PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Title of Study:
A phase 2 multi-centre randomized double-blind placebo-controlled parallel group study to examine the effects of 24 weeks tezepelumab 210 mg sc q4wks on methacholine airway hyperresponsiveness in participants with mild allergic asthma.

Principal Investigator: Dr. Donald Cockcroft, MD FRCP(C)
Department of Medicine
Division of Respirology, Critical Care and Sleep Medicine
University of Saskatchewan
don.cockcroft@usask.ca 306-844-1446

Co-Investigators: Dr. Beth Davis, PhD.
Dr. Brianne Philipenko, MD FRCP(C)
Department of Medicine
Division of Respirology, Critical Care and Sleep Medicine
University of Saskatchewan

24-Hour Emergency Contact Beth Davis (306-229-8709 call/text) or email beth.davis@usask.ca

Sponsor:
McMaster University

Funding:
AstraZeneca Canada

You are being invited to participate in a research study because you have mild asthma that does not require any regular medications. In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision. Feel free to discuss it with your friends and family, or your family physician.

The University of Saskatchewan and Dr. Cockcroft will receive funding to conduct this research study. Dr. Cockcroft will not receive personal financial benefit for conducting this study.

WHY IS THIS RESEARCH BEING DONE?

Asthma is a condition where small inhaled particles can cause inflammation in the lung leading to constriction of airways and wheeze. Mast cells are immune cells in airways that can release chemical causing constriction of the airways and wheeze. If we prevent inflammation, we can also prevent airway constriction. Tezepelumab is an injectable medication that improves asthma by stopping inflammation, but we do not yet know the effect on mast cells.

WHAT IS THE PURPOSE OF THIS STUDY?

Tezepelumab was approved in Canada July 2022 for treatment of severe asthma. Tezepelumab is not approved for treatment of mild asthma by any health authority, except for use in research studies like this. We would like to study the effect of tezepelumab on mast cells and airway constriction to understand the mechanisms of asthma, and which patients will benefit most from drugs like tezepelumab.

Mast cells play an important role in immune responses. In asthma, mast cells release many different mediators that lead to various detrimental effects including airway constriction (i.e. bronchoconstriction) and airway inflammation. The number of mast cells in the airway is associated with both asthma severity and magnitude of bronchoconstriction.

In those with poorly controlled asthma, tezepelumab has been shown to decrease bronchoconstriction induced by inhalation of mannitol, a stimuli that causes mast cells to release mediators. In allergic asthmatics, allergen exposure causes mast cell mediator release that results in bronchoconstriction and airway inflammation. Tezepelumab has been shown to inhibit these responses. In addition, allergen exposure leads to an increase in the airway response to inhaled methacholine, a stimuli that directly causes airway smooth muscle contraction (i.e. bronchoconstriction). Tezepelumab has also been shown to inhibit this response however the study was not specifically designed to look at this and the number of individuals studied was small. More data are needed.

Our study will provide additional data regarding the effect of tezepelumab on mannitol and methacholine induced bronchoconstriction and extend our knowledge regarding the role of mast cells in these responses.

WHAT WILL MY RESPONSIBILITIES BE IF I TAKE PART IN THE STUDY?

This is a placebo-controlled study. That means you will be assigned by chance (like a flip of a coin) to a group of people who receive either tezepelumab or a placebo. A placebo is an inactive substance, like a sugar pill. In this study you have a 50% chance of receiving the placebo and a 50% chance of receiving tezepelumab. During this study you may not co-enroll in any other studies to test other medications.

If you volunteer to participate in this study, you will attend 13 study visits over a period of about 27 weeks. These visits are divided into a Screening period to assess your eligibility for the study, a Treatment period in which study drug will be administered and various testing will be performed, and a Follow up period to assess your general health before exiting the study.

All procedures are conducted for research only, in the Asthma Research Lab facilities at the University of Saskatchewan, Rooms 346 and 348 Ellis Hall, Saskatoon, SK. During these study visits we will ask you to do the following things:

Screening and Baseline period Week -1
Testing will be performed on 2 different days separated by 48 hours to determine your eligibility for the study.

- Day 1 you will have a physical examination, and ECG (test of your heart function), a skin prick test and a methacholine breathing test. You will provide samples of blood, urine, sputum and nasal tissue. This entire visit will take approximately 2 hours.
- Day 2 you will have a mannitol breathing test. You will provide samples of blood, urine, and sputum. This entire visit will take approximately 2 hours.

If you do not meet the study requirements, you will not be invited for the remaining study visits.

Treatment period Week 0 to 24
Weeks 0, 4, 8, 12, 16 and 20 you will be administered study medication. This will take approximately 30 minutes.
Weeks 8, 16 and 24 you will have testing performed on 2 different days separated by 48 hours. On Weeks 8 and 16 study medication will be administered after the Day 2 tests have been performed.

- Day 1 you will have a methacholine breathing test and you will provide a sample of sputum. Only at Week 24 you will provide a nasal sample. This entire visit will take approximately 2 hours.
- Day 2 you will have a mannitol breathing test. You will provide samples of blood, urine, and sputum. This entire visit will take approximately 2 hours.

Follow up period Week 26
You will have a physical examination, and ECG (test of your heart function), and provide samples of blood and urine. This entire visit will take approximately 1 hour.

Use of certain medications are not allowed during the study (e.g. inhaled corticosteroids). These medication restrictions will be discussed with you. Use of a rescue inhaler (e.g. Ventolin®) will be allowed to prevent/treat asthma symptoms although use must be withheld for 8 hours prior to study visits. In emergency situations, do NOT withhold any medication(s) (i.e. use medication as needed and contact study staff as soon as possible to determine how to proceed, for example, re-schedule study visits).

WHAT ARE THE STUDY PROCEDURES, POSSIBLE RISKS AND DISCOMFORTS?

A description of the study procedures and their risks are below.

Blood draw: Blood will be collected from a vein in your arm to ensure you are healthy (Week -1 and Week 26), to look for specific variations in a small part of your DNA called a single nucleotide polymorphism (Week -1, and to measure markers of inflammation (Weeks 0-24). During testing at Weeks -1, 8, 16 and 24 we will collect blood 6 times with not more than 60 mL (4 tablespoons) total volume. Through the entire 27 week study period we will collect up to 280 mL (19 tablespoons) of blood. Obtaining blood may sometimes cause pain at the site where the blood is drawn from, bruising, occasional light-headedness and, rarely, fainting.

Urinalysis: Urine will be collected to ensure you are healthy and in females for pregnancy testing (Week -1 and Week 26), and to measure markers of inflammation (Weeks 0-24). During testing at Weeks -1, 8, 16 and 24 we will collect urine 4 times.

Electrocardiogram (ECG): This is a test of your heart function that requires attachment of sticky pad to your chest to record electrical signals in your heart. ECG electrodes and gel may cause local irritation or redness.

Skin prick test: This test identifies the specific substance that you are allergic to. It is performed by applying an extract of an allergen to the skin, scratching or pricking the skin to allow exposure, and then evaluating the skin's reaction. Skin prick tests cause itch and swelling that normally stops within 1 to 2 hours. More prolonged or severe swelling may be treated with an oral antihistamine, topical corticosteroid cream, and an ice pack. Severe allergic reactions from allergy testing are very rare, but can result in a decline in blood pressure and difficulty breathing shortly after the test, and can be potentially fatal.

Methacholine and mannitol breathing tests: This is a breathing test where you will inhale increasing doses of methacholine or mannitol to determine how your airways react to the agents. Both substances provoke narrowing of the airways. You will have to blow into a spirometer before and after each dose, and you will inhale increasing doses until your lung function has decreased by 15 to 20% from your normal capacity. You will be given a bronchodilator (quick-acting medication to help you breathe better) after the test to reverse the narrowing of your airways. During the methacholine and mannitol challenges, you could experience cough, chest tightness, wheezing, and difficulty breathing. Symptoms, if they occur, are mild and resolve following the inhalation of a bronchodilator medication which will be provided to you. During the mannitol breathing test we will measure how often you cough with the assistance of a cough monitor that will record all sounds during the test. After the mannitol test this recording will be reviewed to confirm the number of coughs, then the recording will be deleted. The test is carried out in a way to minimize the danger of a severe asthmatic reaction, however there is still a very small possibility of severe narrowing of your airways. If this occurs, you will be immediately treated.

Sputum sampling: This procedure is used to obtain mucus from the lungs. You will inhale increasing concentrations of a saline aerosol over a period of approximately 20 minutes. This will increase the secretion of mucus in the airways, promote coughing and in this way produce a specimen. Sputum will be used for measuring inflammation in your airways. Inhalation of a salty mist during a sputum induction may cause cough, and in some patients, may cause the narrowing of the airways and wheezing. Cough usually stops shortly after you stop inhaling the salt water solution and wheezing is reversible with a bronchodilator that is provided. Study staff will stop the procedure if your symptoms become bothersome.

Nasal sampling: A plastic curette is rubbed across the inside of your nose and the nasal sample that sticks to the curette will be used for measuring inflammation in your airways. This procedure may cause minor discomfort including pressure while sampling the area.

Drug administration: The study drug is given as an injection under the skin of arms, thighs or stomach. Putting the needle under your skin may sometimes cause redness, swelling or pain where the needle is placed. Rarely injections under the skin may cause skin infection. Placebo does not contain active substance, but contains other substances that can cause an allergic reaction.

Risk from study drug: There are always risks with taking a research medication. Your study doctor will carefully check your health for your safety. It is important that you tell your study doctor if you have any symptoms or if your asthma worsens. In a medical emergency, please go to a hospital emergency department and contact the study doctor/study staff as soon as possible.

The study medication, tezepelumab, has been approved in Canada for treating patients with severe asthma. Tezepelumab may cause some side effects. You may experience none, some or all of those listed below. There may be risks involved in taking this medication that have not been identified in the studies done so far.

- Allergic reactions: To other similar medications, some people may have allergic reactions. These reactions can sometimes happen hours or days after the injection. Symptoms may include swelling of the lips, breathing problems, fainting, dizziness, hives or rash, or drop in blood pressure. Allergic reactions can potentially be life threatening and require immediate medical treatment. Serious allergic reactions could occur in patients taking tezepelumab. No cases of serious allergic reactions related to tezepelumab treatment have been reported in previous studies with tezepelumab. Please inform your physician immediately if you think you may be having a reaction.

- Based on the information about side effects in the patients from other studies in adults, the following side effects are considered to have a reasonable possibility of being related to treatment with tezepelumab: Sore throat (pharyngitis), joint pain (arthralgia), rash and reactions at or near the injection site used to give the study medication (Injection site reactions)

- The most common (greater than or equal to 5% occurrence) side effects reported by asthmatic patients taking tezepelumab include asthma exacerbation, common cold, headache, bronchitis, skin reaction at the place of injection, diarrhoea. These side effects may have been due to the study drug or may have been due to other reasons such as a subject's other diseases or other medications.

- Other risks from study drug: Because tezepelumab blocks the effect of thymic stromal lymphopoietin (TSLP), a molecule that plays a role in your immune system, receiving tezepelumab could increase your risk for infection. You will not be allowed to enroll in this study if you have a recent or current infection. If you do take part in this study, you will have routine blood tests performed periodically to evaluate your general health including any signs of infection. A severe immune reaction called immune complex disease can occur in patients taking drugs like tezepelumab. Immune complex disease can lead to inflammation of various tissues in the body such as the blood vessels, the membrane

around the heart, the lining surrounding the lungs, the brain and the kidneys and could result in death. No cases of immune complex disease have been reported in previous studies with tezepelumab.

- It is not known whether tezepelumab may cause side effects to pregnant females, to an unborn child (an embryo or a fetus), or to children of breastfeeding females. Because of these unknown risks, if you are pregnant or trying to become pregnant you cannot enter the study. If you are breastfeeding a child, you cannot enter the study. If you can have children, you are required to have a negative pregnancy test result before enrolling in the study. You are a female who can have children if:
    - you have not completed menopause;
    - you have not had a hysterectomy;
    - you have not had surgery to become sterile (i.e., a tubal ligation);
    - your sexual partner has not had surgery to become sterile (i.e., a vasectomy).

  If you are sexually active and can have children, you must not become pregnant during the time you are participating in the study, and for a period of 16 weeks after the last dose. You must use either of the following forms of birth control: true sexual abstinence, a vasectomized partner, Implanon®, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or Nuvaring® during this study. You must use an effective method of birth control, as defined above, from the first visit, throughout the study duration and through 16 weeks after the last dose of the study medication.
  If you or your partner become(s) pregnant during the study, you must tell the study doctor immediately. If you are a woman, you will stop receiving the study medication immediately. You should report any pregnancy occurring during the study immediately to the study doctor. The study doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. Your pregnancy will be followed until its conclusion. By signing this consent form, you are agreeing to this follow-up.
  If you miss a menstrual period or think you might be pregnant during the study, you must tell the study doctor immediately.

If you choose to take part in this study, you will be told about any new information which might affect your willingness to continue to participate in this research.

WHAT WILL BE DONE WITH MY BIOLOGICAL SAMPLES?

Your blood and urine samples will be used during the study to measure safety. All stored samples of blood, urine, sputum and nasal curettage will be de-identified and remain at the site of collection until the end of the study. Stored blood and sputum from both sites will be shipped to and analyzed at McMaster University at the end of the study to measure inflammation.

Urine and nasal samples will also be sent to specialized laboratories in the USA and Sweden for testing. No personal information will be sent with these de-identified samples. All leftover

biological materials will be retained at McMaster University for making measurements related to this study for up to 10 years. Samples will be discarded afterwards. You will not receive the results of any testing.

The samples will be used for research and such use may result in inventions or discoveries that create new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the researchers/sponsor. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

DOES THE STUDY INVOLVE ANY GENETIC TESTING?

Pharmacogenetic testing is a planned component of this study. However, participating in the pharmacogenetic research is optional. If you decide to participate, you will be required to provide an additional blood sample (one tube) at visit 1. There are two statements on the signature page of this document where you will indicate whether you agree or not to participate in the genetic research component of this study.

The blood sample will be used to obtain your DNA and to look for a specific genetic sequence in the TSLP gene, called a single nucleotide polymorphism, the gene that codes for the protein targeted by tezepelumab. This genetic test will not reveal anything else about your DNA, and your blood will not be used for any other genetic testing.

WHO WILL TAKE PART IN THIS STUDY?

The research study is planned to go on for approximately 2 years and includes 34 participants with mild asthma, from 2 sites in Canada (McMaster University and University of Saskatchewan).

WHAT ARE THE POSSIBLE BENEFITS FOR ME AND/OR FOR SOCIETY?

We cannot promise any personal benefits to you from your participation in this study. Your participation may help other people with asthma in the future.

IF I DO NOT WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

Your participation in this study is voluntary. You can choose not to participate in this study. Choosing not to participate in this study will in no way affect your current or future medical care, treatment or academic standing.

WHAT INFORMATION WILL BE KEPT PRIVATE?

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information, nor mentioned in any study report, nor be made

available to anyone except the research team (i.e. non-identifying codes will be used for identifying your study data. For example, if you are participant 1, your data/documentation will be coded with TEZAR01; TEZAR is an acronym for tezepelumab airway responsiveness which is a code we created specifically for this study. Your de-identified information will remain under lock and key in the Asthma Research Lab at the University of Saskatchewan for a minimum of 15 years per Health Canada regulations after which time it will be shredded in a confidential manner. In addition, there is a requirement for all clinical study data and regulatory documentation to be reviewed by a study monitor. A study monitor is a representative of the study sponsor, who reviews all study records:

- to ensure participant safety and respect of participant rights
- to ensure the collected data are accurate, complete and verifiable; and
- to ensure the study is conducted in compliance with the protocol and applicable clinical trial regulations

While study monitoring is usually performed in person at the study site, this study will employ a remote monitoring process. In this study, all study data and regulatory documentation will be uploaded to a secure web-based platform (McMaster University Microsoft Sharepoint) for remote/virtual review by the study monitor. Only those individuals involved with the study (e.g. local site staff, study Sponsor, study monitor) will be able to access the platform via a secure url (i.e. a secure website). Access to the website will require the Sponsor to provide the secure url to the user. The user will be prompted to request a numerical code be sent to them via email and the code will then need to be entered to access the site. Apart from the consent form signature page, the documentation being uploaded to the site will not include information that can identify you but will be coded/de-identified as noted above.

As indicated on page 5, leftover biological samples will be stored for a maximum of 10 years. This is an acceptable timeframe for sample stability and will allow for repeat testing or additional testing with new technologies. Note that no guarantee can be made for complete confidentiality.

For quality assurance and/or auditing purposes, the University of Saskatchewan Biomedical Research Ethics Board, a representative of Health Canada or other regulatory body may inspect research records and medical records that may identify you in the presence of the investigator or his or her designate. By signing this consent form, you agree to allow third party access.

Your identifiable data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, address and phone number will be removed from the data and will be replaced with the study code. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed, will be securely stored in a locked office at the research site.

It is the intention of the research team to publish results of this research in scientific journals and to present the results of the study at related conferences and workshops however, your identity will not be revealed in any publication or presentation. If the results of the study are published, your name will not be used and no information that discloses your identity will be released or

published without your specific consent to the disclosure.

CAN PARTICIPATION IN THE STUDY END EARLY?

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your future medical care, treatment or academic status will not be affected.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment will be retained for analysis.

In addition, the study doctor may withdraw you from the study if:

- Your health changes, and the study is no longer in your best interest, or you are unable to tolerate the study treatment.
- New information becomes available, and the study is no longer in your best interest.
- You are unable to complete all required study procedures.
- For females: You become pregnant while on the study.
- If your treatment assignment becomes known.
- The study is stopped by Health Canada, the Research Ethics Board (REB) or the study sponsor.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

You will be reimbursed for out-of-pocket expenses such as parking, public transit and meals etc. These expenses will be reimbursed by an honorarium in the amount of $975. The honorarium will also provide compensation for your time and the inconvenience of being a research participant. If you enroll in the study but are not eligible or if you withdraw from the study after agreeing to participate, the honorarium will be prorated accordingly at $75/visit. The honorarium will be tax reportable; your social insurance number will be required and the University will issue you a T4 for tax purposes.

WILL THERE BE ANY COSTS?

There will be no cost to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your Provincial Health Insurance Plan or private health insurance plan.

WHAT HAPPENS IF I HAVE A RESEARCH-RELATED INJURY?

If you suffer an injury from participation in this study, medical care will be made available to you by your study doctor, or you will be referred for appropriate medical care. However, if you sign this consent form it does not mean that you waive any legal rights you may have under the law, nor does it mean that you are releasing the investigator, institution and/or sponsor from their legal and professional responsibilities.

IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions or concerns regarding this study before or during participation, you may contact Dr. Davis at beth.davis@usask.ca or 306-229-8709 or Dr. Cockcroft at 306-844-1446 or don.cockcroft@usask.ca.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975 (out of town calls 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

CONSENT STATEMENT

Title of Study: A phase 2 multi-centre randomized double-blind placebo-controlled parallel group study to examine the effects of 24 weeks tezepelumab 210 mg sc q4wks on methacholine airway hyperresponsiveness in participants with mild allergic asthma.

- I have read the information in this consent form.
- I understand the purpose, procedure and possible risks of the study.
- I was given sufficient time to think about it.
- I have had the opportunity to ask questions and have received satisfactory answers.
- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care or academic status.
- I agree to follow the study staff's instructions and will tell the study staff at once if I feel I have had any unexpected or unusual symptoms.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I understand that by signing this document, I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.

☐ _____ yes, I will participate in the pharmacogenetic testing.
initial

☐ _____ NO, I will NOT participate in the pharmacogenetic testing.
initial

I agree to participate in this study:

Printed name of participant	Date
Signature of participant	Phone number
Printed name of person obtaining consent	Date
Signature of person obtaining consent	