BEAM-302: Targeting AATD-related Liver and Lung Disease with Base Editing

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Beam Therapeutics
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Disclosure/Forward looking statements

- I am a Beam employee and shareholder
Overview

- Introduction to Base Editing with BEAM-302
- *In vivo* data for correction of the PiZ mutation
- Summary and Next Steps
Base editing is a next-generation approach to gene editing with single base precision

<table>
<thead>
<tr>
<th></th>
<th>Nuclease</th>
<th>Base editing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precise targeting?</td>
<td>Yes (guide RNA or ZF/TALE)</td>
<td>Yes (guide RNA)</td>
</tr>
<tr>
<td>Durability of edit?</td>
<td>Permanent</td>
<td>Permanent</td>
</tr>
<tr>
<td>Double strand breaks?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Applications?</td>
<td>Primarily knockout</td>
<td>Correct, modify, activate, multiplex</td>
</tr>
<tr>
<td>Editing predictability</td>
<td>Random insertions and deletions, 100s of uncharacterized edits</td>
<td>Single base edits, All edits fully characterized</td>
</tr>
<tr>
<td>Efficiency of precise edit?</td>
<td>Low – dividing cells only</td>
<td>High – any cell type</td>
</tr>
</tbody>
</table>
Base Editors Chemically Modify Target Bases, Permanently and Predictably

Base editor binds the target DNA and exposes a narrow editing window

Deaminase chemically modifies target base, permanently and predictably

CRISPR-Cas protein → Guide RNA-driven targeting
  ▶ Leverages established DNA targeting ability of CRISPR
  ▶ Modified to not cause double-stranded breaks

Deaminase → Single base editing
  ▶ Completes desired chemical modification at target DNA base
  ▶ Adenine Deaminase for A-to-G editor (“ABE”)
  ▶ Cytidine Deaminase for C-to-T editor (“CBE”)

PiZ allele is due a G-to-A mutation

CRISPR-Cas protein

Guide RNA

Target DNA

Deaminase

A-to-G base editor (“ABE”)

PiM

AATD

PiZ
Alpha-1 Antitrypsin (AAT) Deficiency

<table>
<thead>
<tr>
<th>Normal AAT Function</th>
<th>Genetics</th>
<th>Liver</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type SERPINA1 gene</td>
<td>AAT protein is secreted, protecting lungs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AAT Deficiency</th>
<th>Genetics</th>
<th>Liver</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>E366K (PiZ) mutation</td>
<td>Z-AAT aggregates and causes liver damage/failure</td>
<td></td>
<td>Low functional AAT and presence of Z-AAT polymers in circulation causes lung damage, emphysema, etc</td>
</tr>
</tbody>
</table>

Direct correction of the PiZ mutation through base editing can:
1. Reduce liver toxicity caused by mutant Z-AAT protein aggregates (referred to as polymers)
2. Restore circulating functional AAT and decrease circulating Z-AAT polymers to protect the lungs
Lipid nanoparticle delivery for *in vivo* base editing in liver

**Formulate LNP**
- Lipid
- Base editor mRNA
- gRNA

**LNP uptake**
- i.v. infusion

**Editor+gRNA RNP**
- Nuclear import
- Target DNA (PiZ) binding
- Correction editing
- Expression of corrected A1AT
- Release of mRNA & gRNA
- Translation of editor protein

**Functional AAT secretion**
BEAM-302 treatment led to *in vivo* correction of the PiZ mutation in AATD mouse model

**Liver editing**
- **Corrected alleles**
- **Additional base-edited alleles**
- **Indels**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Max A&gt;G %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>4.8</td>
</tr>
<tr>
<td>0.05mpk</td>
<td>10.9</td>
</tr>
<tr>
<td>0.1mpk</td>
<td>28.0</td>
</tr>
<tr>
<td>0.25mpk</td>
<td>37.3</td>
</tr>
<tr>
<td>0.5mpk</td>
<td>48.7</td>
</tr>
<tr>
<td>0.75mpk</td>
<td>49.2</td>
</tr>
<tr>
<td>1mpk</td>
<td>47.8</td>
</tr>
<tr>
<td>2mpk</td>
<td></td>
</tr>
</tbody>
</table>

**Sequence for correction editing**

ATCGACAAGAAAAGGACTGAAGCTGCTG

**Editing window**

I D K K G T E A A
BEAM-302 resulted in both increased serum total & corrected AAT and decreased serum PiZ AAT in vivo.

Measure secreted AAT in blood 1-week post-dose.
Correction of the PiZ mutation led to decreased liver Z-AAT polymers in NSG-PiZ mice.

Reduction in toxic liver polymers

Liver Z-AAT levels by LC-MS being established
Increased serum AAT from BEAM-302 dosing corresponded to increased functional serum AAT

Collect serum from dosed NSG-PiZ mice

Incubate with human neutrophil elastase

Measure inhibition of neutrophil elastase activity as functional AAT

Functional AAT

![Graph showing functional AAT levels](image)

* P<0.05, ***P<0.005, ****P<0.0005
One-way ANOVA with Sidak's Multiple Comparison test
In vivo correction of the PiZ mutation with BEAM-302 was durable

BEAM-302 LNP

i.v. delivery

NSG-PiTZ Mouse (>10 PiZ copies)

1-week, 13-week

Sequence for correction editing

Liver editing (correction)

Max A>G %

0 20 40 60

Vehicle BEAM-302 0.25mpk Vehicle BEAM-302 0.25mpk

1-week 13-week

Corrected Alleles
Additional base-edited alleles
Indels

Increased editing likely due to survival advantage of corrected hepatocytes

A novel knock-out/knock-in humanized PiZ rat

**Targeted Rat Serpina1**

- Knock-out WT PiM allele(s)
- Insert mutant PiZ allele(s)

**KO-KI SERPINA1 allele**

- huSERPINA1 c.1096G>A (PiZ)
- SV40-pA

**hSERPINA1 PiZ rat**

- Background strain: Sprague-Dawley
- Immunocompetent: Yes
- Rat AAT: No
- AAT genes (copy number): Human PiZ (1:1 replacement)
- hAAT serum levels: 3.6 uM (18 wks)

**AAT protein (LC-MS)**

- Normalized MS Peak Area
- Human AAT
- Rat AAT

**Background strain**

- Sprague-Dawley

**Immunocompetent**

- Yes

**Rat AAT**

- No

**AAT genes (copy number)**

- Human PiZ (1:1 replacement)

**hAAT serum levels**

- 3.6 uM (18 wks)
Correction of the PiZ mutation with BEAM-302 in PiZ rats was dose dependent

Sequence for correction editing

Liver editing

Max A>G %

- Corrected alleles
- Additional base-edited alleles
- Indels

PiZ Rat (2 copies of PiZ)

1-week

i.v. delivery

BEAM-302 LNP
PiZ mutation correction by BEAM-302 resulted in both increased serum total & corrected AAT and decreased serum PiZ AAT in rats.

Measure secreted AAT in blood 1-week post-dose.
Summary

AAT Deficiency

BEAM-302

✓ Corrects the PiZ mutation to restore SERPINA1 gene function
✓ Decreases Z-AAT polymers in liver
✓ Increase circulating functional AAT and decrease Z-AAT in two rodent models

Next steps

▸ Complete CTA/IND-enabling studies: Efficacy, Biodistribution, Safety and Toxicology
▸ Submit a CTA/IND application in early 2024 to investigate BEAM-302 in first-in-human clinical studies
Together,

with our partners in the AAT deficiency community, academia, industry, and regulators, we hope to bring new treatment options to patients and families living with AAT deficiency.
Questions?