods and study progress

- As of August 25, 2026, the BEAM-302 investigational Phase 1/2 clinical study enrolled 38 patients with both AATD-associated lung and liver disease in Part A and Part B
- **Herein, as of the June 24, 2026, data cut, results are reported for 29 patients: n=21 in Part A and n=8 in Part B (Figure 2); safety results include all 29 patients, and efficacy results include 17 patients from Part A and Part B 30 and 60 mg cohorts**

Figure 2: BEAM-302 clinical study design

Key eligibility criteria

- 18–70 years of age; homozygous for Z mutation; FEV_1 ≥40% (Phase 1) or ≥35% (Phase 2) of predicted
- Blood AAT level <11 µM and clinical diagnosis of emphysema; no evidence of liver disease (**Part A only**)
- Clinical diagnosis of AATD-related liver disease along with evidence of METAVIR F1, F2, or F3 liver fibrosis (**Part B only**)

PART A: AATD-associated lung disease				PART B: AATD-associated liver disease with or without lung disease	
Phase 1 15 mg N=3	*Phase 1* 30 mg N=3	*Phase 1* 60 mg N=6	*Phase 1* 75 mg N=9	*Phase 1* 30 mg N=3	*Phase 1* 60 mg N=5

Key endpoints

- Rates of TEAEs and serious TEAEs
- Blood levels of total AAT, Z-AAT and M-AAT, and functional AAT
- Blood HNE activity and Z-polymer levels

See NCT06389877. ClinicalTrials.gov for full study design
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; FEV_1, forced expiratory volume in 1 second; HNE, human neutrophil elastase; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis scoring system; TEAE, treatment-emergent adverse event

Disclosure

J.H. served as an investigator in this study and declares no other conflicts of interest related to the study, the sponsor, or alpha-1 antitrypsin deficiency

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Acknowledgments

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Results

Patient disposition and baseline characteristics

- Median exposure follow-up was 15.0 (6.9–24.2) months and 6.2 (1.0–10.2) months, in pooled **Part A** and pooled **Part B** cohorts, respectively
- Baseline characteristics were largely comparable across cohorts; as expected, **Part A** patients had evidence of reduced lung function as measured by FEV_1 and **Part B** patients had increased liver stiffness as measured by FibroScan (**Table 1**)

Table 1: Demographics and clinical characteristics

	Part A (N=21)				Part B* (N=8)	
	15 mg (N = 3)	30 mg (N = 3)	60 mg (N = 6)	75 mg (N = 9)	30 mg (N = 3)	60mg (N = 5)
Age (year), mean (SD) *min, max*	46.3 (8.3) *37, 53*	57.3 (4.0) *53, 61*	50.7 (8.9) *38, 62*	57.6 (5.5) *51, 64*	51.7 (15.0) *35, 64*	54.8 (10.9) *40, 69*
Sex, *n* (%)						
Male	2 (66.7)	2 (66.7)	5 (83.3)	6 (66.7)	2 (66.7)	3 (60.0)
Female	1 (33.3)	1 (33.3)	1 (16.7)	3 (33.3)	1 (33.3)	2 (40.0)
Race, *n* (%)						
White, Not Hispanic	3 (100.0)	3 (100.0)	6 (100.0)	9 (100.0)	3 (100.0)	5 (100.0)
BMI (kg/m²), mean (SD) *min, max*	26.9 (1.7) *25.7, 28.8*	25.5 (1.4) *24.7, 27.1*	26.13 (3.0) *22.7, 29.7*	26.5 (1.9) *23.7, 29.7*	32.7 (9.9) *21.4, 39.9*	24.9 (3.0) *21.8, 29.7*
Total AAT† (µM), mean (SD) *min, max*	4.1 (0.4) *4.0, 4.8*	5.3 (0.4) *4.8, 5.7*	5.0 (0.7) *3.9, 5.8*	4.7 (1.8) *2.4, 8.4*	5.1 (0.8) *4.3, 5.9*	4.7 (1.2) *3.3, 6.2*
FEV_1 % predicted, (post-bronchodilator) mean (SD) *min, max*	57.5 (12.5) *45.1, 70.0*	61.2 (7.5) *54.0, 68.9*	54.7 (13.4) *46.9, 80.9*	53.7 (13.2) *38.8, 80.1*	88.3 (18.7) *66.9, 101.5*	73.2 (19.4) *56.4, 99.8*
FibroScan liver stiffness, (kPa), mean (SD) *min, max*	4.9 (1.4) *3.3, 5.9*	5.0 (1.2) *3.6, 5.8*	5.3 (1.3) *3.8, 7.0*	5.0 (0.8) *3.8, 5.9*	9.9 (2.2) *7.6, 11.9*	8.1 (1.7) *5.7, 9.5*

Data cutoff June 24, 2026;*METAVIR fibrosis stage for patients enrolled in Part B were F1 (n=4) and F2 (n=4); †total blood AAT measured by turbidimetry
AAT, alpha-1 antitrypsin; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; kPa, kilopascal; SD, standard deviation

Safety

- BEAM-302 safety profile is consistent with LNP-based therapies (**Table 2**)
- Mild-to-moderate infusion-related reactions (IRRs) were the most common drug-related TEAEs, occurring in 41.4% of all patients
- Liver transaminase elevations were predominantly Grade 1. One Grade 3 elevation was observed; bilirubin remained normal and elevations resolved without intervention

Table 2: Safety summary

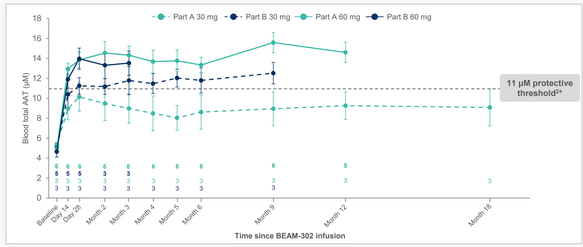
	Part A (N=21)				Part B (N=8)	
n (%)	15 mg (N=3)	30 mg (N=3)	60 mg (N=6)	75 mg (N=9)	30 mg (N=3)	60mg (N=5)
Any TEAEs	3 (100)	3 (100)	6 (100)	8 (88.9)	3 (100)	5 (100)
Related to BEAM-302	2 (66.7)	0	3 (50.0)	5 (55.6)	1 (33.3)	3 (60.0)
Any TEAEs Grade ≥3	0	0	0	0	0	1 (20.0)*
Related to BEAM-302	0	0	0	0	0	1 (20.0)*
Serious TEAEs	0	0	0	0	0	1 (20.0)†
Related to BEAM-302	0	0	0	0	0	0
IRRs	2 (66.7)	0	3 (50.0)	5 (55.6)	1 (33.3)	1 (20.0)
Grade 1	2 (66.7)	0	1 (16.7)	1 (11.1)	0	1 (20.0)
Grade 2‡	0	0	2 (33.3)	4 (44.4)	1 (33.3)	0
ALT/AST elevations§	3 (100)	1 (33.3)	6 (100)	7 (77.8)	2 (66.7)	3 (60.0)
Grade 1	3 (100)	1 (33.3)	6 (100)	7 (77.8)	2 (66.7)	2 (40.0)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	1 (20.0)*

Data cutoff June 24, 2026; *ALT/AST elevation above baseline began on Day 14 and reached Grade 3 on Day 25; bilirubin remained normal and resolved without intervention; †shortness of breath, assessed as unrelated to BEAM-302 and related to underlying disease; ‡Grade 2 IRRs required treatment intervention and/or infusion interruption; §ALT/AST elevations were identified from laboratory data during the dose-limiting toxicity monitoring period and graded per CTCAE v5.0. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRRs, infusion-related reactions; TEAEs, treatment-emergent adverse events

Efficacy

- A single 60 mg dose of BEAM-302 led to sustained total AAT levels above the protective threshold (≥11 µM; **Figure 3**)
- Following a 60 mg dose, functional AAT levels increased and >80% of participants in **Part A** had at least one human neutrophil elastase (HNE) activity measurement below the lower limit of quantification of 87.8 ng/mL; in **Part B**, functional AAT also increased and HNE activity decreased (**Figure 4**)

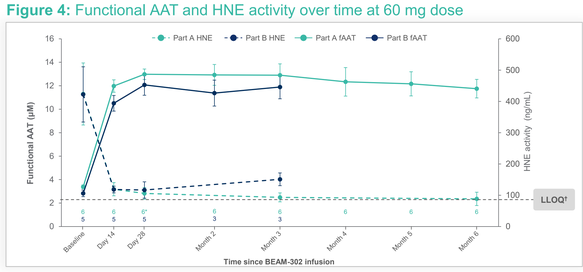
Figure 3: Blood total AAT over time



Total AAT (µM)	Part A: 60 mg (N=6)	Part B: 60 mg (N=5)
Baseline,† mean (SEM)	5.0 (0.3)	4.7 (0.5)
Steady state,‡ mean (SEM) *Median (min, max)*	14.4 (0.9) *15.2 (11.0, 16.4)*	13.5 (0.9) *13.8 (11.1, 15.4)*

Data cutoff June 24, 2026; total blood AAT was measured by turbidimetry; bold typeface indicates N numbers for 60 mg doses; *protective serum AAT concentration above which protease-mediated lung damage is reduced, and which serves as a therapeutic target; †baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion; ‡steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; SEM, standard error of the mean

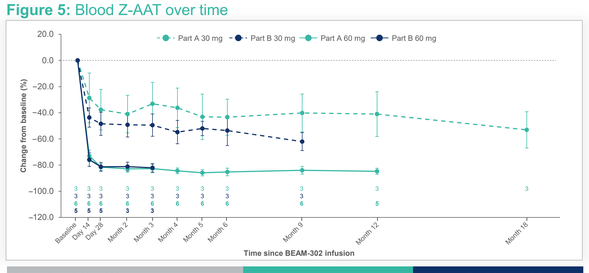
Figure 4: Functional AAT and HNE activity over time at 60 mg dose



Data cutoff June 24, 2026; functional AAT irreversibly binds and inhibits HNE activity; therefore, reduced HNE levels indicate functional AAT activity. *n=5 for Part A HNE activity at Day 28; †values below the LLOQ of 87.78 ng/mL were set to LLOQ/2 for analysis. AAT, alpha-1 antitrypsin; HNE, human neutrophil elastase; LLOQ, lower limit of quantification

- A single dose of BEAM-302 (60 mg) led to an 84% reduction in circulating Z-AAT (**Figure 5**) and corresponding decrease in plasma Z-polymers (**Figure 6**)

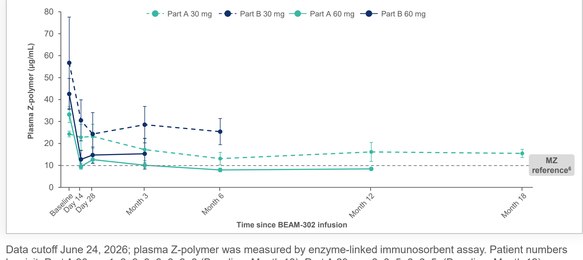
Figure 5: Blood Z-AAT over time



Blood Z-AAT (%)	Part A: 60 mg (N=6)	Part B: 60 mg (N=5)
Percentage change from baseline,* mean (SEM)	−83.9 (2.6)	−83.5 (2.7)

Data cutoff June 24, 2026; Z-AAT was measured by liquid chromatography-mass spectrometry; bold typeface indicates N numbers for 60 mg doses; *measured at steady state, defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin

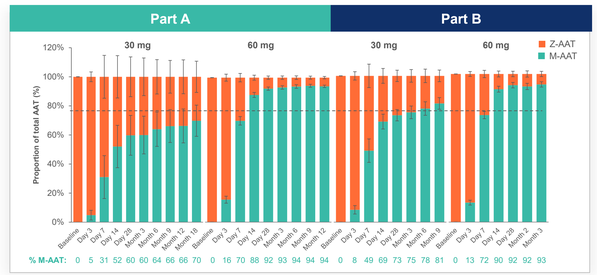
Figure 6: Plasma Z-polymer over time



Data cutoff June 24, 2026; plasma Z-polymer was measured by enzyme-linked immunosorbent assay. Patient numbers by visit: Part A 30 mg 1: 3, 3, 3, 3, 3, 3, 3 (Baseline–Month 18); Part A 60 mg: 6, 6, 5, 6, 6, 5 (Baseline–Month 12); Part B 30 mg: 3, 3, 3, 3, 3 (Baseline–Month 6); Part B 60 mg 2: 5, 5, 5, 3 (Baseline–Month 3)

- Treatment with BEAM-302 (60 mg) led to sustained circulating M-AAT levels of >90% (**Figure 7**)

Figure 7: Blood M-AAT and Z-AAT isoform levels over time

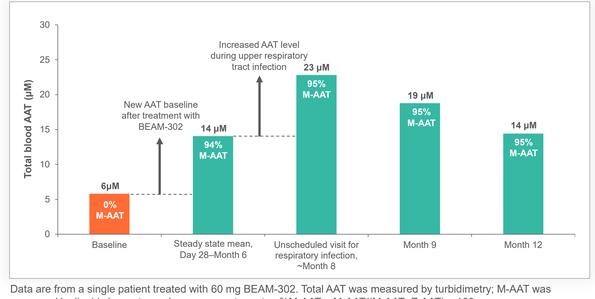


M-AAT, as a proportion of total AAT	Part A: 60 mg (N=6)	Part B: 60 mg (N=5)
Baseline,* mean (SEM)	0 (0)	0 (0)
Steady state,† mean (SEM)	93.6 (1.1)	93.3 (1.5)

Data cutoff June 24, 2026; M-AAT/Z-AAT were measured by liquid chromatography-mass spectrometry; %M-AAT = M-AAT/(M-AAT+Z-AAT) × 100
*Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion; †steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; SEM, standard error of the mean

- BEAM-302 restored physiological AAT inducibility in a patient following a respiratory infection (**Figure 8**)

Figure 8: Blood total AAT and proportion of M-AAT in one patient who experienced inflammation from a respiratory infection



Data are from a single patient treated with 60 mg BEAM-302. Total AAT was measured by turbidimetry; M-AAT was measured by liquid chromatography-mass spectrometry; %M-AAT = M-AAT/(M-AAT+Z-AAT) × 100
AAT, alpha-1 antitrypsin

Conclusions

- **BEAM-302, the first therapy in pivotal development to correct a disease-causing mutation, offers a potential one-time treatment for both the lung and liver manifestations of AATD by restoring *SERPINA1* and AAT function**
- BEAM-302 at 60 mg dose in **Part A** and **Part B**:
  - Was well tolerated, with mainly transient Grade 1 transaminase elevations and mild-to-moderate IRRs
  - Achieved durable increases in total AAT above the protective range, reduced Z-AAT and Z-polymer, and induced M-AAT production (>90%) in circulation
  - Led to an increase in AAT to ~23 µM (~95% M-AAT) during a respiratory infection, indicating AAT protein production is under normal physiological control
  - Increased functional AAT levels and decreased HNE activity levels in circulation
- Based on safety and efficacy across cohorts, 60 mg BEAM-302 has been selected as the optimal biological dose for the pivotal cohort study

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