PARTICIPANT INFORMATION SHEET AND CONSENT FORM

AN ASSESSOR-BLIND, RANDOMIZED, PARALLEL NON-INFERIORITY TRIAL TO COMPARE MULTIPLE SWITCHING OF BRENZYS (ETANERCEPT BIOSIMILAR) AND ENBREL (ETANERCEPT-REFERENCE PRODUCT) VERSUS NON-SWITCHING ENBREL (ETANERCEPT-REFERENCE PRODUCT) IN MAINTAINING EFFICACY IN PARTICIPANTS WITH RHEUMATOID ARTHRITIS ON ENBREL (ETANERCEPT REFERENCE PRODUCT) – ER2017-00 IIS

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INTRODUCTION

You are being invited to take part in a clinical research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what you will need to do. Take time to read the following information carefully. The purpose of this informed consent document is to tell you about the study so that you can decide whether or not you want to be part of the study.

Tell your study doctor or someone from the study staff if there is anything in this information sheet that is not clear, or if you would like more information. Make sure you have all your questions answered, so you understand what the study is about. We encourage you to discuss study participation with your family, friends and medical advisers.

WHAT IS THIS STUDY ABOUT AND WHY IS IT BEING DONE?

You are being asked to take part in this research study because you have been diagnosed with Rheumatoid Arthritis (RA) and you are currently being successfully treated with Enbrel.

This study will look at whether Enbrel and its biosimilar Brenzys are interchangeable in the treatment of rheumatoid arthritis. In other words, multiple switching of treatment between Enbrel and Brenzys is not expected have any impact on your RA in terms of effectiveness nor is it expected have any impact on expected side effects.

A **biosimilar** is a biologic medical product which is almost an identical copy of an original product that is manufactured by a different company.

The specific aim of the study is to test whether multiple switching between Brenzys and Enbrel is equal with regard to disease control and clinical immune response, compared to no switching, that is, continuing on Enbrel.

Both Enbrel and Brenzys have been approved by the Australian Therapeutic Goods Administration, (TGA) for treatment of RA.

There are two treatment arms in the study. You will be randomised (like flipping a coin) to one of the two treatments arms. There will be equal numbers (44) in each treatment arm. One treatment arm will receive Enbrel for the entire 12-months of the study. The second

treatment arm will commence on Brenzys (two months) and then swap between Enbrel and Brenzys each two months for the 12-months of the study.

HOW MANY PEOPLE WILL BE IN THE STUDY AND HOW LONG WILL IT TAKE?

Approximately 88 participants will take part in this research study. The total time you will be in the study is 12 months. There will be 7 study visits and each clinic visit for the purpose of the study will last approximately 1 hour.

WHAT IS THE STUDY DRUG/THERAPY?

Australia's Pharmaceutical Benefit Advisory Committee (PBAC) allows doctors and pharmacists to give patients the option of substituting biologic medicines at the chemist if there is a less expensive replacement available.

Enbrel is a biologic medicine approved in 1998 for the treatment of RA. Brenzys is a biosimilar of Enbrel approved for the treatment of RA in Australia in July 2016.

Consumer Product Information is available for both Enbrel and Brenzys as both are registered for the treatment of RA and commercially available in Australia.

WHAT HAPPENS TO ME IF I AGREE TO BE IN THIS STUDY?

If you decide to take part, you will be asked to sign this informed consent document. You will then be given a copy of the signed document.

Tests, examinations, and procedures that will be done during the study are listed below:

- During your first study visit (the Screening visit), the study staff will ask you questions about past and present medical conditions, diseases, surgeries, allergies and all medicines that you are now taking. You must tell the study staff about all of the medicines you are taking, including those prescribed by a doctor and those that you can buy without a prescription.
- Weight, Height and Vital signs – your weight will be recorded and your height will be measured. Vital signs will include your temperature, respirations, pulse, and blood pressure.
- Complete Physical Examination – A complete physical examination will include examinations of your skin, respiratory (your lungs), cardiovascular (your heart), gastrointestinal (your digestive system) and musculoskeletal systems (your muscles and bones). You will only be required to remove the outer layer of clothing for this examination.
- Limited Physical Examination – A limited physical examination will be undertaken according to the symptoms you report at other study visits.
- Pregnancy Test – if you are a female who engages in activity that would allow you to become pregnant, you will be required to have a pregnancy test during the first study visit. If the pregnancy test is positive you will not be able to participate in the study.
- An assessment of your joints will be performed.

Study Questionnaires will be completed – Health Assessment Questionnaire (HAQ) Quality of Life Questionnaire –SF-36. You will also be asked about your pain and your general health.

In addition, you will complete a Pen Preference Questionnaire as the device used to inject Enbrel is different to the device used to inject Brenzys. You will receive training on how to use the Brenzys injecting device.Blood will be collected for routine testing – full blood examination (FBE), liver function tests (LFT), urea and electrolytes (U & E), erythrocyte sedimentation rate (ESR), study drug levels and anti-drug antibodies at selected study visits.

- At this visit you will be randomized to one of the two arms of the study. You will either remain on Enbrel or be part of the multiple switching arm, where you will switch each two months between Brenzys and Enbrel for the 12-months of the study.
- All study assessments and the schedule of the study visits are outlined in Figure 1 below.

Visit Schedule

Visit	**1**	**2**		**3**		**4**		**5**		**6**		**7**
Months	1	2	3	4	5	6	7	8	9	10	11	12
Screening	S											
Control n=44	E	E	E	E	E	E	E	E	E	E	E	E
Intervention n=44	B	**B**	E	E	**B**	**B**	E	E	**B**	**B**	E	E
Consent, eligibility criteria, medical history, smoking history, demographics, concomitant medications, physical examination, height & weight.	✓											
Measures												
Vital signs	✓	✓		✓		✓		✓		✓		✓
28 Joint count: 28 swollen 28tender	✓	✓		✓		✓		✓		✓		✓
Questionnaires: VAS Pain, *VAS general health (Participant Global Assessment - PGA), HAQ, Physician Global Assessment of disease activity (PGA)*	✓	✓		✓		✓		✓		✓		✓
SF-36	✓									✓		✓

Safety /Adverse Events		✓		✓		✓		✓		✓		✓
Labs: FBE, ESR U&E, LFT	✓	✓				✓						✓
Blood stored: anti-drug antibodies, drug levels	✓	✓		✓		✓		✓		✓		✓
Pen preference questionnaire		✓										✓

Figure 1. Randomization schedule/ switching sequences and visit schedule

WHAT ARE THE POSSIBLE RISKS, DISCOMFORTS AND SIDE EFFECTS?

Blood Sample Collection Risks

You may have discomfort or pain when your blood is collected. You may feel faint or pass out. There is a risk of infection, bleeding, or bruising at the puncture site. You may develop a small scar at the puncture site where several blood samples are taken.

Enbrel and Brenzys

Switching from Enbrel to Brenzys has been studied previously. No problems were found either in the control of arthritis or side-effects, but there has been no research looking at the effect of switching repeatedly. The studies done up to now have also not found an increase in risk of developing anti-drug antibodies as a result of the switching between Enbrel and Brenzys.

Pregnancy

The effect of Enbrel or Brenzys on your fertility, including future fertility, may not be known. The effects of Enbrel or Brenzys on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project.

You must not participate in the research if you are pregnant or trying to become pregnant, or breastfeeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least [number] months after the last dose of study drug. Both male and female participants must avoid pregnancy during the course of the research and for a period of 3 months after completion of the research project, as there is potential risk for an abnormal child being born. The study doctor must discuss effective methods of avoiding pregnancy with you.

Female participants. If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

Male participants. It is highly recommended that you inform your partner of your participation in the study and the need to avoid pregnancy. You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

Possible Benefits

You may or may not receive any direct medical benefit from being in this study. Your condition may get better, it may get worse, or it may stay the same. The information that is obtained during this study may be useful scientifically and thus be helpful to others with rheumatoid arthritis in the future.

Alternatives to Participation

You do not have to take part in this study to be treated for your RA.

Voluntary participation/withdrawal

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop taking part in the study at any time without giving reasons, and without a penalty or loss of benefits to which you are otherwise entitled

Other relevant information about the research project

A description of this clinical study will be available on http://www.ClinicalTrials.gov

Confidentiality

If you agree to become part of this study, your name will be held in confidence. You will be allocated a unique study code to protect your privacy. Unless required by law, only the study doctor and staff involved in this study, the Bellberry Human Research Ethics Committee and personnel from government regulatory agencies may have direct access to your medical records to check the study information. By signing this consent form, you are granting permission for the study staff to have access to your medical records.
All study information will be archived as paper in Australia for 15 years as required by the regulatory guidelines.

You may withdraw from the study at any time for any reason. You may also take away your permission for use of your health information at any time. To take away your permission for use of your health information you would need to write to the study doctor. If you withdraw your permission, you will not be able to continue being in this study. When you withdraw your permission and you have had your final study visit, no new health information that might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Payment/costs

Emeritus Research will receive funding from Merck Sharp and Dohme (MSD) to cover the cost of undertaking the study. MSD markets Brenzys in Australia.

Participant Reimbursement of Travel Expenses

You will not be paid for your participation in this study. You will be reimbursed for reasonable travel expenses for study required visits. Reimbursement will be paid periodically.

Compensation for Injury

In the event that you suffer any injury attributable to the procedures required under the study that would not have occurred but for your inclusion in the study, you will be compensated in accordance with the Medicines Australia Guidelines for compensation for injury resulting from participating in a company-sponsored research project. A copy of the Medicines Australia Guidelines is available to you from the research staff on request.

If you think that personal injury has occurred as a result of your involvement in this study, you must contact your study doctor immediately.

It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards compensation for injury.

New information arising during the 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, he/ she will explain the reasons and arrange for your regular health care to continue.

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 Bellberry 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

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 any of the following people:

Clinical contact person

Name	A/Professor Stephen Hall
Position	Principal Investigator/ Director
Telephone	03 9509 6166
Email	stephenhall@emeritusresearch.com

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	Michelle Nash
Position	Clinical Research Manager
Telephone	03 9509 6166
Email	michellenash@emeritusresearch.com

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 approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Human Research Ethics Committee
HREC Executive Officer	Committee Chair, Bellberry HREC
Telephone	08 8361 3222
Email	bellberry@bellberry.com.au

CONSENT FORM

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Principal Investigator (Study Doctor): **A/Professor Stephen Hall**

Address of Research Site: **1180 Toorak Road, Camberwell VIC 3124**

- I have read and understand this consent form and its contents were explained. My questions have been answered to my satisfaction.
- I consent voluntarily to participate in this research study and I will receive a signed and dated copy of this consent form for my records.
- By signing this consent form, I am not giving up any of my legal rights.
- I am at least 18 years of age.
- By signing this informed consent form, I am authorizing access, use and transfer of my personal data as described in this informed consent.
- I consent to my GP and/or specialist being notified of my participation in this study and of any clinically relevant information.
- I give permission for my doctors, other health professionals, hospitals or laboratories outside Emeritus Research, to release information to the staff of Emeritus Research concerning my medical condition/disease and treatment that is needed for this study. I understand that such information will remain confidential.

_____

Name of Participant (Printed)

_____ _____

Signature of Participant **Date**

I attest that the participant named above had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be in this study.

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Name of Investigator (Printed)

_____ _____

Signature of Investigator **Date**