FREQUENTLY ASKED QUESTIONS

PHASE I BCG HUMAN CLINICAL TRIAL

What was the design of the Phase I study?

The Phase I, double-blind, placebo-controlled clinical trial was conducted at Massachusetts General Hospital (MGH) to test BCG vaccination as a treatment for advanced type 1 diabetes. It is part of the BCG Human Clinical Trial/Cure Diabetes Now Program at MGH. The study was conducted with FDA oversight.

Patients with long-term diabetes were enrolled (n=6) as well as simultaneously studied clinical trial controls (n=6). Participants had been living with type 1 diabetes for an average of 15 years prior to enrollment and had good blood sugar control and no evidence of insulin secretion upon enrollment in the trial.

Safety was the primary endpoint but four efficacy endpoints were also studied:

- Levels of autoreactive T cells (cells that destroy the insulin-secreting cells of the pancreas)
- Levels of regulatory T cells (Tregs) (cells that help control the immune response)
- GAD autoantibodies (a marker of pancreas activity)
- Levels of C-peptide (a marker of restored insulin secretion)

Participants were randomly assigned to receive two injections of either BCG or a placebo, spaced four weeks apart. Blood samples were taken weekly or bi-weekly for 20 weeks and analyzed for the four outcome measures. Each patient was serially followed and compared to self, compared to a matched nondiabetic (n=6) control and compared to the reference population of serially followed cohorts (58 individuals with type 1 diabetes and 17 without diabetes) that were not treated with BCG nor placebo injections. A total of 1,012 blood samples were studied.

What were the safety findings?

The safety findings were announced in June 2010. There were no serious adverse reactions and only mild inflammation at the injection site, as expected. The U.S. FDA and the Massachusetts General Hospital (MGH) data safety monitoring committee both confirmed that Phase I testing adequately confirmed that BCG vaccination was safe for people with longstanding type 1 diabetes as used in the Phase I human clinical trial.

What were the additional findings?

Data on four outcome measures were presented at the American Diabetes Association's 71st Scientific Sessions in June 2011. The data were presented in two abstracts:

- BCG Treatment of Long-Term Type 1 Diabetes (ADA Abstract 2240)
- EBV Infection May Influence Therapeutic Potential of αCD3 Therapies (ADA Abstract 1311ADA11D1LB)

These data showed that induction of tumor necrosis factor (TNF) using BCG in individuals with long-term diabetes appears to briefly:

- selectively eliminate the autoreactive T cells that destroy the pancreas.
- increase the number of regulatory T cells (Tregs).
- transiently restore insulin production as measured by C-peptide.

Fluctuations in GAD autoantibodies were also observed, suggesting BCG was having a positive effect on the pancreas, i.e., islet cell regeneration may have been starting to occur.

These results were also seen in one participant in the placebo group who unexpectedly developed an infection with the Epstein-Barr virus (EBV) after enrollment in the trial. Like BCG vaccination, EBV infection is also known to boost TNF levels.

The research team's conclusion is that BCG or a treatment that similarly induces TNF has the potential to reverse, albeit transiently, long-term diabetes and that BCG should be pursued in further studies to test its potential to benefit or even reverse advanced type 1 diabetes with repeat administrations.

Can you discuss the trial design, i.e. small number of participants but intense blood monitoring?
Phase I studies are typically small trials designed primarily to demonstrate safety, but they may also look at additional outcomes that are indicative of drug efficacy, as did the Phase I BCG Human Clinical Trial.

The Phase I trial size and analysis was carefully planned with the clinical trial team at MGH and the FDA. We were able to detect statistically significant outcomes using a "small" sample of randomized participants (n=6) paired with controls (n=6), but a very large number of blood samples and intense blood monitoring (measuring outcomes weekly over the 20-week trial period for each participant). In total, we analyzed 1,012 blood samples, including samples from the randomized participants and paired controls as well as reference samples. Each patient was serially followed and compared to self, compared to a matched control and compared to the reference population of serially followed cohorts.

The intensity of studying the immune and pancreas response – weekly, serial measurement of the four outcomes over 20 weeks – was one of the largest for any type 1 diabetes trial designed to date to our knowledge. With intense serial monitoring, we observed that the participants who received BCG treatment showed a response in at least three of the four outcome measures, even at the low dose used. This suggests that the majority of diabetics will likely be sensitive to the drug as we move forward to additional stages of testing. Overall, a strong statistical significance was reached for the outcome measures, especially for the promising clinical outcome, i.e. a return of C-peptide secretion, which is indicative of a return of insulin secretion.

We were also able to plan and analyze a smaller trial due to the fact that we were testing a generic drug with a long history and well-established safety profile in the general population.

In Phase II, we will study a larger population of patients with advanced type 1 diabetes to further validate our preliminary efficacy findings.

What are the implications of the Phase I trial?
First, this proof-of-concept study demonstrated that BCG, an inexpensive generic drug, is safe to use in advanced type 1 diabetes and appears to have the ability to transiently and partially reverse type 1 diabetes and restore insulin production, even at the low doses used in Phase I and even in individuals who have had type 1 diabetes for over a decade. These data support the hypothesis that the mechanism through which BCG might benefit human type 1 diabetes is by boosting TNF levels.

In addition, looking at the data from the EBV-infected patient shows that TNF induction is key not just for this trial, but that it also may have been the missing component in two recent Phase III trials testing anti-CD3 monoclonal antibodies in type 1 diabetes. These trials specifically used lower drug doses in

Phase III to prevent reactivation of latent EBV infection. We believe this may have negatively affected drug efficacy in those studies.

What is unique about this study?
Most type 1 diabetes trials focus on new-onset disease. This study is investigating a treatment to reverse advanced disease without using immunosuppression or cell transplants. This study is also unique in seeking to repurpose an inexpensive generic drug for a new use, based on a mechanistic understanding of how autoreactive T cells can be eliminated by elevating tumor necrosis factor (TNF) in the body, halting the autoimmune attack.

Why is this research being done? Why is it important?
In type 1 diabetes research, there is a large emphasis on new patches, pills and blood glucose monitoring devices, but relatively little emphasis on cures. Currently available treatments, such as insulin injection or islet transplantation, slow down the disease or alleviate symptoms, but do not address the autoreactive T cells that are part of the underlying cause of disease. In addition, research efforts typically favor newly diagnosed patients, rather than people who have been living with type 1 diabetes for many years.

The BCG Human Clinical Trial Program is focused on people with longstanding diabetes, not just newly diagnosed patients. The goal is disease reversal followed by pancreas regeneration by exploiting the sensitivity of the disease-causing T cells to a protein that is produced by the immune system: tumor necrosis factor (TNF). Importantly, the current clinical trial program is testing whether an inexpensive, generic drug called BCG can eliminate the autoreactive T cells and lead to disease remission and regeneration of the pancreas. If approved for use in type 1 diabetes, BCG could have a tremendous, positive impact not only on the health of those with type 1 diabetes, but also on type 1 diabetes-related healthcare costs.

What is BCG, the drug that was tested in the Phase I study?
BCG (bacillus Calmette-Guérin) is currently approved by the U.S. FDA for vaccination to prevent tuberculosis and for the treatment of bladder cancer. It is a generic drug with ninety years of safety data. BCG is known to elevate levels of the immune modulator tumor necrosis factor (TNF). Previous work in the Faustman lab in both humans and mice has shown that elevating TNF can temporarily eliminate the abnormal white blood cells that are responsible for type 1 diabetes. This was also observed in the Phase I study.

Is BCG a cure for type 1 diabetes?
We do not expect that treatment with BCG will cause a permanent remission of type 1 diabetes with a single treatment. More likely, if this drug is developed for type 1 diabetes, recipients may need intermittent "booster shots" to sustain the beneficial effects of the vaccine, i.e. regrowth of the pancreas and restoration endogenous pancreas activity to some level.

In our mouse studies, we eliminated the autoreactive memory T cells using one treatment (this is what we are trying to replicate in the current BCG human clinical trials) and used a second intervention to "re-educate" a different population of abnormal T cells (naïve T cells) so that they would not become autoreactive and attack the insulin-producing islets. It is likely that once the islets reappear after BCG vaccination or other similar treatment, the abnormal naïve T cells will still convert into killer memory cells. This is why re-dosing of BCG will likely be necessary if it is developed into a type 1 diabetes treatment.

In the Phase I study, we saw that two BCG vaccinations spaced four weeks apart had a transient beneficial effect in advanced type 1 diabetes. In Phase II, we will be looking for a dose and timing of administration that leads to a more sustained benefit. If BCG is developed and approved as a drug for type 1 diabetes, we hypothesize that this will lead to better blood sugar control, fewer long-term complications and less expensive treatment for people with type 1 diabetes.

Has BCG been tested in children?
Children throughout the world have received BCG as a vaccination to prevent tuberculosis. The Phase I BCG Human Clinical Trial conducted at Massachusetts General Hospital did not enroll children. Enrollment of children in future trials will be determined by the FDA.

Is the BCG vaccine used today in the United States?
The BCG vaccine is used for the prevention of tuberculosis under certain circumstances, i.e. in people who were not previously infected with tuberculosis who are at high risk for exposure. However, it is not routinely used in the United States as a vaccination. More information can be found at http://www.cdc.gov/tb/publications/factsheets/prevention/BCG.htm or in discussions with your physician.

Can I just go and get BCG from my doctor now?
BCG is not currently approved for use in type 1 diabetes. We are conducting the BCG Human Clinical Trial Program to see if BCG is an effective treatment for advanced type 1 diabetes, including at what dose and schedule of administration.

What is TNF?
Tumor necrosis factor (TNF) is a type of protein known as a cytokine. It is produced naturally by the human immune system in response to infection and inflammation. Induction or release of TNF can cause certain cells to die, including tumor cells and, as the MGH research team has shown (Ban et al. PNAS 2008; ADA 2011), the self-reactive white blood cells (autoreactive T cells) that attack the specific tissues in people with autoimmune diseases.

PHASE II BCG HUMAN CLINICAL TRIAL

What will the Phase II trial try to accomplish?
The Phase II trial will look at what dose and schedule we need to use to make BCG a functional and sustained type 1 diabetes therapy. In Phase II, we will try to sustain the favorable T cell and pancreas responses in people with long-term diabetes that we observed transiently with limited dosing in our Phase I trial. Trial design and endpoints will be determined with the FDA and MGH clinical trial team.

Is the Iacocca Foundation supporting the Phase II clinical trial?
Yes. The Iacocca Foundation has made a leadership gift for the Phase II study.

Where can I find additional information? How can I enroll in a study?
Additional information can be found at www.faustmanlab.org. Individuals interested in participating in future trials should email DiabetesTrial@partners.org.