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**Participant Information Sheet/Consent Form**

**Interventional Study** - *Adult providing own consent*

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| --- | --- |
| **Title** | Phase IB/II study of Zanubrutinib and Tislelizumab in CNS lymphoma  |
| **Short Title** | BICICL: BTK and Immune Checkpoint Inhibitor in CNS Lymphoma |
| **Protocol Number** | Insert here |
| **Project Sponsor** | Monash Health |
| **Principal Investigator** | Professor Stephen Opat |
| **Location** | Monash Health, 246 Clayton Road, Clayton VIC 3168 |
|  |  |

**Part 1 What does my participation involve?**

**1 Introduction**

You have been invited to take part in this research project. This is because you have a disease called central nervous system non-Hodgkin lymphoma. The central nervous system includes the brain and spinal cord. This type of lymphoma is caused by growth of abnormal B cells. These B cells are an immune cell, a type of white blood cell, that normally helps us to fight infections.

The research project is testing a new combination of drugs called zanubrutinib (BGB-3111) and tislelizumab (BGB-A317).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor. If English is not your first language and you require an interpreter, one will be provided for you.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

* Understand what you have read
* Consent to take part in the research project
* Consent to have the tests and treatments that are described
* Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

**2 What is the purpose of this research?**

You are being asked to participate in this study because you have a disease called B cell lymphoma affecting the brain or spinal cord (CNS Lymphoma). You may have had unsuccessful treatment for this condition before, or your doctor has recommended this study as you are not fit enough to receive strong therapy.

B-cell lymphoma is a type of cancer that occurs when your B cells start to grow out of control. B cells normally help protect the body against bacteria or viruses by making proteins called antibodies.

Zanubrutinib is a medication that inhibits a protein called BTK or Bruton’s Tyrosine Kinase which plays an important role in the growth and survival of normal B cell and lymphoma cells. Blocking BTK with zanubrutinib may slow down or stop growth of lymphoma cells, however, not all participants improve the same way or to the same degree with some participants who may not improve at all.

Another type of cancer treatment is immunotherapy, where antibodies are administered to help the body’s immune system to detect and eliminate certain types of cancer cells. Tislelizumab a humanised anti-programmed death-1 (PD-1) monoclonal antibody, is such a kind of immunotherapy. There is evidence that some patients with CNS lymphoma have some changes in lymphoma cells that prevents their immune system attacking the cancer. Treatment with tislelizumab may overcome these changes.

Zanubrutinib was approved for use in Australia by the Therapeutic Goods Administration (TGA) in October 2021 for the treatment of two different types of lymphoma, namely mantle cell lymphoma and Waldenström’s macroglobulinemia. Tislelizumab has not yet been approved by the TGA for use in Australia. Therefore, both drugs are an experimental treatment for CNS lymphoma. This means that it must be tested to see if it is an effective treatment for this condition.

Both the study drugs are made by BeiGene Aus Pty Ltd, a biotech company in Australia.

Treatment cycles are of three weeks duration. Participants will initially receive only zanubrutinib 320 mg once a day, orally for three cycles i.e. 9 weeks. After 8 weeks of treatment with zanubrutinib alone, a magnetic resonance imaging (MRI) scan of the brain will be performed to assess the response to treatment. In participants who show benefit from zanubrutinib, participants will then receive zanubrutinib 320 mg once a day in combination with tislelizumab from Cycle 4 onwards. Tislelizumab is administered by intravenous infusion, through the vein, at 200mg every 21 days. Treatment will continue up to 2 years in patients demonstrating ongoing benefit.

This research study is a Phase IB/II study. The purpose of this study is to test the safety, tolerability and effectiveness of the two drugs, zanubrutinib and tislelizumab. If you agree to take part in this study, you will be one of 30 participants at 3 sites in Australia.

This research has been initiated by the study doctor, Professor Stephen Opat, and has been funded by BeiGene Aus Pty Ltd.

**3 What does participation in this research involve?**

Before entering this research project, your doctor will discuss it with you in detail and you will be given enough time to review this Information Sheet and Consent Form. You are then totally free to decide whether you want to take part in this research project or not. If you wish to participate, you sign this Information Sheet and Consent Form. Only then the following assessments will take place.

Some medications, as well as some foods like grapefruit, grapefruit juice, and Seville oranges may interfere with the way your body processes zanubrutinib. This interference could cause the amount of either zanubrutinib or your regular medications in your body to be higher or lower than expected. It is also possible that taking zanubrutinib with your regular medications or supplements may change how your regular medications or supplements work. It is important to avoid grapefruit, grapefruit juice, and Seville oranges and tell the study doctor about all medications or supplements you are taking during the study.

The study is expected to last about 4 years. The amount of time you will be on study treatment or be followed up for health information as part of the study depends on how you respond to the study treatment. If you benefit from treatment, you may receive study treatment for 2 years with a discussion at the end of 2 years regarding ongoing treatment. You may stay on study treatment until you decide to stop, or develop a side effect that prevents you from continuing treatment, or until the study doctor believes it is better for you to stop study treatment (for example if the treatment is no-longer helping). After stopping study treatment, the investigators will continue to collect health information to evaluate long-term effects of the study treatment.

**During your participation in this study, you will be asked to come in for the following study visits:**

If you decide to participate in this study and sign this form, you will be asked to undergo certain screening tests and procedures to determine if you are eligible to take part in this study. However, signing this form does not guarantee that you will be able to join this study.

There are up to 4 phases in this study.

* Screening (to determine if you qualify for the study)
* Treatment (when you are receiving study treatment)
* End of Treatment (when you stop study treatment)
* Follow-up (after you permanently stop study treatment)

**Screening Period (within 28 days before starting study treatment)**

This Information Sheet and Consent Form (ICF) must be signed and dated before any trial specific procedure is performed.

Prior to confirming your inclusion in the study, your doctor will arrange for some study specific procedures to be conducted to see if you meet the requirements for being in the research project. You will visit the clinic for approximately 2 to 4 hours. If you meet the requirements, you will have up to 28 days from the Screening Visit to start taking the study drugs.

These examinations, tests or procedures may be part of your regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor:

* Your age (date of birth), gender, race, height, and weight will be recorded.
* You will be asked questions about your general health and well-being, medical history, any other drugs that you are currently taking and how well you can undertake general day to day activities.
* Your height, weight and your vital signs (blood pressure, pulse rate, temperature and respiratory rate) will be measured and recorded.
* You will be asked about any weight loss over the previous 6 months, fever, or night sweats.
* An electrocardiogram (ECG) will be performed to check the activity of your heart. The ECG reading will be repeated three times within approximately five minutes whilst you remain connected to the ECG machine. Small sticky patches will be placed on certain areas of your body while you are lying down. These patches are connected to thin wires connected to a machine which will interpret the electrical activity of your heart and then print a report.
* An echocardiogram (ECHO) or multigated acquisition (MUGA) scan will be performed to check the activity of your heart. An assessment of left ventricular ejection fraction (LVEF) will also be performed to assess your heart function. This is an ultrasound and will take up to an hour to complete.
* Urine and Blood samples (approximately 25 mL or approximately 5 teaspoons) will be collected. These blood samples will be used to assess your general health, the activity of your thyroid gland and to measure certain proteins that cause the blood to clot.
* Blood will also be taken for Creatinine Kinase and Troponin. These routine safety tests will test muscle and heart muscle function. Your doctor will monitor these results and will let you know if any further action needs to be taken.
* If you are suspected or known to have serious respiratory conditions or exhibit significant respiratory symptoms unrelated to your cancer, you will undergo pulmonary function testing which may include to spirometry and assessment of diffusion capacity, which measures the transfer of gas from air in the lung, to the red blood cells in blood vessels in the lungs.
* The blood tests will also include a screening test for HIV and hepatitis. This is because the study doctors need to know about your general health. You will receive information and counselling before the test. If a test shows you have HIV or hepatitis B or C, you will have follow-up counselling and medical advice. If your test results are positive, the study doctors are required by law to notify government health authorities. Signing the consent form means that you agree to have this testing; it will not be done without your consent.
* If you are a woman who is able to have children, you will also be asked to have a laboratory-based highly sensitive pregnancy test (urine or blood). For blood-based pregnancy test, blood sample will be collected.
* A complete eye examination will be performed. This will involve eye drops which dilate or enlarge your pupils to in order to get a better view of the fundus of the eye, the back surface of your eye, and a slip-lamp examination (a lamp which emits a beam of light, used for examining the interior of the eye) will be performed.
* A lumbar puncture or spinal tap and/or Ommaya tap will be performed to assess for any cancer cells in the cerebrospinal fluid (CSF), the fluid that surrounds the brain and spinal cord. CSF collected (5 mL) will be examined for the presence of any disease and to measure protein levels.
* A magnetic resonance imaging (MRI) scan, or a computed tomography (CT) scan if you can’t have an MRI scan, will be performed to assess your cancer.
* If you have had a previous biopsy of your tumour, a sample of that biopsy will be requested. If this sample is unavailable, your participation in the study will not be impacted.

**Treatment Period**

The number of visits that you will need to make to the hospital will vary depending on how many cycles you participate in and how many follow-up visits you have. This will depend on how the study drug affects you. You will continue to be given the combination treatment for up to 2 years at which point further treatment will be decided upon by the study doctor. During the 2 years of treatment, you will continue treatment until there is any worsening of your disease, you experience any intolerable side effects, you withdraw your participation, or your study doctor considers it is in your best interest to stop taking the study drugs. The study will continue until all participants stop taking part in the study for the reasons described above. You must be willing to attend all the scheduled visits to the hospital. Various procedures will be performed each time you visit. The study doctor might need to repeat any of these procedures at times other than those specified below if he/she feels it is necessary for your safety.

**Study Drugs**

Zanubrutinib will be given as a bottle containing capsules to be taken once daily beginning on Day 1 of the first cycle. You will be given a study drug diary for zanubrutinib and asked to write down the date and time you take zanubrutinib and how many capsules you take.

Tislelizumab will be given at a dose of 200 mg as an intravenous infusion (a drip) on Day 1 of every 3-week treatment cycle from cycle 4 onwards in combination with zanubrutinib. The infusion will take a period of 30 – 60 minutes. The time it takes to infuse the drug will depend on whether you have any reaction to the drug. You will be watched closely by the study staff during your first infusion.

If you have a reaction to the tislelizumab infusion, you may be given medication 30 to 60 minutes before you receive the next infusion to help prevent any further reaction you may experience. You may also be given other medicines that your doctor thinks would be helpful.

**Cycles**

Initially you will be given zanubrutinib (a capsule) 320 mg once per day, orally, for the first 3 cycles, i.e. 9 weeks.

From Cycle 4, Day 1 onwards, you will be given the combination of the 2 study drugs, zanubrutinib and tislelizumab (an infusion) at least 30 minutes apart on the first day of each cycle of treatment. A “cycle” is the period of time between your infusions. “Infusion” is a method of transferring fluids, including drugs, into the bloodstream.

All cycles will be 21 days (3 weeks), which means you will receive your first infusion on the first day (Day 1) of Cycle 4 and then 21 days later, you will receive your second treatment on the first day (Day 1) of Cycle 5, and so on, until you have completed 2 years of treatment. You will be given zanubrutinib (a capsule) every day throughout the cycle with or without food.

During Cycle 4 of treatment, you will visit the hospital twice for various tests.

You will visit the hospital on Day 1 of each subsequent Cycle to receive your infusion of tislelizumab and to have repeat tests and procedures.

**Study Visits**

During the treatment period many of the tests and procedures conducted at the screening visit will be repeated. The following tests and procedures will occur at most visits:

* You will be asked about any changes to your health since the last visit, and whether you have started taking any new treatments (new drugs and/or new anti-cancer therapies)
* Recording of your general health and well-being, ability to perform day to day tasks, and any weight loss, fever or night sweats and a physical examination
* You will have vital signs measured.
* Blood samples will be collected to assess your general health, to measure the proteins that cause the blood to clot, the activity of your thyroid gland, your immune response to study drugs and to measure biomarkers in your blood which indicate your body’s response to treatments.
* If you are taking tislelizumab (BGBA317), blood tests will also include Creatinine Kinase and Troponin. Blood for these tests will be taken during all scheduled visits from cycle 4 onwards. These routine safety tests will test muscle and great muscle function. Your doctor will monitor these results and will let you know if any further action needs to be taken.
* If you are a woman who is able to have children, you will also be asked to have a urine or blood pregnancy test.
* The study staff will ask you how you are feeling and measure your vital signs at regular intervals during your infusion.
* A repeat complete eye examination will be performed only if you receive treatment with tislelizumab.
* Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be repeated in patients treated with tislelizumab approximately every 15 weeks.
* An MRI of the brain and/or spinal cord, will be repeated 8 weeks after commencing treatment with zanubrutinib alone, 8 weeks after commencing combination treatment with zanubrutinib with tislelizumab and then every 12 weeks thereafter.
* A lumbar puncture or spinal tap to collect cerebrospinal fluid (CSF) will be performed at screening, Week 8, Week 16 and at progression to assess for cancer cells, measure zanubrutinib concentrations and for special testing, specifically biomarker analysis.
* Quality of life Questionnaires: You will be asked to complete 2 questionnaires about how much your illness is affecting your daily life at the beginning of each cycle. Each questionnaire will take you about 5 – 10 minutes to complete. You will complete the questionnaire preferably at the beginning of your study visits before any other tests or study procedures are done.

**Unscheduled visits**

If your study doctor believes that you should have additional visit(s) for your safety, e.g., in the event of a new symptom or side effect, you may be asked to come for an additional visit. If necessary, additional tests and procedures related to such a safety concern may be done.

**Follow-Up Period**

**End-of-Treatment / Safety Follow-up Visit**

This will be done when you stop receiving study treatment. You will be asked to return to the clinic approximately 30 days after your last dose of study treatment even if you have started another treatment for your disease. At this visit, the following study assessments will be done:

* Your vital signs will be taken, and you will have a final physical examination.
* You will be asked for any symptoms or sickness you have had since your last visit and any medications you have taken.
* Your ability to do daily activities will be assessed. You will be asked if you have had any other anti-lymphoma treatment.
* You will be asked to complete 2 quality of life questionnaires at your end of treatment visit.
* As per your Treatment Study Visits, tests and procedures, including a blood sample, will be repeated. Additionally, a blood sample (approximately 6 teaspoons or 30mL of blood) will be taken for biomarker research.
* If you are taking tislelizumab (BGB-A317), blood will be taken to assess Creatinine Kinase and Troponin. These routine safety tests will test muscle and heart muscle function.

**Long-term Follow-up**

If you stop participating in the study because your disease has worsened or you start a new anti-cancer therapy, you will no longer need to come to the hospital. The study doctor or study staff will follow up to see how you are doing every 3 months by telephone contact or a review of your medical records or other means until you can no longer be contacted or the study is closed.

**4 What do I have to do?**

If you consent to be on the study, you are responsible for:

* Keeping your study appointments. If you miss an appointment, please contact the study coordinator or the study doctor to reschedule as soon as you know you missed the appointment.
* Telling the study coordinator or the study doctor about any new medications, medical procedures, illnesses, new or worsening symptoms, illnesses or injuries, doctor visits, or hospitalisations that you have had since the last visit.
* Telling the study coordinator or the study doctor if you change your mind about staying in the study.
* Telling the study coordinator or the study doctor if your contact information changes.
* Only you should take the zanubrutinib study drug. It must be kept out of the reach of children. Please also keep the study drug away from people who may not be able to read or understand the label.
* You must comply with the storage instructions written on your study drug bottle. The study staff will go over this with you to ensure that you understand.
* You must return all of the used and unused study drug materials (including empty drug bottles).
* You may not eat grapefruit or drink grapefruit juice for the entire time that you are participating in the study.
* If you are male and fertile, you must also agree to use an effective barrier method of birth control from signing this form until 90 days after the last time you take the study drug.
* Telling the study coordinator or the study doctor if you think you might be pregnant or if your partner is pregnant.

**5 Will there be any charge for me to be in this study?**

There are no additional costs associated with participating in this research project. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

**Other relevant information about the research project**

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

If you agree to participate, you may not participate in any other research study of an investigational product while you are in the treatment phase of this study.

**6 Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Monash Health.

**7 What are the alternatives to participation?**

You do not have to take part in this research project to receive treatment at this hospital.

Other options are available; these may include treatment with marketed drugs or other experimental drugs. Alternatively, you may choose not to have any treatment directed at the cancer but supportive care guided by your symptoms. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

**8 What are the possible benefits of taking part?**

We cannot guarantee or promise that you will receive any benefits from this research.

Zanubrutinib and tislelizumab are experimental drugs, and treatment may or may not have any direct medical benefit to you. Others may benefit from the information learned in this study. This study may help to develop a new therapy for others with similar conditions.

**9 What are the possible risks and disadvantages of taking part?**

You may or may not have side effects from the study treatment or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Here are important points about side effects:

* Some side effects may go away soon, some may last a long time, and some may never go away.
* Some side effects may interfere with your ability to have children.
* Some side effects may be serious and may even result in death.

Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect. The study doctor may be able to treat some side effects and possibly adjust the study treatment to try to reduce side effects.

If you live far away or are for other reasons not readily able to travel to the study site, you need to go to your local healthcare providers or local emergency service.

The study treatment may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. Your study doctor will be testing your blood and will let you know if changes occur that may affect your health. Tislelizumab, and other drugs similar to tislelizumab, are thought to act against cancer by activating the immune system to attack cancer. However, in some patients there can be side effects related to an over-active immune system, which can cause damage to your organs or other tissues of your body. In most cases these side effects are temporary and can be treated with stopping tislelizumab and treating you with a medication that suppresses the immune system.

**Side Effects Known to be Associated with Tislelizumab as a Single Agent**

Tislelizumab is being developed for the treatment of human malignancies in multiple organs and tissues as monotherapy or in combination with other therapies. The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 3498 patients (2150 patients treated with monotherapy and 1348 patients treated with combination therapy) as of the cut-off date 20 May 2021.

The most commonly reported side effects seen in participants taking tislelizumab as a single agent are outlined below. In most cases, these side effects are mild and respond to treatment, but in some cases may be serious or require urgent treatment. Some of these side effects may be life-threatening or fatal.

**Very common side effects (*occurring in at least 1 out of 10 people; equal to or more than 10.0%*).**

* Nausea (feeling sick to the stomach)
* Constipation
* Diarrhoea (watery, loose, or soft stools)
* Pyrexia (fever)
* Fatigue (tiredness)
* Aspartate aminotransferase increased/Alanine aminotransferase increased which are liver enzymes produced by liver cells (abnormal liver test [possibly resulting in liver damage])
* Blood bilirubin increased (abnormal liver tests [possibly resulting in yellowing of the skin and/or eyes])
* Rash
* Pruritis (itching)
* Decreased appetite
* Cough

**Common (occurring in at least 1 out of 100 and less than 1 out of 10; equal to or more than 1.0% but less than 10.0%).**

* Vomiting
* Asthenia (weakness)
* Blood alkaline phosphatase increased (abnormal liver test [possibly resulting in liver damage])
* Blood glucose increased/hyperglycaemia (high blood sugar [possibly resulting in diabetes])
* Dyspnea (shortness of breath)
* Pneumonitis (lung inflammation [possibly resulting in difficulty breathing])
* Hypothyroidism (underactive thyroid gland [possibly resulting in weight gain, heart failure, and/or constipation])
* Hyperthyroidism (overactive thyroid gland [possibly resulting in weight loss, heart rate changes, and/or sweating])
* Thyroiditis (inflammation of the thyroid gland [possibly resulting in tenderness in the neck])
* Arthralgia (joint pain)
* Myalgia (muscle pain)
* Hepatitis (inflammation of the liver)
* Infusion-related reaction (may occur soon after drug infusion with flushing, difficulty breathing, feeling faint, chills, itching, and/or skin rash)
* Uncommon serious side effects (occurring in at least 1 out of 1,000 and less than 1 out of 100 people; equal to or more than 0.1% but less than 1.0%).
* Colitis (inflammation of the large bowel)
* Pancreatitis (inflammation of the pancreas)
* Diabetes mellitus
* Adrenal insufficiency (decreased production of adrenal hormones [possibly resulting in weakness and/or low blood pressure])
* Arthritis (joint inflammation and swelling)
* Myositis (muscle inflammation)
* Hepatic function abnormal (abnormal liver function)
* Hyperbilirubinaemia (abnormal liver tests [possibly resulting in yellowing of the skin and/or eyes])
* Myocarditis (inflammation of the heart muscle, usually caused by infection. May be serious and require hospitalisation)
* Uveitis (inflammation inside the eye)
* Nephritis (kidney inflammation)

**Side Effects Known to be Associated with Tislelizumab in Combination with Zanubrutinib**

The side effects observed for zanubrutinib as a single agent are as follows:

**Very common side effects (*occurring in at least 1 out of 10 people; equal to or more than 10.0%*).**

* Infection (66.6%)
* Bleeding (46.3%)
* Neutrophil (a type of white blood cell) count decreased (41.1%)
* Platelet count decreased (39.3%)
* Anaemia (23.4%)
* Upper respiratory tract infection (31.4%)
* Diarrhoea (18.2%)
* Rash (17.4%)
* Cough (17.3%)
* Contusion (bruising) (17.0%), a condition of blood vessels ruptured in a region of injured tissue or skin.
* Urinary tract infection (11.8%)
* Blood in urine (11.0%)
* Fatigue (10.6%)

**Common (*occurring in at least 1 out of 100 and less than 1 out of 10; equal to or more than 1.0% but less than 10.0%*).**

* Low blood potassium (9.1%)
* Second cancer (7.9%)
* Pneumonia (6.6%)
* Lung infection (6.1%)
* Pleural effusion, excessive fluid building around the lung (1.9%)
* Atrial fibrillation and flutter, two types of irregular heart beat (1.8%)

**Uncommon serious side effects (occurring in at least 1 out of 1,000 and less than 1 out of 100 people; equal to or more than 0.1% but less than 1.0%).**

* Toxic epidermal necrolysis (0.1%), a condition of skin rash, extensive skin necrosis and detachment of layers of skin and mucosa

Common side effects observed for zanubrutinib in single-agent therapy may also be side effects in combination treatment.

As of 20 October 2021, a total of 75 participants have received tislelizumab in combination with zanubrutinib treatment in the BGB-3111\_BGB-A317\_Study\_001. In addition to the side effects listed above for tislelizumab as a single agent, the following side effects for this combination observed in ≥ 10% of participants and assessed as related to tislelizumab are listed below.

**Common side effects (*occurring in at least 1 out of 100 and less than 1 out of 10 people; equal to or more than 1.0% but less than 10.0%*).**

* **Anaemia** (low number of red blood cells that can causes tiredness and shortness of breath)
* **Thrombocytopenia** (low blood cell counts [platelets]. A low platelet count increases your risk of bleeding such as nosebleeds, bruising, stroke, and/or digestive system bleeding. You may need a platelet transfusion)
* **Neutropenia** (condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing)
* **Headache**

Your study doctor will notify you if any new and significant side effects become known.

There may also be other side effects related to the study drugs that cannot be predicted. If you experience any adverse reaction while taking the study drugs, you should immediately contact your study doctor. Many side effects go away after the drug is stopped, but in some cases, side effects can be more serious, long-lasting, permanent, or life-threatening.

**Allergic Reactions**

Occasionally, people have allergic reactions (including life-threatening reactions) when taking any medication. Symptoms of an allergic reaction can include: headache, rash, itching, flushing, swelling of the lips, tongue or face, shortness of breath, nausea and sometimes vomiting. Severe allergic reactions can cause dizziness, severe skin reactions, difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening. Immediately get emergency medical care if you have any of these symptoms. Your study doctor will be informed and your scheduled intravenous infusions will be delayed or stopped.

In general, allergic reactions to medicines are more likely to occur in people who already have allergies. If you are allergic to other drugs, foods or things in the environment, such as dust or grass, you should let your study doctor know. Also, if you have asthma, let your study doctor know.

**Infusion Site Reactions**

During the infusion of tislelizumab you may experience an infusion reaction. Symptoms of an infusion reaction include fever, chills, shortness of breath, and flushing. Infusion reactions usually occur during or within 1 day of infusion.

**Blood Draws**

Having blood taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

**CT Scans / MRI Scans**

A CT scan is a procedure that uses computer processed x-rays to produce images of a specific part of your body.

An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used in CT scans. There are no proven long-term risks related to MRI scans as used in this research study. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room. Patients with pacemakers or metal implants must inform the study doctor and technician.

Some people may experience symptoms of claustrophobia from lying in a confined space. If you do experience discomfort at any time during the scan, you will be able to alert staff by pressing on a call button provided to you

Occasionally an injection of “contrast” material is given to produce better CT or MRI images. If contrast material is used during the scan, there is slight risk of developing an allergic reaction. The reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock).

Your study doctor will explain CT, PET and or MRI scans in more detail as needed.

**Risks of Ionising Radiation**

Your enrolment in this research study may involve exposure to an amount of radiation from CT exams. As part of everyday living everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisievert (mSv) each year.

**Lumbar Puncture**

A lumbar puncture (also called a spinal tap) is a procedure to collect and look at the fluid (cerebrospinal fluid) surrounding the brain and spinal cord. During a lumbar puncture, a needle is carefully inserted into the spinal canal low in the back (lumbar area). The entire procedure takes about 30 minutes. You will lie or sit in positions that will help widen the spaces between the bones of the lower spine so that the needle can be inserted more easily.

A numbing medicine (local anaesthetic) is put in the skin. You will probably feel a brief pinch or sting when the numbing medicine is given. A long, thin needle is then put in the spinal canal. You may feel a brief pain when the spinal needle is inserted or repositioned. During the procedure, the needle may touch one of your spinal nerves and cause a tingling feeling, like a light electrical shock, running down one of your legs. Your doctor checks whether the fluid is clear, cloudy, or bloody. Several small samples of fluid are collected and sent to the lab for study.

Up to 25% of people who have had a lumbar puncture develop a headache afterward due to a leak of fluid into nearby tissues. The headache typically starts several hours up to 2 days after the procedure and may be accompanied by nausea, vomiting and dizziness. Drinking extra fluids after the procedure may help prevent or reduce the severity of a headache. You may also feel tired and have a mild backache the day after the procedure. Some people have trouble sleeping for 1 to 2 days.

**ECG**

Small sticky pads will be stuck to your chest, shoulders and hips and a machine will measure the electrical activity of your heart. We may need to shave small patches of your hair in these areas. These sticky pads may cause some local irritation and may be uncomfortable to remove.

**ECHO**

An ECHO is a type of ultrasound test that picks up the echoes of sounds waves as they bounce off the different parts of your heart. This scan does not involve the use of any radiation and it should not be painful or uncomfortable.

**Ommaya Reservoir placement**

This procedure will enable doctors to collect samples of your cerebral spinal fluid to check for certain proteins, study drug levels (if consented), and how the cancer in your CNS is responding to treatment. The procedure conducted under general anaesthesia involves an incision in your scalp to place and secure the reservoir between the skull bones and the scalp. A catheter is also inserted until it can reach a part of the brain called the ventricle before the scalp is closed with sutures or staples. The procedure generally requires a hospital stay of one night and the sutures or staples are removed approximately 10-14 days after the surgery. A CT or MRI may also be done to check for the correct placement of the reservoir. A small bump will remain at the treatment site but normal activities may be resumed as soon as the incision is completely healed. Since the Ommaya reservoir placement is a surgical procedure, and all surgeries carry some form of risk, complications may include bleeding, infection, or very rarely, neurological impairment. In certain cases, the reservoir or catheter may need to be adjusted or repositioned to work properly with a follow-up procedure.

**Pulmonary function tests (PFTs)**

PFTs check how well the lungs are working. The tests measure how much air the lungs can hold, how well you can push air out of your lungs, and how well the oxygen can get into your blood. The machine that performs the PFT is sometimes in a confined space with clear walls and a seat inside. You will be asked to wear a nose plug and blow into a plastic mouthpiece connected to the machine. The machine measures the amount of air breathed in and the force of the air breathed out. You will probably be asked to repeat the test a few times to get an accurate reading. You may also be given a medicine through an inhaler to improve your breathing by widening the airways. To test how well oxygen can get into your bloodstream, you will breathe a harmless gas, called a tracer gas, for a short time. The concentration of the gas in the air you breathe out is measured. This test allows the doctor to estimate how well the lungs move oxygen from the air into the bloodstream. These tests are painless. There is a small risk of collapsed lung (pneumothorax) in people with a certain type of lung disease. You should not undergo this testing if you had a recent heart attack or collapsed lung. Please inform your doctor about your medical condition.

**Eye Exam**

During this exam, the eye doctor may put dilating eye drops in your eyes. These drops widen your pupil and make it easier to examine your retina. The eye drops may cause you to feel a sharp tingling or burning pain or sensation. When your eyes are dilated, they may be sensitive to light for several hours after the exams and it is recommended to wear sunglasses and be accompanied during the exam. You may also experience poor/blurred vision, allergic reaction to the eye drops, eye pain, risk of blood pressure increase, irregular/increased heartbeat, dizziness and increased sweating. During the procedure of retinal scanning there is a potential risk of damage to the eyes with excessive light exposure, but the machine used for this exam is designed to halt testing before this can happen.

**Pregnancy and Breast-feeding**

The effects of zanubrutinib and tislelizumab on the unborn child are unknown. Therefore, women who are pregnant or breastfeeding must not participate in this study. It is important that participants do not become pregnant during the course of this study. If you are or become pregnant, or if your partner becomes pregnant, there may be unknown risks to the baby. You must not participate if you are trying to become pregnant or even occasionally breastfeeding. If you are a female, and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study.

If you are a woman who may be able to have children, you will be given a pregnancy test at screening and the Day 1 for every cycle, and if the result is positive, you will not be able to be in the study. If you are a sexually active man or woman, you must use an accepted form of birth control throughout the study (until 90 days after the last dose of zanubrutinib and until 120 days after the final dose of tislelizumab, whichever is longer).

These highly effective methods of birth control have a less than 1.0% chance of unwanted pregnancy during 1 year, if used according to the instructions of the manufacturer. These include implants, injectable medications, birth control pills, intrauterine devices or systems (IUDs), sexual abstinence (which is defined as refraining from all aspects of heterosexual activity) or a sterilised partner.

The study doctor will discuss methods of birth control with you if needed.

**For female participants**: If you become pregnant or think you may be pregnant during the study or within 90 days after the last dose of zanubrutinib or 120 days after the last dose of tislelizumab, whichever is longer, stop using the study drug and contact the study doctor’s office **immediately**. The study doctor will withdraw you from the research project and advise on further medical attention should this be necessary.

Your study doctor will medically follow your pregnancy until its completion to monitor your and your baby’s health status. BeiGene Aus. Pty Ltd will continue to collect information about your pregnancy and the birth of your baby, and the health of your baby for up to 8 weeks after birth, even after study treatment is stopped.

**For male participants**: If your partner becomes pregnant or thinks she may be pregnant during the study 90 days after the last dose of zanubrutinib or 120 days after the last dose of tislelizumab, whichever is longer, contact the study doctor’s office **immediately**.

Your pregnant partner will be asked to sign a separate consent form to allow the follow-up of her pregnancy and the delivery. The follow-up will be no longer than 8 weeks following the delivery date. Any premature termination of the pregnancy will be reported. The study doctor will discuss this with you further.

**For female and male participants**: If you are in an exclusive same-sex relationship and are not trying to become pregnant or father a child, it is not necessary to use birth control. However, if you are a female, you will still have to have pregnancy tests according to the study protocol.

**Unknown or Unexpected Risks and Discomforts**

In addition to the risks listed above, there are risks that are not known or do not happen often when participants take any study drugs, including severe or life-threatening allergic reactions or interactions with another medication. You will be informed in a timely manner, both verbally and in writing of any new information, findings or changes to the way the research will be done that might influence your willingness to continue to take part in this research project.

**10 What will happen to my test samples?**

Tumour, blood and cerebrospinal fluid samples will be collected as part of this study. They will be used to confirm your diagnosis and routine safety testing, for biomarker research testing (special genetic testing) to help better understand patients’ response to the treatment and measuring zanubrutinib drug levels in the cerebrospinal fluid.

Samples taken will be labelled with a unique code by the staff at the clinic. The laboratories will not know your name or personal details. The staff at the clinic will keep a list which details all participants and the code that they are assigned for the study. This list will be kept in a secure facility so that only the study staff will be able to access this information.

If you withdraw your consent to participate in this research project you are entitled to request that all previously retained identifiable biological samples are destroyed, to prevent further analysis according to national provisions, however data already collected from samples provided prior to withdrawal of consent will not be able to be deleted.

Any future unspecified use of your samples collected during your participation in this study will not occur unless reviewed and approved by the Ethics Committee.

**Samples for confirmation of diagnosis and routine safety testing.**

All blood collected from you will be sent to the site’s local laboratory for routine safety testing, which includes blood chemistry, haematology, coagulation, pregnancy testing (if applicable) and serology. These samples will not be stored for any extended period of time, and are not being used for any procedures other than those outlined in this document. They will be destroyed after completion of the analysis as per local laboratory practices.

Any laboratory data will be kept confidential by your study doctor; however, if the tests reveal any unusual findings your study doctor will discuss these with you and your family doctor, if appropriate.

**Biomarker analysis for this research project**

Some of the blood, cerebrospinal fluid and biopsy samples taken from you will be used to perform biomarker research. This will provide information about how your lymphoma responds to the treatment. This is part of the analysis of the study and will help to find out why some patients respond well to the treatment whilst others don’t respond as well. Individual results of these tests will not routinely be distributed to your doctor.

Samples will be stored up to a maximum of two years after the last participant visit in the study. After, that time they will be destroyed in an internationally acceptable method. These tests will be performed for research purposes only. You will not receive the results, nor will they be included in your medical record or used to make decisions about your future treatment.

**Blood and cerebrospinal fluid testing for zanubrutinib levels**

You may be asked to provide a sample of blood and cerebrospinal fluid to test the level of zanubrutinib, one of the drugs used in this study. This would occur at Week 8, where a sample of cerebrospinal fluid and a blood test will be taken 2 hours after zanubrutinib is administered.

Samples of your cerebrospinal fluid and blood will be transferred to WuXi AppTec in Suzhou China for analysis of zanubrutinib levels. This will enable us to understand how effectively zanubrutinib can get into the brain tissue.

**11 What if new information arises during this research project?**

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, they will explain the reasons and arrange for your regular health care to continue.

**12 Can I have other treatments during this research project?**

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your study doctor about this possibility.

**13 What if I withdraw from this research project?**

Your participation in this study is voluntary. You may discontinue study drug at any time, for any reason, and it will not affect your relationship with the treating team.

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the study investigators up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

With your permission, your study doctor will keep in contact with you to find out your progress.

If you do not want them to do this, you must tell them before you join the research project.

If you decide to leave the research project, you are advised to:

* Tell your study doctor
* Return to the study doctor for one more visit
* Return all unused study drug to the study doctor
* You will be asked for permission to be contacted at a later date by your doctor to collect minimum additional data about your condition.

**14 Could this research project be stopped unexpectedly?**

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

* Unacceptable side effects
* The drug/treatment/device being shown not to be effective
* The drug/treatment/device being shown to work and not need further testing
* Decisions by local regulatory/health authorities.

**15 What happens when the research project ends?**

You will continue the treatment until you have completed two years of combined therapy. You may stop treatment earlier if: there is worsening of the disease, intolerable side effects, you decide to withdraw your participation, or your study doctor considers that it is in your best interest to stop taking the study drugs. Supply of the medication in this study will end after two years of combined therapy, however further access to zanubrutinib beyond two years may be possible through other channels if you are still deriving benefit.

You will still participate in the study after you stop taking study treatment, but study visits will be reduced or eliminated depending on your situation.

This study will continue until all participants stop taking part in the study due to the above reasons.

When the clinical study report is completed, the major findings of the research project will be available to you from your study doctor.

**Part 2 How is the research project being conducted?**

**16 What will happen to information about me?**

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal health information (PHI) about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your PHI includes items such as your name, address, and medical records. Your PHI will be kept confidential as much as possible as required by law. People involved with the study, including doctors, nurses, and researchers, will see your medical records so that they can follow the progress of the study. Information in these records will be shared with people involved with the study in the form of a unique code, but personal identifiers such as your name, address, or date of birth will not be provided for use.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Site Name , or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored for 15 years following completion of the study. It will be disclosed only with your permission, or as required by law.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

**17 Complaints and compensation**

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

**18 Who is organising and funding the research?**

This research project is being conducted by Professor Stephen Opat and is sponsored by Monash Health. Funding is being provided by BeiGene Aus Pty Ltd. BeiGene Aus Pty Ltd. is supplying the zanubrutinib (BGB-3111) and tislelizumab (BGB-A317).

BeiGene Aus. Pty Ltd may benefit financially from this research project if, for example, the project assists BeiGene Aus. Pty Ltd to obtain approval for a new drug.

By taking part in this research project you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Site Name.

Site Name may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to Site Name.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Monash Health, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

**19 Who has reviewed the research project?**

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Monash Health HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

**20 Further information and who to contact**

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects) you can contact the principal study doctor on (03) 9594 4044 or any of the following people:

 **Clinical contact person**

|  |  |
| --- | --- |
| Name |  |
| Position |  |
| Telephone |  |
| Email |  |

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

**Complaints contact person**

|  |  |
| --- | --- |
| Name |  |
| Position |  |
| Telephone |  |
| Email |  |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

|  |  |
| --- | --- |
| Reviewing HREC name | Deborah Dell |
| HREC Executive Officer | Manager, Human Research Ethics Committee |
| Telephone | (03) 9594 4611 |
| Email | Deborah.Dell@monashhealth.org |

**Reviewing HREC approving this research and HREC Executive Officer details:**

**Local HREC Office contact (Single Site-Research Governance Officer)**

|  |  |
| --- | --- |
| Name |  |
| Position |  |
| Telephone |  |
| Email |  |

 *Insert Header with institution’s name or institution’s letterhead*

**Consent Form -** *Adult providing own consent*

|  |  |
| --- | --- |
| **Title** | Phase IB/II study of Zanubrutinib and Tislelizumab in CNS lymphoma  |
| **Short Title** | BTK and Immune Checkpoint Inhibitor in CNS Lymphoma (BICICL) |
| **Protocol Number** | To insert here |
| **Project Sponsor** | Monash Health |
| **Principal Investigator** | PI name |
| **Associate Investigator(s)**( if required) |  |
| **Location** | Site name and address |

**Declaration by Participant**

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Monash Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

• This specific research project

• Other research that is closely related to this research project

• Any future research.

• Genetic testing, as outlined in the relevant Section of the Participant Information Sheet

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

|  |
| --- |
|  |
|  | Name of Participant (please print) |  |  |  |  |
|  |
|  | Signature |  | Date |  |  |
|  |

|  |
| --- |
|  |
|  | Name of Witness\* to Participant’s Signature (please print) |  |  |
|  |
|  | Signature |  | Date |  |  |
|  |

\* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

|  |
| --- |
|  |
|  | Name of Study Doctor/Senior Researcher†(please print) |  |  |
|  |  |
|  | Signature |  | Date |  |  |
|  |

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

 *Insert Header with institution’s name or institution’s letterhead*

**Form for Withdrawal of Participation -** *Adult providing own consent*

|  |  |
| --- | --- |
| **Title** | Phase IB/II study of Zanubrutinib and Tislelizumab in CNS lymphoma  |
| **Short Title** | BTK and Immune Checkpoint Inhibitor in CNS Lymphoma (BICICL) |
| **Protocol Number** |  |
| **Project Sponsor** | Monash Health |
| **Principal Investigator** | PI name |
| **Associate Investigator(s)**(if required) |  |
| **Location** | Site name and address |

**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Monash Health.

|  |
| --- |
|  |
|  | Name of Participant (please print) |  |  |  |  |
|  |
|  | Signature |  | Date |  |  |
|  |

*In the event that the participant’s decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.*

|  |
| --- |
|  |

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

|  |
| --- |
|  |
|  | Name of Study Doctor/Senior Researcher†(please print) |  |  |
|  |  |
|  | Signature |  | Date |  |  |
|  |

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.