BIOMARKER-GUIDED DOSE SELECTION FACILITATED BY A C-PEPTIDE MODEL IN TYPE 1 DIABETES PATIENTS

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Introduction

There is no approved disease-modifying therapy for new-onset Type 1 Diabetes (NOT1D). Although rabbit anti-thymocyte globulin (rATG) is effective at preserving C-peptide and lowering HbA1C, it is limited by safety concerns. SAB-142, a fully human, multi-specific anti-thymocyte globulin, is designed to delay NOT1D onset and progression with low to no immunogenicity, enabling safe maintenance redosing (e.g. every 6 months).

Loss of C-peptide is a key indicator of disease progression in T1D. Declining levels indicate the loss of healthy functioning insulin-producing beta-cells, a disease progression that can take many months to years. As a measure of therapeutic impact, changes in C-peptide levels require long periods of observation. For this reason, we aimed to identify an early biomarker that is predictive of C-peptide response.

C-peptide and immunophenotyping data from two prior clinical studies[1,2] evaluating rATG at 2.5 and 6.5 mg/kg in T1D patients and immunophenotyping data from the first-in-human (FIH) study, SAB-142-101, were used to generate an efficacy profile to guide dose selection for a subsequent Phase 2b study, of SAB-142, the SAFEGUARD Study.

Aims

1. Characterize C-peptide development in T1D patients from two previous rATG studies START and TN-19, including the influence of covariates.
2. Characterize the pharmacodynamic (PD) profile of SAB-142 in humans by assessing its dose-dependent dynamics on lymphocyte subtypes in Study SAB-142-101, particularly those related to slower decline of C-peptide in T1D patients.
3. Provide supportive evidence for the dosing regimen of SAB-142 in the Phase 2b study in T1D patients.

Methods

A longitudinal model of C-peptide decline for rATG or placebo treatment in T1D patients was developed, explaining slower or faster decline in C-peptide by covariates: age, weight, sex, baseline lymphocytes count, rATG treatment and the percentage of exhausted $CD4^+$ T cells at baseline or Week 12 (defined by $PD1^+KLRG1^+CD57^-CD4^+$), as well as the percentage of $CD45RA^+$ non-Treg $CD4^+$ T cells at baseline or Week 12[3]. Only the TN-19 study was considered in the final covariate modelling.

In the FIH study, the treatment effect of SAB-142 on the cell populations $PD1^+$ Tconv, $TIGIT^+$ Treg, and $CD8^+$ CM in healthy volunteers was assessed graphically. At the time of analysis, the available interim immunophenotyping results were generated from a static or fixed gating method, which did not account for batch-to-batch variability. To assess the dose-response relationship, the area under the effect curve (AUEC) was graphically explored.

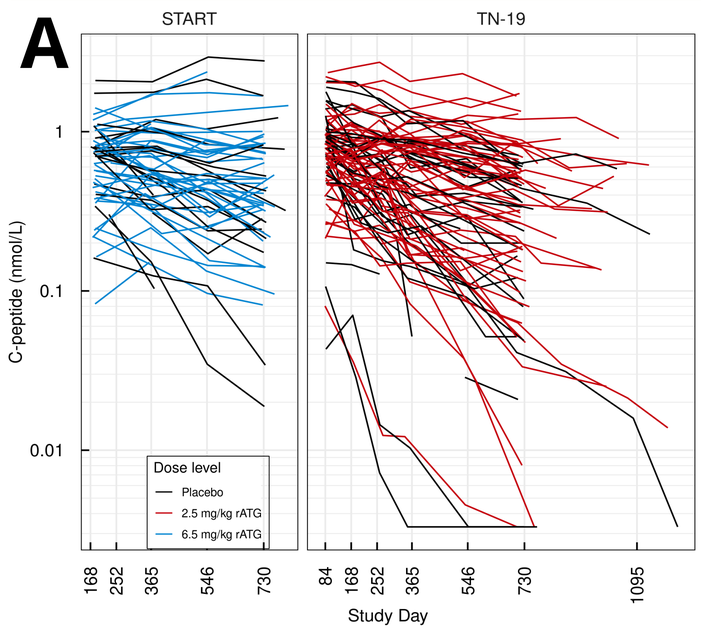
Model estimation was carried out using NONMEM v7.5.0 on the R-based IQRtools[4] platform.

Overview Data Sources

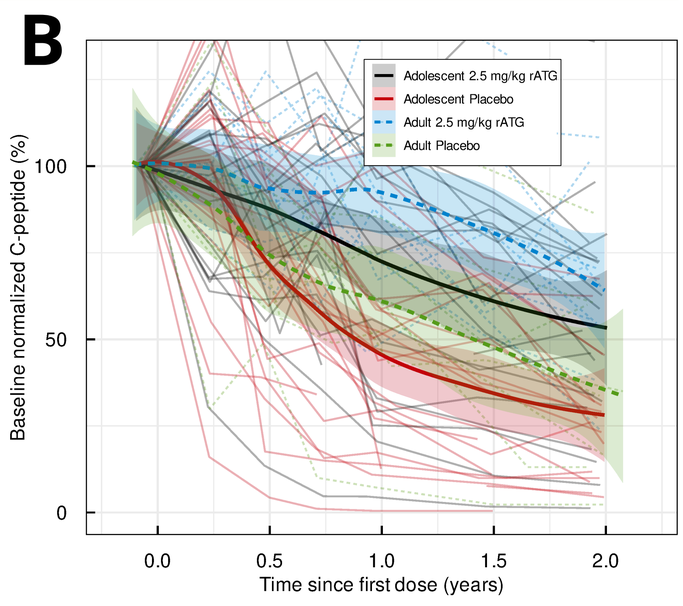
Data source	External	In-house
Study	START, TN-19	SAB-142-101
Drug compound	rATG	SAB-142
Enrolled subjects	T1D patients (n = 58 and 89)	HV and T1D Subjects* (n = 46)
Measure of drug effect	C-peptide	Lymphocyte subtypes

Interim data from cohorts 3, 4, and 5 was used for this analysis (n=18)
*HV: Health Volunteer; One cohort with 6 subjects with T1D was included in this trial

rATG C-peptide Data from T1D Patients



A rATG studies START and TN-19: C-peptide over time
Lines represent subjects' trajectory over time. C-peptide was plotted on a logarithmic scale, Study Day on a linear scale.



B TN-19 Study: adult vs. adolescent efficacy
Thin lines represent subjects' trajectories over time. Thick lines represent smoothed means using the local regression (loess) method, with the shaded area representing a 95% confidence interval.

C-peptide Model in T1D Patients of TN-19 Study

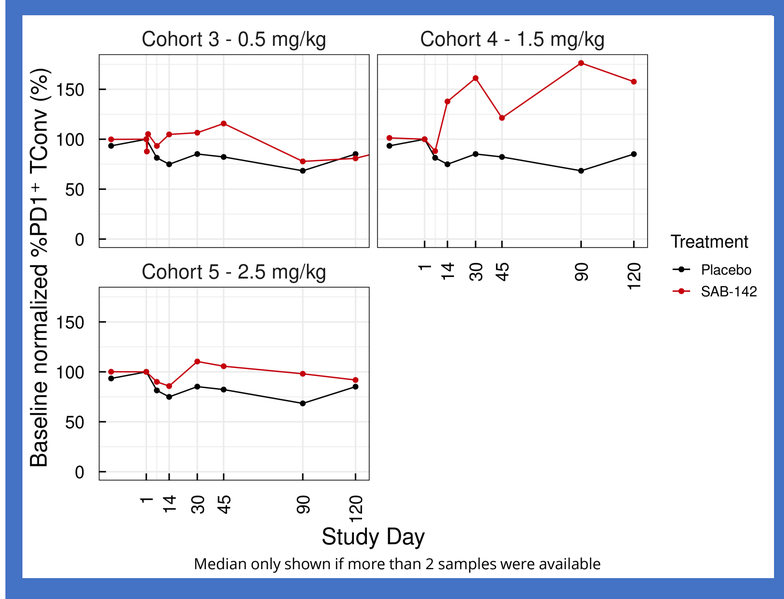
$$d/dt(Cpep) = -ke \cdot (Cpep - Cmin) \cdot decay_{start}$$
$$Cpep(0) = BL$$

DESCRIPTION	NAME	TYPICAL PARAMETERS		IIV* (LOGNORMAL)	
		VALUE	RSE	VALUE	RSE
C-peptide reduction rate (1/day)	ke	0.00203	18.8%	1.07	13.2%
C-peptide baseline (nmol/L)	BL	0.84	1.41%	-	-
Start of C-peptide delay (day)	Delay	55.3	11.2%	0.3 (FIX)	-
Minimum C-peptide value (nmol/L)	Cmin	0.0263	44.6%	1.81	22.2%
Covariate model					
Baseline C-peptide in nmol/L on BL	beta_BL(CPEP0)	1 (FIX)	-		
Baseline Age in years on ke	beta_ke(AGEY0)	-1.54	49.2%		
Week 12 ratio to baseline %exhausted $CD4^+$ on ke	beta_ke(EXHSTRTB)	-0.71	64.9%		
Residual variability					
Proportional Error (fraction) C-peptide	error_PROP1	0.197	3.39%		

*IIV: Inter-individual variability on ke, Delay and Cmin parameters.

The C-peptide model indicated that with an approximately 75% increase over baseline of %exhausted T cells at Week 12, the **C-peptide decline** would be **reduced** by approximately **30% versus placebo** as estimated for the TN-19 study.

PD1+ Tconv cells post SAB-142 dosing



Median only shown if more than 2 samples were available

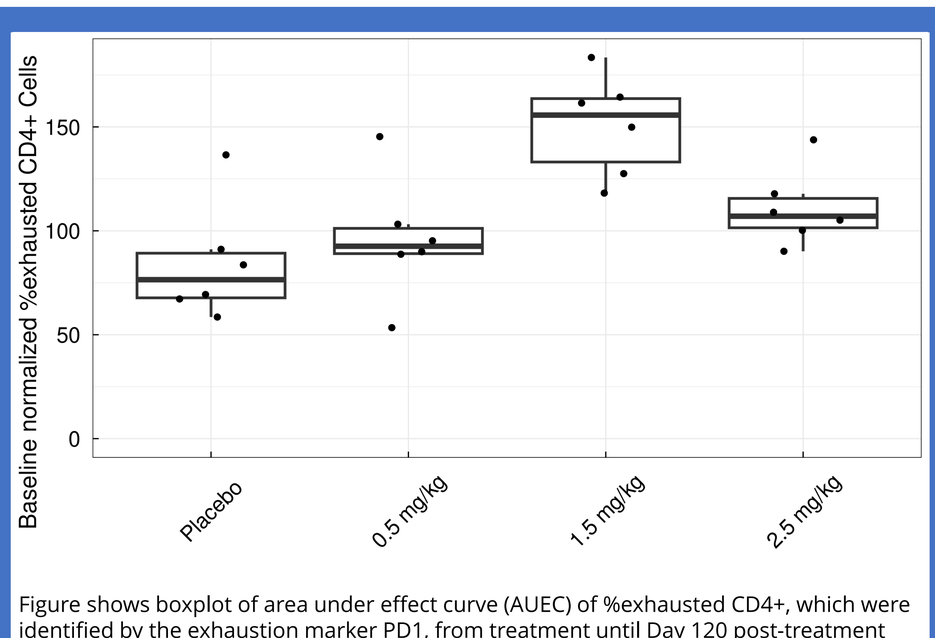


Figure shows boxplot of area under effect curve (AUEC) of %exhausted CD4+, which were identified by the exhaustion marker PD1, from treatment until Day 120 post-treatment

Based on the correlation between increased %exhausted CD4+ cells and C-peptide preservation, as modeled above, the maximum C-peptide response to SAB-142 is expected at doses around 0.5-2.5 mg/kg

Conclusions

In a model with a delayed exponential decline to a lower bound of C-peptide, the long-term C-peptide response to treatment could be linked to short-term biomarkers at a certain timepoint, such as the percentage of exhausted $CD4^+$ T cells, at Week 12. The maximum response based on %exhausted cells ($PD1^+$ Tconv) is expected at doses between 0.5 and 2.5 mg/kg. In conclusion, publicly available databases from prior clinical studies were used to develop a longitudinal model of C peptide preservation to provide supportive evidence for the dosing regimen of SAB-142 in the Phase 2b SAFEGUARD Study.

References:
[1] Haller 2018: Haller MJ, Schatz DA, Skyler JS, et al. Low-Dose Anti-Thymocyte Globulin (ATG) Preserves β-Cell Function and Improves HbA1c in New-Onset Type 1 Diabetes. Diabetes Care. 2018;41(9):1917-1925. doi:10.2337/dc18-0494
[2] Gitelman 2016: Gitelman SE, Gottlieb PA, Felner EI, Willi SM, Fisher LK, Moran A, Gottschalk M, Moore WV, Pinckney A, Keyes-Elstein L, Harris KM. Antithymocyte globulin therapy for patients with recent-onset type 1 diabetes: 2 year results of a randomized trial. Diabetologia. 2016 Jun;59:1153-61.
[3] Jacobsen 2023: Jacobsen LM, Diggins K, Blanchfield L, et al. Responders to low-dose ATG induce $CD4^+$ T cell exhaustion in type 1 diabetes. JCI Insight. 2023;8(16):e161812. doi:10.1172/jci.insight.161812
[4] https://iqrtools.intiquan.com