BCG Clinical Trial Programs in Advanced Type 1 Diabetes – Pediatric and Adult: 2023 Update

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Introduction

- The bacillus Calmette-Guérin (BCG) vaccine, originally introduced a century ago for tuberculosis prevention, has been shown in epidemiological studies and randomized clinical trials to protect humans from diverse infectious diseases
- Recent randomized Phase I-III human clinical trials suggest BCG may also protect humans from immune diseases such as type 1 diabetes (T1D) and multiple sclerosis (MS)
- Immune and metabolic mechanisms account for BCG's durable ability to regulate glucose control in T1D[1-3]:
  - BCG **corrects underlying aerobic glycolysis defects** in the white blood cells (WBC) of subjects with T1D
    - BCG-treated lymphocytes become a major consumer and regulator of blood sugars *in vivo*
    - WBC with accelerated glycolysis stop sugar transport when blood sugar is < 50 mg/dl
    - BCG restores the underlying sugar transport defects in the WBCs of those with T1D to levels closer to normal
  - Gradually (over 3 years) BCG **induces potent regulatory T cells (Tregs)** to suppress autoimmunity
- Multiple randomized human clinical protocols (**Table 1**) are underway at Massachusetts General Hospital (MGH)/Harvard Medical School testing BCG's ability to lower HbA1c, reduce insulin requirements and regulate blood sugars in T1D; studies are also looking at BCG's ability to protect from infectious disease
- Here we present an update on the BCG studies at MGH

Table 1. T1D Patient Enrollment & Follow-Up Timelines for BCG Studies

	Total # Subjects	BCG-Treated (n)	Control/ Placebo (n)	Trial Type	Time Followed/ Duration
Phase I + Crossover	52	9	43	Randomized, Double-Blind	5 or 10 y/10 y
Radiology Study	6	6	0	Open-Label	~3 y/5 y
Phase II Study	150	100	50	Randomized, Double-Blind	~4 y/5 y
Transition Study	29	29	0	Open-Label	1.5 y/5 y
Phase II Crossover	6	NA	NA	Randomized, Double-Blind	2 y/5 y
COVID-BCG Study	143*	95	48	Randomized, Double-Blind	33 mo/33 mo
Phase II Pediatric Study	250	125	125	Randomized, Double-Blind	1 y/5 y
Total:	**636**	**364**	**266**		

- To date, all T1D subjects in randomized trials have long-term diabetes except for the subgroup of new-onset subjects enrolled in the pediatric study
- Current ongoing studies use multi-dose BCG; Tokyo 174 strain
- Study groups include: 1) 10-year follow up of a Phase I adult study to evaluate the durability of lowered HbA1c values after BCG treatment; 2) Randomized, double-blind Phase II adult clinical trial to demonstrate the reproducibility of Phase I findings; 3) Radiologic study to quantify and identify organs/organ systems with higher sugar utilization after BCG treatment; 4) Adult study comparing 2 vs 6 doses of BCG over 5 years of observation; 5) Pediatric trial of BCG in subjects with ≥ 2 years T1D and with new-onset T1D

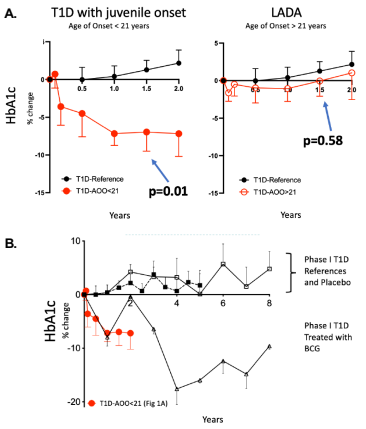
*The COVID-BCG study uses the randomized Phase II subjects for infectious disease monitoring.

Current Clinical Trial Updates

Adult Trials

- In an 8-year, Phase I randomized clinical trial in adults with longstanding T1D (no pancreas C-peptide), BCG vaccinations induced long-term improvements in glycemic control
- In an open-label trial, subjects with T1D, but not latent autoimmune diabetes of adults (LADA), responded to BCG vaccinations with HbA1c lowering within two years (**Fig. 1**)
- In a randomized, double-blinded, placebo-controlled Phase II/III trial, BCG had 92% efficacy vs placebo against COVID-19 (**Table 2**)

Figure 1. Open-label trial: *In vivo* BCG vaccinations decrease HbA1c in T1D, not LADA



In an open-label clinical trial in adults with longstanding T1D (n=62), the HbA1c response in subjects with T1D with juvenile onset (age of onset [AOO] ≤21), LADA (AOO >21), and untreated controls were evaluated.

(A.) Juvenile-onset T1D subjects (n=6; mean AOO=11±3 y) (*left*) were compared with LADA subjects (n=10; mean AOO=31±2 y) (*right*) for responsiveness (% change from baseline HbA1c) to BCG Tokyo strain vaccines over a 2-year period and to a T1D reference population not receiving BCG. The fall in HbA1c in juvenile-onset T1D is a significant trend (repeated-measures ANOVA p=0.01; left). The trend in LADA was not significant (repeated-measures ANOVA p=0.58; right). Mean current chronological age of the study groups: 28±3 y (T1D) and 45±4 y (LADA). Mean duration of diabetes: 18±3 y (T1D) and 19±2 y (LADA).

(B.) HbA1c percent change from baseline in T1D subjects with juvenile onset receiving Tokyo BCG treatment is shown in red (n=6) and compared with previously published Phase I clinical trial data using Sanofi BCG in patients with similarly early onset (11±5.8 y) (black, open triangle). Also shown are the Phase I placebo group (open squares) and a reference population (closed squares).

Table 2. U.S. COVID-BCG study: BCG primary vaccinations provide protection from COVID-19

	BCG (n=96)	Placebo (n=48)	Surveillance duration (months)	Vaccine efficacy	Posterior probability (Vaccine efficacy > 30%)
COVID-19 cases (Confirmed by point of care + SARs CoV-2 antibodies)	1 (1.0%)	6 (12.5%)	15	92%	0.99
COVID-19 cases (Confirmed by PCR)	0 (0.0%)	5 (10.4%)	15	100%	0.99

Pediatric Trial

- A Phase II double-blind, placebo-controlled, randomized trial has enrolled 90/150 planned long-term subjects (ages 11 to <18 y; ≥ 2 y of T1D; 45 have received BCG) and enrollment 100 of new-onset subjects is underway (ages 8 to <18 y; ≥ 3 mo to < 1 y of T1D)
- Trial will evaluate BCG's ability to restore aerobic glycolysis, improve blood sugars and induce Tregs to stop pancreas-driven disease; will also evaluate pancreas preservation in those with significant C-peptide

Conclusions

- In longstanding T1D, the primary mechanism for BCG vaccine efficacy is correction of underlying aerobic glycolysis defects in WBCs, restoring regulated glucose transport for lowered and improved HbA1c values; BCG also gradually induces Tregs
- The impact of multi-dose BCG vaccination in MS and T1D takes approximately 2 years to manifest, but effects appear durable without further treatment to > 8 years
- BCG vaccine therapy may offer a safe, affordable intervention in longstanding autoimmunity; new pediatric clinical trials will study the impact of BCG-induced Tregs on pancreas preservation

Refs: 1. Kühtreiber WM, *NPJ Vaccines* (2018); 2. Shpilsky GF, *iScience* (2021); 3. Dias HF, *Vaccine* (2022).
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