Single, Systemic Administration of BEAM-301 Mitigates Fasting Hypoglycemia and Restores Metabolic Function in a Transgenic Mouse Model of Glycogen Storage Disease Type-Ia

Yvonne Aratyn-Schaus

May 16, 2022
I am a Beam employee and shareholder
Base-editing strategy to treat Glycogen Storage Disease Type Ia

- GSDIa is a genetic disease caused by mutations in the G6PC gene encoding G6Pase, a predominantly liver-expressed enzyme vital to glucose metabolism.

- Beam’s base editing technology has the potential to permanently correct these mutations and restore regulation of glucose metabolism.

Fasting hypoglycemia can be acutely fatal

No cure

Strict regimen of slow-release glucose required

Long-term complications include,
  - Hyperlipidemia
  - Elevated lactic and uric acid
  - Hepatic steatosis, HCC
Base Editors Generate Permanent and Predictable Single Nucleotide Substitutions

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

Deaminase chemically modifies target base, A>G edit made permanent by DNA repair/replication.

Gene Correction – Direct repair of point mutations to restore gene function.

A-to-G base editor (“ABE”)
What is BEAM-301?

- **BEAM-301 is an *in vivo* base-editing development candidate**
- BEAM-301 is a lipid nanoparticle (LNP) formulation containing a mRNA encoding an adenine base editor and a gRNA that directs the correction of the *G6PC-p.Arg83Cys* variant
- The mRNA and gRNA are encapsulated in LNPs, which protect and transport them to hepatocytes
Single BEAM-301 dose yields robust rate of R83C correction in livers of transgenic huR83C mouse model

- The huR83C GSD-la mouse model harbors human G6PC- p.Arg83Cys transgene in place of mouse G6PC
- BEAM-301 administered via tail vein (adult) or temporal vein (newborn) in heterozygous or homozygous huR83C mice (due to pre-weaning lethality in homozygotes)
- NGS analysis in total liver extracts yield
  - ~40% base-editing efficiency in adults
  - A range, up to ~60% in newborns
- Next step: Functional benefit via base-editing in newborn homozygotes

* Base-editing evaluated at 7d post dose in adults, 3wks post dose in newborns
BEAM-301 improves long-term survival and restores normal growth in homozygous huR83C mice

- Homozygous huR83C mice on glucose-supplementation exhibit growth impairment relative to wild-type and heterozygous littermates
- Single-dose of BEAM-301 yields **improved survival and normal growth trend**
Reduction in liver size in BEAM-301-dosed homozygous huR83C mice

- Glucose-supplemented huR83C homozygotes exhibit enlarged livers, hepatocyte size, and elevated lipids
- BEAM-301-induced base editing is associated with **reduction in liver size and lipid deposition**
Restoration of hepatic G6Pase activity at single-digit base-editing rates for R83C correction

- Restoration of G6Pase activity at clinically-relevant levels achieved at single-digit base-editing efficiencies for R83C correction
- Durable effect; correlation maintained to early adulthood
Decline in hepatic Glucose-6-Phosphate (Glc-6-P) levels at ≤10% base-editing rates for R83C correction

- Decline in hepatic Glc-6-P levels, approaching average healthy (WT) levels
- Will restoration of glucose homeostasis mitigate fasting hypoglycemia? Restore serum metabolites?
Homozygous huR83C mice survive a 24h fasting challenge more than 8 weeks after BEAM-301 dose

- 100% of homozygous mice survive a 24-hr fasting challenge, some with as little as 1% base-editing
- Blood glucose levels maintained above hypoglycemic threshold, at levels of healthy control animals
- Ongoing long-term studies include successful fasting challenge at 20wk and 35wk (data not shown)
Durable maintenance of near-normal serum metabolites in BEAM-301 treated homozygous huR83C mice

- Glucose-supplemented huR83C homozygotes exhibit elevated serum metabolites
- Through early adulthood, huR83C homozygotes administered BEAM-301 exhibit near-normal secondary serum metabolites (including subjects with single-digit base-editing rates)
Summary and Next Steps

- **BEAM-301 Preclinical Pharmacology**
  - Up to ~60% base-editing efficiency
  - Long-term survival, with normal body weight and liver weight
  - Restoration of clinically-relevant hepatic G6Pase activity
  - Survival through a 24hr fast with single-digit base-editing rates
  - Normal secondary serum metabolites in adult mice

- **Preliminary low-risk off-target profile (ongoing)**
  - Guide-dependent off-target base editing detected at 3 intergenic sites in primary human hepatocytes (<0.9% editing at a saturated dose)
  - No evidence of upregulated guide-independent A>G mutagenesis in WGS of clonally expanded immortalized cells

- **Next steps**
  - Ongoing durability studies in BEAM-301-dosed huR83C mice
  - Continued off-target evaluation
  - IND-enabling studies
Thank You

NIH
• Irina Arnaoutova
• Lisa Zhang
• Janice Chou

Beam Therapeutics, Inc.
• Dominique Leboeuf
• Steven Boulé
• Monique Otero
• Tom Fernandez
• Thomas Leete
• Raymond Yang
• Lauren Young
• Yingying Zhang
• Ka Wai Mok
• Minglun Wang
• Luis Barrera
• Maya Sen

• Lo-I Cheng
• Genesis Lung
• Krishna Ramanan
• Faith Musenge
• Delai Chen
• J. Robert Dorkin
• Jeremy Decker
• Sarah Smith
• Michael Packer
• Francine Gregoire
• Giuseppe Ciaramella