START
STUDY OF THYMOGLOBULIN TO ARREST TYPE 1 DIABETES

Frequently Asked Questions

1. What is the purpose of this research study?

When someone is diagnosed with type 1 diabetes, between 60-85% of the cells that produce insulin (called "beta cells") have been mistakenly destroyed by the immune system. The START trial will test whether a drug called Thymoglobulin® can reset the immune system so that it learns to spare the remaining 15-40% of beta cells that can still produce insulin. If successful, improved daily blood sugar control and reduced risk of long-term complications from type 1 diabetes would result.

2. Who can participate?

Participation in the START trial is voluntary. Individuals 12-35 years old with type 1 diabetes who are not more than 100 days (about 3 months) past the date of their diagnosis with diabetes may be eligible to participate. Additional criteria will be evaluated during a screening appointment to see if all study eligibility requirements are met.

3. How is the medication given?

Thymoglobulin® (and the placebo) is administered by infusion. An infusion requires placing an intravenous needle (known as a catheter) in the arm and then the appropriate dose of the drug is slowly given over time. In the START trial, participants will receive an infusion each day for four days at the beginning of the trial. Each infusion will take place over 8-12 hours. Receiving the study medication requires staying in the hospital for at least 5, and possibly as many as 8 days.

4. Are there any other medications administered as part of the trial?

Before each Thymoglobulin (or placebo) infusion, you will be given medications to reduce potential side effects. All participants will be given an antihistamine (Benadryl) and acetaminophen (Tylenol) by mouth in order to reduce potential side effects from Thymoglobulin. You may also be given Methylprednisolone (a steroid) or a placebo intravenously depending on what group you were randomized to. Following the infusion, participants will take antibiotics by mouth each day for about 3 months in order to reduce the risk of infection. Participants in the placebo group will also receive placebo antibiotic tablets to take for about 3 months (placebo tablets look like the active drugs but do not contain any medication).

5. Will I/my child need to be hospitalized?

Yes. All participants are admitted to the hospital to receive the study drug (or placebo), which is given intravenously in four infusions. Participants can expect to spend a total of 5-8 days in the hospital.

6. What does intensive diabetes management involve?

All participants in the START trial will receive intensive diabetes management, which is commonly used to improve blood glucose control and lower the risk of long-term complications from type 1 diabetes. The goal of intensive diabetes management is to keep daily blood glucose levels as close to normal as possible. Participants will work closely with the diabetes research study team, as well as their primary care physician and current diabetes care provider. Participants will be expected to check their blood sugar levels at least 4 times a day, and use insulin as prescribed. Each participant will receive individualized treatment plans from the diabetes research team (which includes a nurse educator, dietician, and diabetes physician) in order to develop a comprehensive care plan to manage their diet, exercise, and lifestyle. A member of the diabetes care team will contact participants every 2

weeks. For the five days immediately prior to each study appointment, participants must keep track of their blood sugar levels and insulin doses. A diary will be provided for this purpose.

7. How often do I need to visit the clinic?

A schedule of study appointments is provided in the table below. There are a total of 14 separate visits over two years, with more visits occurring in the early part of the study and one visit every 3 months near the end of the study. Throughout the study, participants will have biweekly contact with study staff (either as part of an appointment or via telephone) to monitor diabetes management progress, discuss concerns and answer questions. Participants may also make arrangements for additional, unscheduled visits at their request.

Type	Visit #	Time	Purpose	Assessments
Screening	-1		To assess eligibility for trial. Asked to sign informed consent	medical history, medication use, physical exam, blood sample, urine sample, MMTT*
Baseline	0		Randomization (assignment to 1 of the 2 study groups)	Medication use, adverse events, blood samples
Treatment	1-5	days 1-5	Thymoglobulin/placebo infusion	Medication use, adverse events, physical exam, blood samples
Study visit	6	day 10	Progress, diabetes management	Medication use, adverse events, blood sample, urine sample
Study visit	7	day 15	Progress, diabetes management	Medication use, adverse events, blood sample, urine sample
Study visit	8	month 1	Progress, diabetes management	Medication use, adverse events, physical exam, blood samples
Study visit	9	month 2	Progress, diabetes management	Medication use, adverse events, blood sample
Study visit	10	month 3	Progress, diabetes management	Medication use, adverse events, physical exam, blood samples
Study visit	11-18	months 6-24 (every 3 months)	Progress, diabetes management	Medication use, adverse events, physical exam, blood samples and/or MMTT

*MMTT = mixed meal tolerance test. This involves drinking a special drink, similar to a milkshake, and collecting blood samples over a 4-hour period

8. How long do study visits take?

The screening visit will last approximately five hours. Regular study visits should take no more than 1-2 hours in most cases. If a visit involves mixed meal tolerance test (MMTT), the visit will last up to 5 hours.

9. What happens during study visits?

Study visits are appointments that take place at the study site. They include meetings with the study staff (physicians, nurses and diabetes educators) and discussing progress in meeting diabetes management program goals. At the study visits, participants can expect to provide blood and/or urine samples, have a physical exam, answer questions about potential side effects and insulin/other medication use, and/or perform a mixed meal tolerance test.

10. What is a Mixed Meal Tolerance Test?

A Mixed Meal Tolerance Test (or 'MMTT' for short) tells doctors how much insulin your body is still making. It involves drinking a special drink called 'BOOST' that tastes like a milkshake, and contains a mixture of protein, fat and carbohydrates. The drink raises your blood sugar, causing insulin to be released from your beta cells. Over a four hour period after drinking the Boost, eleven blood samples are taken at specific time points. An intravenous catheter (an IV) will be placed in a vein your arm at the start of the procedure through which all blood samples will be obtained. The samples are sent to a lab for analysis.

11. What are the laboratory tests for?

Tests done during the trial will be used to measure several things: how your whole body responds to the treatment; how your immune cells respond and grow back following the treatment; to assess the health of your beta cells and status of your diabetes; to look for signs of possible infection; and to provide other information that might help learn more about how Thymoglobulin affects type 1 diabetes.

12. When are the clinical centers open?

Each clinical center has different hours, however, every attempt has been made to be flexible in order to accommodate busy schedules.

13. Does it cost anything to participate?

Participation in the START trial is at no cost to you. You will receive reimbursement for parking or other travel expenses incurred in attending study visits. Blood glucose monitors and testing supplies are provided free of charge for the duration of the study (generously supplied courtesy of LifeScan, Inc.).

14. Will I or my child receive payment for participating?

Compensation is available to participants in the trial for study visits that include mixed meal tolerance testing, due to the time involved in these tests. Study staff can provide you with the exact amounts and schedule of compensation.

15. What does it mean that START is a 'controlled' study?

A controlled study means that some patients will receive the study drug (Thymoglobulin), while others will receive an inactive form (or "placebo"). Patients that receive the drug are in the "treatment" group; patients that receive the placebo are in the "control" group. By comparing the results in the treatment group with results in the placebo group allows doctors to better determine how effective the study drug is. In START, 2/3 of participants (the treatment group) will receive Thymoglobulin, while the other 1/3 (the control group) will receive a placebo.

16. What does it mean that START is a 'blinded' study?

A "blinded" study means that the participant (as well as their parent/guardian) does not know whether they are receiving the active or placebo formulation. In this study, the diabetes management team will also not know which group participants are in.

17. Can I choose to receive the study drug?

Whether a participant receives the placebo or active formulation is random – that is, it is left completely to chance (like flipping a coin). Neither participants nor study staff are able to choose which group a participant will be

assigned to. If you enroll, there is a 2 in 3 chance that you will receive the study drug and a 1 in 3 chance that you will receive the placebo.

18. Will my/my child's privacy be protected?

START investigators take the privacy of study participants very seriously. The confidentiality of all patient records is maintained according to regulations set by the Food and Drug Administration and the Department of Health and Human Services. The results of all tests, assessments and evaluations performed during the course of the study will remain confidential and will not be released to third parties without prior written consent of the participant and/or their parent/guardian. Prior to release of the study results, all personal identifying information will be stripped so that results may not be associated with any one individual.

19. Will my primary care physician and current diabetes provider be involved?

Your current health care providers have much to offer in helping you manage type 1 diabetes. The START study team will work closely with your current health care providers to develop, manage and track your progress in the intensive diabetes management program.

20. What are the potential risks/benefits of participating?

The health and safety of participants in the START trial is the highest priority of the study investigators and sponsors. The START trial has been designed to minimize potential risks to study volunteers. However, as with any medication, there is the risk of developing side effects from the medications provided as part of the START trial. Depending on the person, these side effects can vary in both type and severity. Taking part in the START trial may or may not make your health better. While doctors hope that Thymoglobulin will be effective in treating diabetes, there is no proof of this yet. If you are in the treatment group, and Thymoglobulin proves to work, your diabetes may improve, but this cannot be guaranteed.

Every participant in the study will receive intensive diabetes management - research has shown that following an intensive diabetes management program and keeping your blood sugar levels close to normal can help to preserve beta cell function and decrease the risk of long-term complications from diabetes. Your participation in this study may improve our understanding of Thymoglobulin, and the information learned in this study may help future patients with type 1 diabetes.

21. If I agree to participate, can I change my mind?

Participation is completely voluntary. If you decide to participate and at any time during the study you change your mind, you are free to stop participating. Your decision to stop being in the study will not have any effect on your ability to continue to get the health care you need.