IXEHEAL: IXEKIZUMAB FOR CHRONIC VENOUS ULCERS

Protocol: Version 1

Protocol number:

13st November 2019

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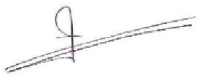
Protocol Authorisation:



sign | 13/11/2019 *date*

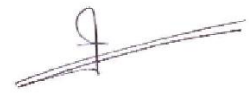
Investigator Statement of Compliance

This protocol was designed and will be conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines, as well as in accordance with all national, state, and local laws of the appropriate regulatory authorities and the Declaration of Helsinki (October 1996).

I agree to conduct the study in accordance with the most current Human Research Ethics Committee (HREC) approved version of the protocol and informed consent, Good Clinical Practice (GCP) and ICH Guidelines, and applicable local, state, and federal laws and regulations. I further agree to maintain direct supervision of this study and to ensure that all sub-investigators, associates, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

All individuals responsible for the design and conduct of this study are deemed appropriately qualified to be conducting this research prior to the enrolment of any patients.

Investigator Name (Printed): Kiarash Khosroteharani

Investigator Signature: 

Date: 13/11/2019

Trial management Committee

Role /Affiliation	Name
Trial Chairperson	Professor Kiarash Khosrotehrani
Principal Investigator	Professor Kiarash Khosrotehrani
Translational Researcher	Professor Kiarash Khosrotehrani
Research Assistant	Charlotte Cox
Research Nurse	Kirsty Fry
QiDerm Manager and Administrative Services	Jane Parbery
Research Nurse	Stephanie Armstrong

Foreword

This document is intended to describe a University of Queensland (UQ) trial and to provide information about procedures for screening, enrolling and treating trial participants. It is not intended that the protocol be used as a guide for the treatment of patients who are not enrolled on this trial.

UQ will not accept any data for analysis unless each Trial Site has HREC approval for patient enrolment and participation in this trial.

Abbreviations

AE	Adverse Event
CRF	Case Report Forms
QOL	Quality of Life
DLQI	Dermatology Quality of Life Index
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
PI	Principal Investigator
PICF	Participant Information Sheet and Consent Form
PRO	Patient Reported Outcome
QA	Quality Assurance
QiDerm	Queensland Institute of Dermatology
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
TGA	Therapeutic Goods Administration
TMC	Trial Management Committee
UAE	Unexpected Adverse Events
UQ	University of Queensland

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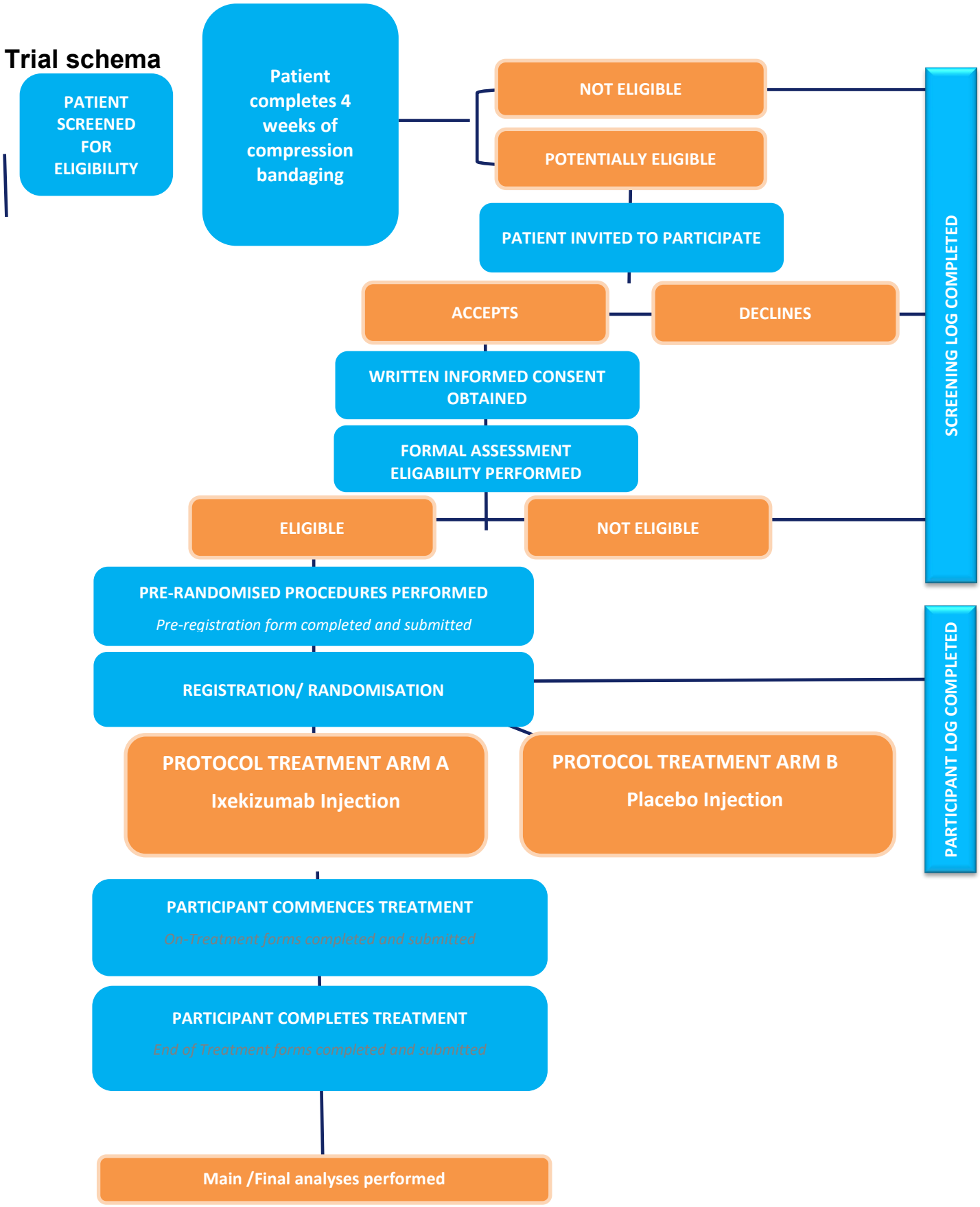
Trial Summary

Data category	Information	
Trial Registry	Registry Name	Australian New Zealand Clinical Trials Registry (ANZCTR)
	Trial Identifying No	TBC
	Date of registration	TBC
	Registry Name	ClinicalTrials.gov
	Trial Identifying No	TBC
	Date of registration	TBC
Secondary identifying numbers		
Source(s) of monetary or material support	The University of Queensland	
Primary sponsor contact details		
Contact for public queries	Prof Kiarash Khosrotehrani k.khosrotehrani@uq.edu.au	
Contact for scientific queries	Prof Kiarash Khosrotehrani k.khosrotehrani@uq.edu.au	
Public title	IxeHeal	
Scientific title	Phase II Study of Ixekizumab for Chronic Venous Ulcers	
Countries of recruitment	Australia	
Health condition(s) or problem(s) studied	Treatment of Chronic Venous Ulcers	
Intervention(s)	To perform a Phase II randomized double blind placebo controlled trial, using Ixekizumab, in patients with treatment-resistant chronic venous ulcers	

Key Eligibility criteria	**Inclusion** 1. Aged 18 years or older. 2. Patients who are willing to read or comprehend and sign a voluntary consent for research 3. Patients with Chronic Venous Ulcers that have failed to respond to Standard Therapy including Compression for 4 weeks **Exclusion** 1. Arterial insufficiency: Ankle-Brachial pressure index <0.7 2. Diabetes 3. Pregnancy 4. Crohn's Disease 5. Ulcerative Colitis 6. Infection or excessive colonization of ulcer in past 2 months 7. Patients whose neutrophil count is not WNL 8. Patients who have active Tuberculosis (positive QFT-G) 9. Patients currently being treated for malignancy 10. Patients with chronic or recurrent candidiasis infection 11. Patients who have inflammatory bowel disease (IBD) 12. Women of childbearing age 13. Any contraindication to therapy 14. Life expectancy of less than 6 months due to chronic illness Any other condition as defined by the investigator which significantly impact the patient's suitability in this study such as the use of cytotoxic medication, inability to present to study visits due to distance.

Study type	Phase II randomized double blind placebo controlled trial
Target sample size	28 patients
Primary outcome(s)	A 40% reduction in ulcer size after 12 weeks compared to the initial wound size.
Key secondary outcomes	Drug related adverse events and serious adverse events at 12 weeks. Percentage reduction in ulcer size at 12 weeks compared to the initial wound size. Percentage patients with healed ulcers Time to ulcer healing Percentage and absolute reduction in Pain score (0-10) Dermatology life Quality Index DLQI Compliance with compression Treatment-related reduction of IL17 levels in wound fluid and biopsies* Wound-infiltrating macrophage phenotype change from M1 to M2* Alterations in wound microbiome
Trial analyses timelines	**Interim Analysis:** After the first 14 patients have completed the 12 weeks of Intervention **Final Analysis:** After the full 28 patients have completed the 12 weeks of Intervention

Trial schema



1 INTRODUCTION AND BACKGROUND

Inflammation is one of the early phases of wound healing and is an evolutionarily conserved process. It is mainly driven by macrophages and neutrophils, as well as a small sub-population of T cells. Many studies have demonstrated that inflammation is an essential phase of the healing process and depletion of macrophages classically results in delayed healing. At the same time, however, many chronic wounds display excessive inflammation which has been shown to impede healing. Excessive inflammation is established as an etiologic factor in venous leg ulcers as a result of iron oxide deposition in the dermis due to venous hyper pressure and red blood cell extravasation. This excessive inflammation results in matrix and growth factor degradation through the action of proteases and reactive oxygen species. Additionally, in diabetic wounds, excessive inflammation down modulates insulin/IGF1 signalling, preventing the proper response of epidermal cells to growth factors.

Wound closure requires the transition of macrophages from an inflammatory state (M1) to a pro-healing state (M2) during the course of healing. Using gene expression array studies on sorted M1 and M2 macrophage populations from skin wounds we have demonstrated that IL17-IL23p19 signalling maintains wound macrophages in an inflammatory stage and promotes excessive recruitment of neutrophils.

1.1 Previous Studies

Our preclinical experiments have demonstrated the following points of validation:

1. IL17-/- mice heal faster than wild-type (Rodero et al. 2013).

2. IL17-/- mice on an obese diabetic background heal faster than wild-type (Lee et al. 2017)

3. Diabetic mice treated with anti-IL17 blocking antibodies heal faster than wild-type (Rodero et al. 2013).

4. p19-/- mice do not display any IL17 in their wounds (Lee et al. 2017)

5. Diabetic mice treated with anti-p19 antibodies have reduced IL17 in their wounds and heal faster than wild-type (Lee et al. 2017).

6. IL12 (p35) and IL12/23(p40) deficient mice have delayed healing (unpublished).

Results of a recent, small clinical pilot study by others showed that TNF blocking antibodies promoted closure of chronic wounds (Fox et al., 2016), providing preliminary support for the hypothesis that excessive inflammation prevents chronic wound healing.

Taken together, these preclinical data and preliminary clinical findings provide strong support for our idea of using p19 or IL17 blocking antibodies to promote chronic wound healing.

2 TRIAL OBJECTIVES

2.1 Research Hypothesis

HYPOTHESIS: The IL23(p19)-IL17 axis is strongly involved in the maintenance of macrophages in an inflammatory state (M1) in chronic wounds, preventing wound progression to a repair stage. By stimulating the transition of macrophages from the pro-inflammatory (M1) to pro-healing (M2) phenotype, blockade of IL17 or IL23 (p19) will, therefore, accelerate closure of treatment-resistant chronic wounds.

2.2 Objectives

To evaluate the safety and efficacy of Ixekizumab over placebo at 12 weeks in a randomized double blind trial on patients with chronic venous ulcers failing well conducted standard of care therapy.

The evaluation encompasses wound size reduction, pain reduction, quality of life improvement as well as biological measures of inflammation reduction.

Regarding safety, specific emphasis will be on infections and changes in microbiome.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary endpoints are

- A 40% reduction in ulcer size at 12 weeks as compared to initial size. Size changes are measured using digital 3D photography and wound size evaluation device.
  It is expected that significantly more patients will achieve the primary end-point at 12 weeks in the Ixekizumab group compared to the placebo group.

2.3.2 Secondary Endpoints

- Drug related adverse events and serious adverse events at 12 weeks.
- Percentage reduction in ulcer size at 12 weeks compared to the initial wound size.
- Percentage patients with healed ulcers
- Time to ulcer healing
- Percentage and absolute reduction in Pain score (0-10)
- Changes in Quality of life DLQI score
- Compliance with compression
- Treatment-related reduction of IL17 levels in wound fluid and biopsies*
- Wound-infiltrating macrophage phenotype change from M1 to M2*
- Alterations in wound microbiome

3 TRIAL DESIGN

Patients with a diagnosis of venous ulcer at the participating wound clinics will be considered and treated with standard compression therapy and dressing for 4 weeks. Those not responding to treatment with wound surface reduction <20% will be included and randomly assigned, using double blind technique, to treatment and placebo groups. All participants will receive standard of care treatment for chronic, non-healing wounds, comprising compression dressings changed as required. In addition to standard of care treatment, participants will receive either Ixekizumab or placebo via subcutaneous injection.

3.1 Dosing Regimen

Cohorts of patients with chronic venous ulcers (n = 28) will be randomly assigned to treatment and placebo groups, both receiving compression treatment and standard dressing and therapy of wounds.

Ixekizumab or placebo will be injected subcutaneously (prefilled syringe format) in two 80 mg injection at week 0, followed by single 80mg injections at weeks 2, 4, 6, 8, 10 and 12. This corresponds to standard dosing regimen performed in psoriasis.

3.2 Choice of Comparator

Patients receiving placebo will be the comparators in this study.

4 PARTICIPANT SELECTION AND ELIGIBILITY

4.1 Source of participants

Participants will be recruited for the study the Queensland Institute of Dermatology Brisbane and other reliable Wound Care Clinics in Brisbane.

4.2 Accrual Numbers and Timelines

It is anticipated it will take 9 months to complete target accrual of 28 participants. Duration for individual patients on study will be approximately 16 weeks this includes the cinclusion criteria of 4 weeks of unsuccessful compression bandaging.

4.3 Eligibility Criteria

Patients (or a representative) must provide written, informed consent before any screening or study procedures occur.

Patients will be eligible if they meet all of the inclusion criteria and none of the exclusion criteria. Inclusion and exclusion criteria will be checked at prior to and at randomisation, and only those patients that still meet the criteria will be included. No exceptions, waivers or exemptions will be granted.

4.3.1 Inclusion Criteria

1. Aged 18 years or older.
2. Patients who are willing to read or comprehend and signed a voluntary consent for research.
3. Patients with at least one venous leg ulcer defined as any break in the skin that had either been present for longer than 6 weeks or occurred in a person with a history of venous leg ulceration. Ulcers are judged purely venous if no other cause is suspected. The ulcer is required to be venous in appearance (moist, shallow, and of an irregular shape) and to lie wholly or partly within the gaiter region of the leg where varicosities or purpuric and pigmented skin can be identified.
4. Patients with Chronic Venous Ulcers that have failed to respond (<20% closure) to Standard Therapy including Compression 4 weeks

4.3.2 Exclusion Criteria

1. Arterial insufficiency: Ankle-Brachial pressure index <0.7
2. Diabetes
3. Pregnancy
4. Crohn's Disease
5. Ulcerative Colitis
6. Infection or excessive colonization of ulcer in past 2 months
7. Patients whose neutrophil count is not within normal limits
8. Patients who have active Tuberculosis (positive QFT-G)
9. Patients currently being treated for malignancy
10. Patients with chronic or recurrent candidiasis infection
11. Patients who have inflammatory bowel disease (IBD)
12. Women of childbearing age
13. Any contraindication to therapy
14. Life expectancy of less than 6 months due to chronic illness

Any other condition as defined by the investigator which significantly impact the patient's suitability in this study such as the use of cytotoxic medication, inability to present to study visits due to distance.

5 SCREENING

5.1 Screening Log

Appropriately, qualified personnel at the trial site will screen patient health records for potentially suitable patients according to the eligibility criteria in the protocol. The trial site will then record de-identified information relating to each patient screened on the screening log (including ineligible patients) screening will continue until the target population is achieved. The screening log will be requested by the Sponsor on a regular basis for the purpose of monitoring accrual.

5.2 Informed Consent

Written Informed consent from each patient must be obtained prior to initiating any study procedures in accordance with the ICH GCP. All potential study participants will be given a copy of the HREC approved Participant Information Sheet and Consent Form to read and discuss with family, general practitioners, specialists etc. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study prior to signing consent. If the patient decides to participate in the study, they will be asked to sign the Informed Consent documents. One photocopy of each of the Participant Information Sheets and signed Informed Consents must be given to the patient to keep, the originals must be retained in the Investigator Site File. The completed and signed Informed Consent documents for all patients at the site must be available in the case of data audits. Patients who choose not to participate or who withdraw from the study will be offered appropriate treatment options reflecting the current standard of care without prejudice.

5.3 Participation in Other Research

Participation in other research will be considered on a case by case basis by the Trial Management Committee.

6 ENROLMENT AND RANDOMISATION

Every patient will undergo a period of 4 weeks of standard of care treatment and the ulcer will be measured at the start and end of this period.

Only patients who do not respond to standard of care therapy with less than 20% wound size reduction will be enrolled.

Following written informed consent, cohort of patients with chronic venous ulcers (n = 28) will be randomly assigned to treatment and placebo groups, both receiving concomitant compression treatment and standard dressing and therapy of wounds.

Patients will be stratified according to wound duration more or less than 6 months.

Randomisation will be done with a prevalidated computer program and participants will be stratified by ulcer duration (≤6 months or >6 months) with permuted blocks (block sizes 4), because this criteria is a known predictor of ulcer healing.

Ixekizumab or placebo will be injected subcutaneously (prefilled syringe format) in two 80 mg injection at week 0, followed by single 80mg injections at weeks 2, 4, 6, 8, 10 and 12.

This corresponds to standard dosing regimen performed in psoriasis.

7 TRIAL PARTICIPANT ASSESSMENTS

7.1 Trial Participant Assessment Table

Assessment	Compression Bandage Treatment				Pre Screening	Drug Loading dose	Ixekizumab + CBT / Pacebo + CBT Study					
	Week 1	Week 2	Week 3	Week 4		Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Patient has completed 4 weeks of Unsuccessful Compression Therapy	✓	✓	✓	✓	✓							
Informed Consent					✓							
Medical Hx inc smoking Hx					✓							
Bloods (screening for TB,Hep B & C, HIV)					✓							
Concomitant Medications					✓							
Observations (Weight, BP, Temp)					✓							
Perinuclear Cellulitis (possible exclusion from trial if confirmed)					✓							
Ulcer Assessment + Bx + Swab					✓							
Photos both limbs					✓							
DLQI					✓							
Eligible for the Study												
Ulcer Assessment						✓	✓	✓	✓	✓	✓	✓
Smell / Exudate / Colour							✓	✓	✓	✓	✓	✓
Perinuclear Cellulitis (possible exclusion from study if confirmed)						✓	✓	✓	✓	✓	✓	✓
Photos both limbs						✓	✓	✓	✓	✓	✓	✓
Blood Sample												✓
Skin Bx (All Participants)												✓
Swabs									✓			✓
Collection of Exudate where applicable												
Compression Therapy						✓	✓	✓	✓	✓	✓	✓
Ixekizumab or Placebo S/C Injection						160mg	80mg	80mg	80mg	80mg	80mg	80mg
DLQI												✓
Adverse Events						✓	✓	✓	✓	✓	✓	✓

7.2 Participant Assessments Pre- Registration

- **Assessment of eligibility** – Full skin assessment and has to undergo 4 weeks of compression bandaging for venous ulcer
- Complete medical history including Smoking History
- **Assessment of concomitant medications** will be performed at baseline, during treatment and at all follow-up points throughout the study.
- **Blood Sample** will be taken to screen for (TB, HEP B, C and HIV).
- **Physical examination (weight, temperature, blood pressure)** will be assessed at baseline and at all follow-up points throughout the study
- **Photograph of the Ulcer** will be measured using standard medical photography and will be measured at baseline and follow-up points throughout the study. The size of the ulcer will be monitored from these images.
- **Skin biopsy (all patients)** will be performed on all patients at Baseline and at 12 weeks. Skin Biopsy will not be performed on a participant that has achieved full wound healing.
- **Swab** a swab will be taken of the ulcer at baseline, 6 weeks and at week 12 of the study.
- **Saliva sample (all patients)** will be taken for all patients at Baseline and 12 weeks.
- **Leg circulation** will be assessed by looking for signs of pitting oedema, leg ulcer or intermittent claudication, lower limb pulse palpation. Leg circulation will be assessed by the clinician at baseline and at all follow-up points throughout the study.
- **DLQI** assessment will be completed by patients at baseline and at 12 weeks.

8 DISCONTINUATION / WITHDRAWAL / TRANSFER

A Trial Participant may discontinue trial treatment for any of the following reasons:

- Intercurrent illness which prevents further treatment
- Withdrawal of consent for treatment by participant
- Any alterations in the participant's condition which justifies the discontinuation of treatment in the investigator's opinion
- Non-compliance with the compression bandaging
- Not attending the scheduled follow-up appointments

Discontinuation of treatment does not necessarily indicate withdrawal from the trial. The distinction between discontinuation of treatment and withdrawal from the trial is shown by the definitions in the following subsections.

8.1 Protocol Treatment Discontinuation

A participant would be considered to have discontinued treatment where trial related treatment is ceased according to the reason(s) outlined above. The participant may however still agree to further follow-up assessments as scheduled in Section 7.1.

The participants' discontinuation of treatment must be documented in the medical records and transcribed onto the relevant Case Report Form (CRF).

8.2 Withdrawal from Trial

Trial Participants have the option to completely withdraw from the trial at any time without giving a reason. Total withdrawal would occur in the circumstance that the participant decides to completely withdraw from all treatment aspects of the trial and does not agree to any further scheduled follow up assessments. The participants' total withdrawal must be documented in the medical records and transcribed onto the relevant CRF. No further information will be collected from this participant for the purpose of this trial.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

Treatment effect on wound size will be tested between treatment and placebo groups and across wound types by ANOVA.

Estimated number of 28 patients in 2 equal groups gives an 85% power at a significance level of 0.05 to detect an improvement of 40% in wound healing rates at 12 weeks (20% standard deviation). Based on preclinical studies, a 50% improvement is expected.

9.2 Analysis of the Objective

Primary objective

- To compare the proportion of patients achieving a 40% reduction in wound size at week 12 between Ixekizumab and placebo groups.

Secondary Objective

- To compare the average wound size reduction in treated versus placebo group.
- To compare the number and proportion of patients achieving wound closure.
- To compare in an actuarial survival analysis the time to closure between placebo and treatment group.
- To compare average pain score and reduction in pain score at 12 weeks (Pain score 0-10) between placebo and treatment group.
- To compare average Quality of life (QOL) (measured by DLQI) and improvement in QOL at 12 weeks between placebo and treatment group.
- Compliance with compression will be compared as a patient reported outcome.

*these biological endpoints will depend on availability of funding

9.3 Analysis of Exploratory Endpoints

Comparisons between wound healing in the treatment ulcers vs participants receiving placebo. Differences in the ulcer size will be compared by ANOVA

- We will compare IL17 levels in wound fluid and biopsies between placebo and treatment group.
- We will compare Neutrophil infiltrating and wound macrophage phenotype change from M1 to M2 on immunostaining.

10 PATIENT REPORTED OUTCOMES AND HEALTH ECONOMICS

10.1 Patient Reported Outcome Questionnaires

The following Patient Reported Outcome (PRO) questionnaires will be used in this trial to assess Quality of Life (DLQI) outcomes in accordance with the time points as specified in Section 0:

10.1.1 DLQI questionnaire

The DLQI (see appendix Section 18.4) is a validated, copyrighted QOL assessment tool that is designed for use in adults and focuses on physical limitations rather than the psychological impact of the skin disease. It is self-explanatory and can be handed to the patient who is asked to fill it in without the need for detailed explanation. It may be used without seeking permission by clinicians for routine clinical purposes. The aim of the questionnaire is to measure how much the patients skin problem has affected their life over the last week. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of zero. The higher the score the more quality of life is impaired.

10.1.2 Pain Score questionnaire

Pain score tool 1-10 will be used access participants level of pain during the trial.

11 TRIAL ADMINISTRATION AND QUALITY ASSURANCE

11.1 Participating Centres

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place, and a site initiation has taken place.

11.2 Data Acquisition

Case Report Forms (CRF) will be used for the collection of trial data. The Trial Management Committee reserves the right to amend or add to the CRF template suite as appropriate. Such changes do not constitute a protocol amendment.

11.3 Data Management Plan

A Data Management Plan (DMP) will be established in this study to outline the collection, use and plan for persevering and sharing data collected during this study. It will be recorded in the TMF.

11.4 Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

11.5 Archiving

Essential trial documents and source documentation (including medical histories, laboratory tests, treatment records and photographs) must be retained for 15 years after completion of the trial in accordance with ICH GCP Guidelines. Documents should be securely stored and access restricted to authorised personnel.

11.6 Study Monitoring

The sponsor will be responsible for monitoring this study in accordance with ICH GCP guidelines and other appropriate regulatory guidelines. By signing this protocol, the investigator grants permission to the sponsor and appropriate regulatory authorities to conduct onsite and remote monitoring of all relevant study documentation essential documents and source data. To ensure accuracy of data captured on the case report forms, it is mandatory that the monitor have access to original source documents used in the completion of case report forms. During the review of these source documents, patient anonymity will be maintained with strict adherence to professional standards of confidentiality.

The sponsor will be responsible for monitoring relevant study documentation at regular intervals throughout the study, as defined by the pre-study risk-assessment and monitoring plan. The purpose of monitoring the study will be to verify adherence to the protocol, GCP and completeness and correctness of all case report form entries. The investigator agrees to cooperate with the sponsor to ensure that any items arising in the course of these monitoring visits are resolved.

11.7 Study Audits

The sponsor or an external party may undertake a routine audit of the study site dependent on risk assessment pre-study and/or ongoing study conduct. During the course of the study and after its completion, it is likely that one or more quality assurance audits will be undertaken by authorised sponsor representatives or external parties. The purpose of the audit, which is independent of and separate from routine monitoring, will be to evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements.

11.8 Quality Assurance Reviews

11.8.1 Eligibility Reviews

11.8.1.1 Informed Consent and Other Eligibility Reviews

As per GC requirements, reviews of consent forms will be performed to determine that Informed Consent was obtained before registration on the trial. Throughout the trial, copies of relevant documents (such as clinical history notes, pathology/histology reports, etc.) may be requested for source data verification.

12 ADVERSE EVENT REPORTING

12.1 Definitions

Adverse Event (AE): An AE is any untoward medical occurrence (toxicity, sign or symptoms) in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE): An SAE is any untoward medical occurrence that occurs after administration of the Ixekizumab .

- Results in death
- Is life-threatening (an event in which the participant was immediately at risk of death *at the time of event*)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event (events may be considered a serious adverse experience if they require medical or surgical intervention to prevent one of the listed definitions, e.g. an 'allergic bronchospasm' which required intensive treatment in an emergency room or at home)

An event will not be considered to be a SAE if;

- Hospitalisation is due to pre-trial scheduled elective surgery
- Out-patient hospitalisation for procedures such as:
    - Elective day surgery
    - Convenience purposes (e.g. transportation difficulties)

Serious Adverse Reaction (SAR): A serious adverse reaction is an SAE that is suspected as having a causal relationship to the trial treatment, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Related Unexpected Serious Adverse Event: An adverse event that meets the definition of serious and is assessed by the Principal Investigator or nominative representative delegated and trained by the Principle Investigator as:

Related	that is, it resulted from administration of any of the research procedures
Unexpected	that is, the type of event is not listed in the protocol as an expected occurrence

Definitions of causality:

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

12.2 REPORTING

12.2.1 Adverse Events (AE)

Adverse events are to be reported following any injection of Ixekizumab, which must be graded according to The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Appendix) by a study investigator. For each AE, the highest grade observed since the last visit should be reported on the relevant CRF.

All adverse events shall be recorded in the trial database via adverse event CRFs. Internal statistical analysis of these data shall be performed at the times specified in the protocol and investigators and responsible HRECs will be advised of any safety issues which emerge during this process.

Of note, all serious adverse events are to be reported within 24 hours to Lilly Ltd who provides the drug for this study.

12.2.2 Serious Adverse Events (SAE)

SAEs are to be reported by the trial site immediately and no more than 24 hours of being notified, from the commencement of injection until the last visit. Date of the SAE occurrence and date notified must be documented.

The investigator at the trial site is responsible for;

- grading the event according to the NCI CTCAE v 5.0
- identifying the seriousness of the adverse event
- identifying the causal relationship to the treatment and
- determining the expectedness according to the treatment

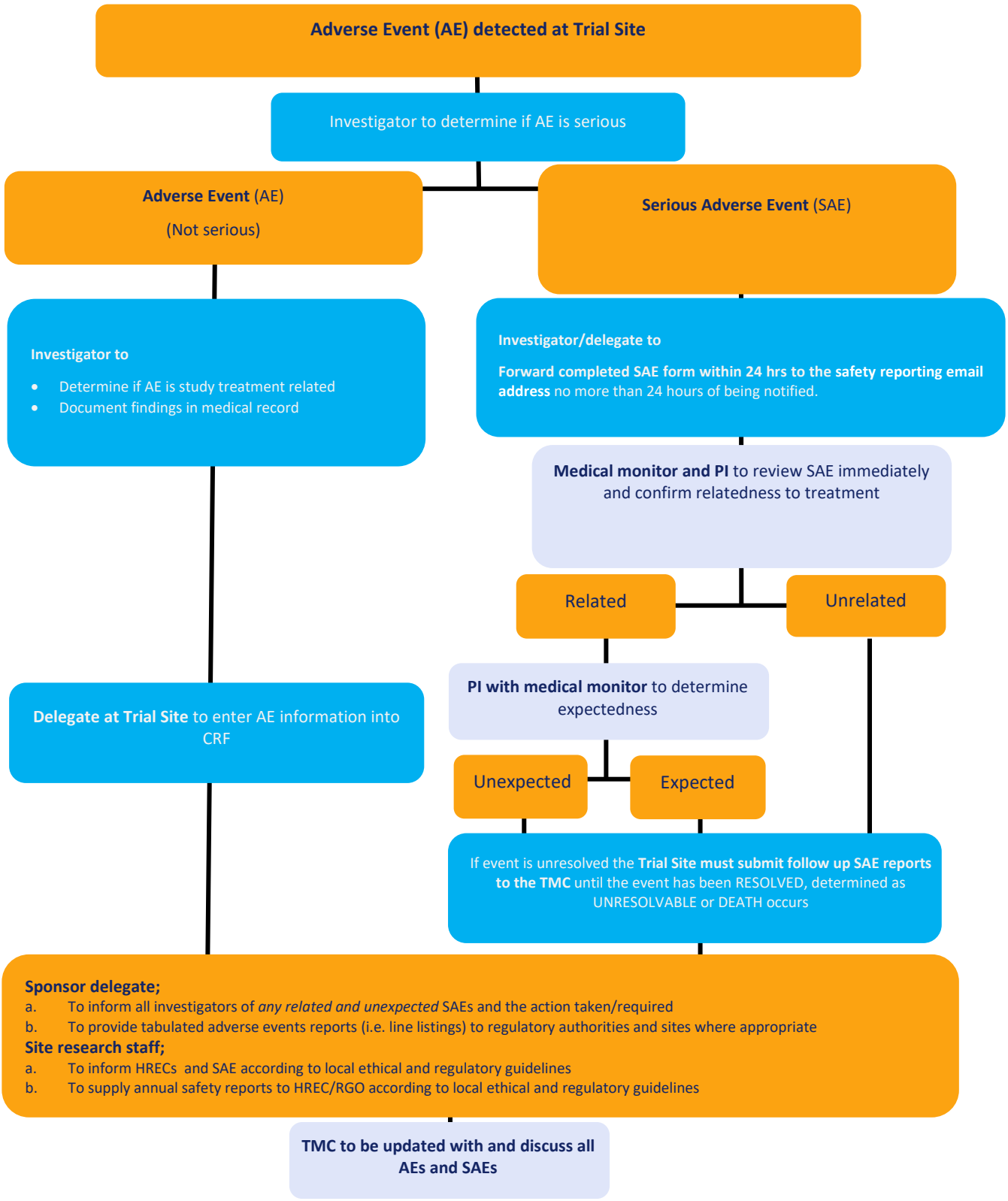
The investigator is also responsible for notifying responsible HRECs, Research Governance Officers or other appropriate regulatory authorities of the SAE according to local ethical and regulatory guidelines. They are also to follow up the event (with regular reporting) until resolved. Please see figure 1.

The Sponsor shall;

- Arrange for the trial chairperson and/ or a clinical reviewer to review the event and confirm causal relationship and expectedness
- Report applicable events to the regulatory authorities (e.g Therapeutic Goods Administration of Australia (TGA))

Notify all other participating investigators of any serious unanticipated related adverse events and any action taken

Figure 1: Adverse Event reporting requirements



13 RESEARCH GOVERNANCE

13.1 Sponsor and Funder

This trial is sponsored by University of Queensland and Eli Lilly is donating the required medication and some of the study funds, however, have no monitory input in the trial

13.2 Trial Chairperson

The trial chairperson will have overall responsibility for the design and conduct of the trial. Further details regarding the responsibilities and delegations are set out in the Clinical Trial Agreement.

13.3 Trial Management Committee

The TMC will be responsible for monitoring of the progress of the trial, decision making, education and information services and reporting. TMC members are listed at the beginning of the protocol. SAE and AE reports will also be discussed and documented during the meetings to ensure ongoing monitoring of patient safety.

13.4 Independent Data Safety Monitoring Committee

Independent Data Safety Monitoring Committee (IDSMC), will independently review accrual rate, ineligibility rate and the conduct of the study. Their review of documented AEs/SAEs and monitoring reports will autonomously analyse the conduct of the trial to ensure patient safety is maintained. The Committee will also review safety and toxicity data and efficacy information during the accrual phase after the first 14 patients. The committee will be made aware immediately of any serious adverse events.

13.5 Principal Investigator

At Queensland Institute of Dermatology a Principal Investigator (Consultant Dermatologist) will be responsible for identification, recruitment, data collection and completion of Case Report Forms along with follow up of study patients and adherence to the study protocol.

14 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

14.1 Ethical Principles and Regulatory Compliance

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the sponsor and in accordance with relevant national guidelines.

14.2 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the trial participant requires that an alternative treatment be used, the trial will be

conducted exactly as per the terms and instructions described in the approved protocol. No protocol exceptions, waivers or exemptions will be granted. If the protocol constraints cannot be met, then the participant will be treated off trial.

14.3 Aboriginal and Torres Strait Islander Values and Principles

UQ/Lilly/QiDerm recognises and commits to the respect of Aboriginal and Torres Strait Islander cultural values and principles.

Although this trial is not targeted specifically to Aboriginal and Torres Strait Islander peoples, a person from one of these communities may be invited to participate if they meet the eligibility criteria of this trial. This decision will be at the discretion of the Principal Investigator at the Trial Site who shall consent and treat the participant according to the principles set forth in the Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research and any specific requirements of the approving Human Research Ethics Committee.

14.4 Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant. An exception is where the trial participant has provided written consent for his/her records to be included in source document verification. In this instance, the records may be inspected by (a) a representative of Elli Lilly for the purposes of source document verification or quality audit as stipulated in the ICH GCP Guidelines, or (b) a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to trial participants will be treated in strict professional confidence.

15 PUBLICATION AND PRESENTATION POLICY

The Trial Chair and Trial Management Committee are responsible for presentations and publications arising from this trial. No data from the trial can be presented until it is agreed on by the Trial Management Committee.

Publications and presentations resulting from this trial will comply with recognised ethical standards concerning publications and authorship, including Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. Furthermore, publications and any kind of presentations of any results from the trial shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with Eli Lilly Publication Policy.

16 REFERENCES

- Ref 1. Rodero MP, Hodgson SS, Hollier B, Combadiere C, Khosrotehrani K. Reduced Il17a expression distinguishes a Ly6c(lo)MHCII(hi) macrophage population promoting wound healing. J Invest Dermatol. 2013 Mar;133(3):783-92.

- Ref 2. Fox JD, Baquerizo-Nole KL, Keegan BR, Macquhae F, Escandon J, Espinosa A, Perez C, Romanelli P, Kirsner R. Adalimumab treatment leads to reduction of tissue tumour necrosis factor-alpha correlated with venous leg ulcer improvement: a pilot study. International Wound Journal, 2016, 13(5): 963-966.
- Ref 3: Ashby et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. The Lancet. March 8 2014, 383: 871-9.

- Ref 4: Squadrito et al. The effect of PDRN, an adenosine receptor A2A agonist, on the healing of chronic diabetic foot ulcers: Results of a clinical trial. J Clin Endocrinol Metab, May 2014, 99(5):E746–E753.
- Ref 5: Lee J, Rodero MP, Patel J, Moi D, Mazzieri R, Khosrotehrani K. Interleukin-23 regulates interleukin-17 expression in wounds, and its inhibition accelerates diabetic wound healing through the alteration of macrophage polarization. FASEB J. 2018 Jan 5:fj201700773R. doi: 10.1096/fj.201700773