Safety and Pharmacodynamic Effects of Novel Fully Human Anti-Thymocyte Polyclonal IgG Antibodies in an IND Enabling GLP Toxicology Study

First in Class, Human ATG (SAB-142) Therapeutic Developed to Delay Onset and Progression of Type 1 Diabetes

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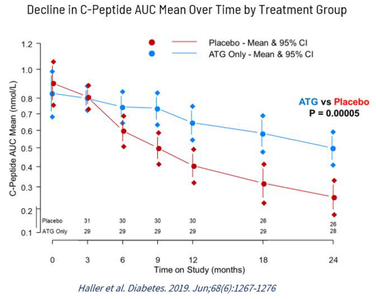
Abstract

- SAB-142 is a first-in-class fully human polyclonal immune modulating anti-thymocyte immunoglobulin (hATG) produced in SAB Biotherapeutics' proprietary Transchromosomic (Tc) Bovine platform.
- SAB-142 is expected to be efficacious, non-immunogenic, and well tolerated when used in humans, as previously demonstrated by several clinical phase investigational products produced in the in the Tc Bovine™ platform. In contrast, other anti-thymocyte immune modulating agents currently on the market, such as rabbit ATG (rATG, Thymoglobulin) or equine ATG (ATGAM), are known to cause serum sickness and severe hypersensitivity reactions in humans.
- Tc bovines that produce fully human polyclonal antibodies underwent a series of immunizations with human thymocytes. Post immunization plasma was processed into (SAB-142). *In vitro* characterization of SAB-142 demonstrated minimal red blood cell binding, higher complement-dependent cytotoxicity (CDC) and similar binding to human PBMCs as compared to rabbit ATG (rATG).
- In an IND-enabling GLP NHP study, a single infusion of SAB-142 was administered at 1, 5, and 10 mg/kg (6 animals per dose) and rATG was administered at 5 mg/kg (6 animals). All 24 animals were assessed for safety and pharmacological activity with clinical assessments, clinical labs and PBMCs collected at various timepoints. Analysis of peripheral blood lymphocyte populations post-treatment showed dose-dependent impact on total lymphocytes and memory $CD4^+$ and CD^+8 T lymphocytes through day 28.
- Our data suggest that SAB-142 (hATG) demonstrates safety and dose-dependent pharmacological activity in NHPs. These results support an Investigational New Drug (IND) application for clinical investigation of SAB-142 in clinical trials as a potential disease-modifying treatment for Type 1 Diabetes (T1D) and other autoimmune diseases.

Background

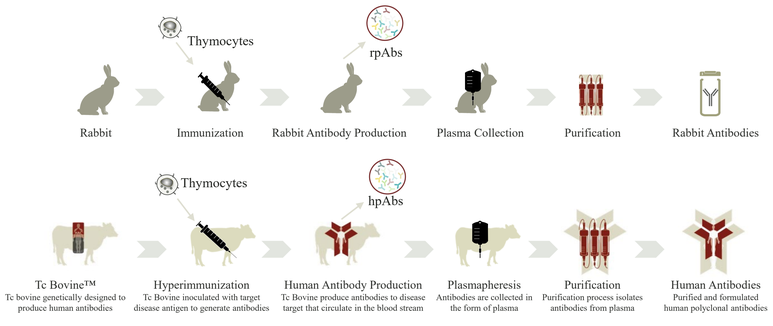
Type 1 Diabetes and Clinical Intervention with Anti-Thymocyte Immunoglobulin (ATG)

- Type 1 Diabetes (T1D) affects 1 in 300 Children and accounts for 1 in 7 health care dollars.
- Since 2000, the prevalence of T1D has increased at four times the rate of the global population.
- As of 2021, an estimated 8.4 million people are living with T1D globally with a predicted increase to 13.5-17.4 million by 2040.
- T1D is currently not preventable nor curable and is only managed via life-long administration of insulin.
- Rabbit ATG, FDA-approved for kidney transplantation, was used experimentally in clinical trials and showed a delay progression of T1D but is associated with significant adverse reactions such as serum sickness related to animal origin of antibody.
- **SAB-142 is a first in class fully human ATG therapeutic produced in SAB's Tc Bovine platform.**



Haller et al. Diabetes. 2019. Jun;68(6):1267-1276

- **SAB-142 was produced using a process similar to rATG but is expected to be non-immunogenic and well-tolerated when used in humans,** as previously demonstrated in several Phase 1-3 clinical trials with investigational products produced in SAB's Tc Bovine platform.



IND-Enabling GLP NHP Toxicology Study Design

A single infusion of SAB-142 (hATG) or rATG was administered to cynomolgus monkeys, and all 24 animals were assessed for safety and pharmacological activity with clinical assessments, clinical labs and PBMCs collected at various timepoints.

Group No.	Test Material	Dose Level (mg/kg)	No. of Males	No of Females
1	rATG	5	3	3
2	SAB-142	1	3	3
3	SAB-142	5	3	3
4	SAB-142	10	3	3

Results

SAB-142 (hATG) has Potential for a Best-in-Class Safety Profile with Higher Potency Compared to rATG

A) Better Safety Profile

Red Blood Cell Binding

Sample	Activity (µg/mL)
rATG	20
SAB-142	**280**

B) Higher Potency

Complement-dependent cytotoxicity (CDC)

Sample	Mean EC_{50} ±SD (µg/mL)
rATG	162 ± 8
SAB-142	**22 ± 2**

Figure 1. Red Blood Cell Hemagglutination and Complement-Dependent Cytotoxicity (CDC)

A) The Hemagglutinin (HA) Titer was determined by the following formula: (Protein conc/endpoint titer/dilution)*1000 = relative active concentration of antibody to cause complete agglutination of the red blood cells. (Higher number = decreased RBC binding (desired). **B)** CDC activity was measured in human PBMCs using human complement. N=4 replicates (Lower number = higher activity/potency)

SAB-142 (hATG) Demonstrates Proportional Binding to Human T Cell Subsets as rATG

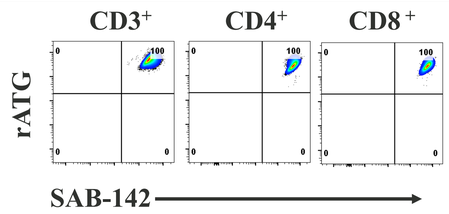


Figure 2. Binding affinity of SAB-142 and rATG to $CD3^+$, $CD4^+$, $CD8^+$ T lymphocytes

PBMCs were co-incubated with the respective fluorescently labeled CD marker and fluorescently labeled preparations of SAB-142 and rATG. Cell populations were gated for the respective CD marker and assessed for labeling by SAB-142 and rATG

SAB-142 (hATG) Demonstrates Similar Immunomodulatory Effect on Human T Cell Subsets *in vitro* as rATG

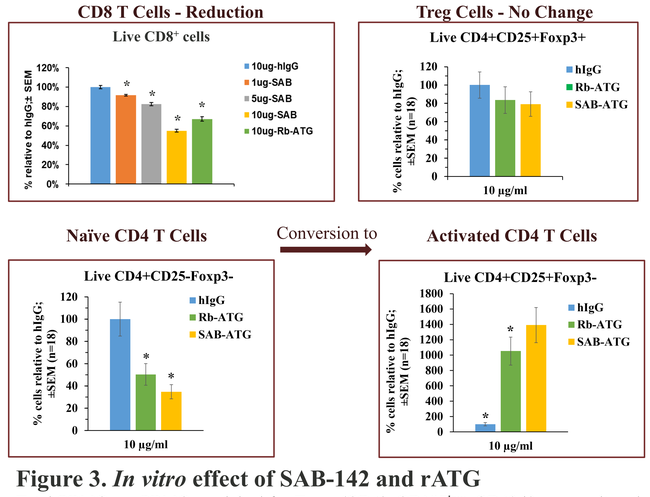


Figure 3. *In vitro* effect of SAB-142 and rATG

Total PBMCs or PBMCs enriched for Tregs ($CD4^+$, $CD127^{low}$, $CD49d^-$) were cultured with SAB-142 or rATG overnight. Cells were then stained as indicated and analyzed by flow cytometry. * Indicates $p<0.05$ compared to negative control hIgG.

SAB-142 (hATG) modulates $CD4^+$ and $CD8^+$ Memory T cell subsets *in vivo* similarly to rATG in an NHP GLP Study

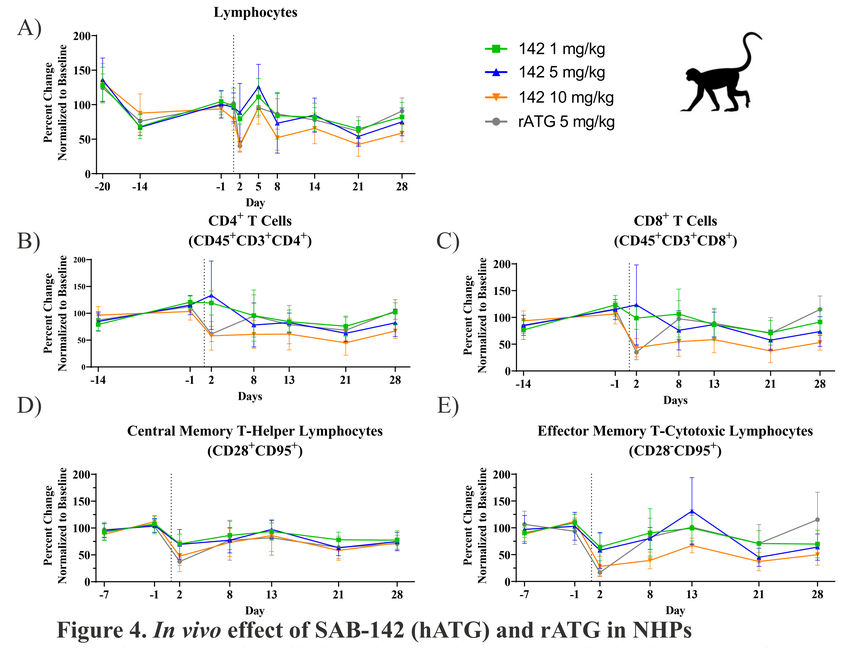


Figure 4. *In vivo* effect of SAB-142 (hATG) and rATG in NHPs

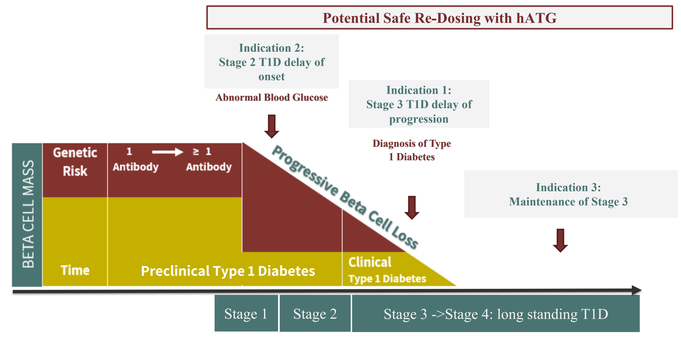
A) Lymphocyte counts, obtained by hematological analysis, were normalized to the average pre-dose counts (collected on days -20, -14, -1 and 1). **B-E)** Absolute counts of the indicated subsets were normalized to the average pre-dose counts (collected on days -14 and -1 or days -7 and -1 as indicated). Vertical dotted line indicates time of dosing with either SAB-142 or rATG. Error bars show standard deviation.

Conclusions

- SAB-142 is a first in class, fully human polyclonal ATG that demonstrates safety and dose-dependent anticipated pharmacologic effects in NHPs in a GLP Toxicology Study.
- SAB-142 demonstrates the following:
  - Minimal Red Blood Cell binding and higher CDC activity compared to rATG, suggesting less potential adverse effects with higher potency.
  - Proportional binding to human T Cell subsets ($CD3^+$, $CD4^+$, and $CD8^+$) as rATG.
  - Similar *in vitro* immunomodulatory activity in T lymphocyte subsets as rATG.
  - Modulation of central memory $CD4^+$ and effector memory $CD8^+$ T lymphocyte populations *in vivo* in cynomolgus monkeys, similarly to rATG.
- The successful completion of a GLP Tox study is a significant IND enabling milestone in the development of SAB-142.

Future Clinical Impact

These data support clinical trials to determine if SAB-142 can prevent and/or delay the progression of Type 1 Diabetes with an enhanced safety profile over current approaches.



Acknowledgements

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