REWRITING THE CODE: PRECISION DELIVERY VECTORS AND GENE THERAPY FOR PULMONARY VASCULAR DISEASES

The potential for base editing to treat diseases impacting the lungs: Ongoing data from the BEAM-302 clinical trial in alpha-1 antitrypsin deficiency (AATD)

ATS
American Thoracic Society

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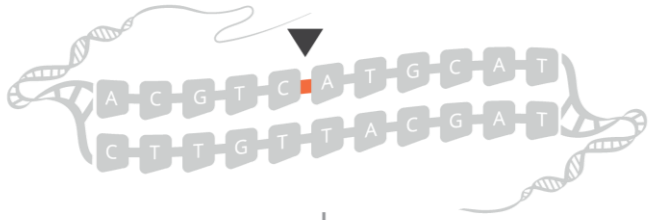
Base editing

Base editing is an efficient, predictable, and potentially best-in-class gene editing technology

NUCLEASE CRISPR, ZFN, TALENs

Precision targeting with CRISPR



Double-stranded breaks

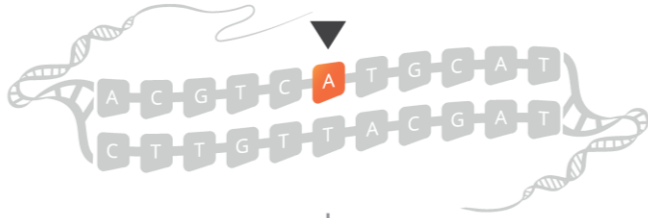
Lack of control of gene sequence outcomes

…A C G - - - - G C A T…
…A C G T C **G C T T** A T G C A T…
…A - - - - - T G C A T…
…A C G T C **T** A T G C A T…
…A C - - - - - - - A T…
…A C G T C **A A C** - - G C A T…
Etc.

- - - - - Deletions
A G C T Insertions

BASE EDITING

Precision targeting with CRISPR

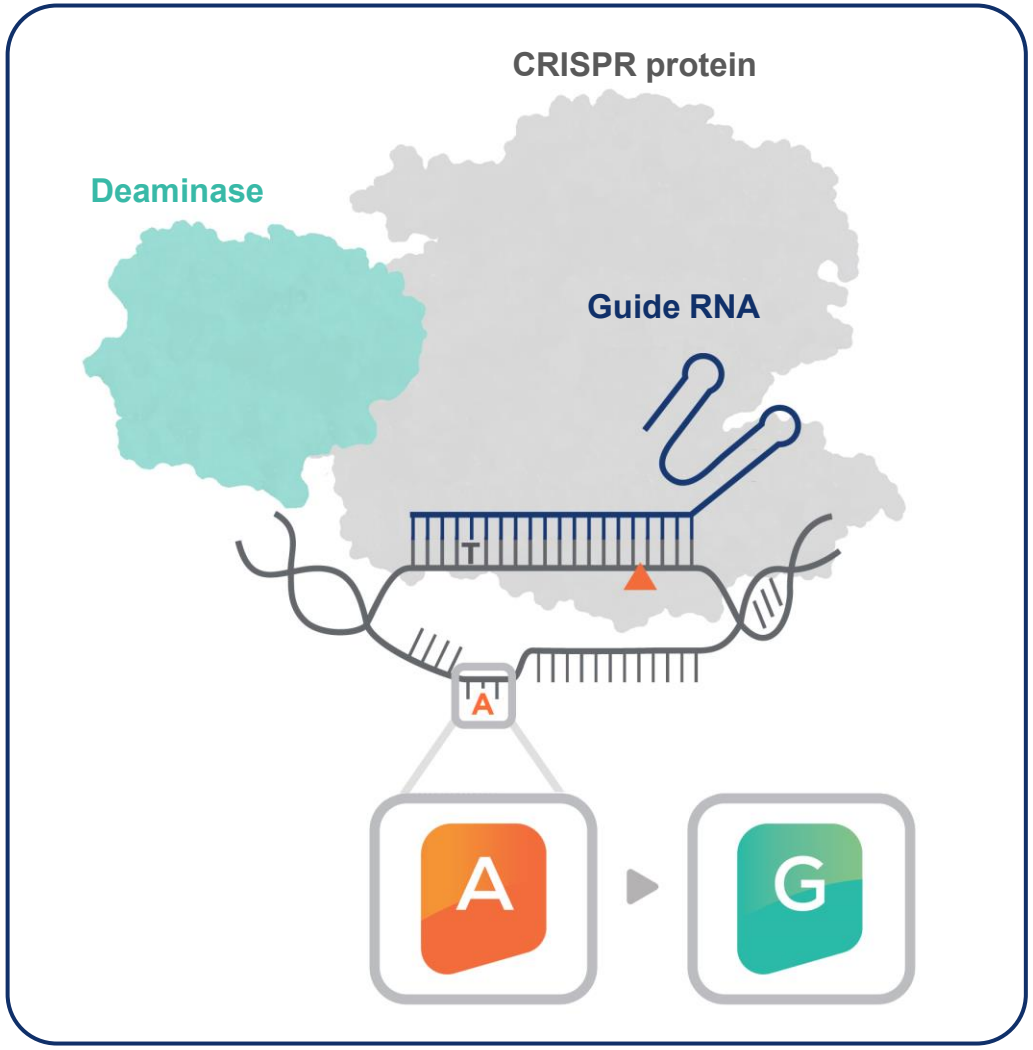


Enzymatic base conversion

Highly efficient, with predictable gene sequence outcomes

CRISPR, clustered regularly interspaced short palindromic repeats; TALEN, transcription activator-like effector nuclease; ZFN, zinc finger nuclease

Base editing technology has multiple, highly versatile applications



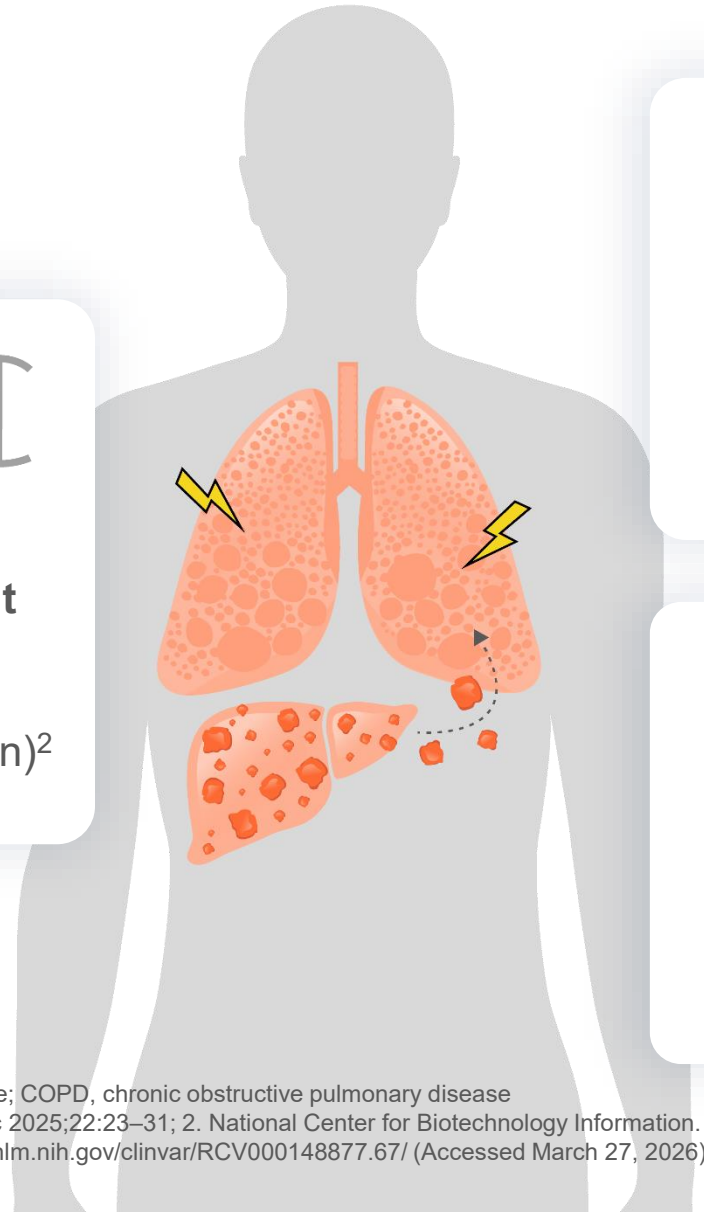
Correct mutations	Repairs the most common type of gene mutation, single base changes
Silence proteins	Turns off gene with disease-causing activity
Activate expression	Turns on genes to restore or increase the function
Modify proteins	Alters how proteins bind or signal without disrupting their function
Multiplex edits	Targets multiple pathways simultaneously with high efficiency

CRISPR, clustered regularly interspaced short palindromic repeats. Beam Therapeutics Inc. Base editing applications. Available from: https://beamtx.com/science/base-editing-applications (Accessed March 24, 2026)

What if we could use base editing to correct disease-causing mutations *in vivo?*

Severe AATD (ZZ genotype) impacts ~100,000 individuals in the US, with limited treatment options[1]

Single G to A point mutation in the SERPINA1 gene (Pi*Z or “Z” mutation)[2]



Progressive lung disease due to:[3]

- Low and poorly functioning systemic M-AAT levels
- Circulating Z-AAT aggregates, causes inflammation

- Routine **COPD care**[4]
- Intravenous augmentation therapy given **weekly is only approved option**[3,4]

Progressive liver disease with fibrosis and cirrhosis due to:[3]

- Aggregation and accumulation of mutant Z-AAT

- **Supportive care and liver transplant** for advanced disease[3,4]
- **No approved treatments** for liver disease[3]

AATD, alpha-1 antitrypsin disease; COPD, chronic obstructive pulmonary disease

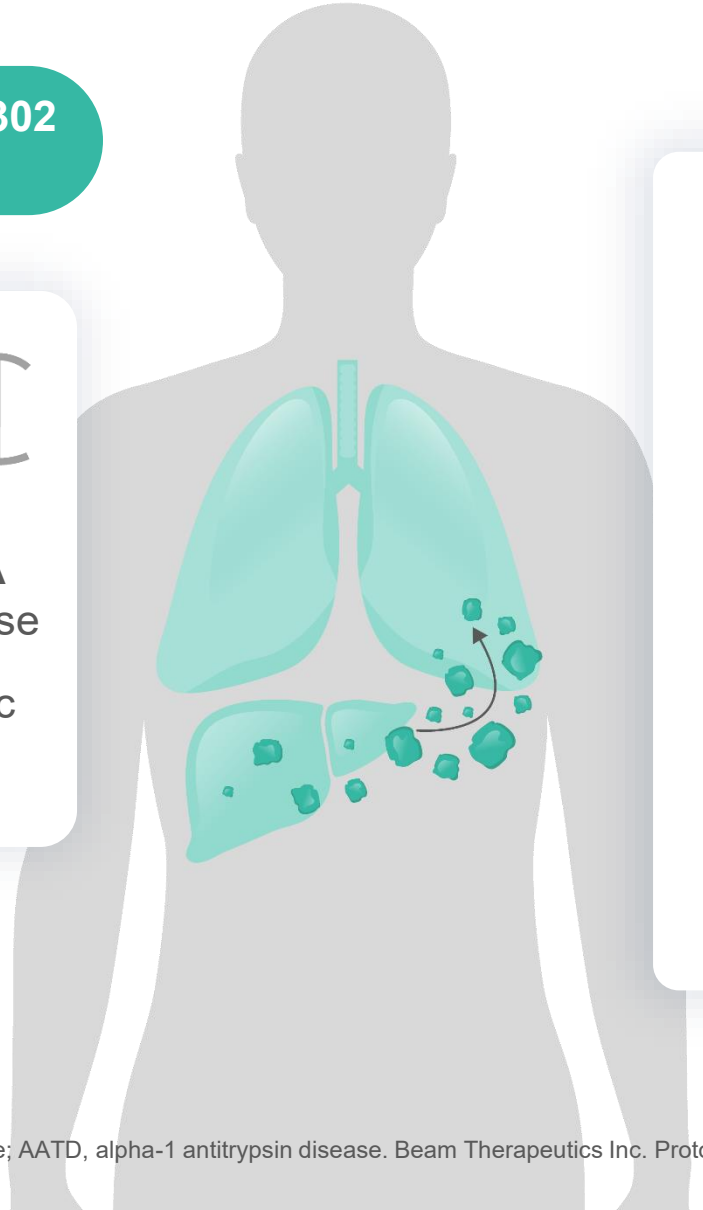
1. Stoller JK. Ann Am Thorac Soc 2025;22:23–31; 2. National Center for Biotechnology Information. NM_001127701.1(SERPINA1):c.1096G>A (p.Glu366Lys) AND alpha-1-antitrypsin deficiency. Updated February 2, 2025. Available from: https://www.ncbi.nlm.nih.gov/clinvar/RCV000148877.67/ (Accessed March 27, 2026); 3. Dasí F. Med Clin (Barc) 2024;162:336–342; 4. Feitosa PH. Drugs Context 2023;12:2023-3-1

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

GOALS OF BEAM-302 TREATMENT

Correction of DNA root cause of disease

Restore physiologic control of AAT



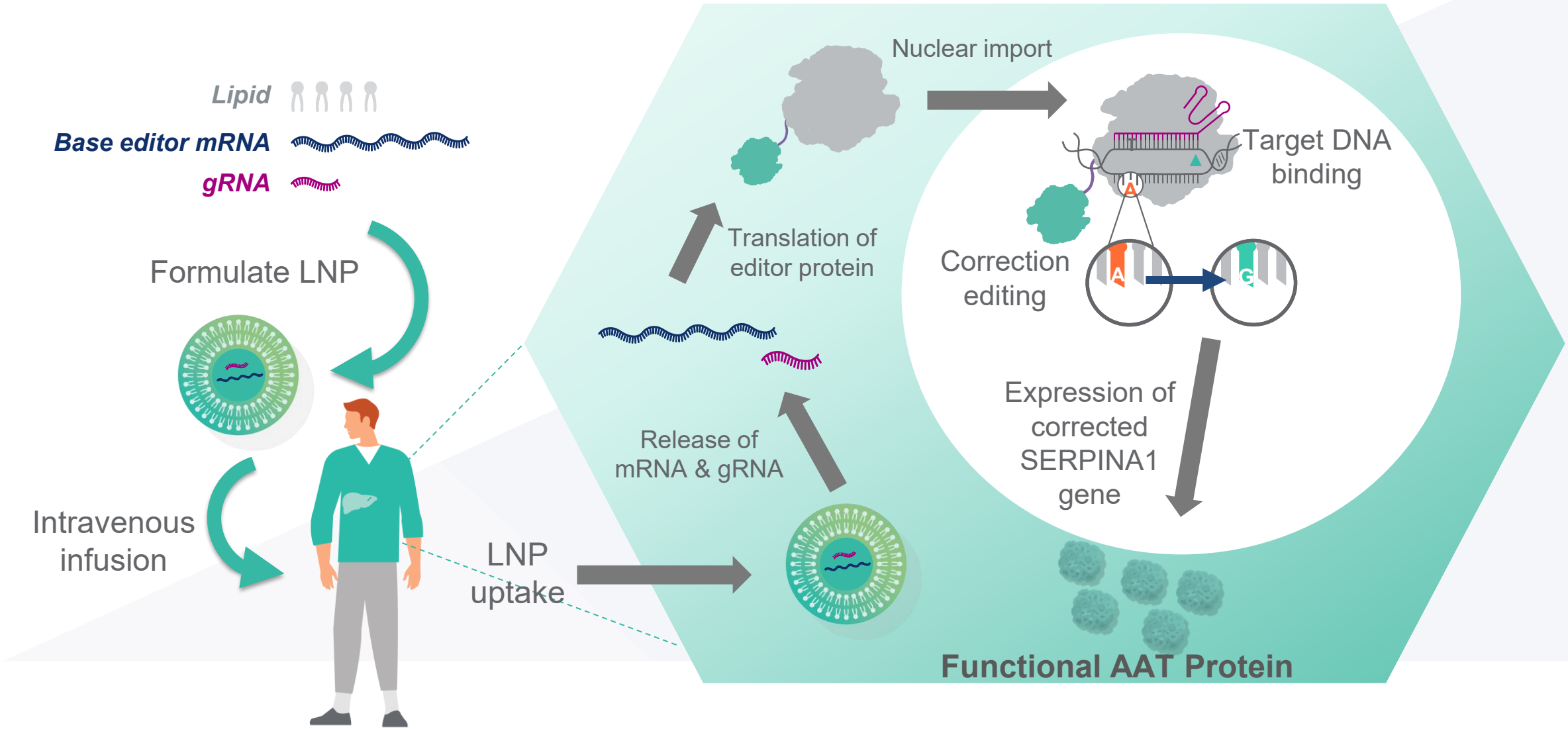
- **Liver produces M-AAT** for the first time
- Significantly **reduces Z-AAT**
- Total AAT **above 11 µM protective threshold**
- Increased total **AAT is functional**
- AAT increases with **inflammatory response**

✔ **Durable, single-course** treatment

✔ **Address both lung and liver** manifestations

AATD, alpha-1 antitrypsin disease; AATD, alpha-1 antitrypsin disease. Beam Therapeutics Inc. Protocol BTX-302-001

BEAM-302 utilizes non-viral, lipid nanoparticle (LNP) delivery to target the liver and correct the *SERPINA1* gene



AAT, alpha-1 antitrypsin; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA. Beam Therapeutics Inc. Protocol BTX-302-001

Initial data from the Phase 1/2 study of BEAM-302

Key elements of BEAM-302 phase 1/2 study design

PART A:

AATD-associated lung disease

DOSE ESCALATION

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
15 mg	*30 mg*	*60 mg*	*75 mg*	*2 × 60 mg*

PART B:

AATD-associated liver disease with or without lung disease

DOSE ESCALATION

Cohort 1	Cohort 2
30 mg	*60 mg*

- **Goal:** assess early safety and efficacy and identify optimal dose for pivotal study
- **Key eligibility criteria:**
  - 18-70 years of age; homozygous for PiZZ mutation; blood AAT level <11μM; FEV1 ≥40% predicted
  - 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)

NCT06389877. Data cutoff February 10, 2026. AATD, alpha-1 antitrypsin deficiency

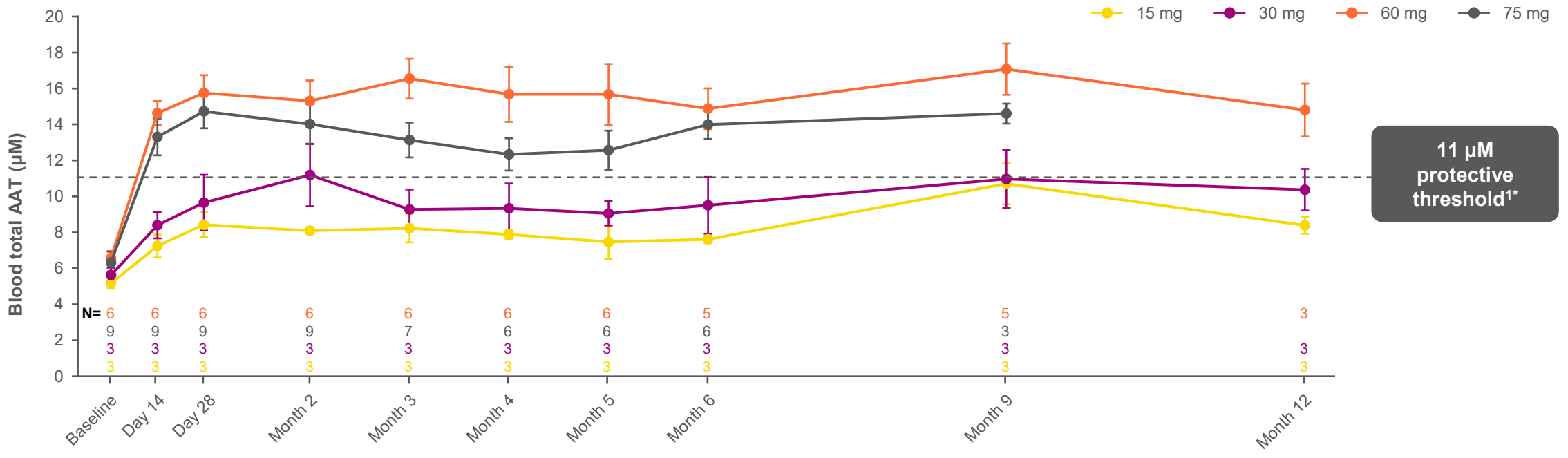
No serious adverse events or dose-dependent safety trends were observed in BEAM-302 single-dose cohorts

	Part A			
Patients, n (%)	**15 mg N=3**	**30 mg N=3**	**60 mg N=6**	**75 mg N=9**
At least 1 TEAE	3 (100.0)	3 (100.0)	6 (100.0)	8 (88.9)
Related to BEAM-302	2 (66.7)	0 (0)	3 (50.0)	5 (55.6)
At least 1 TEAE ≥Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Related to BEAM-302	0 (0)	0 (0)	0 (0)	0 (0)
At least 1 serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)
Related to BEAM-302	0 (0)	0 (0)	0 (0)	0 (0)
At least 1 IRR (by max severity)	2 (66.7)	0	3 (50.0)	5 (62.5)
Grade 1	2	0	1	1
Grade 2	0	0	2	4
Grade 1 ALT +/− AST elevations*	2/3	1/3	6/6	7/9

Data cutoff February 10, 2026. *ALT/AST elevations identified during the DLT monitoring period were graded per CTCAE v5.0; none were assessed and reported as a TEAE by investigators.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRR, infusion-related reaction; TEAE, treatment emergent adverse event

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

Part A

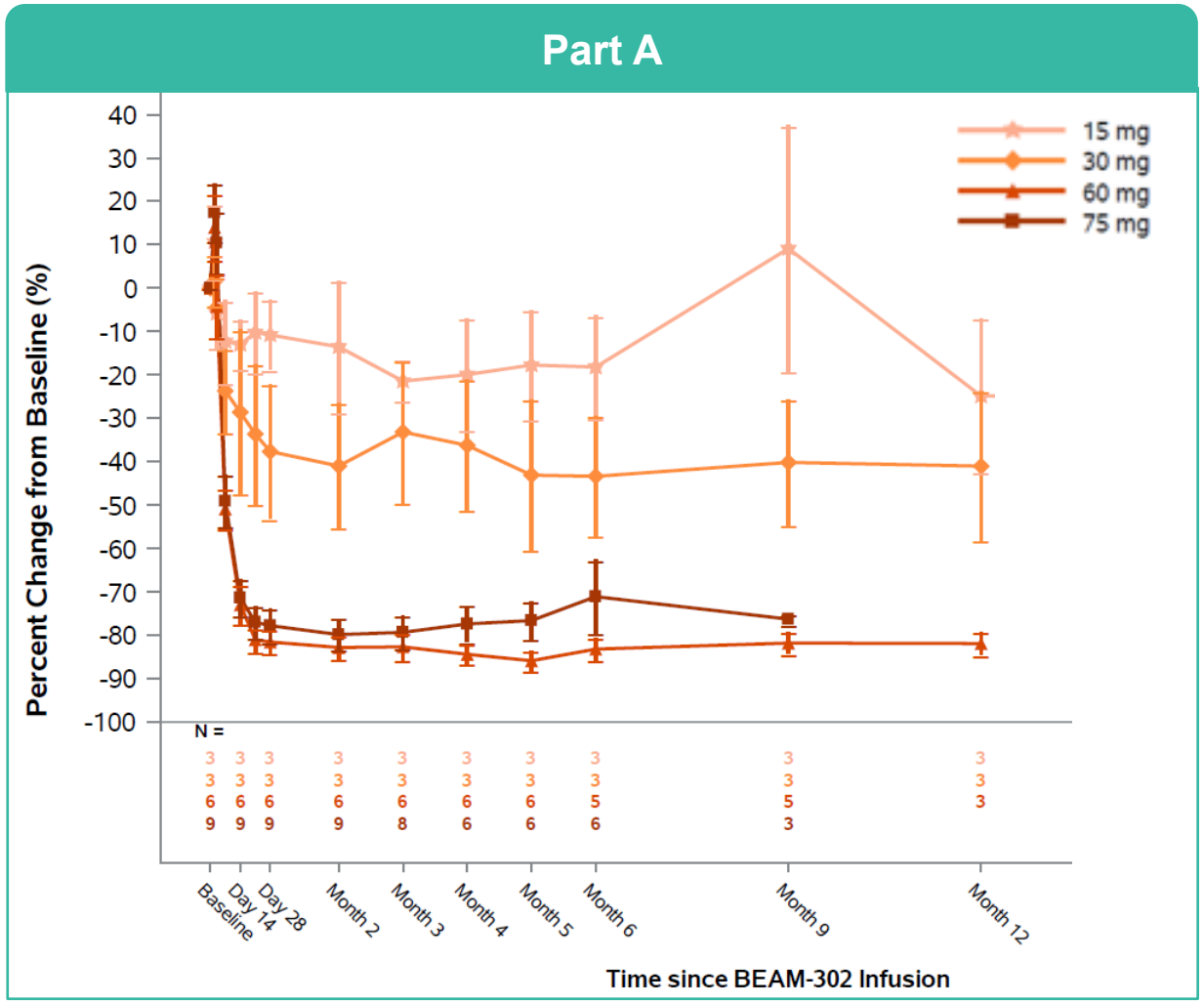


Blood total AAT (µM)	60 mg (N=6)	75 mg (N=9)
Baseline, mean (SD)	6.6 (0.97)	6.3 (1.80)
Steady state,† mean (SD)	16.1 (2.78)	14.4 (2.94)

Data cutoff February 10, 2026. Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion. Total AAT was measured by LC-MS.
*Protective serum alpha-1 antitrypsin concentration above which protease-mediated lung damage is reduced, and which serves as a therapeutic target; †steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; LC-MS, liquid chromatography-mass spectrometry; SD, standard deviation

1. Franciosi AN, et al. Eur Resp J 2022;59:2101410

A single dose of BEAM-302 (≥60 mg) led to ~80% reduction in circulating Z-AAT

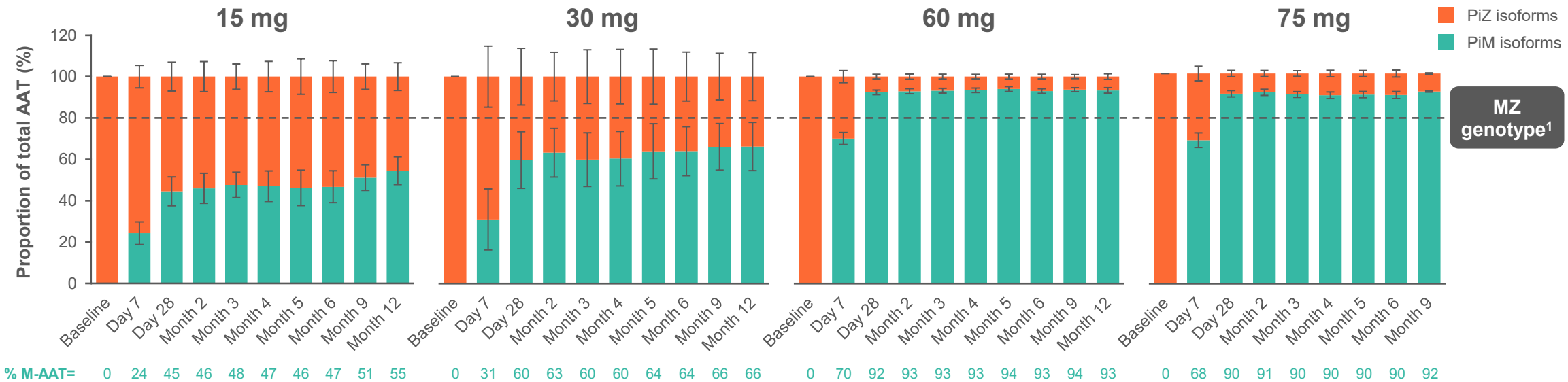


Blood Z-AAT (%)	60 mg (N=6)	75 mg (N=9)
Percentage change in steady state,* mean (SD)	-84% (6.2%)	-79% (11.8%)

Data cutoff February 10, 2026. Z-AAT was measured by LC-MS. *Steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; LC-MS, liquid chromatography-mass spectrometry; SD, standard deviation

BEAM-302 treatment led to production of M-AAT for the first time in circulation that was sustained (green bars)

Part A



M-AAT as a proportion of total AAT	60 mg (N=6)	75 mg (N=9)
Baseline, mean (SD)	0 (0)	0 (0)
Steady state,* mean (SD)	93.5 (2.72)	91.2 (4.14)

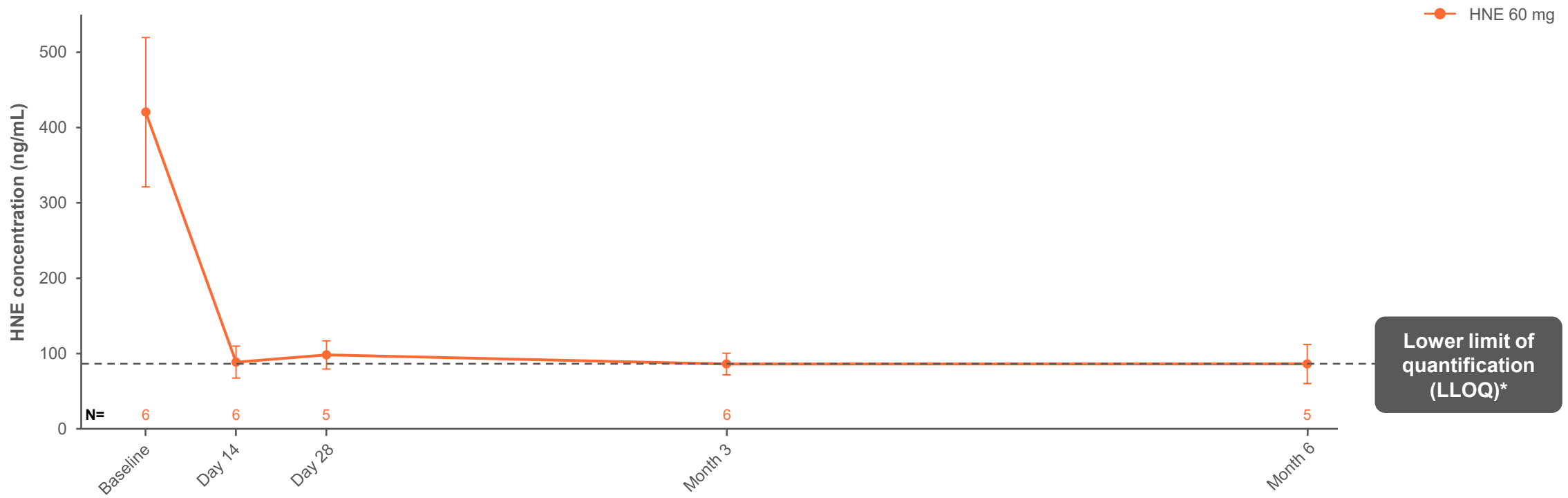
Proportion of M-AAT of >90% post-BEAM-302 at ≥60 mg doses was greater than that of MZ genotype[1]

Data cutoff February 10, 2026. *Steady state is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; SD, standard deviation

1. Donato LJ, et al. Respir Res 2015;16:96

Human neutrophil elastase (HNE) activity was reduced in all participants following BEAM-302

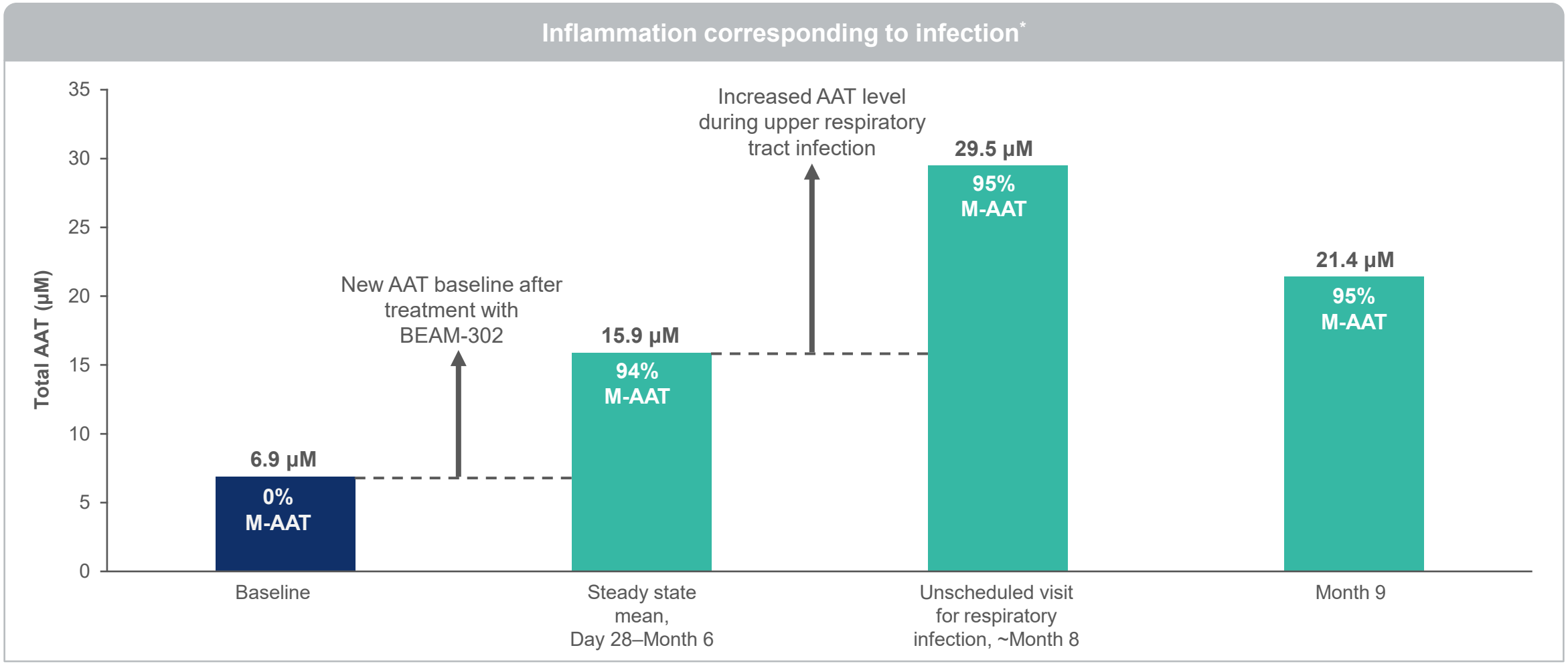
Part A



At 60 mg dose, ~80% of participants had at least one measurement below LLOQ

Data cutoff February 10, 2026. Functional AAT irreversibly binds and inhibits HNE; therefore, reduced NE levels indicate functional AAT activity. *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

BEAM-302 restored physiologic AAT inducibility in a patient following a respiratory infection



Data cutoff February 10, 2026. *Data from a single patient treated with 60 mg BEAM-302. AAT, alpha-1 antitrypsin

Novel scientific discoveries, such as base editing, can provide new approaches to target the underlying cause of serious genetic diseases

Base editing represents a promising new way to treat genetic diseases *in vivo* at the root cause

BEAM-302 is a **therapeutic base editor** and the **first to correct a disease-causing mutation *in vivo***. It has the potential to **address both the liver and lung disease manifestations of AATD simultaneously**

BEAM-302 was **well tolerated in single-dose cohorts up to 75 mg** with transient Grade 1 transaminase elevations and Grade 1–2 IRRs

BEAM-302 achieved durable levels of total AAT in the protective range

- In the 60 mg cohort, mean steady state total AAT reached **16.1 µM**, Z-AAT was reduced by **84%**, and newly produced M-AAT **comprised 94% of total AAT***

AAT was under **normal physiologic control** as evidenced by inducibility during an upper respiratory tract infection in a patient, **with AAT levels reaching ~30 µM** (~95% M-AAT)

Data cutoff February 10, 2026. *Values reported are the mean of subject-level steady-state mean values, which is defined as the period beginning on a patient's Day 28 visit through their last available visit. AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin disease; IRR, infusion-related reaction

Next steps

- **A pivotal cohort to support accelerated approval** is scheduled to begin in second half of 2026
- Based on the strong, consistent safety and efficacy profile across single dose cohorts, **60 mg of BEAM-302** selected as the **optimal biological dose for the pivotal cohort**
- Plan to present **updated study data** later in 2026

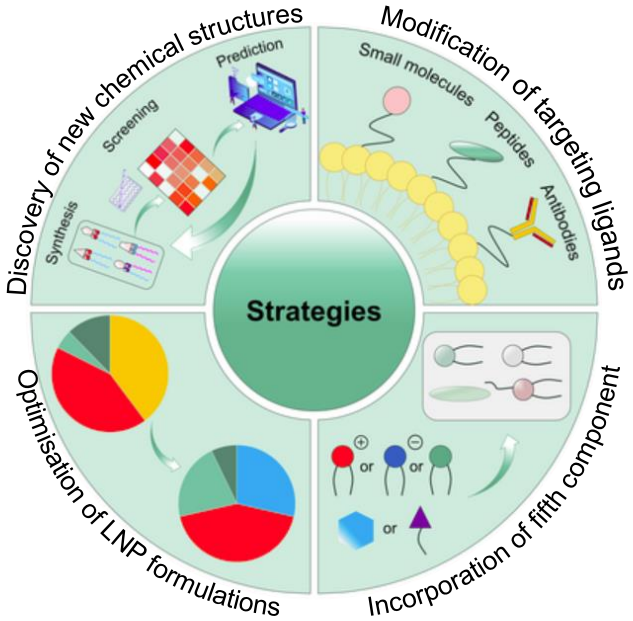
Dan, living with AATD

Gene editing could potentially address genetic targets of pulmonary vascular disease

- High value genetic targets such as *BMPR2* and *KCNK3* have been identified in pulmonary vascular disease

- Next generation LNPs are being developed to target extrahepatic tissues such as heart, lung and brain

- Imagine what is possible with gene editing technologies that can access:
  - Pulmonary vascular endothelial cells?
  - Pulmonary vascular smooth muscle cells?
  - Or both



Liao H, et al. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2024;16:e2004; Pulmonary Hypertension Association. What is pulmonary hypertension? Available from: https://phassociation.org/pulmonary-hypertension/what-is-ph/ (Accessed May 11 2026)

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