Musgrove Park Hospital

Participant Information Sheet

Type 1 Diabetes TrialNet Protocol TN-18

CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus

INTERVENTION

Principal Investigator:	Dr Isy Douek
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You (you means you or your child) have been participating in the TrialNet Natural History Study (Pathway to Prevention). You are now being invited to take part in another TrialNet research study which is a diabetes prevention trial. You have had blood tests that show you have certain markers associated with an increased risk of developing type 1 diabetes. You have also had an Oral Glucose Tolerance Test (OGTT) and other screening tests. These showed that your blood glucose levels are normal and you meet the requirements to enter the study.

This information sheet tells you about the study and what people in the study will be asked to do. Please take time to read the following information carefully. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please talk to

others about the study if you wish. The study will be explained to you and you will be given the chance to ask questions. You will be given a participant handbook that explains the overall study. Taking part in this study is your decision.

If you agree to take part in the study, you will be asked to sign the consent form. You will be given a copy of the consent form to keep for your records.

What is the purpose of this study?

We know that development of type 1 diabetes occurs over time as the immune system destroys insulin producing cells. As this takes place, blood glucose values increase gradually until they are high enough to diagnose diabetes. Before this, blood glucose values may be higher than normal but not high enough to diagnose diabetes. We call these “abnormal glucose levels”.

The purpose of this study is to see whether giving a medication called abatacept can help delay or prevent can help delay or prevent the development of abnormal glucose levels and diabetes in people with have markers associated with risk of diabetes.

What is the drug that is being tested?

The medication is an intravenous infusion containing abatacept. Abatacept is approved as a treatment for rheumatoid arthritis and juvenile idiopathic arthritis. In a previous TrialNet study abatacept was shown to have some effect on preserving insulin secretion after diagnosis.

There is also a placebo (dummy drug) group in this study. This group will be given an infusion of saline which contains no active ingredient. This is a ‘blinded’ randomised trial so that neither you nor the researchers will know which infusion you are taking until the study has been completed.

What will happen during the study?

This study will have two phases, a treatment phase for the first year and then a monitoring phase. During the treatment phase, you will receive the study medication 14 times over a year. During the monitoring phase you will have visits every six months.

All study visits:

At the study visits we will ask questions about your health, diet and activity, and experience as a research participant. From time to time we will perform a physical examination and take blood for testing. Females will also give regular urine samples to be checked for pregnancy.

The blood tests will help us check for diabetes, your immune system, and your general health. They will also be used to better understand what causes type 1 diabetes, to look for new ways to identify people at risk for disease, and to get ideas about new treatments in the future. While TrialNet is ongoing, these samples will be used only by TrialNet-approved researchers. We will be collecting blood samples, including genetic samples, for these studies at most of your visits. You will not routinely be provided with test results from these studies.

The total amount of blood drawn for tests done at each visit will not exceed the amount that is safe for your age and weight. More information about the specific blood tests can be found in the participant handbook.

Treatment phase

At the first study visit, you will be put into one of two groups. One group will receive abatacept through a vein. The other group will receive placebo instead of abatacept. A placebo looks like medicine, but has no medicine in it so that people in the study will not know whether they are receiving the drug or placebo. You will be placed into one of these groups by chance (similar to tossing a coin). You will have a 1 out of 2 chance of getting abatacept or placebo. Neither you nor your doctor will be able to choose the group in which you will

be placed. Neither you nor your doctor will know who is getting abatacept and who is getting placebo.

After you are assigned to a study group, you will receive three doses of either the abatacept or the placebo through a vein in your arm during the first month and then monthly doses. The first dose of study medication will be given as part of your first visit; the second dose will be given 2 weeks later, and the third dose will be given two weeks after that. The remaining doses will be given every 4 weeks. You will have a total of 14 infusions over a period of one year. Administering the study medication will take about 30 minutes. You will need to stay for observation at the study site for an hour after each infusion.

During the treatment phase of the study, in addition to monthly visits to receive the study infusion, you will have an Oral Glucose Tolerance Test (OGTT) every six months (described below). At visits with an OGTT you will be there an extra 2 hours. Even if you do develop abnormal glucose levels, you will still come in for treatment visits monthly.

Monitoring Phase

After you have completed with treatment phase, you will come in every six months for OGTT visits. Even if you do develop abnormal glucose levels, you will still come in for visits every six months.

In addition to study visits every six months, we will monitor you for risk of diabetes at three month intervals by phone contact. We will ask you about possible symptoms of diabetes such as blurry vision, unintended weight loss, increased hunger, thirst, or frequent urination. In addition we will ask you to have a blood test every three months. If you have any of these symptoms or abnormal blood tests, we may ask you to come to the study site for extra testing including an OGTT.

Other Study Procedures:

- **Oral Glucose Tolerance Test (OGTT)**

You have had OGTTs as part of the TrialNet Natural History - Pathway to Prevention Study. An OGTT is done in the morning after an overnight fast (not eating during the night). Your blood glucose (sugar) will be measured after you drink a sweet liquid that contains glucose over a 5-minute period. To make the blood sampling easier, we will place a cannula in a vein in your arm. This cannula will stay in your arm until the end of the test. Blood samples will be drawn through the cannula before you drink the liquid and then at several times after you have finished drinking it. A total of about 1 tablespoon of blood will be drawn for the OGTT. The visit for the OGTT takes about 3 hours

In some cases you will be asked to repeat the OGTT within one month to confirm the results.

- **Immunisations:**

During the treatment phase you will receive a flu vaccine (given at the appropriate time of the year). Children less than 9 will need two flu vaccines (to be given one month apart) if they have not received a flu vaccine before. By testing your blood after the flu vaccine we can learn about how abatacept affects the response to vaccines.

What are the risks of taking part?

The treatment and tests involved in this research project have the known risks listed below. There may be other risks that are not possible to predict.

Common Side Effects:

Abatacept can cause side effects that occur while it is being given. They are called infusion-related reactions. Possible reactions include nausea, dizziness, and high blood pressure, or low blood pressure. Other possible reactions include flushing, itching, coughing, wheezing, difficulty breathing, and fatigue. For your safety, the research staff will watch you closely for these effects. For example, you will have your blood pressure, heart rate, and temperature taken regularly while you are receiving abatacept and during the observation period following the infusion.

Uncommon Side Effects:
Abatacept affects your immune system. Although unlikely, it is possible you could be at increased risk of certain types of infections including respiratory, urinary and skin infections. We will carefully check you for signs of infection during the study. If we see signs that you developed a new infection we will temporarily discontinue giving you monthly infusions until the infection has resolved. You should contact your doctor if you develop any infections, any flu-like symptoms, or are not feeling well at any time. You will not receive an infusion if you have an infection. Other uncommon, but possible, side effects include gastrointestinal irritation, diarrhoea, abdominal pain, blurred vision, dizziness, rashes, hair loss, depression and anxiety.

Rare Side Effects:
Medications like abatacept that alter responses by the immune system can possibly lead to an increased risk of certain types of cancer. This has not been seen in previous studies of abatacept. In very rare instances, anaphylaxis (a severe allergic reaction) can occur which could be life-threatening. There may be increased infections or reappearance of previous infections. Very rarely these infections could be severe or even fatal.

- **Birth control and pregnancy**

It is not known whether abatacept can damage unborn babies. Women must not become pregnant for at least 3 months after completing the treatment phase of the study. If you could become pregnant, you must agree to use a reliable and effective form of birth-control while you are having monthly infusions during the study. You will need to provide a urine sample for pregnancy testing regularly during this study. If you become pregnant, you must tell the study doctor right away. We will stop your study medicine.

- **Intravenous Cannula and Blood Drawing**

While on the study you may have side effects from having your blood taken or intravenous cannula placed. The risks of side effects from these procedures are very small. There is sometimes soreness and/or a bruise at the site where the needle goes through the skin.

Once in a while, people faint. It is rare, but some people may get an infection, a small blood clot, swelling of the vein and the area around it or bleeding where the needle goes through the skin.

- **Oral Glucose Tolerance Test (OGTT)**

Some people may feel sick when they have the OGTT.

- **Immunisations**

Like all immunisations flu vaccines have a small risk of allergic reactions that can be severe. If you had a severe reaction to flu vaccine before, you will not be given that immunisation during this study. You will also not get the flu vaccine if you are allergic to eggs. If you have an illness with a fever, you will not get the vaccinations until you recover. The injections of vaccines may cause redness, swelling, and pain or soreness in the muscle where the injection is given. Immunisations may also cause a slight fever. Rarely, a mild flu-like illness and muscle aches may occur. All effects are usually mild and go away without treatment.

It is not known what effect abatacept may have on other vaccines. If you need any routine vaccinations, you should not get them during the first 15 months of the study (during the treatment phase and the following 3 months). After that time, be sure you let us know if you have received any vaccines as part of your usual medical care.

Are there any benefits of taking part?

If you decide to take part in this study, there is no guarantee that your health will improve. Abatacept may help the body to delay abnormal glucose or diabetes, but there is no guarantee.

How long will the study last?

The exact duration of the study is not known. We anticipate that your participation will be no longer than 5-6 years. If you do develop diabetes, you will no longer be in this study. However, we will let you know if there are other TrialNet studies are available to you. There will be about 206 research volunteers enrolled in the study

What is the alternative?

Before you decide to take part in this study, we will talk with you about the other options available to you. You may choose not to participate in this study. At present, there is no approved medical treatment that will delay or prevent abnormal glucose or diabetes. There may be other research studies that you can choose to be in.

Who is funding the study?

The US National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) is providing major funding for this study. The study is also sponsored by National Institute for Allergy and Infectious Diseases (NIAID), the National Institute for Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation (JDRF), and the American Diabetes Association (ADA). Bristol Meyers Squibb will provide the abatacept medication for the study.

Will I receive anything for taking part?

If you decide to be in this study you will receive a small amount to cover your expenses for each study visit you attend. By signing the consent form, you understand and agree that, if this research project results in the development of any product that can be sold, you will not receive a share of any money that is made.

Do I have to stay in the study?

No. It is up to you to decide whether or not to take part. Participation in this study is voluntary. If you are eligible but choose not to be in this study, you can remain in the Natural History Study (Pathway to Prevention) to be monitored.

You can withdraw your consent at any time. If you chose to stop being in the study, tell a study staff member. Your current or future care will not be any different if you decide not to be in this study or to stop being in this study at any time. Your doctor may choose to take you out of the study at any time, even without your consent. You will be told of any new findings that may affect your being in this study.

Invitation for Questions

You will receive a copy of this Information sheet. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, doctor, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may direct any questions to Prof Polly Bingley and the TrialNet team on 0117 414 7920.

This completes Part 1 of the information sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What will happen to my data?

Your consent to be in this study gives the TrialNet researchers permission to collect study information related to the study and to use it for research purposes. This information may be shared with other TrialNet centers as needed to help with the study. Your consent also includes permission for the sponsor of this study (NIDDK) and the UK and US regulatory agencies (the Medicines and Healthcare products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA)) to review your records.

Information from your research records will be sent to our central coordinating centre at The University of South Florida, USA for statistical analysis. No personal information that directly identifies you will be included with these data. Personal information is information such as your name that directly identifies you. Instead you will be assigned a unique study code. This personal information will be kept in a database at the UK TrialNet Coordinating Centre at the University of Bristol. The key to the code, linking your personal information to you, will be kept in a locked file here at the University of Bristol. Only Prof. Polly Bingley and her research staff will have access to the key to the code.

When TrialNet is completed, your data (but not your personal identifying information) will be moved to another location that will be under the supervision of the NIDDK. Once this happens, it will no longer be possible to link your code to your name or other personal identifying information.

An agreement between the Department of Health and the UK Insurance industry is in place until 2017 (Concordat and Moratorium on Genetics and Insurance). This is intended to further protect the confidentiality of information that we obtain about you. By having this agreement we cannot be forced to give information about you to insurance companies. You do not have to disclose results of clinical research to insurance companies. They may impose underwriting

terms if there is a family history of illness and you must disclose this family history if asked.

TrialNet researchers are not prevented from disclosing information about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

TrialNet researchers will consider your records private. Rarely, representatives of the MHRA, U.S. Department of Health and Human Services (DHHS) or TrialNet may review or ask for a copy of your study records. If this happens, we will provide your records. Also, employees of the University of Bristol, the NHS Trust R&D group or its agents could be allowed to see your study records to make sure that the study is being done properly.

Please understand that we will maintain the confidentiality of your research record. Our procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

The results of this study may be published for scientific purposes. By signing this form, you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

Who else will be informed that I am taking part in the study?
With your permission we will contact your GP to inform him that you are taking part in a research study. He or she will be sent some information about the study. We will not routinely send results of the study investigations. We may need to contact your GP if we find you have developed diabetes during the course of the study. We may also need to talk to other healthcare professionals about your care during the study. With your permission we will inform the diabetes consultant who cares for the person in your family with diabetes.

What will happen to my stored blood samples?

Your blood samples will be stored without your name or any other identifying information on them. You will not routinely be provided with test results from stored samples. Your blood samples could be stored for a number of years, but we cannot say for how long. Even if you do not want to have your samples stored, you can still participate in the rest of the study.

As long as TrialNet continues, your stored blood samples could be used by TrialNet researchers and researchers from outside of TrialNet. However, if researchers from outside of TrialNet want to use your samples, they must first get permission from TrialNet researchers and the sponsor of this study, the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK).

When TrialNet is over, your blood samples will continue to be stored under the supervision of the NIDDK. Researchers would not be able to use your blood samples without the permission of the NIDDK.

Your blood sample will be treated as a gift to the custodian of the NIDDK sample repository. They will assume responsibility for your sample's use, storage and disposal.

What if something goes wrong?

Taking part in this research study may hurt you. If you need to get medical care right away, you should go to your GP or to the nearest Accident and Emergency. Be sure to explain that you are in a research study. If you do not need emergency care, the TrialNet researchers will help you get the care you need.

In the event that something does go wrong and you are harmed during the research study, the University of Bristol has arranged insurance to provide compensation for an injury caused due, on the balance of probabilities, to taking part in this research study. The University will pay compensation where the injury probably resulted from the drug (abatacept) or any test or procedure you receive as part of the research study.

The University would not be bound to pay compensation where the injury results from some cause outside the scope of the research study.
This does not affect your legal rights.
Please ask if you would like to receive more information about this.

How is the study funded?
This study is funded by the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with additional funding from the US National Institute of Allergy and Infectious Diseases (NIAID), the US National Institute of Child Health and Human Development (NICHD), and the National Center for Research Resources (NCRR). Other support is from the Juvenile Diabetes Research Foundation and the American Diabetes Association. Bristol Myers Squibb will donate the abatacept being used in the study and may pay for some of the study's costs.

Who has reviewed the study?
This study was given a favourable ethical opinion for conduct in the NHS by the South West – Central Bristol Research Ethics Committee

Additional Information:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time

Thank you for taking time to read this information.

CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus

Type 1 Diabetes TrialNet Protocol TN-18

INTERVENTION CONSENT FORM

Name of Researcher: Dr Isy Douek, Taunton and Somerset NHS Foundation Trust, Musgrove Park Hospital, Taunton, Somerset, TA1 5DA

Please read the Information sheet before you complete this form.

1. I have read and understood the information sheet (dated 30th March 2015, Version 02) about the study or it was read to me. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the TrialNet Study Group, the University of Bristol, the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to my contact details being sent to the TrialNet coordinating team at the University of Bristol for administrative purposes. These will not be passed on to any third party outside of the TrialNet study team and will be treated in confidence. ☐

6. I agree to take part in the above study. ☐

The following sections are choices you can make. Ticking the "no" box does not mean you cannot take part in the study:

Information about other research

I consent to the research team contacting me about other research for which I may be eligible.

YES ☐ **NO** ☐ **INITIALS** ☐

Storage of Samples in NIDDK Repository

When TrialNet is over, we intend to put any remaining samples into the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) repository for future studies related to type 1 diabetes and its complications. They will be stored there indefinitely without your name or any other identifying information on them. As such, once in the repository you will not be able to have them removed. Researchers must first get permission from the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) to use samples from the repository.

The following checkbox gives you the choice of allowing us to put any remaining blood samples in the NIDDK repository. Even if you decide not to have your remaining blood samples stored, you can still participate in this study.

*I give permission for my blood samples to be stored for further testing as indicated in this form (mark **one** of the options below).*

- **Yes, store all samples including the genetic samples**

  ☐ **INITIALS**

- **Yes, store all samples, but not the genetic samples**

  ☐ **INITIALS**

- **No, I do not give permission to have any samples stored**

  ☐ **INITIALS**

SIGNATURES: By signing this consent form, you agree that you have read the information sheet and consent form and that the study has been explained to you. You also agree that your questions have been answered and that you agree to be in this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a copy of this consent form and the information sheet.

CONSENT FOR SUBJECTS 18 YEARS OF AGE AND OLDER:			
Signature of Subject		**Date**	
Date of Birth			
Print Name of Subject			
Signature of Person Obtaining Consent		**Date**	
Print Name of Person Obtaining Consent			
Role of Person Obtaining Consent	**Research Nurse / Investigator / Co-Investigator**		
CONSENT FOR CHILDREN UNDER 18 YEARS OF AGE:			
Print Name of Subject			
Date of Birth			
Signature of Mother/Guardian			
Print Name of Mother/Guardian		**Date**	
OR			
Signature of Father/Guardian		**Date**	
Print Name of Father/Guardian			
Signature of Person Obtaining Consent		**Date**	
Print Name of Person Obtaining Consent			
Role of Person Obtaining Consent	**Research Nurse / Investigator / Co-Investigator**		