BEAM-302: A potential base editing therapeutic for alpha-1 antitrypsin deficiency (Alpha-1)

2025 Alpha-1 Foundation 7th Global Research Conference and 10th Patient Congress

Nicolas Currier, MD, PhD
Senior Medical Director

DISCLOSURE

- I am a Beam employee and shareholder

Our vision is to provide life-long cures for individuals suffering from serious diseases

To achieve our vision, we have created a strong values-driven organization focused on people, advancing cutting-edge science, and developing a new class of precision genetic medicines

Two locations

Research Triangle, NC

Cambridge, MA

Base editing has potential to treat disease

Hematology, oncology, genetic disease, and more in the future

Three programs in clinic

- Alpha-1
- Sickle cell disease
- Glycogen Storage Disease Type Ia

MA, Massachusetts; NC, North Carolina

Base editing provides a unique opportunity to address serious disease with precision

- DNA is made up of 3 billion bases defined by letters A,T,C,G
- A single spelling error in your DNA, a **point mutation,** can lead to disease
- **Base editing** works like a “pencil and eraser” on the genome, changing:

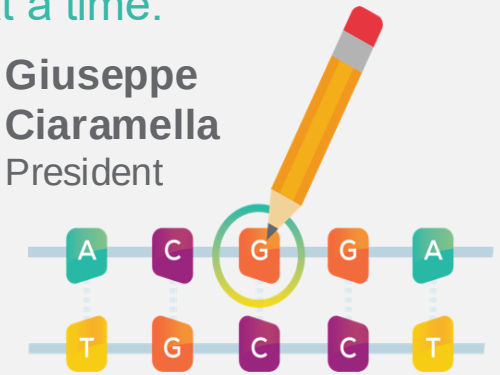
cytosine (C) to **thymine (T)**

or

adenine (A) to **guanine (G)**

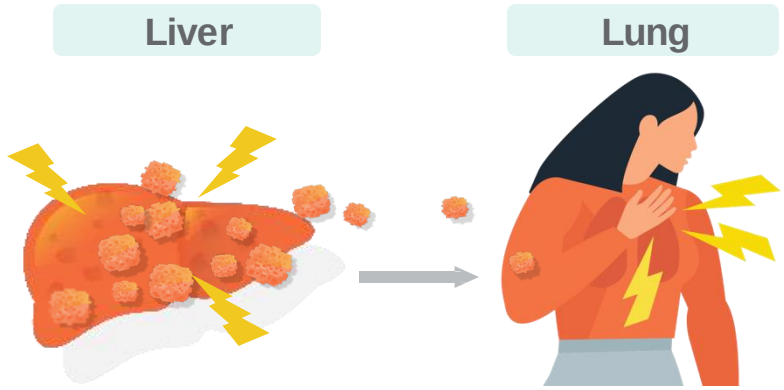
> Many existing gene editing approaches are like ‘scissors’ that cut the genome. Base editors are like ‘pencils’ that enable erasing and rewriting one letter of the genome at a time.”

Giuseppe Ciaramella
President



Alpha-1 lung and liver disease are both caused by a single point mutation (spelling error)

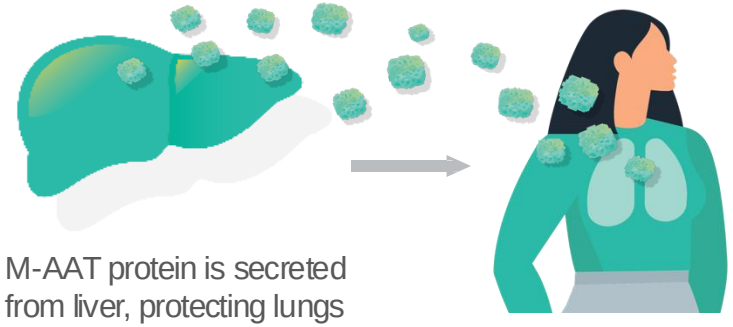
Alpha-1
PiZ



Z-AAT aggregates cause liver damage

Decreased AAT secretion from liver and circulating Z lead to lung damage

Typical AAT:
PiM



M-AAT protein is secreted from liver, protecting lungs

Alpha-1 cause[1–3]

- **PiZ** is caused by a single G → A **point mutation** in the *SERPINA1* gene
- **PiZ AAT causes liver damage** and is **poorly secreted** by the liver into circulation. Decreased circulating AAT and circulating Z causes **lung damage**

Current management[1]

- Plasma-derived AAT (augmentation therapy) is an **approved therapy** available for **lung disease** to maintain patients **above the protective 11 μM threshold,** but this is not available everywhere
- **No approved therapies** are currently available for **liver disease**

Unmet Need in Alpha-1[1]

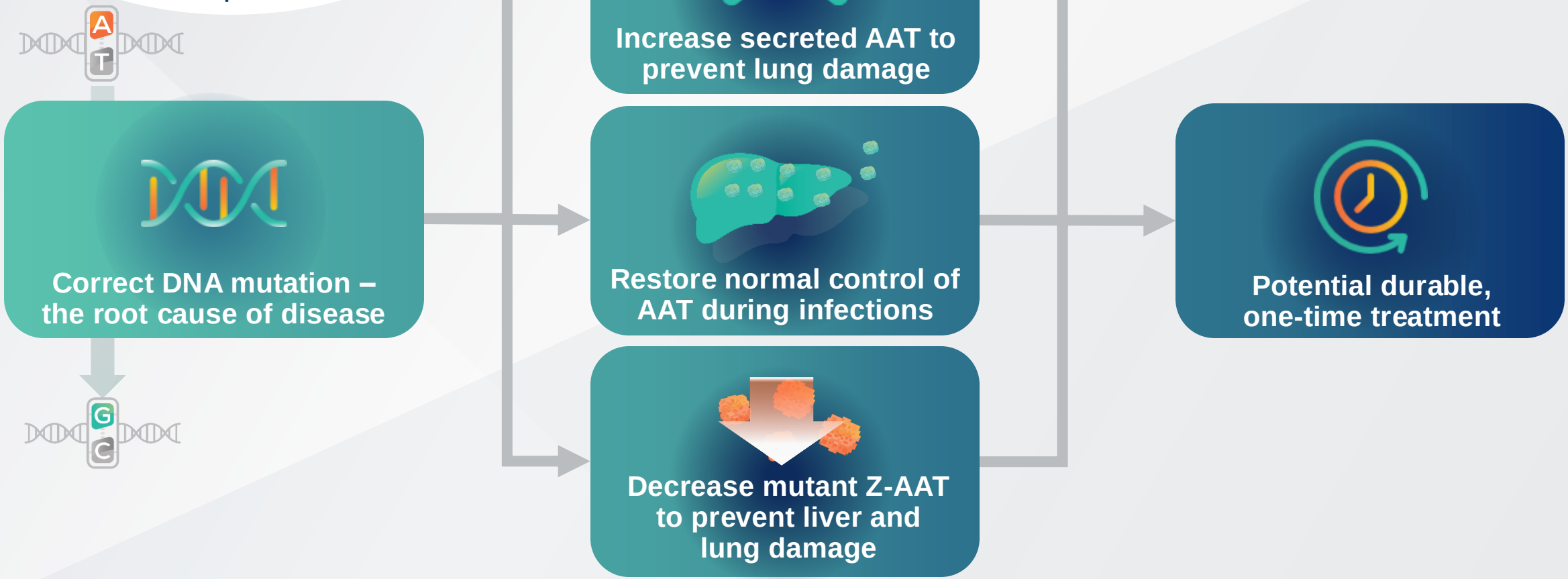
- There is an unmet need for effective therapies that can address **both the lung and liver disease** manifestations

AAT, alpha-1 antitrypsin

1. Stoller JK, et al. Am J Respir Crit Care Med 2003;168:818–900; 2. Abo K, et al. Am J Respir Crit Care Med. 2023;207:A6144; 3. Núñez A, et al. Respir Res. 2021;22:244

BEAM-302 has the potential to be the only one-time treatment for both lung and liver manifestations of Alpha-1

BEAM-302
has potential to address critical aspects of Alpha-1



AAT, alpha-1 antitrypsin. 1. Abo K, et al. Am J Respir Crit Care Med. 2023;207:A6144; 2. Núñez A, et al. Respir Res. 2021;22:244

The Phase 1/2 study aims to evaluate the safety and efficacy of BEAM-302 in people with Alpha-1

Part A: Alpha-1-associated lung disease

Dose exploration | Dose expansion

DOSING COMPLETE in first three cohorts of Part A

- **Cohort 1** *15 mg* *N = 3*
- **Cohort 2** *30 mg* *N = 3*
- **Cohort 3** *60 mg* *N = 3*
- **Cohort 4** *75 mg*

Part B: Alpha-1-associated liver disease with or without lung disease

Dose exploration | Dose expansion

- Up to four dose cohorts
- Patients included with mild-to-moderate liver disease

Clintrials.gov **(NCT06389877)**

PART A: KEY ELIGIBILITY CRITERIA

- 18–70 years of age
- Homozygous for PiZZ mutation
- Blood total AAT level <11µM
- FEV_1 >40% predicted; FEV/FVC <70%
- Confirmed diagnosis of emphysema
- No evidence of liver disease

PART A: KEY OBJECTIVES & ENDPOINTS

- **Phase 1:** Safety and efficacy (AAT, corrected M-AAT, functional AAT, Z-AAT) of BEAM-302
- **Phase 2:** Efficacy and safety of BEAM-302; confirm optimal biologic dose

Data cutoff February 26, 2025.

AAT, alpha-1 antitrypsin; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity

Preliminary data support the safety of BEAM-302 at doses up to 60 mg

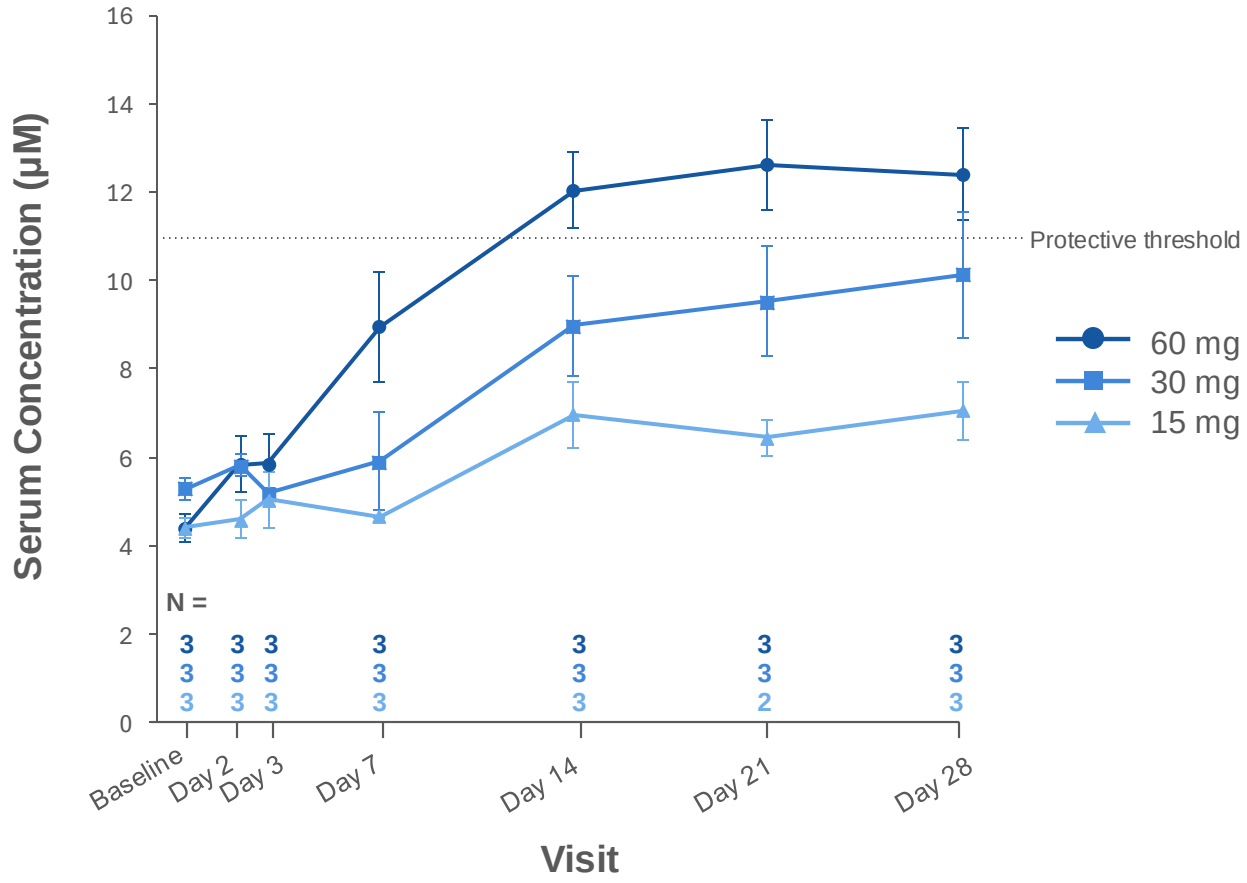
Patients with	15 mg N=3 n (%)	30 mg N=3 n (%)	60 mg N=3 n (%)
Any TEAEs	3 (100)	3 (100)	2 (66.7)
Related to BEAM-302	2 (66.7)	0	1 (33.3)
Any TEAEs ≥Grade 3	0	0	0
Dose-limiting toxicities	0	0	0
Serious TEAEs	0	0	0
Death	0	0	0

- There were no serious adverse events (AEs), dose-limiting toxicities or ≥Grade 3 AEs
- All treatment-related AEs (TEAEs) were mild to moderate
- Three patients had mild infusion-related reactions that went away without stopping the infusion and without treatment
- Grade 1 asymptomatic elevations in ALT (+/- AST) were observed within the first 28 days after dosing in all cohorts

Data cutoff February 26, 2025. Data are based on follow-up exposure data between approximately 28 days and 8 months. Related events include events where investigator has assessed relationship as possibly or definitely related to BEAM-302. Related events include 2 patients at the 15 mg dose each with 1 IRR (mild); 1 patient at the 60 mg dose with IRR (mild) and back pain (moderate)
AE, adverse event; TEAE, treatment-emergent adverse event

BEAM-302 treatment led to a rapid, dose-responsive increase of total AAT above the 11µM protective threshold

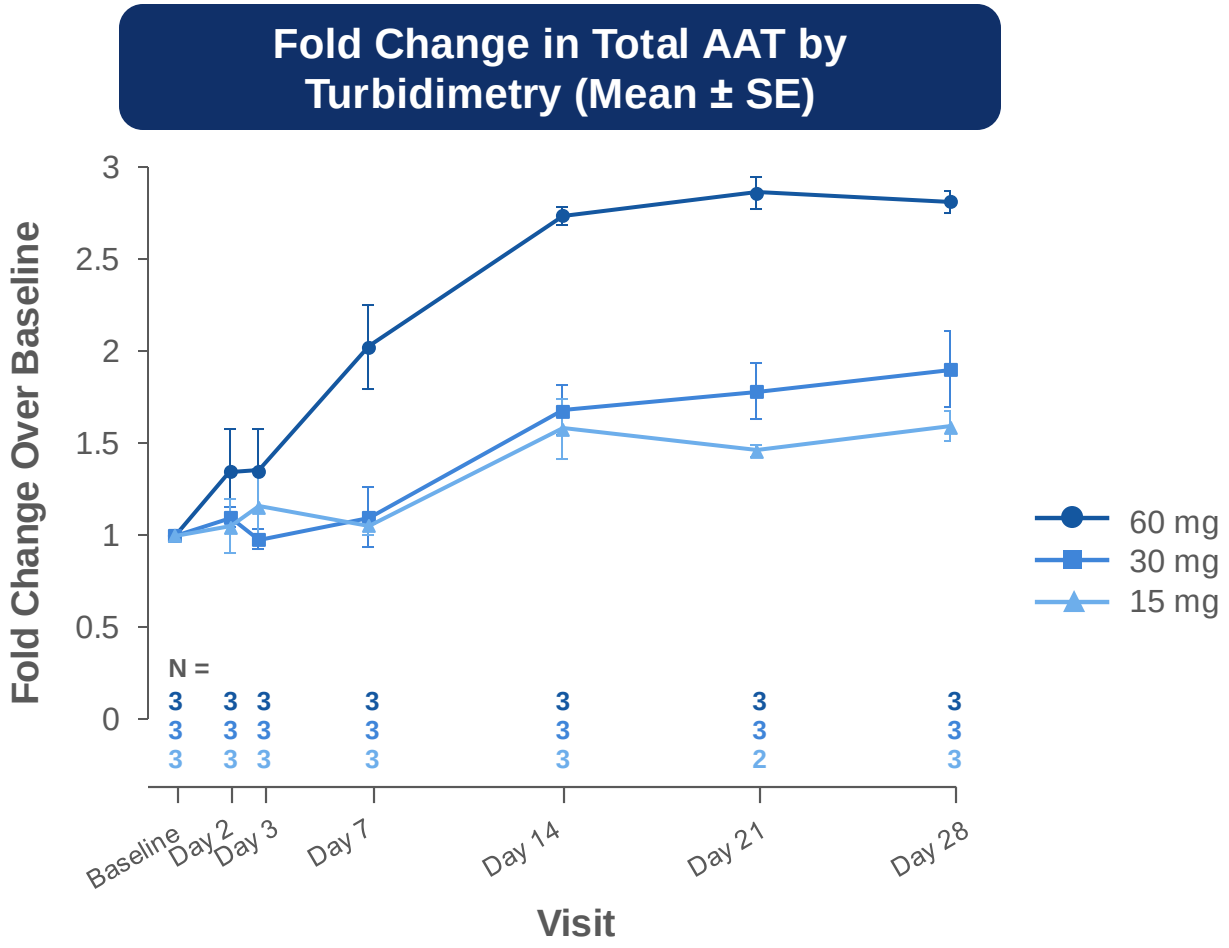
Total AAT by Turbidimetry (Mean ± SE)



Dose	Baseline, mean	Total AAT at Day 28, mean
15 mg	4.4µM	7.0µM
30 mg	5.3µM	10.1µM
60 mg	4.4µM	12.4µM

Data cutoff February 26, 2025
Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion.
One patient in the 15 mg cohort could not attend their Day 21 visit due to a COVID infection.

Dose-dependent increase in fold change in total AAT observed following treatment with BEAM-302

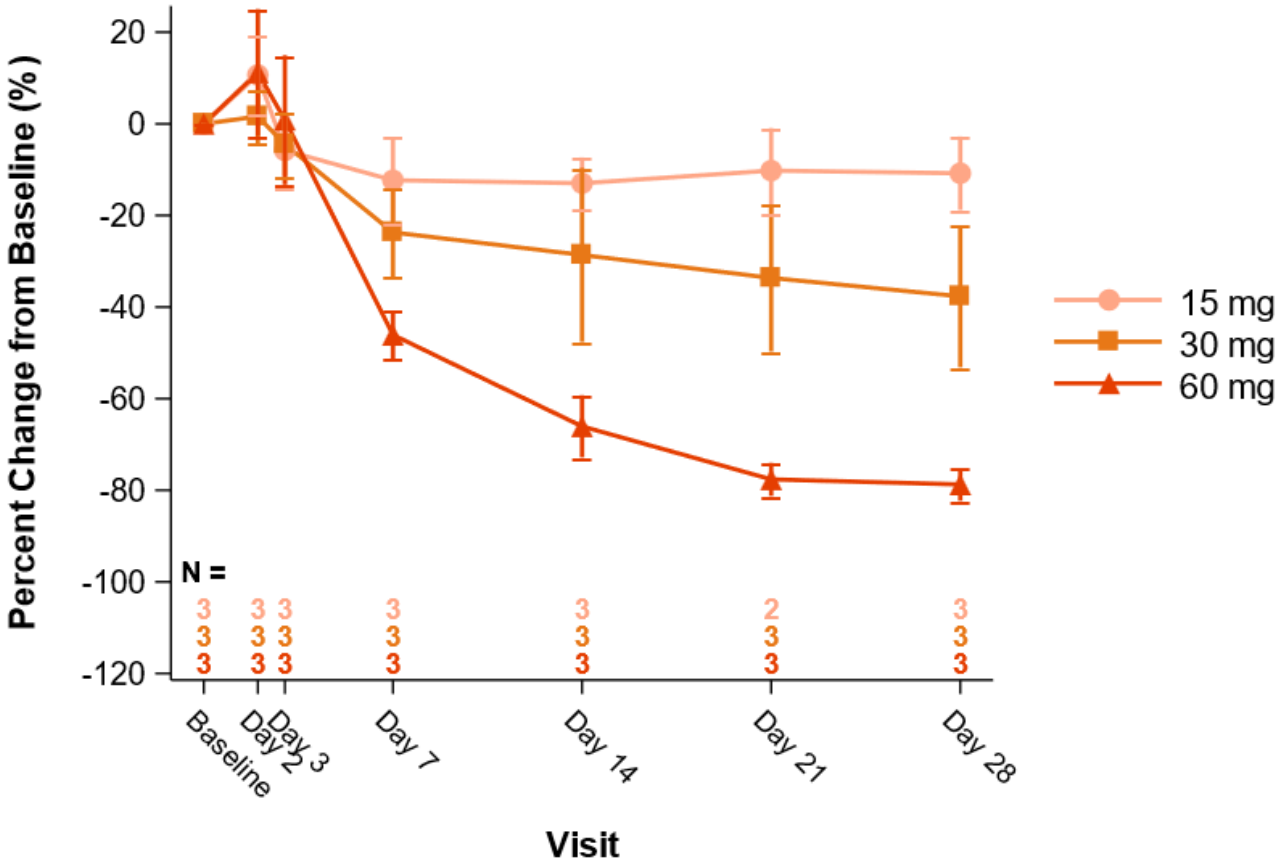


Dose	Baseline, mean	Fold Change in Total AAT at Day 28, mean
15 mg	4.4µM	1.6×
30 mg	5.3µM	1.9×
60 mg	4.4µM	2.8×

AAT, alpha-1 antitrypsin; SE, standard error; µM, micromolar
Data cutoff February 26, 2025. Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion. One patient in the 15 mg cohort could not attend their Day 21 visit due to a COVID infection

BEAM-302 treatment also led to rapid, dose-dependent reductions in circulating mutant Z-AAT

% Change Mutant Z-AAT from Baseline by LC-MS (Mean ± SE)

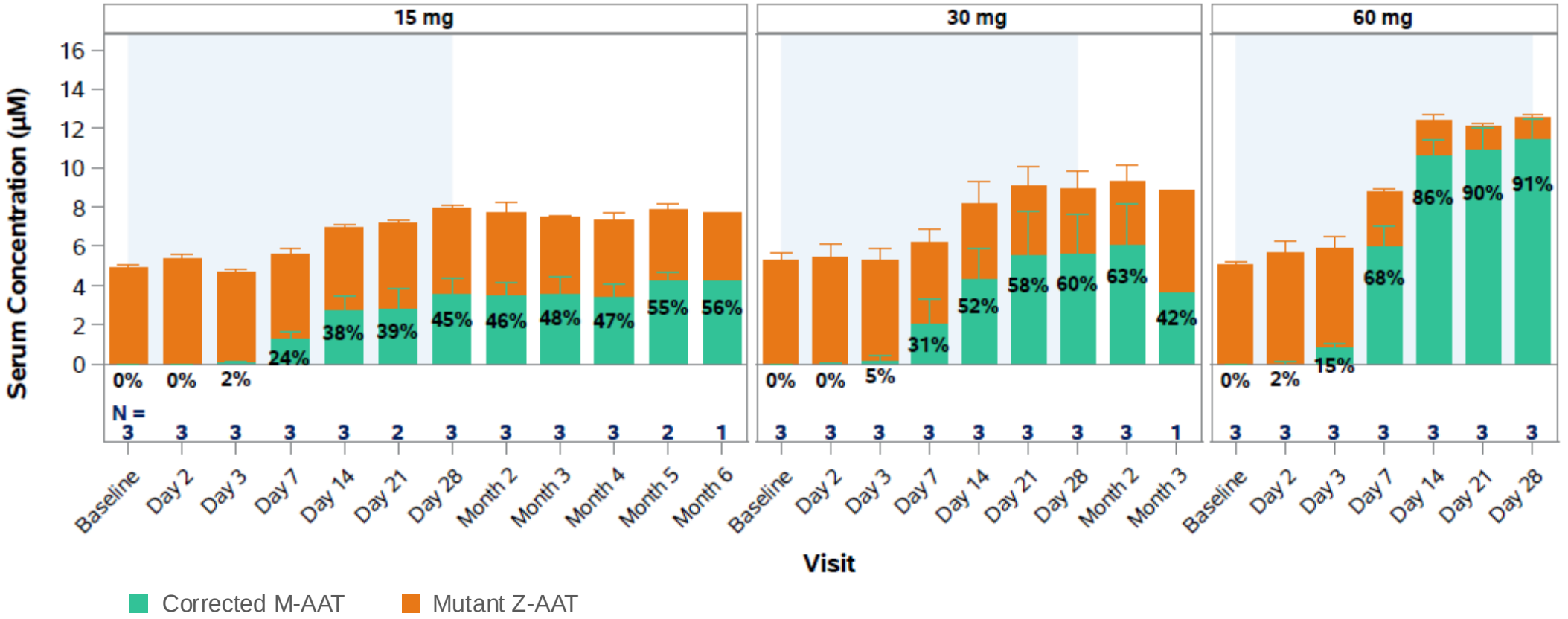


Dose	% change in Z-AAT at Day 28, mean
15 mg	−11%
30 mg	−38%
60 mg	−79%

Data cutoff February 26, 2025. Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion
One patient in the 15 mg cohort could not attend their Day 21 visit due to a COVID infection
AAT, alpha-1 antitrypsin; LC-MS, liquid chromatography mass spectrometry; SE, standard error

BEAM-302 treatment led to up to 91% M-AAT in circulation; correction has been durable up to 6 months

Proportion (%) of Corrected M-AAT and Mutant Z-AAT by LC-MS by Cohort (Mean ± SE)

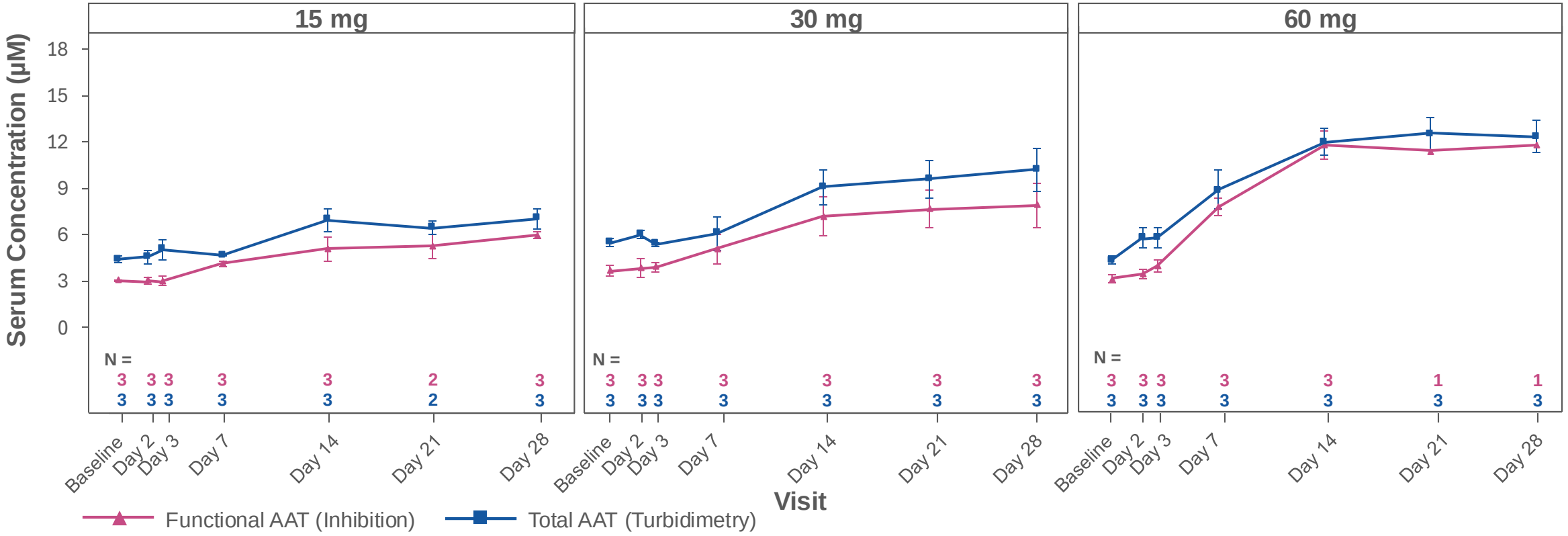


MZ genotype profile:
80% M, 20% Z in circulation

Corrected M-AAT is comprised of both PiM and PiM + an additional edit (PiM + variant) at a neighboring position; both forms are structurally and functionally similar in preclinical studies
Data cutoff February 26, 2025. Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion.
One patient in the 15 mg cohort could not attend their Day 21 visit due to a COVID infection.
AAT, alpha-1 antitrypsin; SE, standard error. Donato LJ, et al. Respir Res 2015;16:1–7

Increased AAT in circulation is functional following BEAM-302

Total AAT (Turbidimetry) and Functional AAT (Inhibition) by Cohort (Mean ± SE)



Data cutoff February 26, 2025. Functional AAT was measured using a neutrophil elastase inhibition assay. Baseline for each patient is defined as the average of all assessments conducted within the 84-day screening period prior to BEAM-302 infusion

AAT, alpha-1 antitrypsin; SE, standard error; µM, micromolar

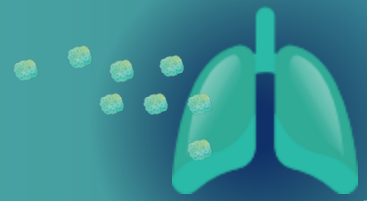
Summary: Initial data from BEAM-302 clinical study demonstrated safety and efficacy in patients with Alpha-1

Correct DNA mutation – the root cause of disease

BEAM-302 corrects the PiZ **point mutation in the DNA** that results in the most severe Alpha-1 (PiZ) deficiency using a precise base editor

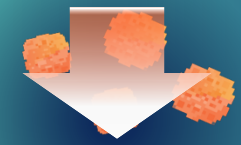
Target the liver (where AAT is produced) with a non-viral LNP

Preliminary data support the **safety of BEAM-302** at doses up to **60 mg**



Increase secreted AAT to prevent lung damage

BEAM-302 treatment led to **rapid, dose-dependent increases in total circulating AAT that is functional and above the protective threshold**



Decrease mutant Z-AAT to prevent liver and lung damage

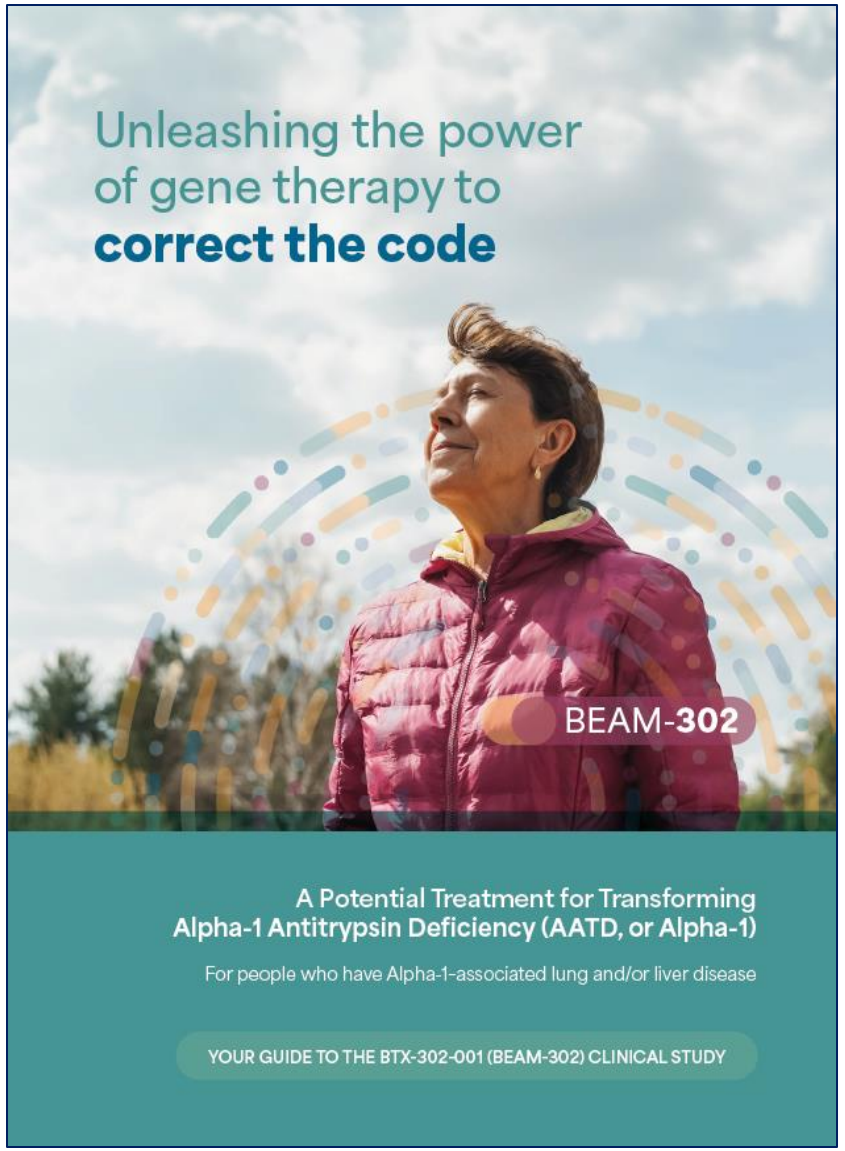
BEAM-302 treatment also led to **rapid, dose-dependent reductions** in circulating **mutant Z-AAT**

Treatment with a single course of BEAM-302 has potential to treat <u>both</u> lung and liver manifestations of Alpha-1

Next steps

- Continue dose escalation to identify the BEAM-302 dose regimen that has optimal safety and efficacy in patients with Alpha-1
- Expand country and site activation:
  - Regulatory approvals obtained in Australia, Ireland, Netherlands, New Zealand, UK, and US
- Presentation of updated study data is planned at a medical conference later in 2025

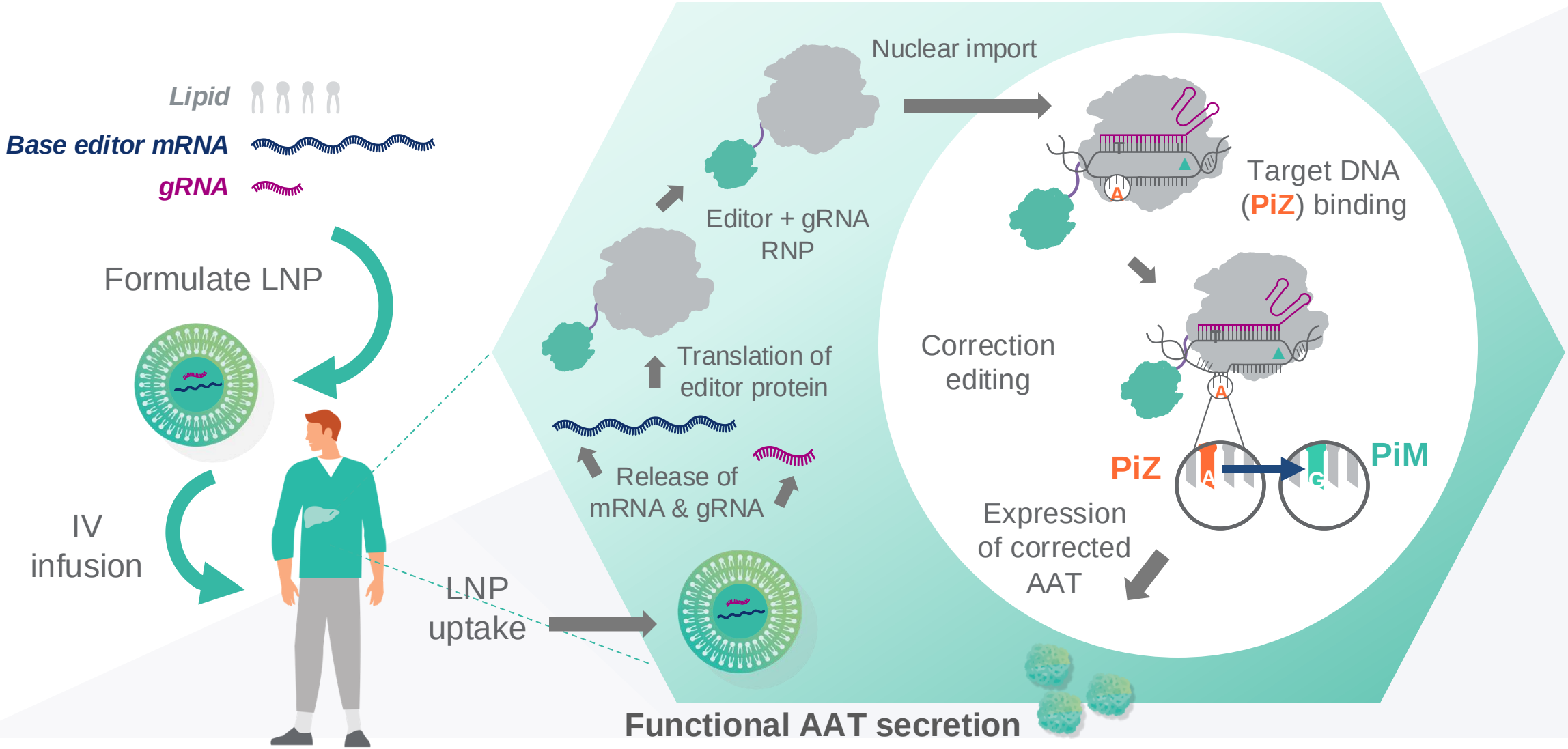
We **thank** the **patients, patient organizations**, **caregivers**, **researchers**, **healthcare professionals**, and **study sites** that have contributed to the BEAM-302 clinical trial



Beam THERAPEUTICS

THANK YOU

BEAM-302 utilizes lipid nanoparticle (LNP) delivery to target the liver and correct the A base mutation back to the typical G

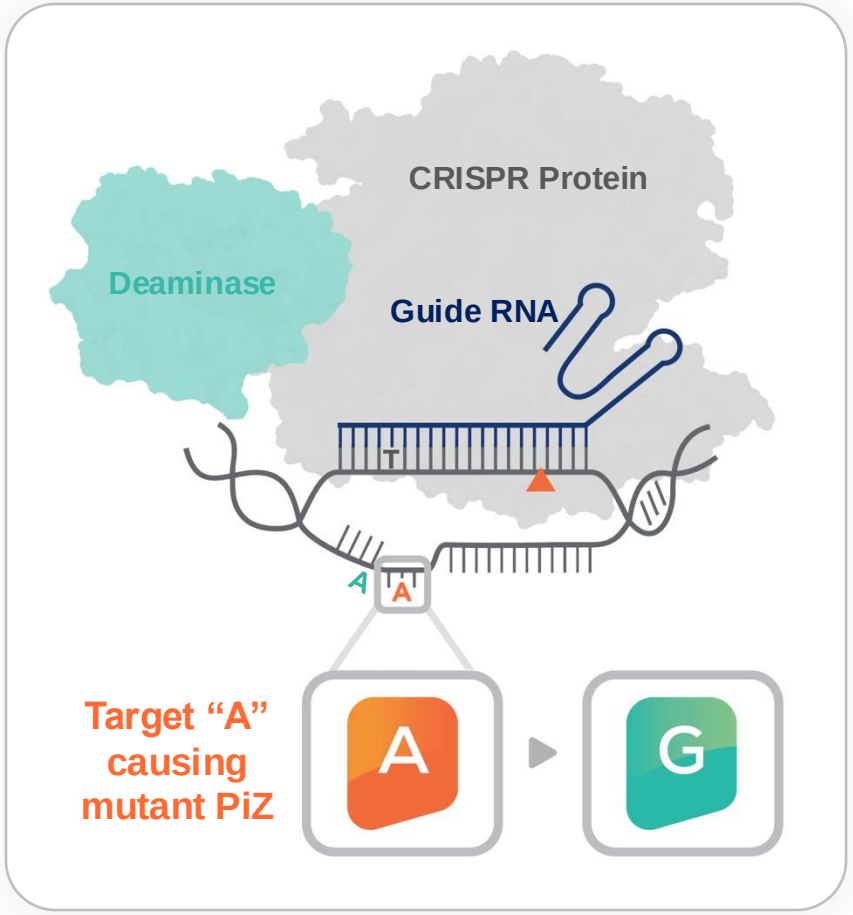


BEAM-302 is a potential one-time therapy that uses base editing to directly correct the E342K mutation causing AATD

BEAM-302 BASE EDITOR

PiZ

E342K mutation



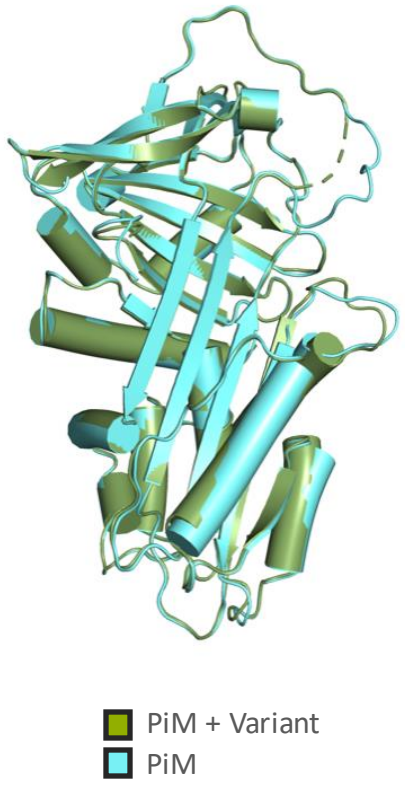
PiM

Corrected SERPINA1 gene

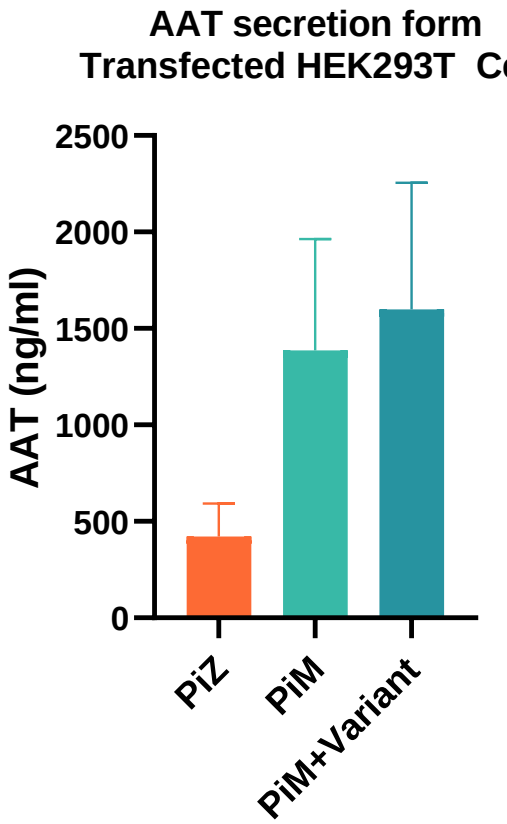
- Presence of an additional "A" within the editing window yields a mixture of corrected proteins:
  - **PiM** (canonical)
  - **PiM + variant** (an additional, naturally-occurring variant at the neighboring 341 position)
- Both PiM forms are functional

Corrected PiM + variant AAT is structurally and functionally comparable to PiM AAT

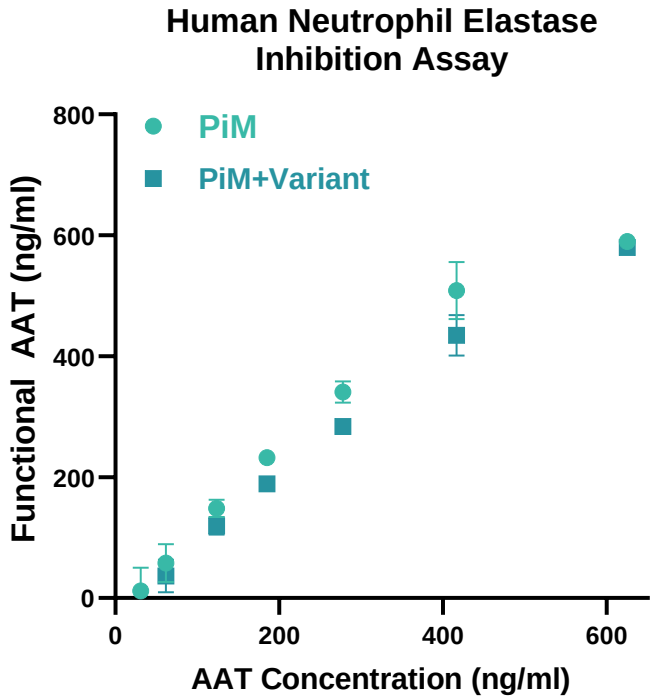
Superimposable structures*



Equivalent secretion in cell culture**



Equivalent Inhibition of Neutrophil Elastase *in vitro*



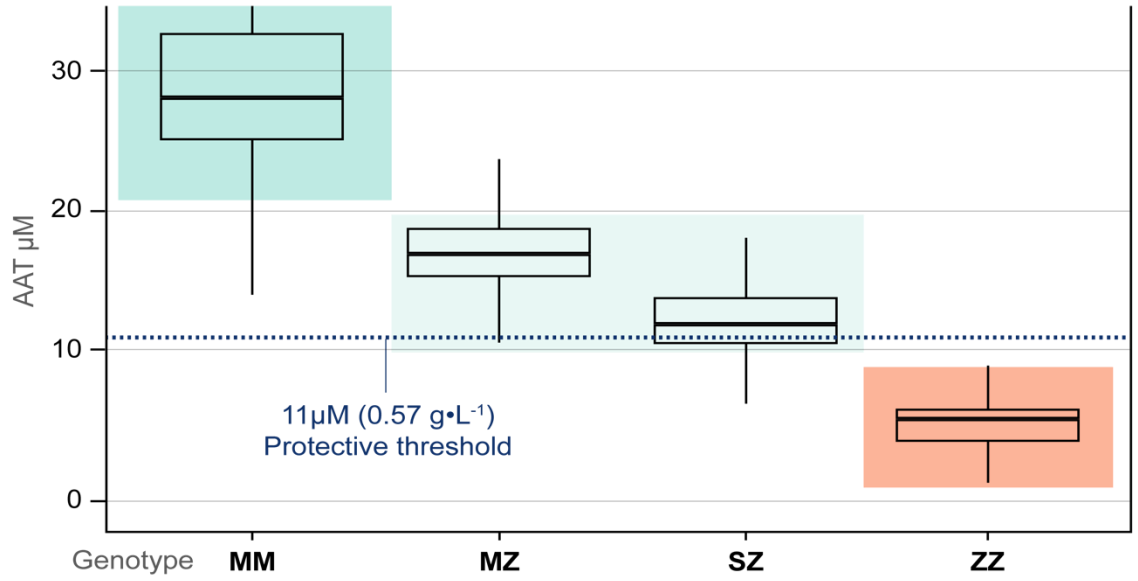
Human genetic validation

- PiM variant is naturally occurring in humans with no reported disease association
- Numerous human SNPs at the same position with no disease association

* Internal BEAM analysis; ** Packer et al. Molecular Therapy (2022) https://doi.org/10.1016/j.ymthe.2022.01.040.

Increasing total AAT levels above protective threshold reduces patients' lifetime risks for lung and/or liver disease

AAT Levels and Disease Manifestations Across Genotypes[1–3]



	No Disease	No Disease Unless Other Risk Factor Present		Disease
Genotype	**MM**	**MZ**	**SZ**	**ZZ**
AAT <11µM	0%	0%	~40%	100%
Emphysema risk	No	Very Low	Low	High
Liver disease risk	No	Possibly	Possibly	High

The goal of treatment with BEAM-302 is to:

- Increase circulating **total AAT** above the 11µM **"protective threshold"**
- **Reduce Z-AAT levels** to prevent ongoing organ damage
- **Restore physiologic control of AAT** during inflammation to minimize lung damage

AAT, alpha-1 antitrypsin; µM, micromolar

1. Franciosi AN, et al. Eur Respir J 2022;59; 2. Vidal R, et al. Arch Bronconeumol (English Edition);42:645–659; 3. Brode SK, et al CMAJ 2012;184:1365–1371