BeCoMe–9: A Phase 1/2 Dose Escalation and Expansion Study of BE-101 for the Treatment of Adults with Moderately Severe or Severe Hemophilia B

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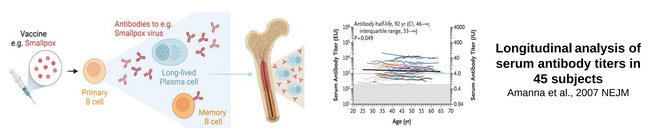
Background

Despite advances in treatment options for people with hemophilia B, significant unmet needs remain, notably disease and treatment burden. To address the unmet need, we developed BE-101 that has the potential to provide durable FIX coverage, while having the option to be titratable and redosable enabling treatment of both adult and pediatric patients and independent of AAV seropositivity. BE-101 is a first-in-class B cell medicine (BCM) comprised of expanded and differentiated B lymphocyte lineage cells that have been genetically engineered to express and secrete Factor IX (FIX). Participants' B lymphocyte lineage cells are collected through leukapheresis, edited ex vivo using CRISPR/Cas9 followed by AAV-mediated homology-directed repair to precisely insert a human *F9* gene encoding full length FIX protein (activity-enhanced Padua variant) into the CCR5 safe harbor gene locus. The terminally-differentiated human plasma cell BCMs derived from these precision gene engineered cells potentially offer natural persistence for decades, the capacity to secrete high levels of protein, the ability to engraft without host preconditioning, and re-dosability, thus making them an attractive platform for durable and titratable therapeutic effects in adolescents and children as well as adults. A robust nonclinical data package including comprehensive genome safety assessments as well as short and long-term *in vivo* studies was submitted and cleared as an Investigational New Drug (IND) application to the US FDA and Clinical Trial Application (CTA) to Health Canada. The FDA later granted orphan drug and fast track designation for BE-101. The clearance of these applications has enabled the initial clinical trial, the **BeCoMe-9** Study, to open to enrollment.

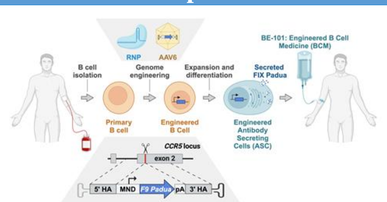
Leveraging B Cell Biology to Create a New Generation of Cellular Medicines with Long-Term Protein Production



Longitudinal analysis of serum antibody titers in 45 subjects
Amanna et al., 2007 NEJM

1. **Constant protein production**; 1000s of molecules/cell/sec
2. **Longevity:** native human plasma cells can persist for decades
3. **Ease of Administration:** engraft without conditioning

Ex-Vivo Gene Edited Cell Therapy, Engineered to Express & Secrete FIX for Hemophilia B

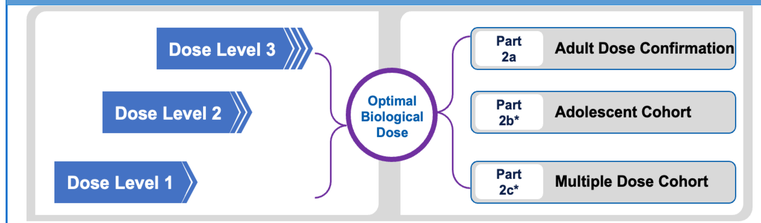


Mechanism of Action:
Restoration of FIX activity via B-cell mediated continuous secretion of active FIX Padua protein

BeCoMe-9: A Phase 1/2 First-in-Human Dose Escalation Study for People with Hemophilia B

The **BeCoMe-9** Study (Study BE-101-01) is a Phase 1/2, first in human, multi-center, open-label, dose-escalation study to evaluate the safety and clinical activity of a single intravenous (IV) dose of BE-101 in adults with moderately severe or severe Hemophilia B (<2 IU/dL FIX). Once infused, BE-101 is designed to engraft and continuously secrete FIX into the circulation to restore clinically meaningful levels of functionally active FIX.

Study Design and Methods



*Additional Part 2 Cohorts to be opened based on safety and activity data collected in Part 1.

The study includes two distinct parts: Part 1 and Part 2. In Part 1, an ascending-dose design will be utilized to enable evaluation of increasing doses in a stepwise manner. The objective for this dose escalation is to identify the dose of BE-101 required to achieve FIX activity at or above 15% of normal activity 28 days after infusion while also minimizing the number of participants who are potentially exposed to subtherapeutic or unsafe doses. Upon identification of a safe and efficacious dose in Part 1 an expansion phase (Part 2) will initiate. The initial cohort in the Part 2 expansion (Part 2a) phase will include up to 6 adult participants to further characterize the safety and activity of BE-101 at the selected dose. Further cohorts (Part 2b and 2c) to evaluate BE-101 both in adolescents and in a multiple dose setting are also planned upon completion of Part 1.

Study Flow and Follow-up

Up to 24 participants will be enrolled across Part 1 (up to 18) and Part 2a (up to 6). Consented participants will complete a screening period to assess eligibility and upon enrollment will undergo leukapheresis collection to support BE-101 manufacturing. Following administration, participants are monitored for safety and clinical activity. The total duration of study participation is approximately 52 weeks (1 year) post-IV administration of BE-101. Following one year, a long-term follow-up program will be opened to evaluate long term safety effects.

Participant Eligibility Criteria

Key Inclusion Criteria

- ❑ Adult males (≥18 yrs.) w/ severe or moderately severe hemophilia B defined as:
  - Plasma FIX activity ≤2% historically & confirmed at baseline
  - Currently receiving prophylaxis treatment
  - Received ≥50 exposure days to FIX products prior to enrollment
- ❑ Adequate organ function and clinical labs
- ❑ Able to tolerate study procedures including leukapheresis

Key Exclusion Criteria

- ❑ Pre-existing or history of specific diseases including:
  - B-Cell malignancy, EBV lymphoproliferative disease
  - Primary immunodeficiency disease or disorder (PIDD) or systemic immuno-suppression
  - Arterial and/or venous thromboembolic events within 2 years prior to dosing
  - History of anaphylaxis or nephrotic syndrome
  - Active infection (HIV, Hepatitis B or C)
- ❑ History of inhibitor to FIX or inhibitor detected during screening
- ❑ History of an allergic reaction or anaphylaxis to FIX products
- ❑ Planed surgical procedure within 6 months from BE-101 administration
- ❑ Previously dosed with gene therapy
- ❑ Participated in an interventional clinical study within 60 days of administration of BE-101 or planned participation in clinical trial within one year after BE-101
- ❑ Administration of a vaccine within 28 days of dosing

Summary

Be Biopharma is developing BE-101, a novel precision engineered B cell medicine, for the treatment of people with moderately severe to severe hemophilia B.

- ✓ A robust nonclinical program has confirmed BE-101's mechanism of action and demonstrated a favorable safety profile.
- ✓ No BE-101-related safety findings were observed in multiple short and long-term *in vivo* studies.
- ✓ U.S. FDA cleared the IND application & granted Fast Track and Orphan Drug Designation for BE-101. Health Canada cleared the CTA application
- ✓ **The BeCoMe-9 Study is now recruiting participants at multiple centers in US (NCT06611436)**

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