PARTICIPANT HANDBOOK

HYDROXYCHLOROQUINE FOR PREVENTION OF ABNORMAL GLUCOSE TOLERANCE AND DIABETES IN INDIVIDUALS AT-RISK FOR TYPE 1 DIABETES MELLITUS

(Protocol TN-22)

Type 1 Diabetes TrialNet

Researchers in this study are part of a larger group called Type 1 Diabetes TrialNet. TrialNet is an international network of centers dedicated to the study, prevention, and early treatment of type 1 diabetes. We have clinical centers in the United States, Canada, Europe, and Australia. The TrialNet Coordinating Center, as well as the TrialNet Hub, help to support TrialNet activities at the centers and other TrialNet study sites.

We are conducting studies to:

• Learn more about the common risk factors among people who get type 1 diabetes.

• Test treatments that could help delay or prevent the start of type 1 diabetes.

• Test treatments that might help people who have recently been diagnosed with diabetes keep producing their own insulin.

TrialNet is supported by: [NIH, NIDDK, JDRF logos]

Your Study Site: _____
Research Physician: _____
Study Coordinator: _____
Tel: _____
Fax: _____
E-mail: _____

Your Clinical Center (if not the same as above)
Research Physician: _____
Study Coordinator: _____
Tel: _____
Fax: _____
E-mail: _____

To learn more about type 1 diabetes studies or to get a referral to a TrialNet study, call toll free 1-800-HALT-DM1 (1-800-425-8361).

You can also learn more about TrialNet at: www.DiabetesTrialNet.org.

Or by contacting the TrialNet Clinical Hub at:
Tel: 206-341-8923
Email: diabetes@benaroyaresearch.org

Table of Contents

Section 1: Study Overview

Introduction

We are trying to learn more about how to delay or prevent type 1 diabetes. In this study, we are testing hydroxychloroquine (HCQ) to see if treatment with HCQ will result in fewer people developing diabetes compared to the people in the study who do not receive HCQ.

In the Pathway to Prevention Study, you had blood tests that show you have autoantibodies, which means you are at risk for developing type 1 diabetes. This does not mean that you will definitely develop diabetes. However, we know that you are at higher risk. Your participation may help researchers learn more about ways to prevent further progression of disease.

After you read this handbook, we will talk with you about the study and answer your questions. We will ask you to take a survey to make sure we've explained everything clearly. We will ask you to sign a consent form if you decide you want to join the study. As you make your decision:

- Ask questions. We are available for questions and to discuss your concerns.
- Talk about the study with your family doctor or health care provider. Your doctor is welcome to call us with questions.
- Talk to your family and friends.
- Take the time you need to make your decision.

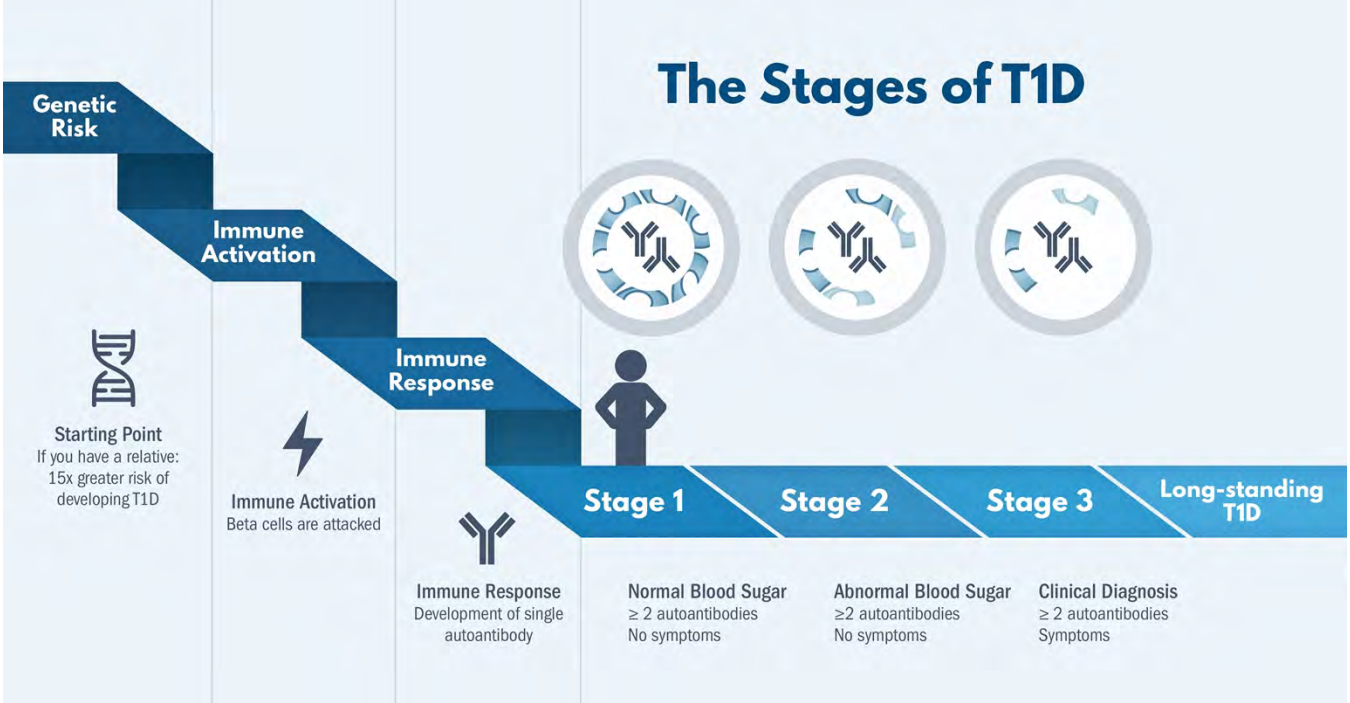
Background

How Type 1 Diabetes Develops

Type 1 diabetes is an autoimmune disease. The immune system mistakenly attacks the cells that produce insulin. These are called beta cells. Beta cells are in your pancreas.

In type 1 diabetes, the body's immune system keeps destroying the beta cells. An early sign that this attack has started is the appearance of autoantibodies. Once many of the beta cells are damaged, blood glucose levels will start to be abnormally high, and eventually this leads to diabetes.

It is now understood that diabetes occurs in stages. Everyone who develops T1D has genetic risk. Only some people with genetic risk will have an immune attack on their beta cells and an initial immune response. The presence of a diabetes-related autoantibody in the blood is a sign that there is an initial immune response. Not everyone with a single autoantibody progresses to multiple autoantibodies. However, we now understand that almost everyone with two or more autoantibodies will eventually develop clinical diabetes. That is why we consider individuals with two or more autoantibodies and normal blood sugar levels as having Stage 1 diabetes. In Stage 1, there are enough beta cells left producing insulin to maintain normal blood sugar levels. Eventually further destruction of beta cells leads to abnormal blood sugar levels, and this is called Stage 2 diabetes. Ultimately, blood sugar levels continue to rise, which leads to the clinical diagnosis of disease - called Stage 3 diabetes.



This study is for people who have two or more autoantibodies and normal glucose tolerance based on an Oral Glucose Tolerance Test (OGTT). There is no treatment that has been proven to protect beta cells after the appearance of autoantibodies. In this study, we are testing whether HCQ will help protect beta cells from being attacked by the immune system, which leads to type 1 diabetes.

The Study Drug

HCQ is approved by the Food and Drug Administration (FDA) and has been in use for over sixty years. HCQ is used in people with such diseases as malaria, rheumatoid arthritis, lupus and certain skin conditions caused by sun exposure. It has not been used in people at risk for or with type 1 diabetes.

HCQ has been studied in other autoimmune diseases. This is the first study being done to see if it can prevent or delay type 1 diabetes in individuals at risk for the disease.

How long will the study last?

This study is starting in 2018. We expect it will take about 4-6 years to complete the study, but it could take a few years longer. We want to see if there is a clear difference in the number of people who develop either abnormal glucose tolerance or are diagnosed with type 1 diabetes in people that are treated with HCQ, when we compare them to controls (the group that does not

receive treatment). We will need to follow people in the study for a number of years before any difference will become clear.

"What do I do to join this study?"

Step 1: Learn about the study and give informed consent.

- We will have you take a survey so we can see if we have explained everything clearly.
- You'll read and sign the Informed Consent.

Step 2: Have screening tests.

These tests are explained in this handbook and in the consent form. We will have the results in about 1 to 2 weeks. You can join the study if the results of these tests show that:

- You have Stage 1 diabetes (the presence of two or more autoantibodies and normal glucose tolerance)
- You will be at least 3 years old at time of randomization in this trial.
- You don't have any medical conditions that might make it unsafe for you to be in this study.
- You are not pregnant and do not plan to become pregnant while participating in the study.
- You do not have G6PD deficiency (this is a rare genetic condition found more commonly in males, which is associated with development of hemolytic anemia).

Step 3: Schedule your first study visit.

You must have your screening visit, including an Oral Glucose Tolerance Test (OGTT), no more than 7 weeks before being randomized and starting study medication.

By volunteering for this study, you are agreeing to the following:

- Screening tests
- Study visits every six months for the duration of the study. If you develop abnormal glucose tolerance, you will continue to be followed in the study but will no longer take study medication and may join another prevention study if you are eligible. If you are diagnosed with type 1 diabetes, you will no longer be in this study but may be able to join a study for people with newly diagnosed type 1 diabetes, or be followed in the TrialNet Long-term Follow-Up Study (LIFT).
- Take study medication as instructed.
- Have a study-specific eye exam to monitor your vision within 3 months of starting the study, and then once a year while taking study medication (TrialNet will pay for these visits.)
- Contact your study team if you have symptoms of high blood sugar (see page __).

- Contact your study team before starting any new medications, as some medications may interfere with the study drug or with the tests which monitor you for diabetes.
- Come to all study visits within two weeks of the required target date.

Randomization

At the first study visit after screening, you will be placed into one of two groups (HCQ or placebo) by chance (similar to drawing straws). You will have a 2 out of 3 chance of getting HCQ. Neither you nor your doctor will be able to choose the group in which you are placed. Neither you nor your doctor will know if you are getting HCQ or if are getting placebo.

Study Capsules

- The study treatment will be given as a capsule. It's very important that you take the capsules as instructed up to once daily as instructed with **food.**

Note: Children must be able to swallow capsules. Your study team can work with children as needed to help them learn how to swallow pills before being enrolled in the study.

- It is recommended that the study capsules be taken with milk or with food. The study medication will be packaged in a "blister pack" to help you adhere to your required medication schedule. You should remove the bubble(s) with the required capsule(s) for each day that you are supposed to take study medication. The bubbles for some days will not contain medication and others will, since you are given a specific amount based on your weight.

You will be given enough study medication to take as prescribed until your next required visit. Be sure to bring the used medication packs with you to each study visit.

Missed Dosage:

- The study medication must be taken as instructed. If you forget to take the medication, you may take it later, up to 12 hours before your next dose is due. If your next dose is due in less than 12 hours, the dose should not be made up, and should be missed permanently.
- Do <u>not</u> take a missed dose in addition to the regular dose the next day.
- **Save your empty** study medication packs. Bring all empty, partial and full packs to all of your visits.

SECTION 2: Study Visits

If you join this study, you are agreeing to:

- take study capsules as directed

- come in for study visits, which include blood tests, for the duration of your participation in the study. It is very important not to miss any study visits. If we do not collect your blood at the required time points, the study findings could be compromised

- have eye exams as needed

- report any changes in your health or medications

- stay in touch with your study team

- stick to the required study visit schedule*. If you are unable to travel to the study site, we may be able make arrangements for you to have some of your blood tests done locally. Your study coordinator will explain how to do this.*

Screening Visit (-1):

- You will need to have an OGTT before starting the study.

When: This may be done at the same time as your Eligibility or Monitoring Visit in the Pathway to Prevention Study, or as a separate visit.

If you chose to join the study, you will need to be randomized within **7 weeks** of your OGTT.

***Before you come*:** See page __ for test preparation.

***Appointment Time*:** Early in the morning (before 10:00 am).

Allow: 3 -4 hours

What: Oral Glucose Tolerance Test (OGTT).

Note: If you already had an OGTT within the past 7 weeks, an OGTT may not be required at this visit.

- Medical history and physical exam
- Urine pregnancy test, as appropriate
- We will draw blood for other blood tests

Oral Glucose Tolerance Test (OGTT)

You had an OGTT in the Pathway to Prevention Study and/or during screening in this study. We will also do this test every 6 months during the study to see if you're developing diabetes.

Test Prep

We will put an IV line in a vein in your hand or arm. We will take all the blood samples from this line. You can have a numbing cream before the IV line is placed.

The Test

- We will draw blood samples at the beginning of the test.
- You will drink about a cup (less for children) of a very sweet drink. You have to drink it all in 5 minutes. Some people may feel sick to their stomachs (nauseated) when they drink this.
- We will draw blood samples for 2 hours after you drink the glucose.
- You will need to sit quietly or rest in bed during the test.

Results

- We will get the results in 1 to 2 weeks. Sometimes the result isn't clear, and we will ask you to come in for another OGTT.

First Study Visit (Visit 0):

***When*:** Must occur within 7 weeks after the screening OGTT.

***Appointment Time*:** Flexible

Allow: *3-4 hours*

What:

- Medical history and physical exam
- Urine pregnancy test as appropriate
- Other blood tests

Randomization:

When: Within 7 weeks of your OGTT

Before your first study visit, a computer will be used to assign you to one of two treatment groups (see page __).

Study Medication:

You will get study capsules.

You will take your first dose at the first study visit. You will be sent home with enough capsules to take until your next study visit.

Study Capsules:

Take the study capsule(s) up to once daily as prescribed.

It's very important that you take your capsules as instructed.

If you forget to take the medication, you may take it later, up to 12 hours before your next dose is due. If your next dose is due in less than 12 hours, the dose should not be made up, and should be missed permanently.

Save your empty blister packs and bring all packs, empty and full, to all of your visits.

Dose Withholding:

There may be times when you should withhold taking your study capsules.

If you are unwell with fever [>101°F (38.3°C)] lasting more than 3 days, you should withhold your study capsules until fever subsides.

Eye exams:

The side effects of HCQ on the eye are rare but we must monitor for these. **To do this you will have a special eye exam within the first 3 months of being on the study and then *at least* once a year while still on study medication.** The exam will be done by an eye doctor. The eye doctor will do tests to check the back of the eye and to monitor you for any possible changes in your field of vision. These eye tests are done for reasons related to the study and are not meant to take the place of routine eye care including evaluation for glasses.

There will be various tests involved in the eye exam. To prepare you for these exams, your eye doctor may put dilating eye drops in your eyes. These drops widen your pupil and make it easier to examine the back of your eye. You may notice that your eyes are sensitive to light for a few hours after the drops and sunglasses may help this.

The tests will include:

- **Retinal photographs**

  Retinal photographs will be done once at the baseline visit to check for any pre-existing eye problems. The eye doctor uses a special camera linked to a microscope, to take a digital image of the retina. *This is a quick test.*

- **Optical coherence tomography (OCT)**

  Optical coherence tomography (OCT) is a test that measures the thickness of the retina. This test will be done on an annual basis. You will sit in front of an OCT machine and use a chin rest to keep your head still. The machine uses a beam of light to scan your eye and take pictures of the back of your eye. *Scanning both eyes takes about 5 – 10 minutes.*

- **Visual field tests**

  Visual field tests measure how wide an area your eyes can see. We normally see a wide area of the space in front of us. Without moving our eyes, we see not only what is straight ahead, but some of what is above, below, and off to either side. Most people are familiar with this as "peripheral vision." The entire area that we see is called the

visual field. A visual field test measures how far the eye sees in any direction without moving and how sensitive the vision is in different parts of the visual field.

Again you will rest your head on a stand and look into a bowl-shaped machine. You will be asked to fix your vision on a point and press a button to indicate when you can see any lights in your field of vision. This test relies on concentration and being able to follow instructions. This can be difficult for young children and the test may have to be repeated. *During the visual field test, one eye is tested at a time. The test takes about 10 minutes for both eyes.*

NOTE:

It may be difficult for younger children to sit for the tests that are required for the eye exam. If the eye exams are not completed, participants can remain in the study but will need to repeat the test(s) the following year. Participants can remain in the study but will need to discontinue taking the study medication if these tests are not completed within 5 years of enrollment.

Since the time to complete all of these eye exams may vary, you should allow a few hours for all the tests together. The time required will depend on whether eye drops are needed and the possibility of waiting time between tests, which may be performed by different examiners.

Month 3 Visit:

When: 3 months after Visit 0 (+/- 2 weeks)

***Before you come*:** See page __ for test preparation.

***Appointment Time*:** Flexible

Allow: 1-2 hours

What:

- Blood tests
- Medical history and physical exam
- Urine Pregnancy test (as appropriate)

Study Medication: you will be given study treatment to continue taking as instructed until your next study visit (in 3 months).

Month 6 and Follow-Up Visits (*every six months*):

When: Every 6 months (+/- 2 weeks)

***Before you come*:** See page __ for test preparation.

***Appointment Time*:** Early in the morning (before 10:00 am).

Allow: 3-4 hours

What:

- OGTT
- Other blood tests
- Medical history and physical exam (limited exam every 6 months; full physical exam every 12 months)
- Urine Pregnancy test (as appropriate)

Other Blood Tests (Immune/mechanistic samples): We will be collecting blood samples, including genetic samples at each of your visits. These samples will also be used to see the effect of HCQ on your immune system, to better understand what causes type 1 diabetes and how individuals respond to treatments, and to get ideas about new treatments in the future. ***You will not routinely be provided with test results from these studies.***

In a small number of adults (18 years and older) who weigh at least 110 pounds (50 kilograms), we will take an extra sample of blood of up to 2 tablespoons. We will use this sample to help us make sure that the test results are accurate.

"How do I prepare for my study visits which require an OGTT?"

For study visits that include an oral glucose tolerance test (OGTT):

Call us if you're taking any prescription or over-the-counter medicines that you haven't already told us about.
Some medicines may change the test results.

Be sure to eat plenty of carbohydrate.
Eat at least 150 grams of carbohydrate (starches and sugars) a day for at least three days before the test. Most adults and children eat 150 grams or more in a usual day, so this will probably not mean a new diet for you or your child. Eating more than 150 grams of carbohydrate is OK. Foods with carbohydrate include:

Grains: breads, pasta, crackers, cereals (hot and cold)
Beans
Starchy vegetables: potatoes, peas, corn
Fruit: fresh, canned, dried, juices
Milk (whole, 2%, 1%, non-fat, chocolate), yogurt
Sweets: candy, cookies, cakes, pies, regular sodas

Each of these has about 15 grams of carbohydrate:
1 slice of bread
6 crackers
1/2 cup pasta
1/3 cup rice
1 cup low-fat milk

1 medium apple

Meats and non-starchy vegetables (leafy greens, broccoli) have little or no carbohydrate. You can have these foods in the amounts that you normally eat.

Drink plenty of water the day before and the day of the test.
It will be easier for us to do your test.

Have no food or drink other than water for 10 hours before your test.
This includes:

- No coffee or tea
- No alcohol
- No diet sodas or sugar-free gum. Even though these have no calories, the flavor can prompt your body to make insulin, and this may change the test results.
- Don't use tobacco (smoking or chewing) or nicotine replacement products for 10 hours before your test.
- Don't exercise for 10 hours before your test.
- Get a good night's sleep before the test.
- Don't schedule the test for the morning after you work a night shift.

Risks:

Risks and Discomforts:
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. You should contact your study team if you experience any of these side effects:

Gastrointestinal:
The most common side effects from taking HCQ are nausea, diarrhea, abdominal discomfort, and vomiting. These happen in 1 to 10 out of 100 people. These symptoms often disappear with continued use of treatment. If you have these symptoms, we may change the dose of your study medication or stop it altogether.

Skin:
Skin changes such as itchy skin and allergic rashes occur in about 1 out of 100 people taking HCQ. These symptoms generally go away within 1-2 weeks of starting treatment. Skin discoloration has also been reported.

Retinopathy (maculopathy):
Fewer than 1 out of 100 people who have been taking HCQ in high doses and for many years may develop eye problems or retinopathy which cause reading and seeing difficulties, blurred vision, light flashes and streaks. Study drug will be stopped if there are any eye problems found.

Ear:
Loss of hearing and ringing of the ears has been reported in a few patients taking HCQ.

Metabolism and Nutrition: HCQ has been suggested to cause low blood sugar in some studies.

Neuromuscular:
Very rarely, people who take HCQ can get muscle problems such as aching and muscle atrophy (weakness).

Hematology:
Very rarely, people who take high doses of HCQ can develop thrombocytopenia (low blood platelets), hemolysis (breakdown of red blood cells), and possibly other severe problems with blood cells.

Cardiovascular:
It has been reported that HCQ can affect the rhythm of the heart. In addition, very rarely, people over age 50 who take high doses of HCQ over a long time can develop heart problems.

Birth control and pregnancy
Many people have taken HCQ during their pregnancy for different reasons and no damage to unborn babies has been seen. However, pregnancy will prevent the study doctors from knowing the effects of the study medication on disease progression. Thus, women who could become pregnant must agree to use a reliable and effective form of birth control and 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 Needle (IV) and Blood Drawing
While on the study you may have side effects from having your blood taken or IV 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.

Drug Interactions:
Some medications interact with HCQ and need to be avoided. You must tell your study doctor all the medications you are currently taking. **Before starting new medications, please discuss this with your study doctor.** It is possible we will need to discontinue the study medicine while you are taking other medications. If so, you will still come for study visits for continued monitoring.

Oral Glucose Tolerance Test (OGTT)
Some people may feel nauseous when they have the OGTT.

Vaccinations
There is no known safety problem of having immunizations while taking HCQ. However, it is possible that some type of vaccines may be less effective. Because of this, it is best if

participants are up to date on their vaccines (including varicella for chickenpox and MMR) prior to enrolling into the study. It is recommended that you take all vaccines at the regularly recommended times and that you let us know when you receive vaccines as part of your usual medical care. We recommend that you get a flu shot (not nasal vaccine) each yearWe also recommend that you have the non-live vaccine for COVID-19 when it becomes available.

Genetic Testing
We will not generally provide the results of your genetic testing to you or anyone else. Although we will try very hard to keep any information about your genetic testing private, there is a very small possibility that someone else could learn about your results.

Watch for Diabetes

It is possible some people could develop Stage 3 (clinical) diabetes while participating in this study. If you develop diabetes, we will probably catch it at an early stage, as we will be in frequent contact. This is one of the benefits of being on this study.

Still, be aware of the symptoms:

- often thirsty
- needing to go to the bathroom (urinate) a lot
- tired
- losing weight without trying

In addition, in a younger child:

- sleeping more than usual
- more cranky than usual
- wetting the bed when he or she used to stay dry at night
- flu-like symptoms, including fever

If you think you might have diabetes, call us right away.

Don't wait until your next study visit or study phone call to tell us. If you have symptoms of diabetes, we will schedule an extra visit right away. You should also talk with your regular doctor.

- It is better for your health to be diagnosed as early as possible.
- It is very important to the success of the study that we do these tests.
- If your regular doctor or another provider outside of TrialNet tells you that you have diabetes:
    - Tell the doctor that you are in a research study.
    - Ask the doctor to call the study site right away. The study site number is answered 24 hours a day. We will want to get as much information as possible about your diagnosis.

Call Us Right Away If…

- You have symptoms of diabetes (see p.__).
- You have any questions or concerns about the study or the capsules.
- You are having any problem taking the study capsules.
- You lose the study capsules. We will send you more study capsules.
- You don't want to be in the study any longer.
- You or your child are always free to stop being in the study. Your future medical care will not be affected in any way.

Please keep coming to the required study visits even if you stop taking the study capsules. We want to monitor you for possible development of diabetes.

In Case of Emergency: Call 9-1-1

Life-threatening emergencies should not arise from the study.

- In the event of a life-threatening emergency, ALWAYS CALL 9-1-1.
- Get medical attention right away rather than calling your study team.

During this study, a group of experts who are not doing the actual study will look at the information being collected. If these experts feel that it's not safe to continue the study, the study will be changed or stopped.

Study Visit Schedule:

	Pathway to Prevention or Screening	Baseline	Month 1	Month 3	Month 6 & every subsequent 6 months	Month 9 & every subsequent 6 months
OGTT	X				X	
Other Blood Tests	X	X		X	X	
Urine pregnancy test (as appropriate)	X	X		X	X	
Complete Physical Examination	X				X (annual visits only)	
Limited Physical Examination		X		X	X (six month visits only)	
Dispense Study Medication		X		X	X	
Eye Exam*		X			X (annual visits only)	
Interim contact**			X			X

* Eye exam will no longer be required if you discontinue study treatment.

** Your study team will contact you over the phone or by email to see how you are doing at 1 month, and then at Month 9 and every 6 months thereafter during your participation in the study.