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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: Potential for BEAM-302 – a one-time treatment that restores gene function to address the spectrum of AATD

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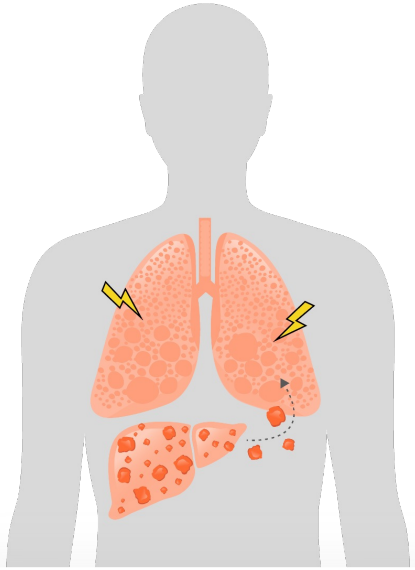


AATD is caused by a single G-to-A point mutation in the *SERPINA1* gene (Pi*Z or "Z" mutation)[1]

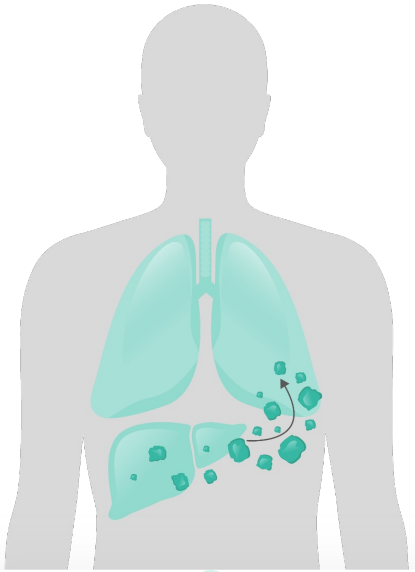
AATD BACKGROUND

Progressive lung disease due to:[2]

- Low and poorly functioning systemic AAT levels
- Circulating Z-AAT aggregates driving inflammation

Progressive liver disease with fibrosis and cirrhosis due to:[2]

- Aggregation and accumulation of mutant Z-AAT



Correction of DNA root cause of disease[3]

Restore typical AAT physiology to potentially address lung and liver disease[3]

GOALS OF BEAM-302 TREATMENT[3]

- **Liver produces M-AAT** for the first time
- Significantly **reduces Z-AAT**
- Total AAT **above 11 µM protective threshold**
- Increased total **AAT that is functional**
- AAT increases with **inflammatory response**

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency. 1. National Center for Biotechnology Information. NM_001127701.1(SERPINA1):c.1096G>A (p.Glu366Lys) AND alpha-1-antitrypsin deficiency. Updated February 7, 2026. Available from: https://www.ncbi.nlm.nih.gov/clinvar/RCV000148877.67/ (Accessed March 27, 2026); 2. Dasí F. Med Clin (Barc) 2024; 162:336–342; 3. Beam Therapeutics Inc. Data on file. Protocol no. BTX-302-001

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METHODS: BEAM-302 clinical study enrolled patients with both AATD-associated lung and liver disease

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PART A:

AATD-associated lung disease

- *15 mg N=3*
- *30 mg N=3*
- *60 mg N=6*
- *75 mg N=9*

PART B:

AATD-associated liver disease with or without lung disease

- *30 mg N=3*
- *60 mg N=5*

NCT06389877 on ClinicalTrials.gov for full study design

- **Select key endpoints:**
  - Rates of **TEAEs**
  - Blood levels of **total AAT**, **Z-AAT** and **M-AAT**, and **functional AAT**
  - **HNE activity** in blood
  - **Z-polymer** levels in blood
- **Baseline characteristics:**
  - **Age range 35–69 years**; homozygous for **PiZZ** mutation; mean post-bronchodilator **ppFEV$_1$: 62.0%** (range 38.8–101.5%)
  - **Mean blood AAT level: 4.8 µM*** (range 2.4–8.4 µM), with clinical diagnosis of **emphysema**; no evidence of liver disease (**Part A only**)
  - Clinical diagnosis of AATD-related liver disease (**Part B only**); METAVIR fibrosis stage F1 (n=4) and F2 (n=4)

Data cutoff June 24, 2026. *Blood AAT was measured by turbidimetry. AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; HNE, human neutrophil elastase; METAVIR, meta-analysis of histological data in viral hepatitis; TEAE, treatment-emergent adverse event

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RESULTS: Initial safety data suggest that BEAM-302 safety profile is consistent with that of LNP-based therapies

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	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; IRR, infusion-related reaction; LNP, lipid nanoparticle; TEAE, treatment-emergent adverse event

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RESULTS: A single dose of BEAM-302 (60 mg) led to sustained increases in total AAT levels to above the 11 µM protective threshold

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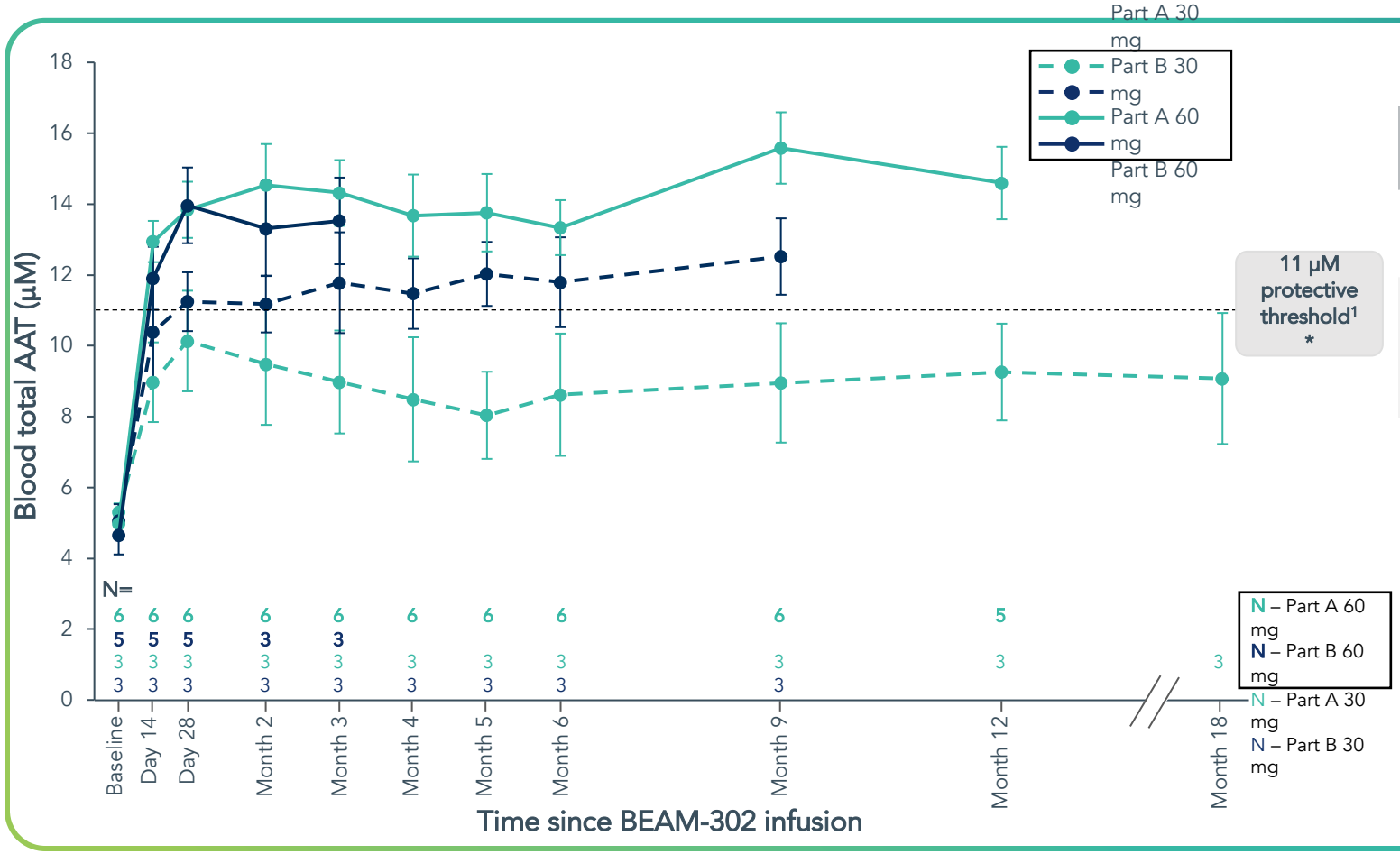

Total AAT (µM)	Part A: 60 mg (N=6)	Part B: 60 mg (N=5)
Baseline,† mean (SEM)	5.0 (0.3)	4.7 (0.5)
Steady state,‡ mean (SEM) Median (min, max)	14.4 (0.9) 15.2 (11.0, 16.4)	13.5 (0.9) 13.8 (11.1, 15.4)

- **Functional AAT** levels increased in a **dose-dependent manner** between the 15 mg and 60 mg dose levels
- **Human neutrophil elastase** activity levels decreased significantly and became **undetectable in 80% of participants** in the Part A 60 mg cohort

Data cutoff June 24, 2026. Total 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; min, minimum; max, maximum. 1. Franciosi AN, et al. Eur Resp J 2022;59:2101410

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RESULTS: BEAM-302 (60 mg) treatment achieved sustained circulating M-AAT levels >90%, with AAT expression under normal physiological control

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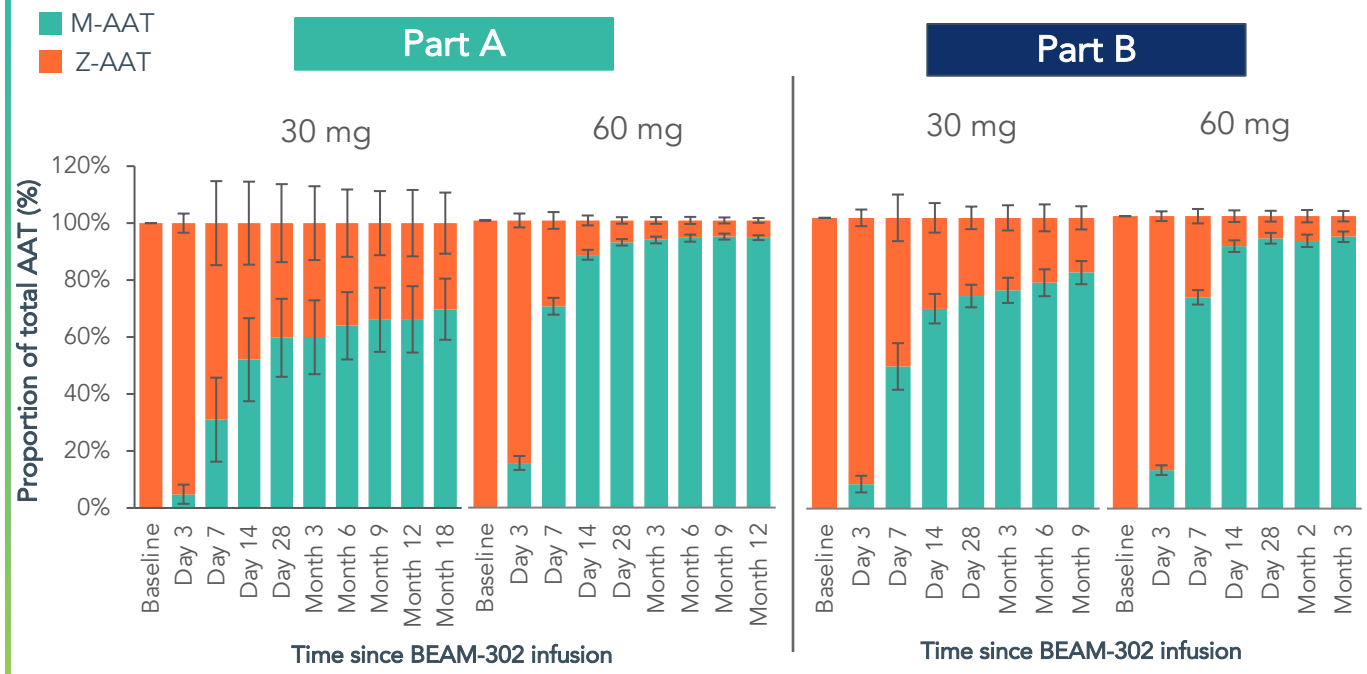
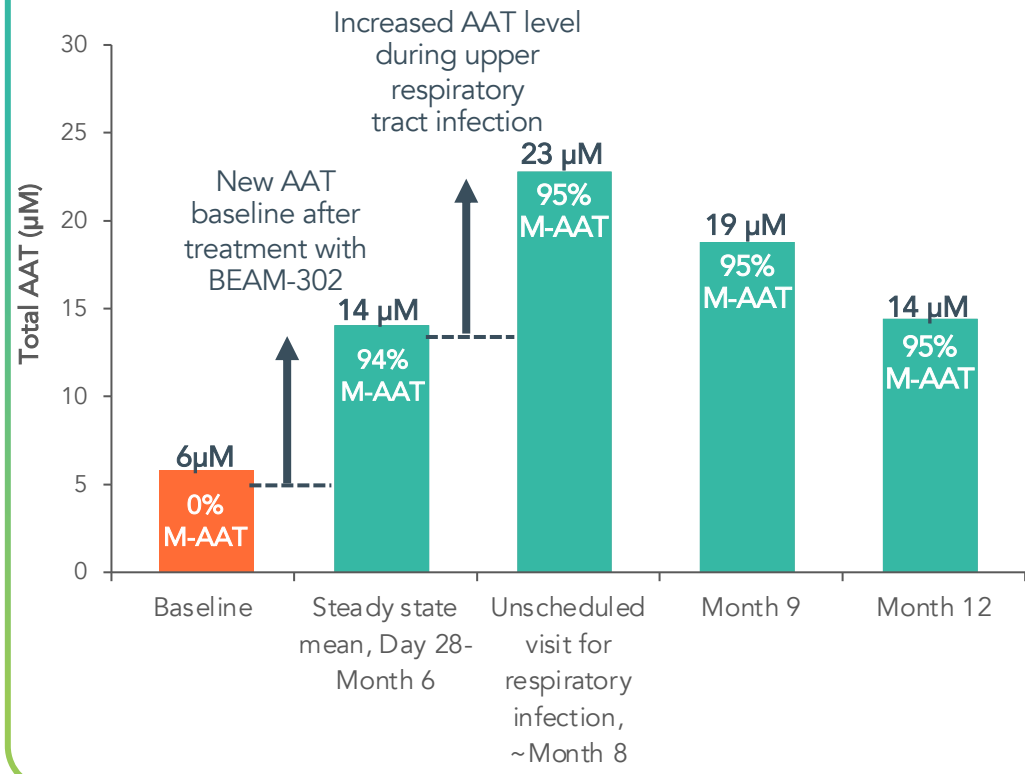
BEAM-302 restored predominant production of the M-AAT isoform



- Proportion of **M-AAT of >90% post-BEAM-302** at 60 mg dose is **greater than MZ genotype (80%)**[1]
- Steady state mean* **reduction in Z-AAT was 84%** with the 60 mg dose in both Part A and B

BEAM-302 resulted in normal AAT regulation during inflammation, while maintaining a beneficial M/Z ratio†



Data cutoff June 24, 2026. M-AAT/Z-AAT was measured by liquid chromatography mass spectrometry. %M-AAT=M-AAT/(M-AAT+Z-AAT)×100. Total AAT was measured by turbidimetry. *Steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit; †data from a single patient treated with 60 mg BEAM-302
AAT, alpha-1 antitrypsin; SEM, standard error of the mean. 1. Donato LJ, et al. Respir Res 2015;16:96

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CONCLUSIONS: BEAM-302 offers the potential for a one-time therapy to correct the mutant Z allele in the *SERPINA1* gene and restore AAT function

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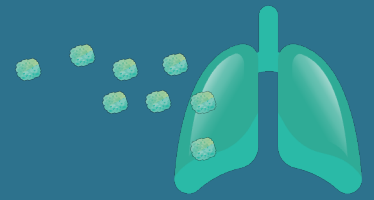
Correct DNA mutation – the root cause of disease

BEAM-302 is the **first therapy** in pivotal development to correct a disease-causing mutation

Safety profile is consistent with LNP-based therapies

Well tolerated at 60 mg, with mainly transient Grade 1 transaminase elevations and mild-to-moderate IRRs



Durable restoration of AAT function

60 mg dose led to: **increased total and functional AAT above the protective threshold** the **majority of which was M-AAT, decreased Z-AAT, and increased circulating AAT** during inflammation

Please see accompanying ePoster (5575) for additional information

The Phase 2 **pivotal cohort** of patients with **AATD-associated lung disease with or without liver disease** (Part C of this study)

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; IRR, infusion-related reaction; LNP, lipid nanoparticle

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Please see accompanying ePoster (5575) for additional information

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