SIG-001 for Hemophilia A: Preclinical Safety and Efficacy Studies Conducted in Mice and Non-Human Primates

PB1153

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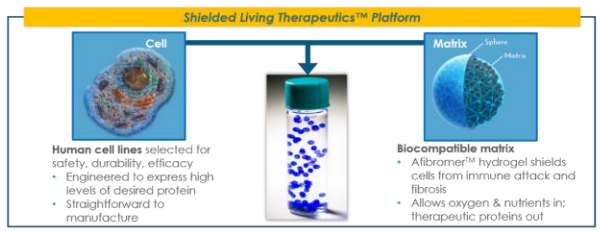
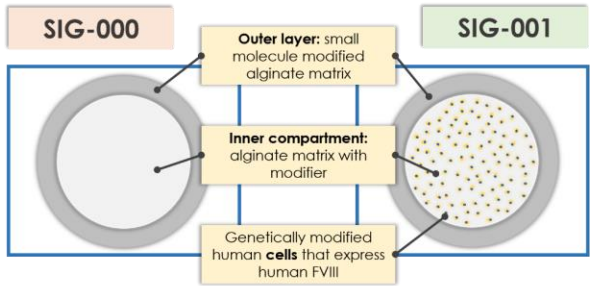
Introduction

- Treatment options for Hemophilia A include frequent IV factor or SC non-factor therapies which have limitations such as:
  - breakthrough bleeds and joint disease due to suboptimal adherence
  - non-ideal factor kinetics/peaks & troughs
  - inhibitor generation
  - risk of thrombotic events and coagulation test interference with newer non-factor therapies
- **Alternative modalities such as cell therapies with genetically modified, human cells are being investigated**
- Various biomaterials, e.g. hydrogels, could serve as the physical barrier between the cells and the host
- However, the host can still activate a foreign body response to the biomaterial resulting in pericapsular fibrotic overgrowth (PFO)
- We have successfully identified a library of proprietary small molecules which reduce PFO when conjugated to alginate spheres (Bochenek, Nat Biomed Eng 2018)

The Shielded Living Therapeutics™ Platform



- **SIG-001**, our most advanced candidate, consists of genetically modified human cell line engineered to produce human FVIII, encapsulated in a two-compartment sphere
- **The objective** of this study was to ensure safety of SIG-001 and its components for entry into the clinic



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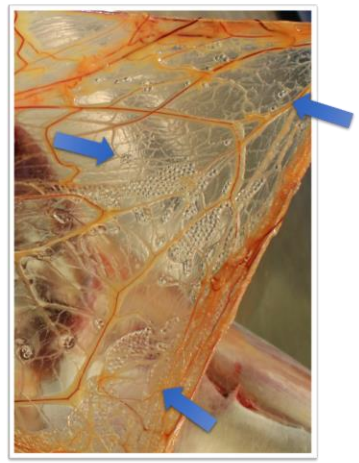
Methods and Results

SIG-000 (Empty Spheres)

- Empty spheres (SIG-000) consist of the outer layer of the sphere and the inner matrix
- Empty spheres do not have genetically modified cells in them

Well Tolerated in Non-Human Primates

- SIG-000 was administered to the Cynomolgus monkey either into the bursa omentalis (lesser sac) or the general peritoneal space (greater sac) via minor laparoscopic surgery
- At the end of the 180-day recovery period, complete necropsy was performed (image of omentum below)



- **The administration of SIG-000 (empty spheres) was well tolerated, with no adverse effects noted**

Genotoxicity and Biocompatibility

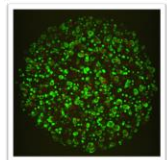
- SIG-000 empty sphere extracts **were neither cytotoxic nor mutagenic** based on the mouse lymphoma forward gene mutation assay and bacterial reverse mutation studies
- The US FDA recognizes alginic acid and alginates as GRAS (generally recognized as safe) per 21 CFR 184.1724
- The **empty spheres were not considered a sensitizer** in the guinea pig maximization test, showed no evidence of causing cell lysis or toxicity to mouse fibroblast cells, were not an irritant following intracutaneous injection in the rabbit and were not pyrogenic in the rabbit

SIG-001 (Final Product)

- SIG-001 consists of genetically modified human cell line engineered to produce human FVIII, encapsulated in a two-compartment sphere
- The multiple integrations of hFVIII-BDD in the modified epithelial cell line are in well-defined sites within open chromatin and will likely result in long-term expression of the transgene

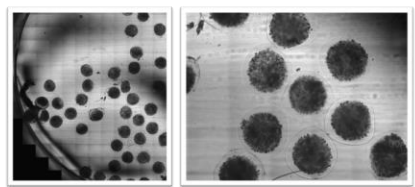
Single Dose Toxicity Study in NSG Mice

- A single dose of SIG-000 or SIG-001 was placed in intraperitoneal space in NSG mice. The mice were followed for 6 months.



Cell viability in the explanted sphere after 6 months

- **There was no impact on:**
  - PFO
  - Mortality
  - Clinical observations
  - Body weight
  - Food consumption
  - Clinical pathology
  - Macroscopic findings
  - Organ weights
  - Histopathology
  - Cell viability



The spheres were intact and without PFO after 6 months in the NSG mice

Broken Spheres Toxicity Study

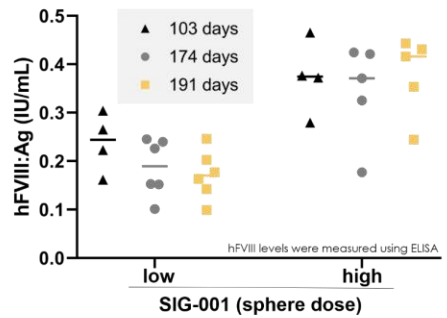
- A single administration of intact or 50% intentionally broken spheres (SIG-001, SIG-000 or spheres containing mouse surrogate cells) did not result in any toxicologically relevant, test article-related changes in mortality, clinical observations, clinical pathology parameters (hematology, and clinical chemistry), gross necropsy findings, organ weights or gross and microscopic anatomic pathology.
- **Thus, integrity of the administered spheres did not alter host tolerability**

Conclusions

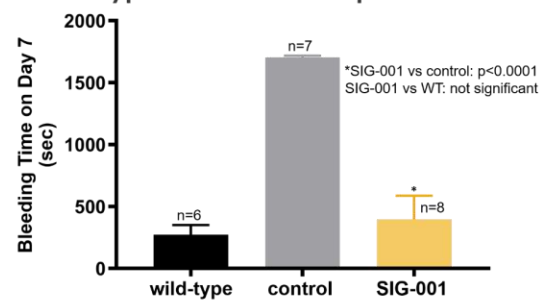
- These safety studies, combined with the *in vivo* efficacy data, indicate no findings in safety/toxicology profile of SIG-001; SIG-001 produces sustained long-lasting hFVIII levels in NSG mice
- The first-in-human trial of SIG-001 in Hemophilia A is planned to open in 2020

Efficacy

SIG-001 Delivers Sustained hFVIII Production in NSG Mice at 6 Months



SIG-001 Corrects the Tail Bleeding Phenotype *in vivo* in Hemophilia A Mice



control: HA mice with spheres containing unmodified cells