



BCG Vaccine Health Impact Profile

Diabetes Care Industry
May 2020

Description

The Bacillus Calmette–Guérin (BCG) vaccine is a tuberculosis immunization that has been widely administered since its discovery in the 1920s. It is currently being studied for an additional application in Type 1 Diabetes treatment. The clinical trials use the Tokyo-172 strain of BCG in a treatment regimen of one annual dose of the vaccine and at a cost of \$200.

Research Facility	The Faustman Lab at Massachusetts General Hospital
Name of Study	Repeat BCG Vaccinations for the Treatment of Established Type 1 Diabetes.
Trial Status	Phase I Completed, Phase II Currently Underway
FDA Application	BCG Tokyo-172 Strain – Investigational New Drug Application (IND) for Type 1 Diabetes Phase II Trials
Website	https://www.faustmanlab.org/

Alignment with SDGs



Good Health and Well-Being



Industry, Innovation and Infrastructure



Reduced Inequalities

Health Impact Score: 6.8/10



Boundless Analysis

- ▶ The analysis compared the Phase I clinical findings for BCG (Tokyo-172 strain) in addition to insulin therapy alone, across available administration devices including syringe-based injection, pen-based injection, and insulin pump.
- ▶ Boundless scores BCG 6.8/10 per patient impact for its public health and socioeconomic benefits. The Health Impact Score is based on performance indicators such as Invasiveness, Efficacy, Quality Adjusted Life Years (QALYs) gained, Severe Complications and Cost Savings. The score rationale can be found in Appendix C.
- ▶ Across all metrics considered, BCG inclusive therapies outperformed regimens that include insulin alone. Based on encouraging Phase I results, BCG has the rare potential to both improve clinical outcomes relative to the current standard of care, and simultaneously reduce systemic costs for Type 1 Diabetes care.
- ▶ If approved, BCG can deliver significant cost savings for patients and payers. A 50% reduction in insulin requirements reduces the annual cost of Type 1 Diabetes care by more than 15%.
- ▶ A reduction in the risk of severe hypoglycemic events accounts for additional savings, considering the cost of inpatient care and glucagon for emergency self-treatment.
- ▶ In a five-year trial, BCG achieved a 1.18% reduction in Hemoglobin A1C compared to the Type 1 Diabetes control group, which experienced a reduction of 0.03%.
- ▶ BCG also had zero reported hypoglycemic events for the entire duration of the Phase I clinical trial. Multiple studies have established the risk of death from hypoglycemia, separately finding that 4-10% of people with Type 1 Diabetes die from severe hypoglycemic events despite insulin therapy.

(REFERENCE: <https://care.diabetesjournals.org/content/35/9/1814>)

Lead Scientist

- ▶ **Denise Faustman, MD, PhD** – Dr. Faustman is Director of the Immunobiology Laboratory at the Massachusetts General Hospital (MGH) and an Associate Professor of Medicine at Harvard Medical School. She is currently leading a human clinical trial program testing the efficacy of the BCG vaccine for reversal of long-term Type 1 Diabetes. Her research accomplishments include the first scientific description of modifying donor tissue antigens to change their foreignness, the identification of interrupted T cell education through MHC class I, and the identification of autoimmune T cell sensitivity to TNF. These achievements have earned her awards including the National Institutes of Health and National Library of Medicine’s “Changing the Face of Medicine Award” as one of 300 American physicians (one of 35 in research) honored for seminal scientific achievements in the United States, the “Oprah Achievement Award” for “Top Health Breakthrough by a Female Scientist,” and the “Women in Science Award” from the American Medical Women’s Association and Wyeth Pharmaceutical Company for contributions to autoimmune disease research. Dr. Faustman has been senior author on over 100 peer-reviewed papers, and her research has been highlighted in publications including *Science*, *Nature*, *The Wall Street Journal*, *The New York Times*, *Los Angeles Times*, *The London Financial Times* and *Scientific American*. She earned her MD and PhD from Washington University School of Medicine, in St. Louis, Missouri, and completed her internship, residency, and fellowships in Internal Medicine and Endocrinology at the Massachusetts General Hospital.

BCG Clinical Trials

Clinical traits of the Phase I clinical trial participants, across the three cohorts:

	n	%Female	Age	Average Age of Onset	Years Since Diagnosis
BCG - T1D	9	44	45 ± 3	26 ± 4	19 ± 3
Placebo - T1D	3	0	49 ± 3	29 ± 3	20 ± 3
Reference - T1D	40	47	40 ± 2	26 ± 2	13 ± 1
p-value (BCG - T1D vs Placebo - T1D)			0.51	0.64	0.93
p-value (BCG - T1D vs Reference - T1D)			0.11	0.99	0.05
p-value (Placebo - T1D vs Reference - T1D)			7	0.53	0.15

Clinical trial results for BCG treatment, placebo treatment and reference/control groups:

HbA1c (%)	Year 0	Year 5	Year 6	Year 7	Year 8
T1D BCG Treated	7.36 ± 0.44	6.18 ± 0.34	6.44 ± 0.34	6.25 ± 0.26	6.65 ± 0.36
T1D Placebo Treated	7.10 ± 0.55	7.07 ± 0.41	7.18 ± 0.62	7.17 ± 0.46	7.22 ± 0.38
T1D Reference Population	7.08 ± 0.07	7.33 ± 0.17			
p-value					
BCG vs Placebo		p=0.02	p=0.02	p=0.0008	p=0.0002
BCG vs Reference		p=0.02			
Placebo vs Reference		p=0.73			

Technology

- ▶ Bacillus Calmette–Guérin (BCG) vaccine was first introduced in 1921 as a tuberculosis (TB) immunization. It is still widely administered in many countries almost 100 years after its initial use and is included on the World Health Organization’s List of Essential Medicines.
- ▶ In addition to its primary use for TB prevention, BCG (in the form of an infusion) has also been the standard treatment option for bladder cancer patients since 1977.
- ▶ BCG is currently being evaluated for new applications in Type 1 Diabetes. Phase I human clinical trials were completed at Massachusetts General Hospital to assess safety and findings were published in 2012.
- ▶ Phase II trials began in 2019 and include 150 patients. The primary readout of clinical findings is expected in 2023.

Operations

- ▶ Massachusetts General Hospital is located in Boston and is the largest teaching hospital affiliated with Harvard Medical School. Its research program is the largest in the world.

Health Highlights

Summarized below are most relevant impact categories and codes that refer to the United Nation's [Sustainable Development Goals](#) (SDGs). The associated metrics highlight the most important factors that explain how this technology is impacting healthcare.



Patient Cost Savings

Patient cost savings are measured as a reduction in direct medical costs to patients, including insulin therapy, administration devices, inpatient and outpatient care and pharmacy expenses. The cost of care for Type 1 Diabetes outcomes and comorbidities is considered on a risk-adjusted basis. Promoting effective, low-cost interventions, when available, can reduce the overall cost burden of Type 1 Diabetes care.

Relevant code: [SDG 3](#)



Quality Adjusted Life-Year (QALY)

The number of healthy life years gained for therapies that include BCG compared to insulin alone. Funding for clinical trials is a scarce resource that must be allocated to treatment options that have the potential to generate impactful outcomes if approved. Reducing HbA1c in a safe manner translates into an improved quality of life and additional life-years. Regained life-years reduce the difference in life-span between a healthy patient and one diagnosed with Type 1 Diabetes.

Relevant code: [SDG 3](#)



Expanding Access to Care Through Innovation

The average annual cost of Type 1 Diabetes care is roughly \$18,000, a price which many uninsured individuals and low-income community members cannot afford. As a result, a sizable share of people with Type 1 Diabetes resort to insulin rationing, the practice of taking less insulin than required, increasing the risk for high blood glucose and ketoacidosis. Interventions that reduce daily insulin requirements safely can decrease the prevalence of this dangerous practice, and reduce the impact of economic inequality among people with Type 1 Diabetes.

Relevant codes: [SDG 9](#) [SDG 10](#)

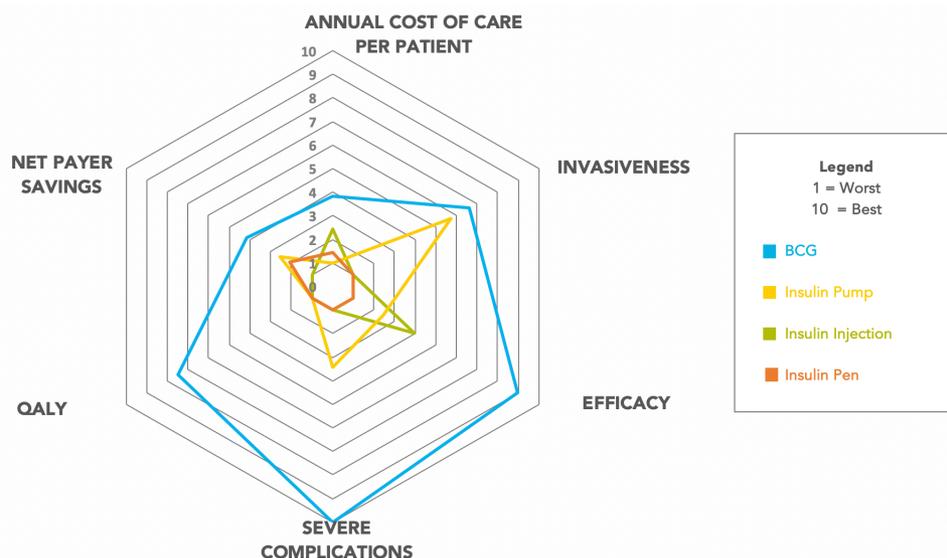


Clinical Improvements

Hemoglobin A1c is the primary measure of blood glucose control in a clinical setting, offering significant insight into the overall state of a patient's management of Type 1 Diabetes. While there are several ways to reduce HbA1c, methods involving the increase of the insulin dosages potentially lead to a higher risk for severe hypoglycemia, both a dangerous and costly consequence. Novel interventions that demonstrate efficacy without daunting side-effects can improve the clinical management of Type 1 Diabetes and become a core element of the new standard of care.

Relevant code: [SDG 3](#)

Benchmarking and Conclusions



The present spider chart depicts the performance of BCG against traditional insulin therapies from 1 (worst) to 10 (best). The values are obtained by comparing the average of each resulting HKPIs for the company against its comparable treatments as well as a baseline of not having diabetes at all (10 out of 10). The scope of this study includes Phase I trial results for BCG treatment compared to the placebo treatment group and broader population of Type 1 Diabetes patients that do not receive BCG. These early clinical findings stand in place of future results of Phase II trials, as the focus of this report is to determine the potential health benefits of funding additional research for BCG as a Type 1 Diabetes treatment. The potential health benefits of BCG are significant. Typically, new treatment options represent a tradeoff between an improvement in the standard of care at a higher cost. Considering the dire need to reduce systemic healthcare costs, BCG could fulfill this objective affordably and without sacrificing the quality of care.

To determine the socioeconomic benefits conferred by BCG, we examined Quality Adjusted Life-Years (QALY's) gained and payer cost savings. Examining the impact of BCG on HbA1c and severe hypoglycemia, the two factors contributed 0.5482 and 0.1700 QALYs respectively, totaling 0.7182 QALYs by year 5. The placebo group, serving as proxy for conventional insulin therapy, only gained 0.0002 QALYs by year five. The cost and savings associated with BCG inclusive treatments were also assessed. A model was constructed using pricing and patient-level spending on insulin, non-insulin pharmacy and medical care. Considering these factors, BCG projects sizable cost savings relative to the current standard of care. The inclusion of BCG and associated 50% reduction in insulin requirements resulted in savings of 16.5% - 22.2% at the patient level, across the three treatments examined. Hypoglycemia was included on a risk adjusted basis, assuming a conservative 30% decline for BCG treatment relative to the broader Type 1 Diabetes patient population. At the payer level, this risk reduction is meaningful, as a single event requiring hospitalization can cost \$16,000, almost doubling the cost of annual care for a patient.

High levels of glucose in the blood can have a multitude of negative effects in the body, especially in blood vessels, which increases the risk of heart disease and stroke, kidney disease, vision problems, and nerve problems. Studies have shown that a 1% reduction in HbA1c, the measure of glucose present in the blood, can cut the risk of microvascular complications by 25%. It was estimated that, on average, BCG could reduce between 85% and 88% of the cost of current approaches used to reduce HbA1c by 1%. On the other hand, when glucose levels are too low, patients can experience severe hypoglycemia, a potentially fatal event where they need another person's assistance to help them increase glucose levels. Approximately 20% of the population with T1D experience at least one severe hypoglycemic event annually, and BCG is expected to reduce this number close to zero. Also, T1D patients must deal with needles on a daily basis. Studies estimate that 28% of the adults managing diabetes with injections have needle fear. It is expected that BCG would reduce invasiveness, considered as injections, pen shots, cannula changes or tests, by 53%.

There are several other factors beyond this study that garner consideration. Insulin rationing is the practice of taking insufficient amounts of insulin when one cannot afford the required dose. This practice can result emergency interventions and even death. Reducing insulin requirements lowers the annual cost of insulin and may allow more patients to move away from rationing. Improving blood glucose control is associated with reduced risk of many other conditions, representing additional benefits in terms of lower costs and improved quality of life.

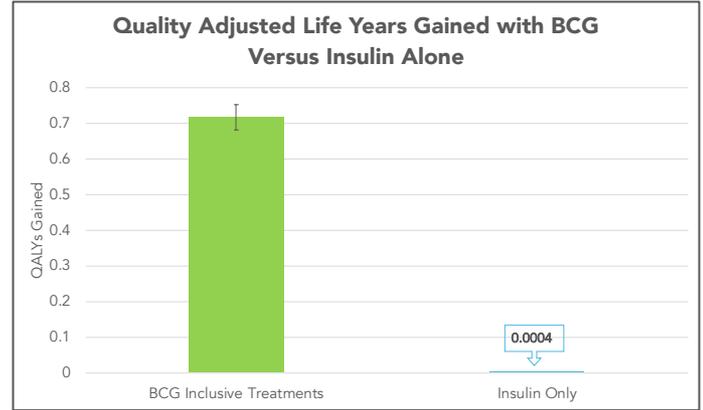
Health Key Performance Indicators (HKPIs)

We evaluated the public health and socioeconomic inputs and impacts for the BCG vaccine considering its ability to reduce HbA1C levels and thus reduce the need for insulin injection.

Quality Adjusted Life Years

Quality Adjusted Life Years (QALYs) are a measure of the additional health and length of life gained by patients from an intervention, adjusted for the quality of life experienced during these years. The estimate of QALYs gained is based on adding BCG therapy to standard treatment.

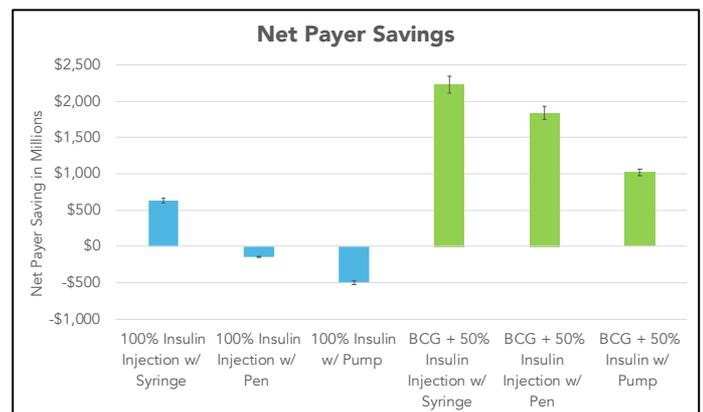
- ▶ Based on estimates of the effect of BCG on HbA1c levels at year five.
- ▶ Drawing on estimates from the Cardiff Type 1 Diabetes Model, a decline in HbA1c levels of 1% accounts for a gain of 0.5482 discounted QALYs.
- ▶ The observed reduction in hypoglycemia frequency contributed an additional 0.17 QALYs, a gain which begins to accrue within the first six months of treatment.
- ▶ Assume annual discount rate of 3.5% per year, based on validated T1D model inputs, and accounting for a 5-year lag in achieving a reduction in HbA1c levels.



Net Payer Savings

Annual projected savings from using BCG therapy in addition to standard insulin therapy. Estimates are provided relative to each of three methods of insulin delivery without BCG.

- ▶ Based on the projected total cost of treating people with T1D in the U.S.
- ▶ Payer spending was calculated by netting outpatient cost sharing. Cost-sharing estimates for insulin were drawn from published statistics on out of pocket expenses for T1D patients enrolled in Medicare Part D. Discounts and rebates are not publicly disclosed as they are determined through private negotiations. An estimated rebate of 22.8% from list price was included.
- ▶ Actual savings may vary across payers, as each payer has its own unique cost-sharing arrangements and bargaining power for treatments considered in this model.



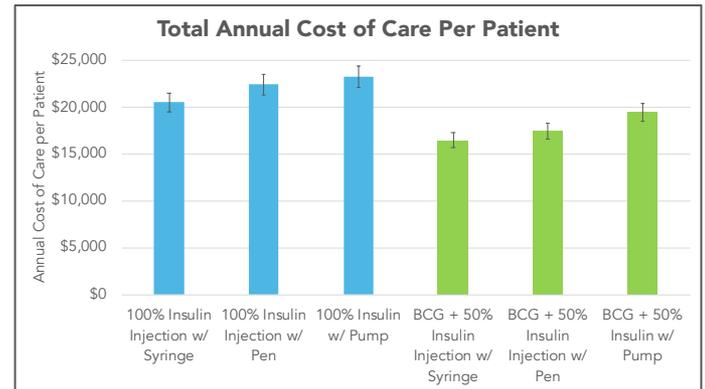
Health Key Performance Indicators (HKPIs)

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Annual Cost of Care Per Patient

Average annual cost of care for T1D patients by treatment regimen for payers, including insurance companies and government programs. Inputs include insulin, non-insulin pharmacy (other scripts), medical spending (in/outpatient, procedures).

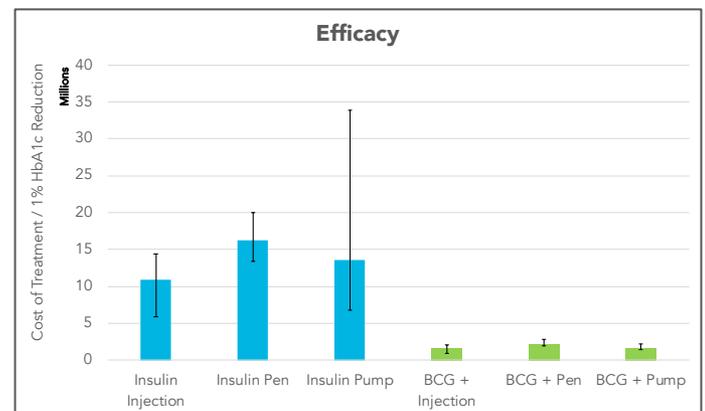
- ▶ Insulin accounted for 31% of total spending for the average patient in 2016 and represents a significant cost saving opportunity if BCG is approved for Type 1 Diabetes.
- ▶ Non-insulin pharmacy (other scripts) is considered a fixed cost across all subsets, due to limited insight into the types medications and conditions that are captured in the data set.
- ▶ Medical spending (in/outpatient, procedures) is the largest component of average total spending, contributing 47% of all costs.
- ▶ Due to the absence of any reported hypoglycemic events during Phase I trials for BCG, average medical spending was adjusted to consider significant reduction in associated expenses, including glucagon and inpatient treatment (on a risk adjusted basis).



Efficacy Cost

Efficacy was assessed in terms of the average cost to payers for a 1% reduction in HbA1c. HbA1c, develops when hemoglobin joins with glucose in the blood becoming 'glycated', part of the natural process when the body processes sugar. An HbA1c test can measure changes in blood sugar levels over a period of weeks/months. For people with diabetes, the higher the HbA1c, the greater the risk of developing diabetes-related complications. A 1% reduction translates to an average reduction in blood glucose levels of 1.6 mmol/L. Studies have shown that a 1% reduction cuts the risk of microvascular complications by 25%*.

- ▶ An average insulin dose of 60 units per day for traditional insulin therapy was assumed, along with a 50% (30 units) reduction after BCG administration.
- ▶ HbA1C reduction for syringe-based injection and pen was considered 0.04% per year, for pump 0.016% to 0.05% per year and for BCG 0.16% per year.
- ▶ On average BCG is projected to reduce 85%-88% of the cost per 1% HbA1c reduction



*Source: UK Prospective Diabetes Study, <https://www.dtu.ox.ac.uk/ukpds/>

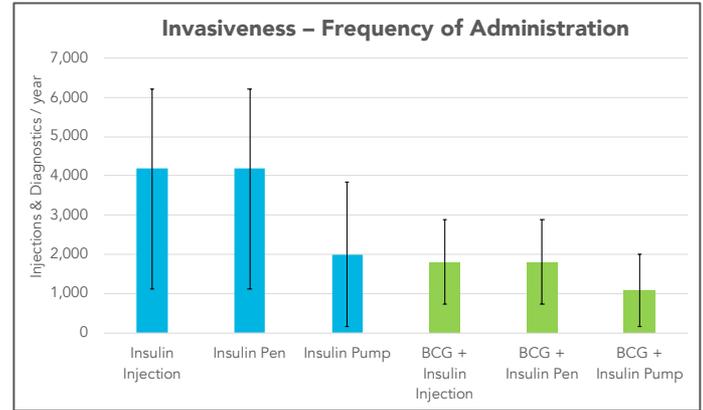
Health Key Performance Indicators (HKPIs)

We evaluated the public health and socioeconomic inputs and impacts for the BCG vaccine considering its ability to reduce HbA1C levels and thus reduce the need for insulin injection.

Invasiveness

Invasiveness measures the number of times the treatment and related procedures (including testing/diagnostics) are needed within a year. Needle phobia is anxiety at the thought of injections or blood glucose testing, leading to attempts to avoid them*. Injections and blood glucose testing can be distressing, as studies estimate that needle fear affect 28% of adults managing diabetes with insulin injections**.

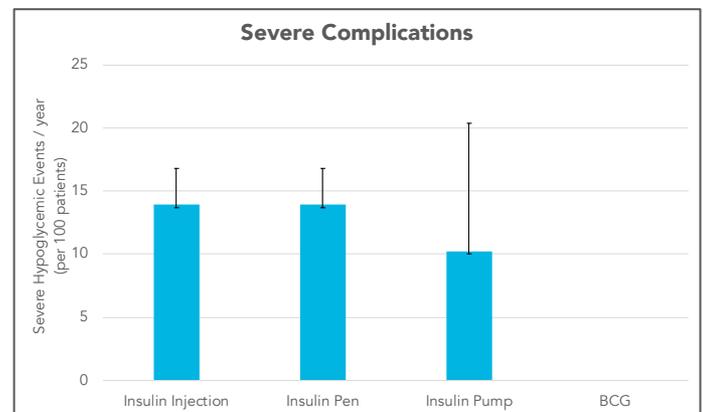
- ▶ Insulin Injection and Pen require 3 to 7 applications per day, while Pumps are changed every 2 to 3 days.
- ▶ For Insulin measurement as a minimum it was considered a Continuous Glucose Monitor changed every 2 weeks, and as a maximum a Self Glucose Monitor 10 times a day. This metric does not measure the potential psychological effect of a patient wearing a Pump inserted under the flesh all day.
- ▶ For BCG, the number of injections and Self Glucose Monitoring applications decreased in half, while the cannula and Continuous Glucose Monitor were unchanged.
- ▶ On average, there is a 53.3% reduction in Invasiveness in comparison to Injection, Pen and Pump when BCG is included.



Severe Complications - Hypoglycemia

This metric measures the annual number of severe hypoglycemic events per 100 patients with T1D. During severe hypoglycemic events, glucose levels are so low that an individual cannot treat his or herself and requires assistance from another person. Patients with severe hypoglycemia get very tired, may lose consciousness and can even experience seizures or convulsions.

- ▶ BCG cohort n=9 reported 0 severe hypoglycemia events over a span of 5 years.
- ▶ Of the 9 participants, 3 reported zero severe hypoglycemic events over an 8-year span (including the original five-year period).
- ▶ Across the broader T1D patient population, around 20% experience on or more hypoglycemic events annually.



*Source: Understanding the psychological impact of diabetes and the role of clinical psychology, <https://www.diabetesonthenet.com/download/resource/4378>

**Source: Prevalence and outcomes of fear of needles and associated psychological conditions among patients managing diabetes, [https://www.valueinhealthjournal.com/article/S1098-3015\(16\)01393-0/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(16)01393-0/fulltext)

APPENDIX A: Methodology

Key Goals

Key goals of this analysis were to:

1. Examine patient healthcare and cost performance in conjunction with financial data to arrive at patient and socioeconomic metrics for the BCG vaccine versus traditional insulin therapies.
2. Provide equitable comparisons among relevant existing practices within healthcare system.
3. Incorporate a variety of methodological considerations that are relevant to the diabetes care industry and which were expected to bear upon the results.

To ensure that these key goals were reached, an independent industry expert reviewed the study and assumptions to ensure that the methodology was coherent with industry standards. The expert review and commentary notes are provided in Appendix C.

Methodology

To address the first goal, Boundless reviewed the BCG clinical trial results as well as performed a detailed diabetes industry analysis to obtain relevant studies and or models. At the core of the methodology is an impact assessment model created by Boundless where we utilized inputs from a model validation study by McEwan et al. based on Cardiff Type 1 Diabetes (CT1DM) Model, which demonstrates the QALY impact of changes in HbA1c and hypoglycemia. Additional studies used to inform this report were conducted by Health Care Cost Institute, Kaiser Family Foundation, Centers for Medicare & Medicaid Services and the American Diabetes Association.

Each metric compares BCG's impact on the need for insulin against conventional diabetes treatments. Metric construction for industry alternatives relies on comparisons, for which we relied on scientific literature, industry reports, white papers, as well as assumptions provided by the industry expert. The impact metrics are reported graphically using bar charts to illustrate a baseline result value, along with sensitivity bars reflecting a range of possible result values around deployment scenarios and key variables.

Research Approach

- ▶ Leveraged industry accepted models and data from diabetes studies previously conducted.
- ▶ Reviewed and incorporated detailed information from the BCG Phase I clinical trials.
- ▶ Identified sources of uncertainty and quantified their impact on results.
- ▶ Included important financial and operational variables to estimate the cost of production.

APPENDIX B: List of Health Key Performance Indicators (HKPI)

HKPI	Metric Description	Unit of Measure	Information Needed
Invasiveness – Frequency of Administration	Number of times the treatment and related procedures (including testing/diagnostics) are needed, within a year.	Invasive procedures (injections & diagnostics) / year	<ul style="list-style-type: none"> Number of doses of BCG in full regimen Total (estimated if necessary) number of insulin injections per year for BCG cohort vs. control group (or individuals w/T1D not in study) Total (estimated if necessary) number of invasive diagnostic test per year for BCG cohort vs. control group (or individuals w/T1D not in study)
Efficacy	Average cost to payers for a 1% reduction HbA1c	Average total cost of treatment / % change in HbA1c	<ul style="list-style-type: none"> HbA1c test results for BCG vs. control group (just insulin) Average cost of BCG and insulin (payer data source)
Quality-Adjusted Life Year (QALY)	Number of years gained from BCG with insulin vs. insulin alone, adjusted for a patient’s quality of life during the additional years gained	Years gained/quality of life	<ul style="list-style-type: none"> Life expectancy for T1D patients across all treatment options Health utility values for T1D complications Validated QALY model for T1D, including HbA1c changes and risk of severe hypoglycemia
Safety – Severe Hypoglycemia	Annual incidence of severe hypoglycemia	Number of severe hypoglycemic events / year	<ul style="list-style-type: none"> Frequency of hypoglycemic events for individuals with T1D (baseline) Frequency of hypoglycemic events for individuals after BCG treatment – or estimates based on improved control of blood glucose levels
Payer Cost Savings	Cost of treatments for all Type 1 Diabetes patients in the US	Average total cost of current treatments – risk adjusted cost of BCG inclusive treatment	<ul style="list-style-type: none"> Average cost of insulin per patient (payers) Projected lifespan of T1D patients based on stage/progression of T1D Change in insulin dose after receiving BCG

APPENDIX C: Independent Expert Review

Independent Industry Expert

Sarah Dykstra, PhD in Health Care Management and Economics at the Wharton School. Sarah's research explores how government and insurance policies influence physician treatment patterns and health outcomes. Her current projects focus on value-based payment reforms and state opioid policies. Sarah has a BA in global health from Boston University and a PhD in health care management and economics from the University of Pennsylvania. She previously worked in policy analysis for the Center for Global Development and for Innovations for Poverty Action managing a maternal and child health impact evaluation in Sierra Leone.

Summary of Expert Review

A recent phase 1 clinical trial demonstrated promising results for the potential of the BCG vaccine to be used as therapy for patients with Type 1 diabetes. Although the results were based on a small sample, with 9 patients in the treated 5-year follow-up cohort, the study found significant reductions in key metrics, including patients' HbA1c levels and likelihood of hypoglycemia events.

Boundless Impact Investing has used the results of this study to evaluate the potential of combining BCG therapy with standard insulin therapy with respect to six indicators. The indicators selected are highly relevant and represent outcomes that are important to both patients and payers. The analysis is well-documented and performed in line with standard health economic analyses.

Due to the size of the clinical trial and limited publicly available data related to spending, the analysis relies on a few assumptions that are worth noting. First, the evaluation of QALYs gained through the introduction of BCG relies on an existing study, the Cardiff Type 1 Diabetes Model, to assess the impact on an outcome via a surrogate endpoint. This study provides estimates of the QALYs gained as a result of a 1% reduction in HbA1c levels, permitting the extrapolation of the clinical trial's results. The key assumption here is that morbidity and mortality resulting from HbA1c reductions achieved through the BCG vaccine are similar to those achieved through existing strategies of glycemic control in T1D patients. Only a future study of the BCG vaccine could validate this assumption. In addition, this analysis uses estimates from 1% reduction in HbA1c levels rather than the estimate of 1.18% from the clinical trial; this represents a conservative estimate of the potential effect on QALYs and is reasonable given the level of uncertainty in the results from the clinical trial.

The analysis of the impact on cost of care per patient and net payer savings relies on published estimates of average annual health care spending among T1D patients in the U.S. across types of care, negotiated rebates for insulin and copayment rates. While the assumptions made are reasonable, it's important to note that these figures may vary substantially based on the payer and patient population examined. Two HKPIs examined, invasiveness and severe complications, rely solely on the results of the initial phase 1 clinical trial.

In sum, this analysis demonstrates that, based on the results of the phase 1 clinical trial, the BCG vaccine may have the potential to achieve both significant improvements in health outcomes and substantial cost savings. Whether these improvements can be realized is dependent upon greater precision in the estimates of the effectiveness of the BCG vaccine.

APPENDIX D: Independent Expert Review

Independent Industry Expert

Dr. John Doupis is a former Fellow of the Joslin Diabetes Center at Harvard Medical School. Currently he directs the Diabetes Division and Clinical Research Center of Iatriko Paleou Falirou Medical Center in Athens, Greece as well as the Internal Medicine and Diabetes Department of the US Naval Hospital in Athens, Greece. Dr. Doupis has also served as a Tutor for Diabetes Diploma and MSc in Diabetes at Cardiff University Medical School in the UK since 2012.

His special areas of interest are Type 1 and Type 2 Diabetes and its complications, especially the Diabetic foot and Obesity, as well as the new glucose sensing technologies and insulin pumps. In these fields, he has participated in a substantial number of studies, most of which have been either published in International journals or presented in international congresses. He is also the instigator of "D-partner," an artificial intelligence app for diabetes management.

Dr. Doupis has given numerous lectures in national and International congresses presenting more than 200 papers. In addition, he has authored many chapters in Diabetes related books, published in the USA and in Europe and is a member of the editorial advisory board of several diabetes related medical journals. He has extensive teaching experience at Harvard Medical School, Athens University Medical School and Cardiff University Medical School. He is a member of the Hellenic Diabetes Guidelines board and serves as Advisor of the National Authority's Committee for Insulin Pumps and Sensors.

Summary of Expert Review

The BCG vaccine is a very well-known and widely used vaccine for tuberculosis prevention. Recent data support evidence for the potential use of this vaccine for the management of Type 1 Diabetes.

Although available data on this topic is relatively limited, and the sample size of the patients in Phase 1 trial is small (9 patients followed up for 5 years), the results come from a high level research center directed by a leading scientist in the field, and are quite impressive and promising, providing a new and safe concept for Type 1 Diabetes management utilizing novel therapeutic pathways.

Boundless Impact Investing analyzed data mainly from this Phase 1 clinical trial and made reasonable assumptions due to limited data availability. The analysis was comprehensively presented helping those not familiar with the topic to quickly understand the diabetes-related health impact of the BCG vaccine as a novel, effective and inexpensive treatment approach for Type 1 Diabetes.

Type 1 Diabetes management requires a continuous effort from both the patient and the physician. Better glucose control with less hypoglycemia rates as proposed by the BCG vaccine use, may consequently lead to the reduction of diabetes related complications and hospitalization. This along with the reduction of daily insulin requirements shows that BCG may also reduce the total direct and indirect costs as nicely analyzed by Boundless Impact Investing, based on published estimates of the average annual health care spending among Type 1 Diabetes patients in the U.S.

Furthermore, estimates of the QALYs from the trial were reasonably calculated as the result of the HbA1c and hypoglycemia rate reduction in the BCG treated group at year five, compared to the control group. Invasiveness calculations were based on reasonable assumptions, as the number of times the treatment and all related procedures are needed within a year.

Overall, I believe that this is a quite efficient analysis of the currently available data of this topic, providing a clear sense of the health-related impact of the BCG vaccine as a promising treatment option for Type 1 Diabetes.

APPENDIX D: Score Rationale & Profile Sponsor

Health Impact Score

The health impact score is a number (1=worst to 10=best). This number represents an overall indicator of a company's health impact performance against its most relevant industry competitors. The value is obtained by comparing the average of each resulting HKPIs for the company against its comparable treatments as well as a baseline of not having diabetes at all (10 out of 10). The score for each metric is also displayed in the summary Spider Chart of the profile of each product.

The BCG Vaccine is ranked as having an overall great performance when compared to traditional forms of insulin therapies. On average BCG is projected to reduce **85-88%** of the cost of achieving a 1% HbA1c reduction, as opposed to traditional insulin. There is a **53.3%** reduction in invasiveness in comparison to Injection, Pen and Pump when BCG is included. A 1 % decline in HbA1c accounted for a gain of **0.5482** discounted QALYs five years after receiving the first dose of BCG. Using a formulaic comparison to measure relative performance across all HKPIs, the BCG Vaccine scored a **6.8** out of 10 on health performance.

FYI Diabetes

FYI Diabetes is a family-founded nonprofit organization dedicated to funding promising research focused on curing diabetes, new innovative technologies that improve the quality of life for diabetics and raising awareness of diabetes through education and health screenings. FYI Diabetes supports the advancement of clinical trials using the Bacillus Calmette-Guérin (BCG) vaccine to prevent and reverse autoimmune diseases including Type 1 Diabetes.

BOUNDLESS

IMPACT INVESTING

About Boundless Impact Investing

Driven by the latest research by independent industry and academic experts, Boundless Impact Investing offers analysis, market trends, and evidence of best practices in a growing number of emerging sectors that address major social and environmental challenges. We are an advanced consulting firm that enables investors to connect with industry leaders and peers for expert analysis, diverse perspectives, and real-time collaboration. Our investor education and expert advisory services offer proprietary access to both subject-matter experts and other impact investors.

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