NCT Number :	NCT 02739412
Official Title:	Efficacy of Low Dose, SubQ Interleukin-2 (IL2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
Document Type:	Informed Consent
Document Date:	06/23/2020

FOR CCI USE ONLY**
Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Consent Approval Date: 09/25/2017

Protocol Number: 2016P000086

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
06/23/2020
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR: Michael Curry MD
PROTOCOL NUMBER: 2016P000086

INTRODUCTION:

- This is a research study;
- Your participation is voluntary;
- A research study includes only people who choose to take part;
- You may or may not benefit from participating in the study. However, your participation may help others in the future as a result of knowledge gained from the research;
- You may leave the study at any time;
- If you choose not to take part, or if you leave the study, your decision will in no way harm your relationship with any member of the research team or any other individuals at Beth Israel Deaconess Medical Center.

Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC AND INVESTIGATORS

This study is being conducted by Michael Curry, MD. The funds used to complete this study have been provided through a private donation from a Grateful Patient to the Beth Israel Deaconess Medical Center and to Principal Investigator, Dr. Michael Curry for use for a special project of Dr. Curry's own choosing. Novartis/Prometheus is providing the study drug.

Neither BIDMC nor Dr. Curry has additional interests in this research project.

WHOM TO CONTACT IF YOU HAVE QUESTIONS OR PROBLEMS

If you have any questions, concerns or complaints about this research or experience any problems, you should contact Dr. Michael Curry at [617] 632 9700.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

PURPOSE

A common complication of organ transplantation is 'rejection' of the transplanted organ. This occurs when the body's immune system tries to attack (or reject) the transplanted organ.

Drugs known as immunosuppressants (anti-rejection medications) are prescribed for patients after transplantation to prevent rejection. But, anti-rejection medications are associated with significant side effects including high blood pressure, high blood sugars, and high cholesterol – all of which may increase the risk of heart and vascular complications. Anti-rejection medications also increase the long-term risk of some types of cancer.

Sometimes, liver transplant patients who stop taking anti-rejection medications do not experience rejection of their transplanted liver and the liver keeps working. These patients are said to "tolerate" the transplanted liver, and this condition is referred to as "tolerance". Doctors are working to learn more about why some liver transplant patients develop tolerance after receiving a transplant, while others do not.

Studies have shown that patients who develop "tolerance" have an increase in a type of immune cell called regulatory T-cells or "T-regs". This means T-regs may be important in preventing rejection of a transplanted organ.

Studies have also shown that a human cytokine (a type of protein), called interleukin-2 (IL-2) aids in increasing the number of T-reg cells in the body, and IL-2 has been given to patients to successfully treat disorders of the immune system such as graft vs host disease – a serious condition sometimes seen in patients after bone marrow transplantation.

The purpose of this investigation is to study if very low dose Interleukin-2 (IL-2), given to liver transplant patients by daily subcutaneous (under the skin) injections, over a 4 week period of time, will cause an increase in the number of T-reg cells in the blood

We are also conducting this study to learn about the kinds of side effects very low dose IL-2 will cause and how severe those side effects will be. This means that you may experience the side effects listed in the "Risks..." section of this consent form.

The study drug involved in this study, IL-2, is investigational. This means that the study drug is still being tested in research studies and is not approved by the Food and Drug Administration [FDA] for the way that it is being used in this study. This particular investigational agent, IL-2, has been approved by the FDA for use in other diseases or conditions, but we do not yet know if it is useful or safe as a treatment for liver transplant recipients.

Use of IL-2 in very high doses is currently approved by the Food and Drug Administration (FDA) for treatment of some types of cancer including malignant melanoma and renal cell carcinoma. For treatment of these cancers, IL-2 is given intravenously (through a vein) in large intermittent doses given over a continuous period of time.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

STUDY PARTICIPANTS

You have been asked to be in the study because you have had a liver transplant, you take anti-rejection medication, and you have stable liver graft function. These are some of the important characteristics that are closely identified with patients who have been successfully withdrawn from anti-rejection medications.

Approximately 12 people will take part in this study at Beth Israel Deaconess Medical Center.

If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen:

1. Screening Procedures: Screening procedures are the tests and procedures that will be done to determine if you are eligible to take part in the research study. Some tests/procedures required for screening have already been completed for your routine care, these will not be repeated; we will obtain these results from your medical record. For this research study, the screening procedures include:

   - **Medical History and Medication Review**: The study doctor will review your medical record and talk with you about your current and past medical history and medications.
   - **Physical exam and vital signs:** A physical exam will be performed and vital signs will be measured.
   - **Blood Tests**: Results from recently completed routine blood tests are required. If these have not been completed recently, they will be completed for the study.
     - ✓ If not completed in the past month, about 2 teaspoons of blood will be collected to complete **kidney** and **liver function tests;**
     - ✓ If not completed in the past 6 months, about 2 teaspoons of blood will be collected for tests to rule out the presence of a **viral hepatitis** infection and **autoimmune disease**;
     - ✓ If you are a woman who is able to become pregnant, approximately 1 teaspoon of blood will be collected to complete a blood pregnancy test (If you are pregnant or breastfeeding you cannot be in the study).
   - **Electrocardiogram**: If not completed in the past 3 months, an **ECG** (electrocardiogram) will be performed to measure the electrical activity of your heart. The ECG will take approximately 10 minutes:
     - ✓ For the ECG, we will ask you to lie down and place adhesive patches (similar to Band-Aids) on your chest, arms and legs.
     - ✓ In some areas, it may be necessary to clip a small area of body hair so the adhesive patches can be properly placed on your body.
     - ✓ Next, wires from the machine will be attached to the adhesive patches. These wires record your heart's electrical activity.
     - ✓ We will ask you to be still during the ECG.
   - **Fibroscan:** Results from a liver biopsy or fibroscan completed in the past year can be used for the research to rule out prior episodes of organ rejection and confirm you do not have cirrhosis. If you

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

have not had a biopsy or fibroscan in the past year, a fibroscan will be completed as part of the study screening.

A fibroscan is a noninvasive imaging test of your liver using both ultrasound and low frequency elastic waves. It is a test to measure the 'stiffness' of the liver to estimate the amount of fibrosis present and to find out if you have cirrhosis. A fibroscan will take about 15 minutes.

After all the screening tests have been completed, the Study Doctor will review all the results and determine if you are eligible to be enrolled into the study.

The screening visit will take about 2 hours to complete.

2. Research Procedures If you qualify to take part in this research study, you will undergo these research procedures:

Baseline: You will come to the BIDMC Harvard Catalyst Clinical Research Center on the East campus on Study Day 1 to initiate the study after the screening visit. This visit will take about 4 hours. Prior to the start of treatment, the following procedures will be completed:

- Vital signs and a review of the medications you take and any new health complaints you may have.
- Blood will be collected (about 5 teaspoons) to complete the following tests:
  - ✓ complete blood count (CBC),
  - ✓ kidney and liver function tests,
  - ✓ blood level of your anti-rejection medication,
  - ✓ blood level of IL-2,
  - ✓ types and amounts of immune cells in the blood .
  - ✓ extra blood will be collected (3 teaspoons) to test for the presence (if any) of specific antibodies prior to the start of treatment:
    - ➢ donor specific antibodies (antibodies against the transplanted liver), and
    - ➢ antibodies against the study drug, IL-2.
- Supervised first dosage of study medication and 2 hour observation for side effects.

Study Treatment: In this study, a very low dose of interleukin-2 (IL-2) will be given as a subcutaneous injection (under the skin) once per day, every day, for 4 weeks.

Study staff will teach you how to give the injections to yourself so you can give them to yourself at home. If you request, study staff will also teach a family member or friend to give you the injections at home.

The daily dose of IL-2 is 0.3 million units per '*body surface area*'. That means the exact dose for you will be based on your height and weight. The study will calculate the dose for you and you will be given the pre filled syringes that contain approximately 1/4 of a teaspoon of sterile fluid. The study doctor will tell you the exact dose prescribed for you and the best time of day for giving yourself the injections.

You will be given a new supply of the pre-filled syringes each time you return for study visits in the treatment period.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

Study Visits during the Treatment Period:

Day 3: You will return to the Center for a study visit on day 3. This visit will last about 1 hour. At this visit we will review how you are doing with self-injections and complete the following measures:

- Vital signs and review of medications you take and any new health complaints you may have.
- Blood will be collected (about 2 teaspoons) to complete the following tests:
  - ✓ complete blood count (CBC),
  - ✓ kidney and liver function tests.

Weekly Visits: After that you will return on day 7 and weekly until the end of treatment (weeks 1, 2, 3, 4). These visits will last about 1 hour. At these study visits the following procedures will occur:

- Vital signs and review of medications you take and any new health complaints you may have.
- An ECG will be completed
- Blood will be collected (about 5 teaspoons) to complete the following tests:
  - ✓ complete blood count (CBC),
  - ✓ kidney and liver function tests,
  - ✓ blood level of your anti-rejection medication (week 4 only),
  - ✓ blood level of IL-2,
  - ✓ types and amounts of immune cells in the blood (Weeks 2 and 4)).
  - ✓ If you are a woman who is able to become pregnant, we will repeat a pregnancy test at week 4.
  - ✓ Extra blood will be collected (2 teaspoons) at week 4 (end of treatment) to test for the presence (if any) of specific antibodies including:
    - ➢ donor specific antibodies (antibodies against the transplanted liver), and
    - ➢ antibodies against IL-2.

At the Week 4 visit, you will have your routine blood draw for standard of care and we will use the results from your standard of care labs for the study (CBC, kidney and liver function, and immunosuppressant blood levels). The Week 4 visit blood draw for study labs will be about 4 teaspoons to measure T cell markers, IL-2 levels and testing for the presence of specific antibodies.

3. Monitoring/Follow-Up Procedures. Procedures performed to evaluate the effectiveness and safety of the research procedures are called "monitoring" or "follow-up" procedures. For this research study, post treatment visits will be completed on week 8, 12 and 36. At these visits we will review how you are feeling, complete a physical exam, and check vital signs. At weeks 8 and 12, you will have blood draw, (about 2 teaspoons) to measure T cell markers and IL-2 levels. If you are a woman who is able to become pregnant, we will repeat a pregnancy test at these visits. At week 36 you will have a blood draw (about 1 teaspoon) to test for the presence (if any) of antibodies against IL-2. These visits will last about 1 hour.

   We will also obtain your routine laboratory results for CBC, liver and kidney function tests, and a blood level of your anti-rejection medication. **See Table 1 for the schedule of study visits, tests and procedures.**

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

Table 1: Study Visits Schedule and Procedures

	Screening & Baseline		Treatment to Week 4					Follow-up to Week 36		
Visit	Screening	Baseline Day 1	Day 3	W1	W2	W3	W4	W8	W12	W36
Study Procedures: Visit #	1	2	3	4	5	6	7	8	9	10
Informed Consent	√									
Full Physical Exam & Medical History	√								√	
Limited Physical Exam & Medical History		√	√	√	√	√	√	√		
Vital Signs	√	√	√	√	√	√	√	√	√	√
Electrocardiogram (ECG)	√			√	√	√	√			
Fibroscan	√[1]									
Study Blood Tests:										
Pregnancy test (for women of child bearing potential)	√						√	√	√	
CBC with Differential		√	√	√	√	√	√[4]	√[4]	√[4]	√[4]
Liver panel (AST, ALT, AP, Total Bilirubin, Albumin)	√[2]	√	√	√	√	√	√[4]	√[4]	√[4]	√[4]
Kidney panel (Na, K, Cl, CO2, Creatinine, Glucose, Ca)	√[2]	√	√	√	√	√	√[4]	√[4]	√[4]	√[4]
Viral hepatitis and autoimmunity panels (HBVsAg, HCVAb, ANA, ASMA IgG)	√[3]									
Immunosuppression drug level		√					√[4]	√[4]	√[4]	√[4]
Donor specific antibodies (DSAs)		√					√			
Antibodies to IL-2		√					√			√
Immune cell counts		√			√		√	√	√	
IL-2 Blood level		√		√	√	√	√	√	√	
T-cell exhaustion markers (only at baseline)		√								

[1] Only if routine fibroscan or liver biopsy unavailable within the last 12 months; [2] Only if liver panel or kidney panel unavailable within last month; [3] Only if viral and autoimmunity tests unavailable within past 6 months; [4] Obtained for standard of care

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

RISKS AND DISCOMFORTS

As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

IL-2:
IL-2 is currently approved by the FDA as a high dose, intravenous (through a vein) treatment for certain types of cancers. The use of IL-2 in low dose, subcutaneous (under the skin) injections is currently not approved by the FDA. Research studies have examined the risks of using IL-2 given as subcutaneous injections in cancer patients, in patients with Graft versus Host disease, and patients with Hepatitis C related vasculitis. The following side effects were observed in these studies and you may experience some of the side effects below:

More Common (more than 5% of subjects):
Fever, shivering, tiredness, loss of appetite, upset stomach, vomiting, diarrhea, headache, dry skin, rash, pain at injection site, inflammation at injection site, skin hardening at injection site, shortness of breath, cough, muscle pain, muscle rigidity (stiffness), insomnia (difficulty sleeping), mood changes, flu like symptoms, dizziness, itchiness, decreased urine output, confusion, changes in blood pressure (low or high), swelling in arms/legs, infection, increase in eosinophils in the blood (eosinophils are one type of white blood cell), mouth ulcer, and sore throat.

Less Common (between 1% and 5% of subjects):
Kidney failure, rising creatinine (substance in the blood used to measure kidney function), digestive tract bleeding (vomiting blood or passing bloody stool), platelet deficiency (thrombocytopenia), increased heart rate, and unusual heartbeat.

Rare (less than 1% of subjects):
Heart attack.

A serious, but very uncommon side effect of IL-2 when given in high doses is "capillary leak syndrome" or "vascular leak syndrome." Capillary leak syndrome is a potentially serious disease in which fluids within the vascular system (veins and capillaries) leaks into the tissue outside the bloodstream. This results in low blood pressure and poor blood flow to the internal organs. The study doctor will monitor you for these side effects.

The makers of IL-2 recommend against use of IL-2 in patients who have received organ transplants. This recommendation is based on use of IL-2 in very high doses for FDA approved treatments for certain types of cancers (malignant melanoma and renal cell carcinoma). While there is a theoretical risk of transplanted organ rejection with high dose IL-2 treatments, there have been no documented cases of organ rejection reported with use of IL-2.

Although the drug manufacturer recommends against use of IL-2 for patients with organ transplantation, participants in this study will take very low dose IL-2 as this study is testing if very low dose IL-2, taken by healthy liver transplant patients will increase the number of T-reg cells in the blood. If this study discovers

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

that very low dose IL-2 **does** increase T-reg cells, Investigators will plan a follow-up study to investigate if healthy liver transplant patients develop 'tolerance' for their transplanted liver. Patients who develop 'tolerance' may be candidates to decrease or discontinue anti-rejection medications.

For up to several months after IL-2 treatment has ended, you may have a reaction to the iodine-containing contrast material used for CT scans (a type of radiology scan similar to an x-ray and sometimes called a CAT scan). These reactions may include fever, chills, nausea and vomiting, itching, rash, diarrhea or swelling.

You must not undergo routine radiology scans (such as CT scan) that require iodine containing contrast for the duration of the study (up to week 12). Please notify the study doctor if you require a CT scan with contrast during the study.

There may be risks that are currently unknown. You will be made aware of these risks as they occur.

Taking your study medicine: It is very important that you give yourself the IL-2 injections every day as instructed by the Study Doctor and staff. Do not miss any injections. Tell the Study Staff about all the other medicines you are taking during the study. This includes prescription drugs, vaccinations, over-the-counter medicines, vitamins and supplements. This is very important. Please tell your Study Doctor or Study Staff if you have any unusual symptoms.

Drug interactions: Other doctors you might see for your health care may prescribe new medicines which might interfere with the effect of the antirejection medications or the study drug, IL-2. **You should not take any new medicines or receive any vaccinations without talking to your Study Doctor.** Please inform any physician who prescribes a drug to you that you are taking IL-2 as part of a research study and show then the Study Drug Card we provide.

Blood draws:
The risks and discomforts of blood drawing from a vein include the possibility of pain or bruising at the site of the blood draw, occasional feeling of lightheadedness, and rarely, infection at the site of the blood draw.

Electrocardiogram (ECG):
You may experience temporary redness or a rash on the skin where the adhesive pads are placed.

Pregnancy:
Because the effects of interleukin-2 on the developing fetus are not known, you may not participate in this study if you are pregnant or breastfeeding. If you are a woman capable of becoming pregnant you will be required to take a pregnancy test to verify that you are not pregnant before receiving your first dose of IL-2.

Furthermore, if you are a woman capable of becoming pregnant, you must agree to use adequate birth control for the duration of the study. For the purpose of this study, use of adequate birth control includes one of the following:

1. oral hormonal contraceptives;
2. implanted hormonal contraceptives;

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

3. diaphragm with spermicide;
4. Intrauterine device;
5. condoms used with another form of contraception as listed above;
6. abstinence.

If you are a man capable of fathering children, you must use adequate contraception while participating in this study. For the purposes of this study, adequate birth control means;

1. use of a condom
2. your partner must use an approved method of birth control as listed above.

The effect of IL-2 treatment on your fertility (your ability to conceive a child or impregnate a female) is not known. It is also unknown what effect IL-2 may have on future pregnancies. If you choose to be sexually active during the study period, you must accept the risk that pregnancy could result and the effect of IL-2 is unknown on either the pregnancy or the fetus.

If you believe you have become pregnant while participating in this study, you must inform your study investigators immediately. They will have you take a pregnancy test. If the results demonstrate that you are pregnant, you must withdraw from the study, and the study investigators will ask to monitor your pregnancy. To monitor your pregnancy may include (but not limited to) office visits, blood work, and questionnaires.

LOSS OF CONFIDENTIALITY
There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information.

CONFIDENTIALITY
Information learned from your participation in this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, and by the drug manufacturer Novartis, accreditation agencies, the Committee on Clinical Investigations, the Human Subjects Protection Office and others involved in research administration of the Beth Israel Deaconess Medical Center with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

POSSIBLE BENEFITS

It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research.

OTHER AVAILABLE OPTIONS
Taking part in this study is voluntary. Instead of being in this study, you have the following options:

- Continue with your standard care treatments and immunosuppression drugs as prescribed by your doctor.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE COMMITTEE ON CLINICAL INVESTIGATIONS
06/23/2020
APPROVAL EXPIRATION DATE

This research study is not meant to diagnose or treat medical problems. Participation in this research study does not take the place of routine physical examinations or visits to your regular doctor.

We recommend that you discuss these and other options with the investigator and your regular doctor so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY

Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. Your decision to not participate will not result in any penalties or loss of benefits to you. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with the research team or any other individual at Beth Israel Deaconess Medical Center.

INVESTIGATORS RIGHT TO STOP THE STUDY

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU

COSTS COVERED BY STUDY

You will not be charged for the physical exams, ECG, blood tests, fibroscan, or study drug that are part of this research study. However, you and your insurance company will be charged for other tests, procedures or medications of this study that are considered standard treatment for your medical condition.

CO-PAYMENT/DEDUCTIBLE STATEMENT

You will be responsible for any co-payments or deductibles that are standard for your insurance coverage.

PAYMENTS TO YOU:

You will be paid $30 for each study visit with the exception of the four hour Baseline visit where you will be paid $60.

If you complete the study, you will receive a total of $300 in study payments.

It may take up to 8 weeks for you to receive payment by check.

Any payments made to you may be taxable income to you. This does not include any payments you may receive to reimburse (pay you back) you for certain expenses like parking fees or travel. We are required to obtain your name and social security number for preparation and submission of Internal Revenue Service

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

(IRS) Form 1099-Misc. You may receive an Internal Revenue Service Form 1099 from BIDMC if you receive more than $600 or more in one calendar year for taking part in one or more research studies at BIDMC. Questions about your own tax status should be referred to your personal tax advisor.

COST OF RESEARCH RELATED INJURY:
If you are injured as a direct result of your participation in this study you should contact the Investigator at the number provided under the section "Whom to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. You or your insurance company will be billed for medical care and/or hospitalization related to this injury. You will be responsible for all co-payments and deductibles required under your insurance. BIDMC will consider reimbursement of injury related expenses not covered by your insurance on a case-by-case basis. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

OTHER IMPORTANT INFORMATION

A description of this clinical trial will be available on www.ClinicalTrials.gov as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

As part of this study, we will be collecting, using and sharing with others information about you. Please review this section carefully as it contains information about the federal privacy rules and the use and disclosure of your information.

PROTECTED HEALTH INFORMATION [PHI]
By signing this informed consent document, you are allowing the investigators and other authorized personnel to use [internally at BIDMC] and disclose [to people and organizations outside the BIDMC workforce identified in this consent] health information about you. This may include information about you that already exists (for example: your medical records and other sources of health information, demographic information, the results of any laboratory tests, and mental health records if applicable including social worker and counseling notes, as well as any new information generated as part of this study. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC WHO WILL SHARE AND USE YOUR PROTECTED HEALTH INFORMATION
Your Protected Health Information may be shared with and used by investigators working on this study, including the supporting research team (such as research assistants and coordinators, statisticians, data managers, laboratory personnel, pharmacy personnel, and administrative assistants), and may also be shared and used by other health care providers at BIDMC who have treated you in the past and have information relevant to the research, or who provide services to you in connection with the research. Your Protected Health Information may also be shared with the members and staff of the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center, which is responsible for reviewing studies for the protection of the research subjects.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

PEOPLE/GROUPS OUTSIDE OF BIDMC WITH WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE SHARED
We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this study:

- The company that manufactures the study drug, IL-2, Novartis/Prometheus and, where applicable, the people and companies that the manufacturer use to oversee, administer, or conduct the research (for example, clinical research organizations are companies that are sometimes hired by research sponsors to help manage and run a clinical research study)
- Your health insurance company
- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], the National Institute of Health [NIH], the Office for Human Research Protections [OHRP], and other federal and state agencies that may have jurisdiction over the research
- Hospital and Clinical Research Accrediting Agencies

Those who receive your Protected Health Information during the course of the research may not be required by the federal privacy regulations to protect it, and they may make further disclosures to others and use your information without being subject to penalties under those laws.

WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION
The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document. There are many other reasons beyond the research for which BIDMC may use or disclose your Protected Health Information. Not all of these reasons require your express written authorization. For example, we will use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities. The various ways in which BIDMC may use and disclose your protected health information without your authorization are explained in a document called the Notice of Privacy Practices. If you have not received a copy of BIDMC's Notice of Privacy Practices, please ask us for one and review it before signing this form. In addition to signing this document, you may also be asked to sign a BIDMC General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION
Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to:

Michael Curry, MD
110 Francis St – 7th Floor
Boston, MA 02215

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
06/23/2020
APPROVAL EXPIRATION DATE

Please be aware that the investigators in this study will not be required to destroy or retrieve any of your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter, and they are permitted to continue to use and disclose your previously collected information as necessary to complete the research.

REFUSAL TO SIGN

Your clinical treatment may not be conditioned upon whether you sign the Authorization for Research. However, if you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI

If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

ADDITIONAL CONTACT FOR QUESTIONS OR CONCERNS

You may contact the Human Subjects Protection Office at [617] 975-8500 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE
COMMITTEE ON CLINICAL INVESTIGATIONS
06/23/2020
APPROVAL EXPIRATION DATE

THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO).

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided for in this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

Signature of Subject or Legally Authorized Representative (Parent if the subject is a minor) Date

_____

Relationship of Legally Authorized Representative to Subject

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/Co-Investigator's NAME

A signing co-investigator must be listed on the study's approved Research Staffing Form at the time of consent.

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Efficacy of Low Dose, Subcutaneous Interleukin-2 (IL-2) to Expand Endogenous Regulatory T-Cells in Liver Transplant Recipients
PRINCIPAL INVESTIGATOR'S NAME: MICHAEL CURRY, MD
PROTOCOL #: 2016P000086

THE FOLLOWING SECTIONS ARE NOT NEEDED FOR ALL STUDIES AND SHOULD BE UTILIZED AS INDICATED:

If the subject is able to speak and understand English but is not able to read or write

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is able to understand English but is not physically able to read or write or see

I was present during the entire oral presentation of the informed consent and witnessed the subject's agreement to participate in the study.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

If the subject is not English speaking and signed the translated Short Form in lieu of the English consent document.

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Signature of Interpreter: _____

Printed name of Interpreter: _____

Date: _____