Title of Trial: PROACTIVE: Phase II Single Center Open Label Study for Prevention of Acute and Chronic GVHD Using Tocilizumab in Combination with Standard GVHD Prophylaxis After Allogeneic Transplantation

Clinical Trials.gov Number: NCT03699631

Date of Consent: January 28, 2020

EFFECTIVE

1/28/2020

MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

IIT-CHHABRA-PROACTIVETOCI-5; Phase II single Center Open label study for prevention of Acute and Chronic GVHD using Tocilizumab in combination with standard GVHD prophylaxis after allogeneic transplantation

Saurabh Chhabra
Froedtert & Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee, WI 53226
414-805-6700

You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Allogenic HCT: unrelated donor bone marrow transplant
ECG: electrocardiogram
GVHD: Graft versus Host Disease: a complication that can occur after an allogenic bone marrow transplant
HLA: human Leukocyte antigen. Proteins that help the body's immune system tell the difference between its own cells and foreign, harmful substances
MUGA: Multiple Gated Acquisition scan
PFT: Pulmonary function test

Purpose

This project is being done to determine the probability of GVHD/relapse-free survival after matched related/unrelated donor peripheral blood or bone marrow.

Length

1. You will be in this research project for about 18 months.

Procedures

You will receive the Tocilizumab in combination with standard GVHD prophylaxis.

List of visits:

- Screening Visit
  - Total Number: 1
  - Total Time: approximately 2 to 4 hours
- Study drug Treatment Visits
  - Total Number: 2
  - Total Time: 2 hours
- End of Treatment Visits
  - Total Number: 1
  - Total Time: approximately 2 to 4 hours

Procedures that will occur at various visits:

Invasive Procedures

- Drug administration, blood sample collection, and bone marrow/aspirate collection

Non-invasive Procedures

- Full medical history exam, physical exam, questionnaires, stool sample collection and ECGs.

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Tocilizumab and Standard GVHD Prophylaxis risks:

Tocilizumab:

- Hypersensitivity reactions
- Respiratory: upper respiratory tract infections, nasopharyngitis, bronchitis
- Gastrointestinal: mouth ulceration, upper abdominal pain, gastritis, gastrointestinal perforations, pancreatitis.
- Hepatic: transaminases elevation

Tacrolimus:

- Cardiovascular: hypertension
- Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think
- Gastrointestinal: nausea, vomiting
- Hematologic: microangiopathic hemolytic anemia, thrombocytopenia

Methotrexate:

- Neurologic: fever, dizziness, chills, undue fatigue
- Gastrointestinal: ulcerative stomatitis, nausea, abdominal distress, diarrhea
- Hematologic: leucopenia, anemia

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

1. Joining a different project
2. Routine care for this condition
3. Getting no treatment for this condition

If you have more questions about this project at any time, you can call Dr. Chhabra at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you have a type of cancer that will be treated with an allogenic HCT. Developing acute or chronic GVHD is a risk of this type of transplant. Because of your condition, you may be eligible for a research project using a new drug combination of tocilizumab and standard GVHD prophylaxis to treat your disease.

A total of about 32 people are expected to participate in this research at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Saurabh Chhabra, MD in the Division of Hematology & Oncology. A research team works with Dr. Chhabra. You can ask who these people are.

There are Investigator Funds supporting this study.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

In this study we want to find out if giving Tocilizumab in combination with the standard GVHD prophylaxis; Tacrolimus and Methotrexate will help prevent acute and chronic GVHD. We also want to find out whether the new drug combination is safe to use and whether it reduces the symptoms of acute and chronic GVHD.

Everyone in this study will receive the combination of tocilizumab and standard GVHD prophylaxis, which is still experimental and is not approved by the U.S. Food and Drug Administration.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Treatment Schedule

	Days											
	pre-transplant	-1	0	+1	+3	+5	+6	+11	+35	+90	+100	+180
Conditioning	x											
Transplant			X									
Methotrexate				X	X		X	X				
Tocilizumab		X									X	
Tacrolimus	X				X					Taper*		Stop*
G-CSF						Start^						

*If there is no evidence of GVHD
^G-CSF begins on day +5 after stem cell infusion and continues until engraftment is seen.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

Screening procedures:
If the screening information shows that you meet the requirements, then you will complete the following:

- Medical History, which includes questions about your health, current medications.
- Physical Exam**,** which includes your height, weight
- Your performance status, which evaluates how you are able to carry on with your usual activities.
- Routine Blood tests (about 4 tablespoons)
- Pregnancy test if you are able to have children
- Infections disease markers
- HLA typing
- PFT: to test the function of your lungs
- ECHO: which is a test that uses sound waves to create pictures of your heart. This test measures the size and shape of your heart and how well the chambers and valves are working.
- MUGA: takes pictures of your heart using and ultrasound to see how strong your heartbeat/heart muscles are
- Bone marrow biopsy and/or aspirate**,** to evaluate the extent of your disease. For this test, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. If a bone marrow biopsy is needed, a small piece of bone and the attached bone marrow is removed. These tests may be done under local anesthesia. Any time a bone marrow exam is done in the study, a sample will also be sent to a laboratory for research studies
- Quality of Life questionnaires which will take about 30 min to complete

If the screening information shows that you cannot be in the research, the research doctor will discuss other options with you and/or refer you back to your regular doctor.

Summary of Procedures: Day 0 to 365
(See Table 1 for more detail)

- Physical Exam**,** which includes your height, weight
- Review of any side effects that you may be experiencing
- Routine Blood tests about 1 to 4 tablespoons at each timepoint listed on Table 1.
- PFT: to test the function of your lungs
- Bone marrow biopsy and/or aspirate**,** to evaluate the extent of your disease. For this test, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. If a bone marrow biopsy is needed, a small piece of bone and the attached bone marrow is removed. These tests may be done under local anesthesia. Any time a bone marrow exam is done in the study, a sample will also be sent to a laboratory for research studies
- GVHD Assessments will be performed to determine if you are developing side effects as a result of the treatment you have been given. This assessment will be part of the physical exam.
- Research (stool) samples will be collected and shipped to Memorial Sloan Kettering Cancer Center. To test the use of tocilizumab which has been shown to lower gastrointestinal GVHD rates preserves the stomach bacteria diversity. Additional analysis on your sample will be done to determine the impact of stomach bacteria on transplant outcomes.

Table 1

Routine Tests	Screening Within 30 days prior to infusion	Day -1	Day 0 (infusion day)	Day +1 ± 2	Day +8 ±2	Day +15 ± 2	Day +21 ±2	Day + 28 ± 7	Day +56 ± 7	Day +100 ± 14	Day + 180±± 14	Day +365 ± 28
Medical History	X		X	X				X	X	X	X	X
Physical Exam	X		X	X				X	X	X	X	X
Vitals	X							X	X	X	X	X
Karnofsky Test	X											
Fasting Lipid Panel									X		X	
Pulmonary Function Test	X										X	X
Infectious Disease Markers^	X											
LVEF	X											
Disease Evaluation*	X									X	X	X
Pregnancy Test	X											
Laboratory Tests	X							X	X	X	X	X
Chimerism tests								X				
Assessment of AEs	X			X				X	X	X	X	
Immune Reconstruction Panel								X		X	X	X
GVHD assessments								X	X	X	X	X
Research (stool) sample collection		X		X	X	X	X	X				

*For acute leukemia, CML and MDS, this includes a bone marrow aspirate and biopsy and cytogenetics. For lymphomas, this includes imaging studies.
^CMV antibody, Hepatitis panel (HepA, HepB Sab, HepB)

B2. HOW LONG WILL I BE IN THE PROJECT?

You will be in this research project for about 12 months

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

⇒ The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.

⇒ You might be asked to come back for one more visit to check your health.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

- While you are participating in this study (during treatment), you can participate in other research studies as long as they are NOT GVHD prevention or treatment.

- You should also report to your doctor any changes in your health or side effects that you may be experiencing.

- You will be asked to receive all study-required treatments and complete all study-required procedures.

- You will also be fasting on the Day you have your pre-transplant evaluation, Day +100 and Day +180.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get a drug combination that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from the combination of tocilizumab and standard GVHD prophylaxis themselves, or how they combine with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** If you have signs of fever or other new abnormal symptoms, call Dr. Chhabra immediately at 414-805-6700. In an emergency, call 911.

C2. RISKS OF TOCILIZUMAB IN COMBINATION WITH STANDARD GVHD PROPHYLAXIS

The research drugs themselves may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

The side effects that other people have experienced so far with the drug combination are:

Tocilizumab:

- Hypersensitivity reactions: allergic reactions
- Respiratory: upper respiratory tract infections, nasopharyngitis, bronchitis
- Gastrointestinal: mouth ulceration, upper abdominal pain, gastritis, gastrointestinal perforations, pancreatitis.
- Hepatic: abnormal liver tests elevation
- Neurologic: headache, dizziness
- Cardiovascular: hypertension
- Dermatologic: skin rash
- Serious infections

Tacrolimus:

- Cardiovascular: hypertension
- Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think
- Gastrointestinal: nausea, vomiting
- Hematologic: microangiopathic hemolytic anemia (possible destruction of red blood cells), thrombocytopenia
- Endocrine and metabolic: hypomagnesemia (low blood level of magnesium), hypokalemia (low blood level of potassium), hypocalcemia (low blood level of calcium), hyperlipidemia (increase lipid level in blood)
- Miscellaneous: unwanted hair growth, changes in vision, liver problems, reversible renal insufficiency, infections and posttransplant lymphoproliferative disorders

Methotrexate:

- Neurologic: fever, dizziness, chills, undue fatigue
- Gastrointestinal: ulcerative stomatitis (painful swelling and sores inside the mouth), nausea, abdominal distress, diarrhea
- Hematologic: leucopenia (decreased number of white blood cells), anemia (decreased number of red blood cells)
- Miscellaneous: abnormal liver tests, kidney failure and pulmonary complications after transplantation

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Blood Draws
Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In rare cases, a blood draw can cause fainting. If you have fainted before when your blood was drawn please let the person drawing your blood know. Only trained people will draw your blood.

Bone marrow biopsy and bone marrow aspirate
Bone marrow aspirate and/or biopsy are each performed using a hollow needle to remove a small sample of bone marrow. Before the biopsy, a local anesthetic is used to numb the area where the needle(s) will be inserted. The sterile procedure may cause discomfort, pain, bleeding, scarring or infection at the site of the aspirate and/or biopsy.

Electrocardiogram (ECG)
There are no major risks associated with an ECG. An electrocardiogram (ECG) checks your heart's electrical activity. To do an ECG, we will put electrodes on your chest. You might get a small skin rash and feel itchy where the electrodes are placed. This does not happen very often. It may also feel uncomfortable when we take the patches off.

Multigated Acquisition (MUGA) Scan
MUGA scans expose you to radiation. You may have a MUGA scan done as part of the study.

A MUGA scan creates video images of the lower chambers of the heart to check whether they are pumping blood properly. It shows any abnormalities in the size of the chambers and in the movement of blood through the heart.

When these scans are done, you will be given a contrast material by mouth or injected into a vein so that certain organs and tumors can be seen. The most common contrast materials used are barium sulfate (taken by mouth) and iodine compounds (injected in the vein). Rarely, some patients may develop an allergic reaction to the contrast material that could cause rash, hives, shortness of breath, wheezing, itching, and rarely cardiac arrest.

The contrast material injected into your vein may cause some damage to your kidneys, but this damage is usually reversible. The radiation exposure from exams using radiation could increase your risk of developing a radiation-induced cancer, years from now.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant
The drugs in this project might affect a baby, before or after the baby is born. We do not know if the drugs cause(s) harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

If you become pregnant during the project, you will be dropped from participation for safety reasons. If you become pregnant while you are taking this experimental drug we ask that you inform the research doctor immediately. The research doctor will ask you for written permission to obtain information from you or your obstetrician on your pregnancy and the health of the baby.

Risks of fathering a child
You should not father a baby while taking part in this project because it is unknown if the drugs could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the research doctor right away if you think your partner is pregnant.

If you think that you have fathered a baby while you are taking this experimental drug, we ask that you inform the research doctor immediately. At that time, the research doctor will ask permission of your partner for the use and disclosure of her health information regarding the pregnancy. She will be asked to sign a separate consent form. She can choose to do this or not. She will be asked to sign this form to allow your research doctor to contact her obstetrician to collect information on the progress of the pregnancy and its outcome. The research doctor will make this information available to the sponsor for safety monitoring.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project. This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms (“double barrier”)
- Limiting sexual activity to a male partner who has had a vasectomy

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don’t know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us develop better treatments for acute and chronic GVHD.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier.

Activities / costs that are part of the project will not be billed to you or your insurance company. These are the study drug, Tociluzumab, research samples and the process and shipping of research samples. Some insurers will not pay for drugs, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Chhabra.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Joining a different research project
- The procedure or drug offered to you may also be available without being in any research project.

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about the drugs that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Dr. Chhabra, 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Dr. Chhabra at 414-805-6700
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Hospital/Medical Records
- Physician/Clinical Records
- Lab and/or Pathology Reports
- Radiology Reports
- Biological Samples

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- The U.S. Food and Drug Administration (FDA)
- Federal agencies such as the Department of Health and Human Services (the DHHS), the National Cancer Institutes / National Institutes of Health (the NCI/NIH) and the Office of Human Research Protections (the OHRP)
- Other regulatory agencies and/or their Designated Representatives
- Any independent ethics committee, which approved this study

- Those required by law

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information, the information may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to:

Saurabh Chhabra, MD
Froedtert & the Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

A description of this clinical trial will be available on http://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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT03699631) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
Rationale for Use of Witness ☐ Subject has limited/no literacy ☐ Subject has limited English proficiency ☐ Subject has limited/no vision	☐ Sponsor requirement ☐ Other _____	
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*