Immunomodulation without Sustained Lymphodepletion: SAB-142, a Fully Human Anti-Thymocyte Globulin

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Unless otherwise specified, information is current at the date hereof.

SAB-142 is a Fully Human, Multi-Specific, Targeted Anti-Thymocyte Globulin (hATG) for Delaying Onset and Progression of T1D

POTENTIAL DISEASE MODIFICATION

Lead candidate SAB-142 has the **potential to deliver disease modification in newly diagnosed Stage 3 T1D with convenient twice-yearly dosing,** supported by clinical data and a de-risked mechanism of action

POSITIVE PHASE 1 DATA SUPPORTS DE-RISKED MOA

Phase 1 data show SAB-142 has an MOA comparable to rabbit ATG, **with improved safety and potential for repeat dosing**, supporting advancement into the Phase 2b SAFEGUARD study

UNIQUE MULTI-SPECIFIC ANTIBODY PLATFORM

First-ever platform that can generate a diverse repertoire of **multi-specific, targeted, anti-thymocyte human IgG**

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SAB-142-101
Phase 1 Study Design

Randomized, double-blind, placebo-controlled, single- and multiple ascending dose, adaptive design clinical study in healthy volunteers and patients with established T1D

Total n=68 subjects Randomized:

HVs n=62
T1D patients n=6

Repeat dosing	n=8
4.5 mg/kg	n=8
2.5 mg/kg	N=22
1.5 mg/kg	n=8
0.5 mg/kg	n=16
0.1 mg/kg	n=8
0.03 mg/kg	n=6

SAB-142 demonstrated clinically validated multi-specific MOA with sustained immunomodulation

Safety & Tolerability — Data strongly position SAB-142 for potentially safe & reliable chronic dosing

- Does not cause lymphodepletion (no depletion of T-cells including Tregs, B cells, NK cells)
- Does not cause neutropenia, sustained decrease in RBCs or thrombocytes

PK/PD — Data demonstrate sustained "T-cell exhaustion" signature

- Clinically validated by rabbit ATG and other T1D T-cell targeting immunomodulatory drugs
- Proven to correlate with C-peptide preservation based on clinical studies in new onset T1D

No serum sickness & low/no immunogenicity — Data confirm SAB-142 is not immunogenic

- Does not cause serum sickness
- Does not induce anti-drug antibodies

SAB-142-101
Phase 1 Top Line

SAB-142 CD4+ T conv Cell Single Exhaustion Markers

SAB-142 induced sustained expression of inhibitory receptors (PD-1 and TIGIT) on CD4+ T conv cells indicative of an exhausted phenotype.

SAB-142: combined 1.5mg/kg and 2.5mg/kg dosed cohorts

SAB-142 CD4+ T conv Cell Dual Exhaustion Markers

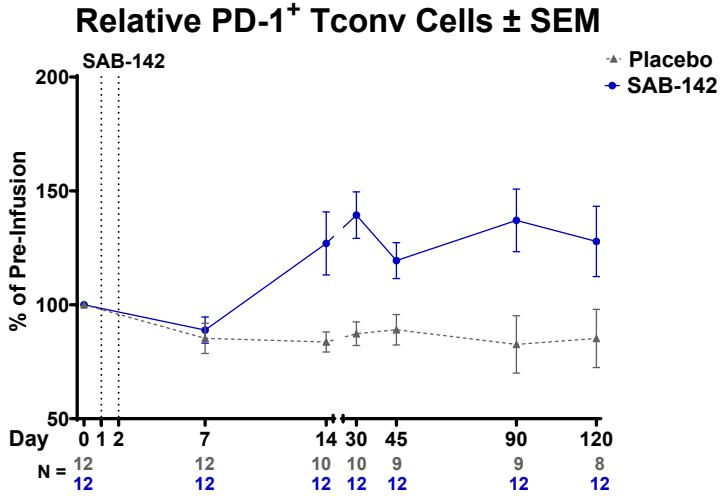
SAB-142 induced sustained expression of co-inhibitory receptors on CD4+ T conv cells.

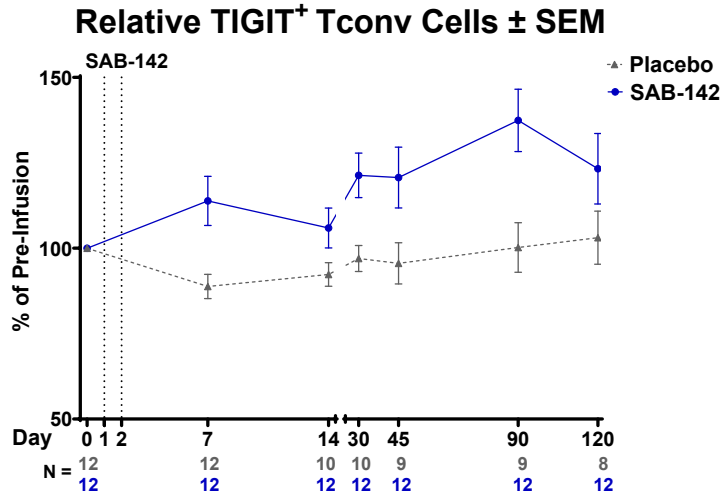
SAB-142: combined 1.5mg/kg and 2.5mg/kg dosed cohorts

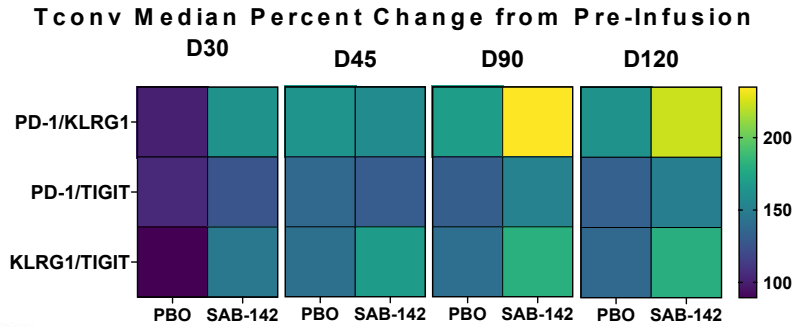
Rabbit ATG CD4+ T Cell Dual Exhaustion Markers

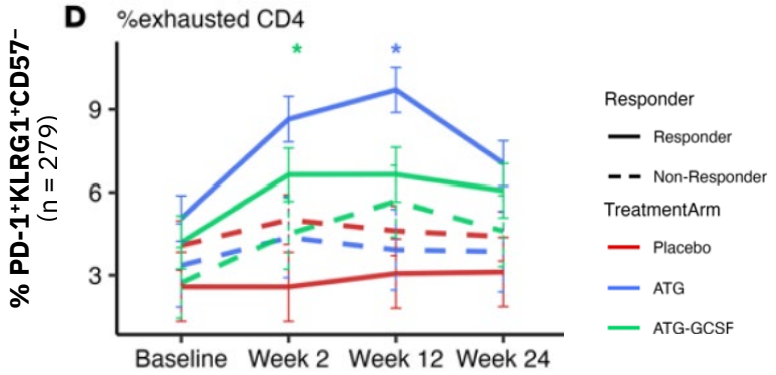
Low-dose ATG induced sustained expression of co-inhibitory receptors (PD-1, KLRG1) on CD4+ cells indicating exhaustion-like phenotype which correlates with C-Peptide preservation.

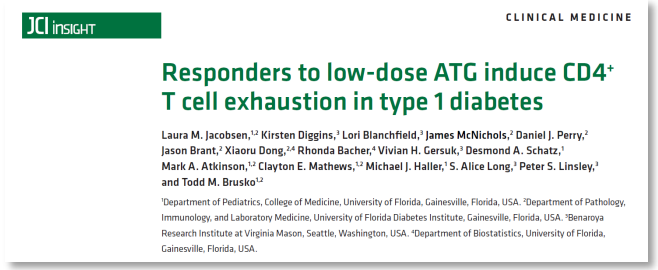
SAB-142 demonstrates sustained CD4+ T conventional cell exhaustion analogous to rATG










JCI insight
CLINICAL MEDICINE

Responders to low-dose ATG induce CD4+ T cell exhaustion in type 1 diabetes

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SAB-142-101
Phase 1 Top Line

No sustained lymphodepletion

- SAB-142: Transient lymphopenia due to lymphocyte margination
- Lymphocytes recover back to baseline by Day 7

Rabbit ATG causes sustained lymphodepletion up to 2 years


JCI insight — CLINICAL MEDICINE

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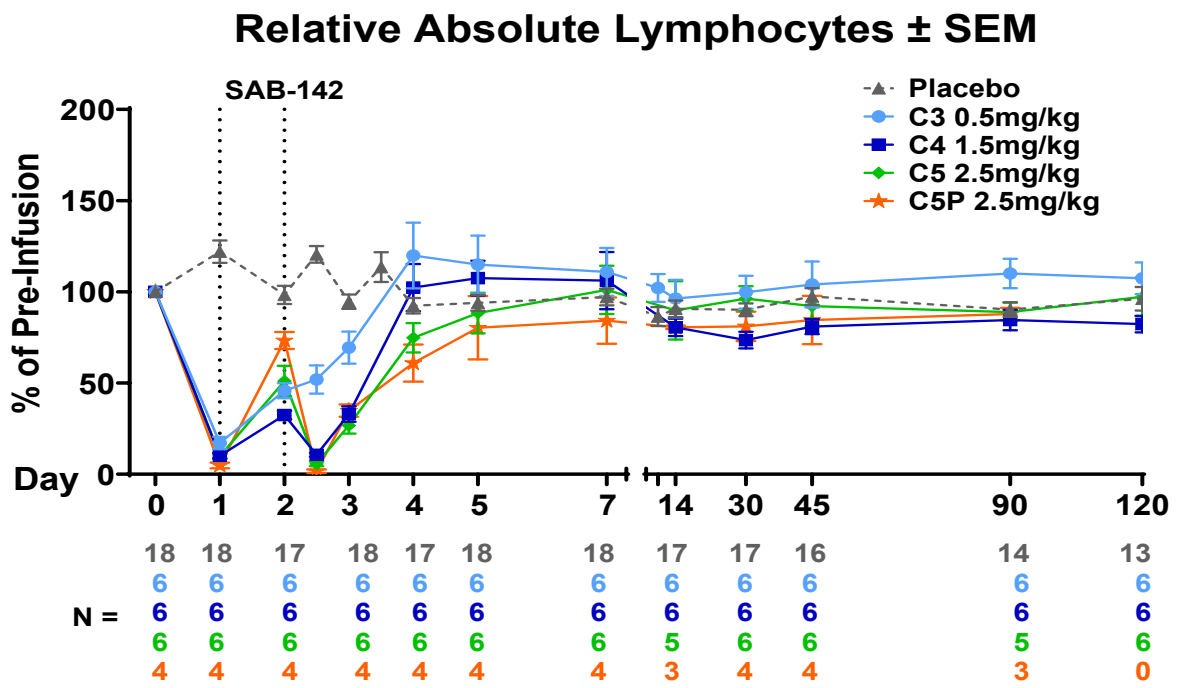
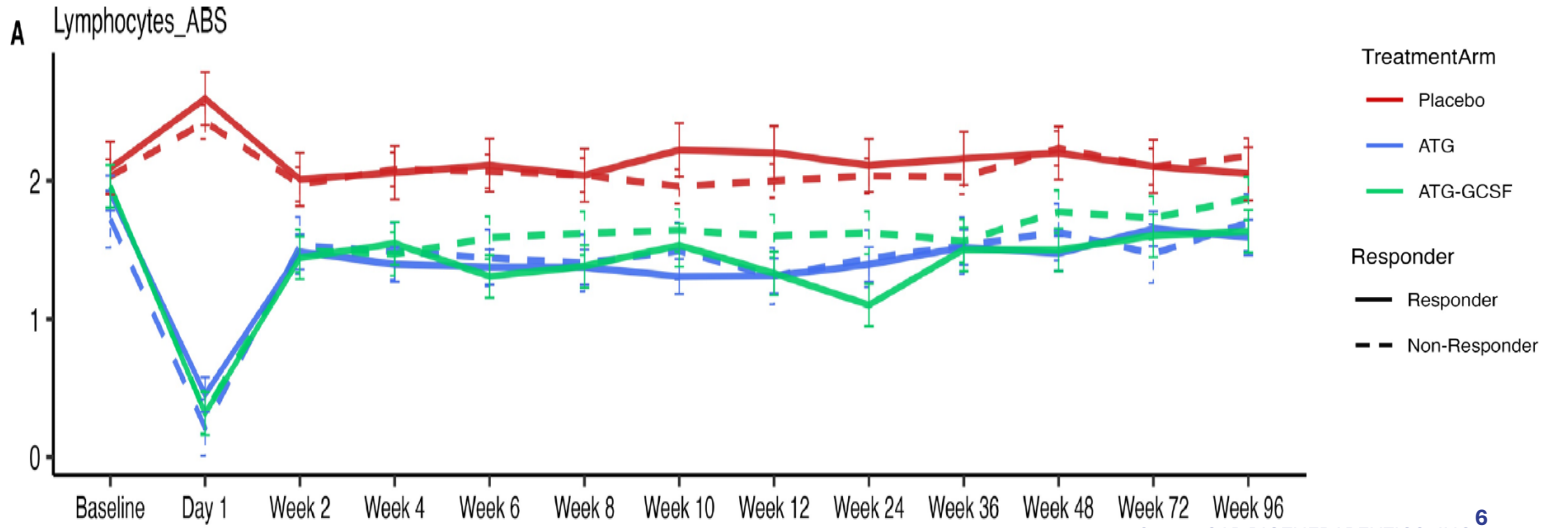
SAB-142 does not cause sustained lymphodepletion





SAB-142-101
Phase 1 Top Line

No loss of CD4+ or CD8+ T Cells

- SAB-142 results in immunomodulation with no depletion of CD8⁺ or CD4⁺ T cells, including T regulatory cells
- SAB-142 demonstrated validated MOA to deliver potentially **Best-in-Class T1D immunotherapy**

Rabbit ATG causes sustained depletion of CD4⁺ T cells.


JCI insight — CLINICAL MEDICINE

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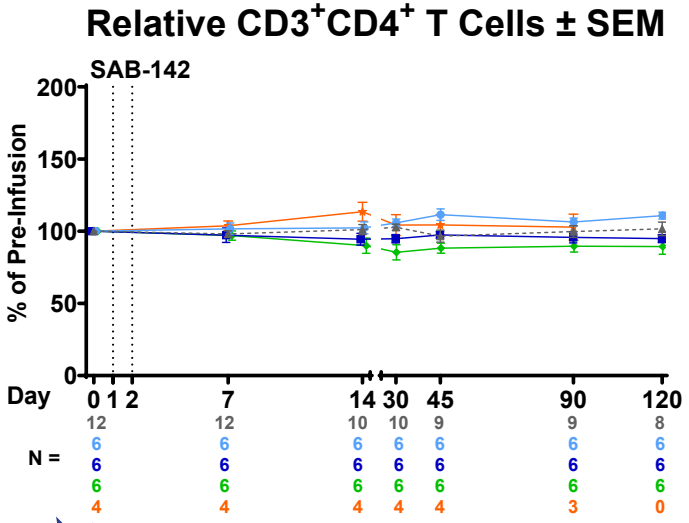
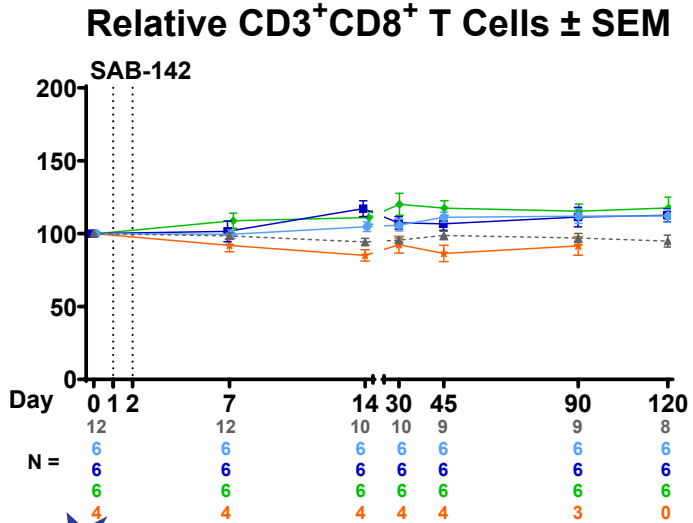
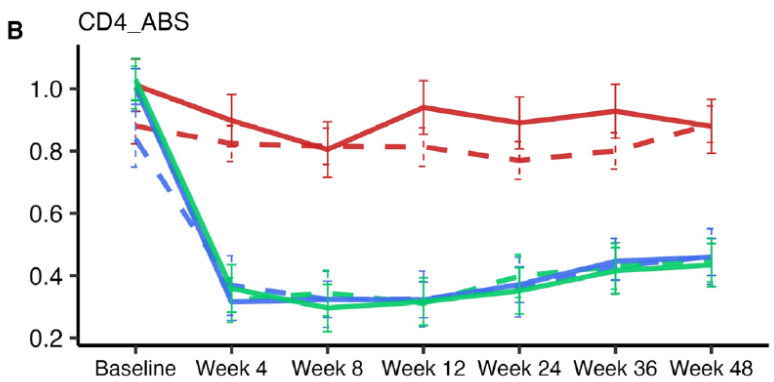
SAB-142 does not cause sustained lymphodepletion

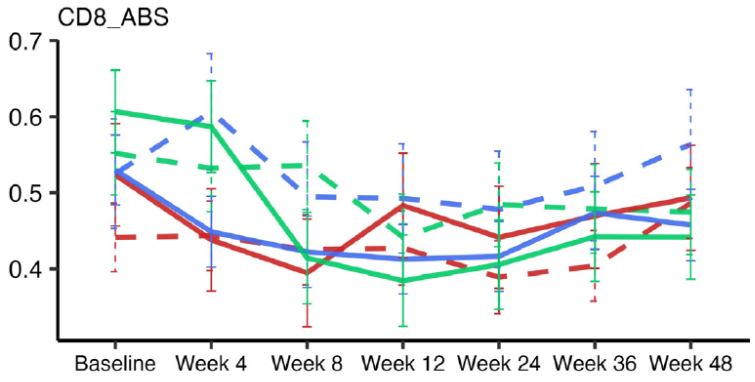


No CD4⁺ T-cell lymphodepletion



No CD8⁺ T-cell lymphodepletion





SAB-142
In Vitro Data

SAB-142 has less binding to FcγRIII and less ADCC activation than rATG

Binding to the FcγRIII on natural killer cells activates cellular pathways leading to antibody dependent cellular cytotoxicity (ADCC)

No ADCC at therapeutic doses of SAB-142 → no lymphodepletion

Similar or better binding to FcRn and FcγRI facilitates immune activation & exhaustion

The human FcRn transports IgG across endothelial barriers; facilitates movement of IgG in both directions

The human FcγRI increases immune activation in multiple immune cell types

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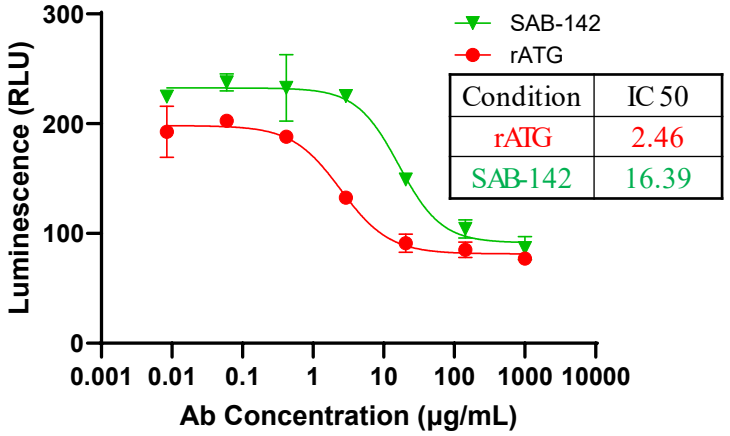
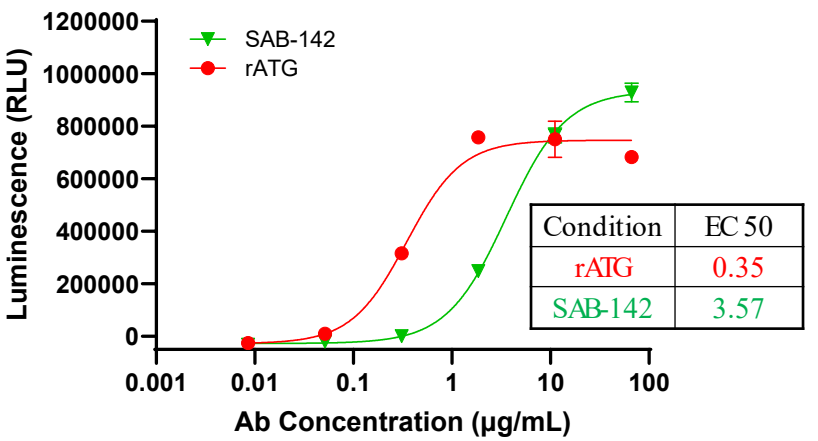
SAB-142 and rabbit ATG (rATG) Binding and Activation of FcγRIII Pathway (ADCC), FcRn and FcγRI

Competitive Inhibition of FcγRIIIa(V158) Binding



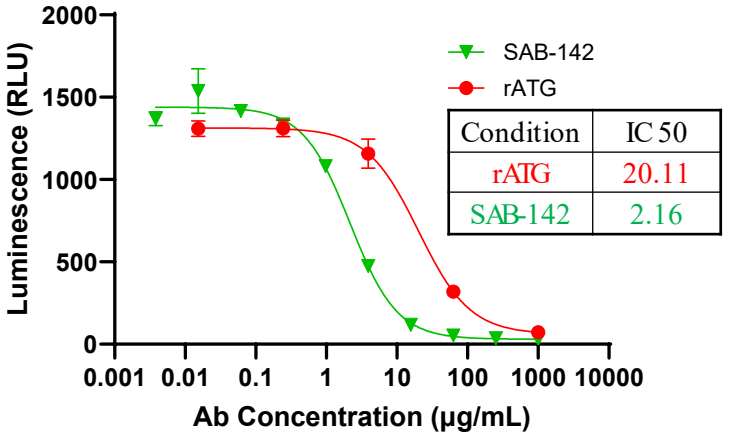
Condition	IC 50
rATG	2.46
SAB-142	16.39

ADCC Activation on Jurkat Cells



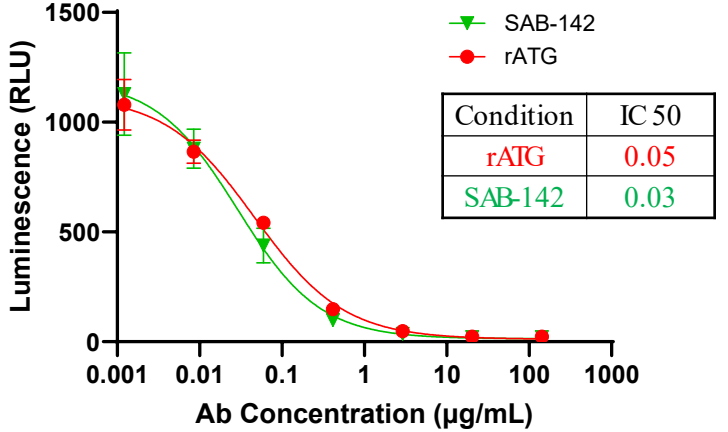
Condition	EC 50
rATG	0.35
SAB-142	3.57

Competitive Inhibition of FcRn Binding



Condition	IC 50
rATG	20.11
SAB-142	2.16

Competitive Inhibition of FcγRI Binding



Condition	IC 50
rATG	0.05
SAB-142	0.03

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CONCLUSIONS

SAB-142 demonstrated a validated MOA to deliver potentially Best-in-Class T1D immunotherapy

- Only transient lymphopenia due to margination was observed during dosing without sustained depletion of major blood cells
- SAB-142 has no ADCC activity at therapeutic concentrations

SAB-142 data in depth at EASD

Thursday, Sep 18

Mechanism of Action of a fully Human Anti-Thymocyte Globulin, SAB-142, for the Treatment of Type 1 Diabetes

- Session: OP 28 Guardians of the Islet Galaxy: Protect and Replace
- Presentation number: 163 | Sofia Hall
- 10:45-12:15

Novel Pharmacokinetic Assay for measuring SAB-142, a fully human Anti-Thymocyte Globulin

- Session: SO 018 Clinical Tales from the T1D Trenches
- Presentation 391 | Station 03, Hall C
- 14:00 - 15:00

Specimen Quality for Multicenter Clinical Trials: Comparing Novel Blood Preservation Methods to Cryopreserved PBMC

- Session: SO 018 Clinical Tales from the T1D Trenches
- Presentation: 392 | Station 03, Hall C
- 14:00 - 15:00

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