First-in-Human Phase 1/2 Clinical Trial of SIG-001, an Innovative Shielded Cell Therapy Platform, for Hemophilia A

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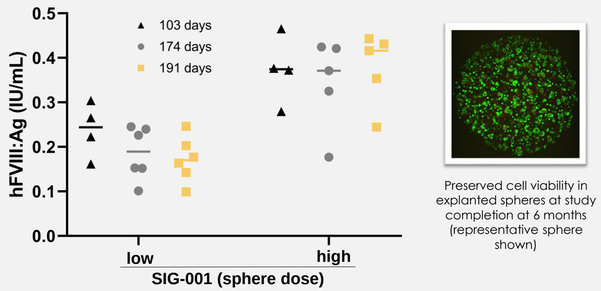
Introduction

- **Hemophilia A** arises from pathogenic variants in the *F8* gene, affecting ~ 1/5000 males.
- Treatment options include frequent IV factor and subcutaneous (SC) non-factor therapies; however they have limitations such as:
  - non-ideal factor kinetics
  - morbidity from breakthrough bleeds, including chronic joint disease
  - impaired quality of life
  - inhibitor development
  - treatment burden (life-long, frequent IV/SC administration)
  - risk of thrombotic events and coagulation test interference with newer non-factor therapies.
- **Cell therapy** with allogeneic, genetically modified cells, is a new potential approach for many diseases, including hemophilia A.
- Genetically modified allogeneic cells have to be physically protected from the host's immune cells as experience in diabetes has shown (Lim Science 1980).
- Biomaterials can physically protect the cells but they themselves activate foreign body response resulting in pericapsular fibrotic overgrowth (PFO).
  - **PFO significantly limits efficacy and durability of these cell-based therapies and is one of major challenges in allogeneic cell therapy development.**
- Sigilon utilized small molecules that avoid PFO when conjugated to alginate biomaterials (Bochenek Nat Biomed Eng 2018) to create a **modular, cell-based platform** (Barney ASGCT 2020) with potential for utilization across a range of chronic diseases, including rare blood disorders.
  - This platform provides both the **essential physical shield** from cell-to-cell interaction, as well as the **prevention of PFO**.
  - The shielded spheres are placed in the peritoneal space where they can absorb nutrients while the released therapeutic protein can enter the blood compartment.

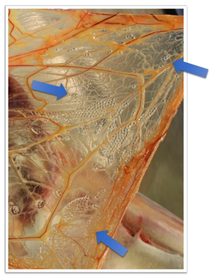
Summary of Preclinical Data for SIG-001



Preserved cell viability in explanted spheres at study completion at 6 months (representative sphere shown)

Given the expected immune response to human FVIII exposure in immunocompetent mice, NSG mice were used in this long-term preclinical study. Low or high doses of SIG-001 were placed in the IP space. hFVIII levels were measured by ELISA. Spheres were explanted at the study completion (191 days) and evaluated for viability and hFVIII productivity.

- SIG-001 can produce functionally **active hFVIII in a dose-dependent manner**, **correct the bleeding phenotype in hemophilia A mice**, and produce sustained long-lasting hFVIII levels (Carmona ASH 2019).
- SIG-001 was further evaluated in IND-enabling studies, including testing in non-human primates (**NHP**).
- Empty spheres were administered to the NHP intraperitoneally via laparoscopic procedure.
- At the study completion (**180 days**) **no PFO observed** (spheres on greater omentum; image to the right).
- In summary, preclinical studies in multiple species showed **no concerning signals in the safety or toxicology profile of SIG-001** (Carmona ISTH 2020).

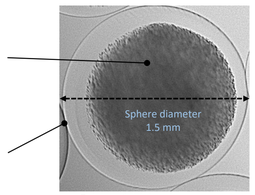


SIG-001-121 Clinical Trial Design

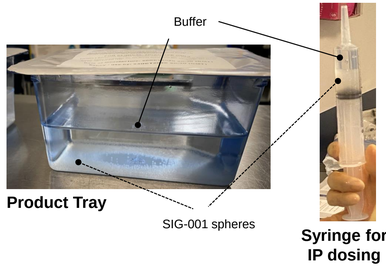
Investigational Product SIG-001: Cell Line Modified with a Non-Viral Vector to Express hFVIII, Encapsulated within Modified Alginate Spheres

Inner Compartment:
- genetically modified human cells that express BDD-hFVIII
- modified alginate designed to optimize cell function

Outer Layer:
- modified alginate chemically linked to small molecule to minimize PFO



Bright field microscope image of a SIG-001 sphere

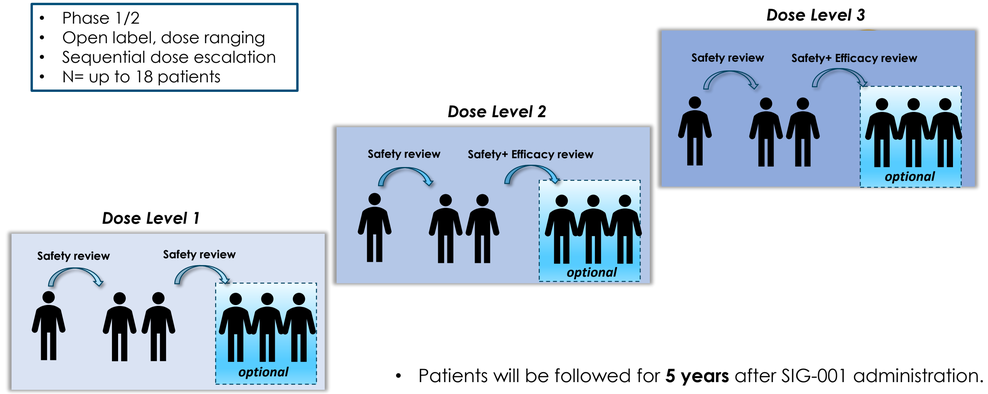


Syringe for IP dosing

- SIG-001 is a **buffered suspension of 1.5 mm alginate spheres** encapsulating hFVIII-expressing human cells (final tray in the middle photo, syringe loaded with sphere suspension on the right).
- **SIG-001** will be administered into the **peritoneal cavity** using a short **laparoscopic procedure**.

SIG-001-121 Study Schema

- Phase 1/2
- Open label, dose ranging
- Sequential dose escalation
- N= up to 18 patients



- Patients will be followed for **5 years** after SIG-001 administration.

SIG-001-121 Study Endpoints

Primary endpoints:
- **Safety**, including clinically significant changes in vital signs, physical exam, hematology and blood chemistry
- Treatment emergent adverse events

Secondary endpoints include:
- FVIII levels by one-stage and chromogenic assays (central lab)
- Annualized bleeding rate
- Annualized FVIII use
- FVIII inhibitors

Exploratory endpoints include changes in:
- Health, QoL, and Physical Activity Questionnaires
- Number and frequency of bleeds in target joints
- Hemophilia Joint Health Score (HJHS)

- Results will be analyzed using descriptive statistics.

SIG-001-121 Planned Study Sites

*as of December 2020

SIG-001-121 Patient Population

Key Inclusion Criteria:
- Adult males (≥18 years of age)
- Severe (<1% FVIII activity) or moderately-severe HA (≥1% - ≤2% FVIII activity)
- ≥150 exposure days to FVIII product(s)
- Normal levels of vWF antigen

Key Exclusion Criteria:
- Current or past FVIII inhibitors or immune tolerance induction (ITI)
- Prior administration of a gene therapy product
- History of allergic reaction to recombinant FVIII products
- Unable to undergo anesthesia or laparoscopy

Contact/Further Information

- **SIG-001** has been granted **orphan designation** by the US FDA
- **ClinicalTrials.gov** Study Number: NCT04541628
- **EudraCT** Study Number: 2019-004210-33
- **Sponsor Contact:** clinicaltrials@sigilon.com

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