A Phase 2a Double-Blind, Placebo-Controlled Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of Deupirfenidone (LYT-100) in Patients with Breast Cancer-Related Upper Limb Secondary Lymphedema

Protocol Number: LYT-100-2020-01-US-02

Authors: Novotech (Australia) Pty Limited

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PROTOCOL AUTHORIZATION

Title: A Phase 2a Double-Blind, Placebo-Controlled Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of Deupirfenidone (LYT-100) in Patients with Breast Cancer-Related Upper Limb Secondary Lymphoedema

As PureTech LYT 100, Inc. ("Sponsor") representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice (GCP).

Michael Chen, PhD, Senior Director PureTech LYT 100, Inc.	Date

INVESTIGATOR'S AGREEMENT

Title: A Phase 2a Double-Blind, Placebo-Controlled Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of Deupirfenidone (LYT-100) in Patients with Breast Cancer-Related Upper Limb Secondary Lymphoedema

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) / Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC, except where necessary to avert an immediate hazard to the patients.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). The conduct of the study will be in accordance with the Integrated Addendum to International Council for Harmonisation (ICH) guideline E6 (R1), Guideline for GCP ICH E6 (R2) and the United States (US) Food and Drug Administration (FDA): Code of Federal Regulations (CFR) Title 21.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

_____

Investigational Site

_____

Printed name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1. Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader and Responsible Physician	Aleksandra Filipovic, MD, Ph.D	PureTech Health LLC 3-8 Bolsover Street, Office 108 | Marylebone W1W 6AB London, UK + 44(0)2073393084
24-Hour Emergency Contact	Aleksandra Filipovic, MD, Ph.D	PureTech Health LLC 3-8 Bolsover Street, Office 108 | Marylebone W1W 6AB London, UK + 44(0) 778 660 7099

2. SYNOPSIS

Name of Sponsor/Company:
PureTech LYT 100, Inc.

Name of Investigational Product:
LYT-100 Capsules

Name of Active Ingredient:
LYT-100 (deupirfenidone)

Protocol Number:
LYT-100-2020-01-US-02

Title of Study:
A Phase 2a Double-Blind, Placebo-Controlled Study to Determine the Safety, Tolerability, Pharmacokinetics, and Efficacy of Deupirfenidone (LYT-100) in Patients with Breast Cancer-Related Upper Limb Secondary Lymphoedema

Study Centers:
Multiple study sites in the USA and Australia

Studied Period (Years):	**Phase of Study:**
Estimated date first patient enrolled: May 2021 Estimated date last patient completed: May 2022	Phase 2a

Study Objectives:

This study is a 26-week randomized, double-blind, placebo-controlled assessment of LYT-100 at multiple study centers in the US and Australia in patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy treatment for breast carcinoma. Screening will be performed up to 28 days prior to administration of the first dose of LYT-100. Only patients who provide written informed consent and meet all of the applicable inclusion and none of the applicable exclusion criteria will be enrolled.

This study will be performed in breast carcinoma patients with secondary mild to moderate lymphedema following axillary node dissection and/or sentinel lymph node biopsy or excision/clearance, with or without radiation, dosed with LYT-100 (750 mg, twice daily [BID]; with food for 26 weeks.

Primary Objectives

- To evaluate the safety and tolerability of LYT-100 on breast cancer carcinoma patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy.

Secondary Objectives

- To explore efficacy signals of double-blinded study medication:
  - Lymphatic obstruction and subsequent edema,
  - Infection (as characterized by cellulitis and/or lymphangitis), and
  - Quality of life (QoL).
- To assess the population pharmacokinetic (PK) profile of double-blinded study medication

– To describe the association between fibrotic and inflammatory biomarkers, in particular transforming growth factor beta 1 (TGF-β1), and disease progression in mild to moderate lymphedema.

Study Design

Treatment Period

This is a double-blind, parallel, placebo-controlled evaluation of the safety and efficacy of LYT-100 compared to placebo. Approximately 50 patients will be randomized to receive LYT-100 or placebo in a ratio of 1:1.

LYT-100 dosing is to be titrated starting at 500 mg BID during the first 3 days of dosing, followed by 750 mg BID thereafter, or matching placebo. Patients will take double-blind-study medication orally with food BID (approximately 10 to 12 hours between the two daily doses) on an outpatient basis for 26 weeks.

Table 2. Dosing Regimens for Days 1 Through 3 and Thereafter

Day 1 to Day 3	Day 4 Through Week 26
[1]LYT-100 **500 mg BID**[2] or matching Placebo × 3 days	[1]LYT-100 **750 mg BID**[2] or matching Placebo × 179 days

Abbreviations: BID = twice a day.

[1]Patients will be administered LYT-100 study medication, or placebo, orally with food with approximately 10 to 12 hours between the two daily doses.

[2]Doses may be adjusted according to safety and tolerability to avoid toxicity by adjusting to lower doses in response to patient safety and tolerability issues. If dosing titration is not well tolerated, adjustments to dosing may be made as follows: reductions to 250 mg BID × 2 days (may be longer if needed), 500 mg BID × 2 days (may be longer if needed), 750 mg BID thereafter versus matching placebo.

Patients with breast cancer-related lymphedema will be assessed for safety, tolerability, clinical endpoints, PK, and biomarkers while receiving LYT-100 or placebo over a 26-week (i.e., 6-month) dosing period. If a patient is using a standard of care compression sleeve, compression pump therapy, and/or manual lymphatic drainage within 4 weeks prior to Screening, they must be agreeable to continuing the same routine care throughout the 6-month study treatment period and throughout 2 weeks post-study drug discontinuation. If a patient is not using a standard compression sleeve, compression pump therapy, and/or manual lymphatic drainage ≥ 4 weeks prior to Screening and are not planning to be using these prior to the study, they must be agreeable to not using the lymphedema therapy(s) throughout treatment and 2 weeks post-study drug discontinuation. Patients will be stratified at enrolment into the standard compression sleeve, compression pump therapy, and/or manual lymphatic drainage stratum versus non-compression/non-lymphatic drainage stratum. In addition, patients will be stratified by higher risk of lymphedema progression (axillary lymph node dissection) versus lower risk of lymphedema progression (sentinel node biopsy).

Table 3. Baseline Randomization Stratification Levels

Compression Sleeve, Compression Pump, and/or Lymphatic Drainage			
Yes		No	
Risk for Progression		***Risk for Progression***	
High (history of axillary lymph node dissection and/or regional lymph node radiation posterior field with or without supraclavicular)	Low (history of sentinel node biopsy or excision/clearance)	High (history of axillary lymph node dissection and/or regional lymph node radiation posterior field with or without supraclavicular)	Low (history of sentinel node biopsy or excision/clearance)

Following confirmation of study eligibility, patients will be seen in the clinic for their final baseline assessments (Day -1). Patients will begin their BID dosing of study medication on the following morning (Study Day 1) and will continue for 26 weeks, with clinic visits at Weeks 1, 2, 4, 8, 12, 16, 20, and 26. The site will contact the patient by phone at Week 23 to check in and assess for compliance to study drug, assess for new concomitant medications and adverse events (AEs) and remind the patient to complete their Patient Diary 1 week prior to the Week 26 study visit.

All patients will be monitored for safety, including assessment of hematology, serum chemistry, coagulation, and urinalysis parameters, ECGs, vital signs, and AEs. Patients will complete the efficacy assessments which will include clinical and QoL measures at time points as delineated in the Schedule of Events. Sparse PK samples will be obtained for population PK analysis to determine the variability of double-blinded study drug concentration data in individual patients across multiple clinical sites. Fibrotic and inflammatory biomarkers will be assessed for changes from baseline. With patients using compression sleeves, pumps, and/or lymphatic drainage as a treatment modality(s) at least 4 weeks prior to and at Screening, they will remain on compression treatments during the treatment period as noted. Compression sleeves will be removed upon arrival at each study visit and until after the bioimpedance assessment is collected. Time of sleeve removal will be noted at each study visit. In addition to routine practices such as diet, exercise, or skin care, use or non-use of compression sleeves, compression pumps and/or lymphatic drainage will be recorded in the Patient Diary 1 week prior to each study visit with lymphedema assessments, including frequency of use and the number of hours used on each occasion. Medication compliance will also be recorded on the Patient Diary.

Follow-Up

Safety and tolerability will be assessed throughout the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology panel, multiphasic chemistry panel, and urinalysis), and review of concomitant treatments/medication use.

Patients will return to the clinic 28 ± 3 days from the last dose of study medication for a safety follow-up visit as delineated in the Schedule of Events.

In the event of premature discontinuation from the study, patients will return to the investigative site and complete an early termination visit with assessments as delineated in the Schedule of Events. Following the early termination visit, patients will be asked to return to the investigative site for one last safety Follow-up visit, approximately 28-days from the last dose of study medication.

Safety Oversight

The study will be subject to oversight by a Safety Review Committee (SRC) comprised of the Principal Investigator (PI), Medical Monitor (MM), and Sponsor representative, at a minimum. Details of the roles and functioning of the SRC will be available in the SRC Charter.

The SRC will convene after 20% of the patients enrolled have completed Week 8 of the Treatment Phase and the double-blind data is available for review. If safety or tolerability issues are identified by the MM for patients while receiving LYT-100 versus placebo at any time, the SRC may meet to review safety and available population PK data and provide recommendations. Options for changes to dosing or protocol assessments may be recommended by the SRC. Ultimate decisions regarding those recommendations remain with the Sponsor.

Number of Patients (Planned):

Approximately 50 patients with breast cancer-related upper limb unilateral secondary lymphedema.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Provides written Ethics Committee approved informed consent prior to any study procedures.
2. Female or male aged ≥ 18 years old at the time of informed consent.

3. At least 6 months and no more than 15 years since the most recent type of surgery performed to treat primary breast cancer including sentinel lymph node biopsy or excision/clearance, axillary lymph node dissection, or any other type of surgery excluding fine needle aspiration biopsy [FNA], at the time of study Screening. No intention to have breast reconstructive surgery, nipple reconstruction, and/or tattooing during the course of the study.
4. At least 3 months since completion of any neoadjuvant therapy, adjuvant chemotherapy, intravenous biologic therapy (e.g., trastuzumab and pertuzumab), radiotherapy, and/or any investigational adjuvant therapy at the time of study Screening.
5. At least 3 months since initiation of anti-hormonal oral adjuvant therapy as well as goserelin and/or adjuvant zolendronic acid.
6. Diagnosis of primary breast cancer, and without evidence of local, locoregional and/or distant recurrence of breast cancer for at least 6 months since completion of adjuvant therapy (excluding anti-hormonal therapy regimens), as determined at Screening and Baseline.
7. Documented evidence of pitting edema in one arm for at least 3 months and also at Screening, and at least one of the following:
    a. Increase in relative limb volume of between 10% to 25% as measured by perometry or the truncated cone method of circumferential tape measurement compared to any prior documented measurement or relative to current measurement of non-affected arm
    b. A bioimpedance measure of > 10 at baseline visit or a change from pre-surgical measure of > +6.5 L-Dex at baseline visit; or
    c. Overt signs of lymphedema in the arm clinically indicating Lymphedema Stage I or II and/or confirmed by asymmetry > 2 via LymphaScan tissue dielectric constant (TDC) in swell spot.
8. Receiving standard of care compression or agreeable to using care compression, i.e., sleeves and/or pumps and/or manual lymphatic drainage, or no compression care and/or no manual lymphatic drainage ≥ 4 weeks prior to Screening and throughout the study.
9. In good general health at Screening and Baseline apart from a history of breast cancer and secondary lymphedema, i.e., free from clinically significant unstable medical, surgical, or psychiatric illness (at the discretion of the Investigator); no acute conditions requiring invasive care or hospitalization; and no conditions or elective procedures requiring invasive intervention within the next 6 months.
10. Vital signs (measured in supine position after 10 minutes rest) at Screening:
    a. Systolic blood pressure ≥ 90 and ≤ 140 mmHg;
    b. Diastolic blood pressure ≥ 50 and ≤ 90 mmHg;
    c. Heart rate ≥ 45 and ≤ 100 bpm;
    d. Vital signs may be repeated once, within a minimum of 10 minutes of the completion of the last set of vital signs (while maintaining supine positions until the repeated set of vital signs are collected), if it is suspected that falsely high or low levels have been obtained.
11. Body Mass Index (BMI) ≥ 18 and ≤ 50 kg/m^2 at Screening.
12. Human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg) negative at Screening.
13. Adequate venous access in contralateral, unaffected limb.
14. Willing and able to comply with all study procedures and requirements including adherence to maintaining routine in either using or not using compression sleeve, compression pump,

lymphatic drainage therapy/self-manual lymph drainage (MLD). Patient should agree to not making extreme changes to their routine, also including diet, exercise, or skin care.

15. Willing and able to abstain from direct whole body sun exposure from 2 days prior to dosing and until final study procedures have been conducted. Patients should be instructed to avoid or minimize exposure to sunlight (including sunlamps), use an SPF 50 sun block, or higher, wear clothing that protects against sun exposure, and avoid concomitant medications known to cause photosensitivity.
16. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must use an acceptable, highly effective double contraception or be abstinent from heterosexual intercourse from Screening until study completion, including the follow-up period (please see Section 10.4.3 for acceptable methods of contraception). WOCBP must have a negative pregnancy test at Screening and Day 1 and be willing to have additional pregnancy tests as required throughout the study. Women not of childbearing potential must be postmenopausal for ≥12 months or be surgically sterile, including a hysterectomy with retention of ovary function is permitted. Postmenopausal status will be confirmed through testing of FSH levels ≥ 40 IU/mL at Screening for amenorrhoeic female patients.
17. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the patient and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period and an additional 12 weeks after the last dose (please see Section 10.4.3 for acceptable methods of contraception).
18. Males must not donate sperm for at least 90 days after the last dose of study drug.
19. Partners of male patients and female patients will report pregnancy occurring within 90 days from cessation of study medication.

Exclusion Criteria:

1. Bilateral lymphedema or history of bilateral axillary lymph node removal (i.e., sentinel lymph node biopsy or axillary lymph node dissection), or primary lymphedema or lymphatic or vascular malformation, determined at Screening.
2. Chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs within 3 months prior to study drug administration; corticosteroids are permitted at the discretion of the PI.
3. Recent history (in the 8 weeks prior to Screening) of cellulitis, lymphangitis, dermatitis, necrotizing fasciitis, or current open wounds or sores in the affected extremity.
4. Fibrotic stranding on affected arm not related to breast cancer-related lymphedema (BCRL); history of breast or arm procedures unrelated to axillary node dissection such as non-cancer-related reconstructive or cosmetic breast surgery, Botox for hyperhidrosis, chronic intravenous use, port, pic-line, etc., for medical or recreational reasons, tattoos (excluding pink ribbon tattoo designated to inform health caretaker not to take blood pressure in affected arm), or other extreme body modifications, determined at Screening.
5. Relative limb volume > 25%, stage III secondary lymphedema, or history of clinically diagnosed secondary lymphedema greater than 4 years, determined at Screening.
6. Initiated use of compression or manual lymphatic drainage or other lymphedema therapies at the start of the study within 4 weeks of the Screening visit. Rescreening is allowed following a course of stable compression regimen of > 4 weeks.
7. Metal implant(s) including implantable cardioverter defibrillators, cardiac resynchronization therapy-defibrillators, and pacemakers that may be affected by assessments used in the trial,

e.g., bioimpedance, and/or that may inconsistently affect collection of secondary lymphedema assessments.

8. Presence of malignancy, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma), carcinoma in-situ of the cervix, or unilateral breast cancer history with completed treatment and with no active cancer at the time of Screening or in the preceding 6 months.
9. Evidence of clinically relevant medical history/illness at Screening, as determined by the Investigator, including stroke, uncontrolled hypertension, and other cardiac disease, vascular disease, pulmonary disease, gastrointestinal disease, hepatic disease, renal failure and other kidney disease, rheumatologic disease, coagulopathy or other hematological disease, uncontrolled diabetes and other endocrine disorders, any progressive neurologic disorder, psychiatric disease, dermatological disorder, or surgical history except for orthopedic and reconstructive breast cancer surgery.
10. Clinically significant infection within 28 days of the start of dosing, as determined by the Investigator.
11. Clinically significant surgical procedure/s, including but not limited to breast cancer reconstruction surgery, within 3 months of Screening, or further breast cancer reconstruction surgery planned during the Study.
12. For baseline liver function tests (LFT) 2.5 × upper normal limit (UNL) or severe hepatic impairment.
13. Positive test for HCV, HBsAg, or HIV antibody at Screening.
14. Currently suffering from clinically significant systemic allergic disease at Screening or Baseline or has a history of significant drug allergies including a history of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
15. Pregnant or lactating at Screening or planning to become pregnant (self or partner) at any time during the study, including the follow-up period.
16. Symptoms of dysphagia or known difficulty in swallowing capsules, determined at Screening.
17. History or presence of cardiac arrhythmia or congenital long QT syndrome determined at Screening.
18. QTcF > 450 msec demonstrated by two ECGs between 30 and 60 minutes apart at Screening.
19. Use of tobacco or nicotine-containing products in the previous 30 days prior to dosing or a positive urine cotinine test at Screening or Baseline.
20. Lack of willingness to abstain from the consumption of tobacco or nicotine-containing products throughout the duration of the study and until completion of the final follow-up visit.
21. Regular alcohol consumption defined as > 21 alcohol units per week (where 1 unit = 284 mL of beer, 25 mL of 40% spirit, or a 125 mL glass of wine), determined at Screening.
22. Positive toxicology Screening panel (urine test including qualitative identification of barbiturates, amphetamines, opiates, and cocaine) or alcohol breath or urine test, determined at Screening. Repeat urine toxicology screenings may be conducted
23. History of substance abuse or dependency or history of recreational IV drug use over the last 2 years, determined at Screening.
24. Use of any over--the-counter medication, herbal supplements, or diet aids within 48 hours prior to dosing without the prior review and approval of the PI and medical monitor
25. Treated with immunosuppressive or antifibrotic drugs, anti-tumor necrosis factor, immunotherapy, or investigational drugs at Screening or within the preceding 30 days.

26. Use of any of the following drugs within 28 days or 10 half-lives of that drug, whichever is the longer, prior to study drug administration:
    a. Fluvoxamine, enoxacin, ciprofloxacin;
    b. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine);
    c. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin);
    d. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol).
27. Use of any investigational drug or device within 28 days or 10 half-lives of the drug, whichever is the longer, prior to start of dosing.
28. Clinically significant blood loss or any blood or blood product donation > 250 mL within 28 days of start of dosing.
29. Any condition (e.g., chronic diarrhea, inflammatory bowel disease or prior surgery of the gastrointestinal tract) that would interfere with drug absorption or any disease or condition that is likely to affect drug metabolism, or excretion, determined at Screening.
30. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
31. As a result of medical review and physical examination at Screening, the Investigator considers the patient unfit for the study.

Dosage and Mode of Administration:

All patients will be randomized to receive LYT-100 or placebo in a 1:1 ratio.

The dose and dosing regimens are presented below in Table 4.

Table 4. Dose and Dosing Regimen

Study Design	Placebo (N)	LYT-100 (N)	LYT-100 dose	Treatment Duration (Days)
N = 50	25	25	LYT-100 BID** (titrate to 750 mg) or matching placebo**	182

** Patients will be administered LYT-100 study medication, or placebo, orally with food with approximately 10 to 12 hours between the two daily doses (BID).

Duration of Treatment with Study Medication:

26 weeks (6 months)

Criteria for Evaluation:

Safety:

Safety and tolerability will be assessed throughout all parts of the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis), and review of concomitant treatments/medication use.

Efficacy:

The following parameters will be measured as per the schedule of assessments (Table 5)

- Limb water content, by bioelectrical impedance spectroscopy (BIS).
- Limb volume (truncated cone tape measure and/or perometry).

- Tissue dielectric constant (MoistureMeterD).
- Tissue firmness (tonometry/SkinFibroMeter).
- Visual analog scales for pain, swelling, discomfort, and function.

Health-related QoL:

The following will be assessed as per the Schedule of Assessments (Table 5)

- LYMPH-Q- Upper Extremity Module see Appendix 2.
- Lymphedema Quality of Life Tool, Arm (LYMQOL); see Appendix 3.

Occurrence of Infection:

The following will be assessed along with AEs:

- Cellulitis
- Lymphangitis

Pharmacokinetics:

Patients will provide blood samples at Baseline (Day -1) for the determination of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 genotype to support exploratory PK analyses. Patients are required to provide consent for genotyping.

Blood samples (4 mL each) for population PK will be collected at specified times at any visit from Week 1 to Week 26 of the study. Each patient will provide a minimum of 1 sample at each timepoint in reference to dosing: Pre-dose, 1 to < 2 hours, 2 to < 4 hours, 4 to < 8 hours, 8 to 12 hours.

Fibrotic and Inflammatory Biomarkers:

The following parameters will be measured at select study visits as per the Schedule of Assessments:

- Fibrotic and inflammatory biomarkers (granulocyte colony stimulating factor [G-CSF], monokine induced by gamma interferon [MIG], fibroblast growth factor-2 [FGF-2], interleukin(IL)-4, IL-10, lymphotoxin-α/ tumor necrosis factor beta [TNF-β], leptin, IL-6, IL-1β, tumor necrosis factor alpha [TNF-α], TGF-β1, matrix metalloproteinase 9 [MMP-9], tissue inhibitor of matrix metalloproteinase 1 [TIMP-1], monocyte chemoattractant protein-1 [MCP-1]).

These data may be reported separately in a supplementary report to the main Clinical Study Report.

Endpoints for the Study are Defined as Follows:

Primary Endpoint:

- Safety and tolerability (AEs, physical examination, vital signs, ECGs, clinical laboratory parameters [hematology, serum chemistry, coagulation, and urinalysis], and concomitant treatments).

Secondary Endpoint:

- Efficacy:
  - Limb water content, by BIS.
  - Limb volume (perometry).
  - Tissue dielectric constant (MoistureMeterD).
  - Tissue firmness (tonometry/SkinFibroMeter).
  - Visual analog scales for pain, swelling, discomfort, and function.
- Infection:
  - Cellulitis.

- Lymphangitis.

- Health-related QoL:
  - LYMPH-Q- Upper Extremity Module (Appendix 2).
  - LYMQOL (Appendix 3).
- Population PK parameters.
- Fibrotic and Inflammatory biomarkers:
  - Fibrotic and inflammatory biomarkers (G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxinα/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP1).

Statistical Methods:

A statistical analysis plan (SAP) will be written that will describe, in greater detail, the analyses to be performed for each part. The sections below provide a summary of the general approach to the analysis. The analysis is consistent with the study design. Note that this study is not hypothesis testing but rather hypothesis-generating, and thus conclusions regarding outcomes will not be based on inferential tests but rather descriptive outcomes, magnitude of treatment effects, and a preponderance of evidence regarding the risk-benefit profile of LYT-100.

Sample Size

Approximately 50 patients with secondary lymphedema will be randomized in a 1:1 ratio to LYT-100 or placebo, as part of this early development and exploratory study of LYT-100. Formal sample size calculations will not be performed; rather, the sample size selected should be adequate for preliminary evaluation of safety, tolerability, efficacy signaling, PK, and fibrotic and inflammatory biomarker parameters in the targeted patient population.

General Statistical Plan

The baseline for all variables will be the last measurement obtained prior to the patient receiving the first dose of study treatment.

Patient disposition (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study) will be tabulated by treatment group. Summary statistics for days of exposure and concentration of exposure will be provided by treatment group.

AEs, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each patient will be tabulated or summarized descriptively, where appropriate.

Demographic information will be presented for each patient and summarized. Treatment-emergent adverse events (TEAEs) and laboratory, vital signs, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will also be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized. ECG results for QTcF will also be classified as < 450 msec, 450 to 500 msec or > 500 msec. Changes in physical exams will be described.

Study Populations

- The Safety Population is defined as all patients who receive LYT-100, or Placebo.
- The Full Analysis Set (FAS) population is defined as all randomized patients who received at least one dose of double-blinded study medication and had at least one post-baseline efficacy assessment. All efficacy endpoints will be assessed using this population.
- The Pharmacokinetic Population (PP) is defined as all patients who receive the double-blinded study medication and for whom an evaluable concentration-time profile is available for the determination of at least one PK variable. Patients with emesis after consuming study

medication will be assessed on a case-by-case basis for eligibility for inclusion in the PK population. In general, patients who vomit after at least 2 half-lives of the given medication will be included in the PK population (as C_{max} will presumably be reached by that time).

- The Fibrotic and Inflammatory Biomarker Population is defined as all patients who receive the double-blinded study medication and who provide biomarker and lymphedema assessment data.

Study-Specific Requirements

Analysis of clinical assessments and potential progression or disease will be explored. Comparisons between LYT-100 and placebo will be based on clinical interpretation of effect, magnitudes of effect, and a preponderance of evidence. Estimates of changes over time from these data may be used to power future clinical studies.

The primary endpoints are safety (clinical laboratory parameters, vital signs, ECGs, and spontaneously reported AEs) and tolerability of the double-blinded study medication. Secondary endpoints include efficacy (lymphedema assessments, infection, and health-related QoL), population PK, and fibrotic and inflammatory biomarkers of the double-blinded study medication.

Change from baseline to each post-baseline visit (through Week 26; on-treatment effect) on the following endpoints will be calculated for the following endpoints: fibrotic and inflammatory biomarkers (G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxin α/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP-1), limb water content (BIS), limb volume (truncated cone tape measure and/or perometry), tissue dielectric constant (MoistureMeterD), tissue firmness (tonometry/SkinFibroMeter), visual analog scales (pain, swelling, discomfort, and function), and QoL (LYMPH-Q, LYMQOL). For select efficacy outcomes, use of a mixed model for repeated measures (MMRM) will be used to provide model-based estimates of changes over time in each of these outcomes. Descriptive statistics will also be provided at each time point. Details for the model (including covariates to be included) will be provided in the SAP.

Data for all endpoints will be tabulated, displayed graphically, or summarized descriptively, as appropriate. No formal hypothesis testing will be performed.

3. STUDY SCHEDULE OF ASSESSMENTS

Table 5. Schedule of Events

	Screening	Baseline	LYT-100 Patient Cohort Double-Blind Treatment Phase[1] (N = approximately 50) [1]										Final Safety Visit
Study Day	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 23**	**Week 26 or Early Termination[2]**	**Week 30 (28 days from last dose)**
Study Drug			**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**D/C Dose**	**n/a**
+/- Days Allowable		**+/-0**	**+/-0**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**
Visit	**1**	**2**	***(no visit)***	**3**	***Phone Call***	**4**	**5**	**6**	**7**	**8**	***Phone Call***	**9**	**10**
Outpatient Clinic Visit	X	X	*(no visit)*	X	*Phone Call*	X	X	X	X	X	*Phone Call*	X	X
Informed Consent[3]	X												
Eligibility Assessment	X	X											
Demographics	X												
Medical History[4]	X												X
12-lead ECG (QTcF)[5]	X			X				X				X	X
Physical Exam[6]	X			X				X				X	X
Vital Signs (Height, Weight, BMI, Body Temp, HR, BP, RR)[7,8]	X	X		X		X	X	X	X	X		X	X
Bioimpedance[8]		X		X		X	X	X	X	X		X	
Limb Volume[8, 20]		X		X		X	X	X	X	X		X	
MoistureMeterD[8]		X		X		X	X	X	X	X		X	
Tonometry/Skin FibroMeter[8]		X		X		X	X	X	X	X		X	
Visual Analog Scales		X		X		X	X	X	X	X		X	
LYMPH-Q		X		X		X	X	X	X	X		X	
LYMQOL		X		X		X	X	X	X	X		X	

	Screening	Baseline	LYT-100 Patient Cohort Double-Blind Treatment Phase[1] (N = approximately 50) [1]										Final Safety Visit
Study Day	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 23**	**Week 26 or Early Termination[2]**	**Week 30 (28 days from last dose)**
Study Drug			**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**	**D/C Dose**	**n/a**
+/- Days Allowable		**+/-0**	**+/-0**	**+/-2**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**
Visit	**1**	**2**	***(no visit)***	**3**	***Phone Call***	**4**	**5**	**6**	**7**	**8**	***Phone Call***	**9**	**10**
Sparse PK Blood Samples [8, 9]				X		X	X	X	X	X		X	
Concomitant Medication[10]	X	X		X	X	X	X	X	X	X	X	X	X
Adverse Events[11]	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test[12]	Urine	Urine						Urine				Urine	
FSH[13]	X												
Genotyping[14]		X											
Hematology [8, 15]	X			X		X		X				X	X
Chemistry[8, 16]	X			X		X	X	X	X	X		X	X
Coagulation[8, 17]	X			X		X		X				X	X
Urinalysis	X	X		X		X		X				X	X
Urine Cotinine, drug screen & alcohol breath test	X	X										X	
Exploratory Inflammatory Biomarkers[8, 18]		X		X			X		X			X	
Review Patient Diary[19]		X		X		X	X	X	X	X	Week 26 diary reminder	X	
Study Drug Dispensing and Drug Accountability		X	*(first dose taken)*	X		X	X	X	X	X	*(cont. dosing)*	*(acct. only)*	*n/a*
Participant Interview[21]	X												X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BID = twice a day; BMI = Body Mass Index; BP = blood pressure; D/C = discontinue; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HR = heart rate; LYMPH-Q- Upper Extremity Module;; LYMQOL = Lymphedema Quality of Life Tool, Arm; n/a = not applicable; PK = pharmacokinetics; RR = respiratory rate.

1. Double-blind treatment is either LYT-100, 750 mg BID or matching placebo by mouth, on an outpatient basis.
2. Early termination is defined as premature discontinuation t
3. Informed consent must be documented before any study-specific Screening procedures are performed.
4. Medical history includes breast cancer, surgical, radiation and therapy history. It should be updated as needed at the final safety visit (# 11).
5. ECG are to be conducted 2.5 hours (+/- 15 minutes) after the morning study drug dose on Week 1 and Week 12 visits.
6. A full physical exam will be conducted at the Screening and final safety visits. Symptom directed physical examinations will be performed at all other indicated visits.
7. Height is collected at baseline while vital signs, weight, and BMI are collected only one time at each designated visit.
8. All breast cancer-related lymphedema (BCRL) assessments should be done toward the end of the study visit. If the patient is using a compression sleeve, it should be removed upon arrival at the study visit and not placed back on until all assessments for the study visit are collected. Where possible, BCRL assessments may be conducted at the Screening (in addition to baseline) visit so that patients do not fail eligibility at baseline.
9. Pharmacokinetic samples are collected at each visit except Screening, baseline, and post-treatment phase. Last dose taken prior to blood collection will be recorded. Population PK will be grouped into the following timepoint ranges post-study med dose administration: Hour 0, Hour 1 to < 2, Hour 2 to < 4, Hour 4 to < 8, Hour 8 to 12.
10. Concomitant medications include all medications taken 30 days prior to the Screening visit.
11. Adverse events include medical conditions such as infections (e.g., cellulitis and lymphangitis) starting or worsening after LYT-100 or placebo administration. All other medical conditions reported around Screening and Baseline prior to study treatment administration will be reported as pre-treatment AEs.
12. Not required for amenorrhoeic female patients (see below); if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
13. Amenorrhoeic female patients only; postmenopausal status will be confirmed through testing of FSH levels (≥ 40 IU/mL).
14. Patients will provide blood samples at baseline (Day -1) for the determination of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 genotyping – Sample to be obtained on Day -1 of the first period only. Patients are required to provide consent for genotyping.
15. Hematology includes complete blood count and differential.
16. Serum chemistry includes glucose, total protein, albumin, electrolytes (sodium, potassium, chloride, total CO_2), calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), ALT or AST, alkaline phosphatase, creatinine, blood urea nitrogen, creatine phosphokinase (CPK). Liver Function Tests (LFTs) will be collected at each visit and includes bilirubin (total, direct), ALT or AST, and alkaline phosphatase.
17. Coagulation includes international normalized ratio (INR), prothrombin time and APTT.
18. Inflammatory markers include: G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxin-α/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP-1.
19. Patient completes the Patient Diary starting 1 week prior to each study visit and returns the diary at the end of the week while attending the study visit.
20. Relative limb volume is measured by perometry. Perometry is a non-invasive technique involving a Perometer (Pero-System), which uses infrared light to scan a limb and obtain measurements of the limb's circumference. The truncated cone tape measure method can be used as a backup if the Perometer is unavailable, or not working at time of the patient visit.
21. Patients will be asked to participate in interviews to discuss their Breast Cancer related Lymphedema either during screening (i.e. to include subjects that are deemed ineligible and not able to participate in the study) or at the end of the treatment period (Week 30 for those that are deemed eligible and complete study treatment)

4. TABLE OF CONTENTS

LIST OF TABLES

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AMP	Amphetamines
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAR	Barbiturates
BASO	Basophils
BCRL	Breast cancer-related lymphedema
BICARB	Bicarbonate
BID	Twice daily
BILI	Total Bilirubin
BILIDIR	Direct Bilirubin
BIS	Bioelectrical impedance spectroscopy
BMI	Body Mass Index
BP	Blood pressure
BZO	Benzodiazepines
CA	Calcium
CFR	Code of Federal Regulation
CL	Chloride
C_{max}	Observed maximum plasma concentration
COC	Cocaine
CPK	Creatine phosphokinase
CREAT	Creatinine
CRO	Clinical Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or Specialist Term	Explanation
ESN	Eosinophils
FDA	Food and Drug Administration
FGF-2	Fibroblast Growth Factor-2
FNA	Fine needle aspiration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GGT	Gamma glutamyl transpeptidase
GLOBUL	Globulin
GLU	Glucose
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-10	Interleukin 10
IL-1β	Interleukin 1 beta
IL-4	Interleukin 4
IL-6	Interleukin 6
INR	International normalized ratio
IP	Investigational product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
K	Potassium
LFT	Liver function test
LYM	Lymphocytes

Abbreviation or Specialist Term	Explanation
LYMPH-Q	Lymphedema Questionnaire- Upper Extremity Module
LYMQOL	Lymphedema Quality of Life Tool, Arm
MCP-1	Monocyte Chemoattractant Protein-1
MDMA	Methylenedioxymethamphetamine
MedDRA®	Medical Dictionary for Regulatory Activities
MET	Methamphetamines
MIG	Monokine induced by gamma interferon
MLD	Manual lymph drainage
MM	Medical Monitor
MMP-9	Matrix Metalloproteinase 9
MMRM	Mixed model for repeated measures
MTD	Methadone
n	Number
n/a	Not applicable
NA	Sodium
NEUT	Neutrophils
OCCBLD	Occult Blood
OCP	Oral contraceptive pill
OPI	Opiates
OTC	Over-the-counter
PCP	Phencyclidine
PD	Pharmacodynamics
PHOS	Phosphate
PI	Principal Investigator
PK	Pharmacokinetics
PLAT	Platelets
PP	Pharmacokinetic population
PROT	Protein
PT	Preferred term
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RETI	Reticulocytes
RR	Respiration rate

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SPGRAV	Specific Gravity
SRC	Safety Review Committee
TDC	Tissue dielectric constant
TEAE	Treatment-emergent adverse event
TGF-β1	Transforming growth factor beta 1
THC	Tetrahydrocannabinol
TID	Three times a day
TIMP-1	Tissue inhibitor of matrix metalloproteinase 1
TNF-α	Tumor necrosis factor alpha
TNF-β	Tumor necrosis factor beta
TROP1	Troponin 1
U	Urea
UROBIL	Urobilinogen
US	United States
WBC	Leukocytes
WHO	World Health Organization
WOCBP	Woman of childbearing potential

6. FACILITIES AND PERSONNEL

Table 6. Facilities and Personnel

Sponsor	PureTech LYT 100, Inc. 6 Tide Street, Suite 400 Boston, MA, 02210 USA
Local Australian Sponsor	Novotech (Australia) Pty Limited Level 3, 235 Pyrmont Street Sydney, NSW, 2009 Australia
Pharmacokinetic Laboratory	Agilex Biolabs 28 Dalgleish Street Thebarton, SA, 5031 Australia
Biomarker Laboratory	Agilex Biolabs 28 Dalgleish Street Thebarton, SA, 5031 Australia
Genotyping Lab	Sonic Clinical Trials 14 Giffnock Avenue Macquarie Park, NSW, 2113 Australia
Biostatistical Analysis, Data Management, Project Management, Monitoring	Novotech (Australia) Pty Limited Level 3, 235 Pyrmont Street Sydney, NSW, 2009 Australia

7. BACKGROUND AND INTRODUCTION

7.1. Introduction

LYT-100 (deupirfenidone) is a selectively deuterated form of pirfenidone. Pirfenidone is an orally active small molecule drug with anti-inflammatory and antifibrotic properties. Pirfenidone has been shown to slow the progression of idiopathic pulmonary fibrosis (IPF) in clinical trials (King et al., 2014; Noble et al., 2011; Rafii et al., 2013; Taniguchi et al., 2010) and has been approved for the treatment of IPF in 30 European countries, Canada, Japan, South Korea, China, India, Argentina, and Mexico and was approved for the treatment of IPF in the United States in 2014. Pirfenidone has been shown to be generally well tolerated; the most common adverse events (AEs) were gastrointestinal symptoms (nausea, diarrhea, dyspepsia, vomiting), fatigue, rash, and photosensitivity reactions.

While pirfenidone has established efficacy in treating fibrotic conditions such as IPF, the short half-life of the drug requires that it be dosed at least three times per day. In addition, metabolism of pirfenidone, primarily by CYP1A2, has the potential to lead to interpatient variability in pharmacokinetics (PK), safety, and efficacy. To address the possible limitations of pirfenidone, a selectively deuterated form of pirfenidone (referred to as LYT-100) has been developed. LYT-100 was designed by substituting three deuterium atoms for hydrogen at the methyl group in the pirfenidone molecule, with the objective of attenuating the rate of drug metabolism and improving the overall PK profile of the drug. LYT-100 is expected to be metabolized more slowly compared with non-deuterated pirfenidone. The possibility of less frequent dosing with LYT-100 therapy and slowed rate of drug metabolism may result in improved tolerability and efficacy compared with pirfenidone.

PureTech LYT 100, Inc. intends to study LYT-100 for the treatment of lymphedema, a chronic condition that is characterized by swelling due to the build-up of lymph fluid and tissue fibrotic remodeling. Lymphedema is a progressive fibrotic and inflammatory disease, and there is no approved pharmacologic therapy for lymphedema. LYT-100 has both anti-fibrotic and anti-inflammatory activity based on *in vitro* and *in vivo* models of fibrotic and inflammatory conditions. Existing treatments focus on reducing the symptoms and using mechanical compression to prevent swelling. However, these treatments do not address the underlying mechanisms of lymphedema and are required chronically for management of the condition. Millions of people worldwide are affected by secondary lymphedema (Rockson et al., 2019), and each year up to 15% of cancer survivors with malignancies ranging from melanoma to sarcoma will develop lymphedema (Cormier et al., 2010). As such, there is an unmet medical need for developing safe and effective new treatments for lymphedema.

The purpose of this study is to evaluate the safety, tolerability, PK, and effect on secondary clinical endpoints of LYT-100 administered twice daily (BID) for 6 months in breast carcinoma patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy, with or without radiation.

7.2. Summary of Nonclinical and Clinical Studies

7.2.1. Nonclinical Studies

LYT-100 has been evaluated in limited pharmacology, PK, metabolism, and toxicity studies via the oral route (along with a pirfenidone comparator arm), since extensive nonclinical and clinical data are available for pirfenidone (Center for Drug Evaluation and Research, 2014) including pharmacology; safety pharmacology; absorption, distribution, metabolism and excretion; and toxicology studies with durations up to 6 months in rats and 9 months in dogs; reproductive toxicity, genotoxicity, and carcinogenicity in mice and rats; and photosafety.

A brief summary of the nonclinical pharmacology, PK, and toxicology of LYT-100 is provided herein. More detailed information is provided in the LYT-100 Investigator's Brochure.

7.2.1.1. Pharmacology

In vitro and *in vivo* pharmacology studies conducted with LYT-100 have verified that deuteration does not alter the pharmacodynamics (PD) of pirfenidone with respect to its anti-fibrotic and anti-inflammatory mechanisms of action.

Safety pharmacology studies have not been conducted with LYT-100, as data on a full battery of safety pharmacology studies are available for pirfenidone including assessments of neurological, cardiovascular, respiratory, and gastrointestinal effects.

7.2.1.2. Pharmacokinetics

Single dose absorption and PK of LYT-100 and pirfenidone and the resulting metabolites have been studied in rats, dogs, and chimpanzees, as summarized in the Investigator Brochure.

In brief, studies of the *in vitro* hepatic microsomal stability of pirfenidone and LYT-100 in human, monkey, dog, rat, and mouse liver microsomes demonstrated that deuteration improved the metabolic stability of pirfenidone in all species. An *in vitro* comparative mass balance study of pirfenidone and LYT-100 in human and rat liver microsomes and a comparative study of pirfenidone and LYT-100 metabolites in rat, dog, mouse, and monkey liver microsomes revealed that metabolism of both compounds was qualitatively similar and showed that deuteration did not introduce novel metabolites (although metabolism of LYT-100 occurred more slowly). No studies have been carried out examining the potential for LYT-100 to interact with human transporter proteins, although pirfenidone does not appear to be a substrate for multiple transporters tested. The major human metabolite of pirfenidone, 5-carboxy pirfenidone, did not inhibit transporters except for OAT1 and OAT3. Metabolite 5-carboxy pirfenidone is a substrate of human breast cancer resistance protein and P-glycoprotein.

7.2.1.3. Toxicology

A comparative dose range finding study of a single dose (male and female rats) or two daily oral doses (female rats) of LYT-100 and pirfenidone (Study AUS-SD-560-NCTP-07) demonstrated findings consistent with previous reports on pirfenidone and supported dose selection for a subsequent 4-/13-week oral toxicity study in Sprague Dawley rats (Study 1322.03), as described briefly below.

The objective of this repeat-dose study was to evaluate the toxicity of LYT-100 or pirfenidone when administered orally once daily for 29 (interim analysis) or 91 consecutive days to Sprague Dawley rats and to evaluate the potential reversibility of any findings following a 4-week recovery period. In addition, the toxicokinetic characteristics of LYT-100 and pirfenidone were determined. The data from the 4-week interim analysis are currently available, as described briefly herein and summarized in greater detail in the Investigator Brochure.

LYT-100 (250, 500, and 750 mg/kg/day) and pirfenidone (750 mg/kg and 875 mg/kg) were administered via an oral gavage once daily for 28 consecutive days to fed male and female Sprague Dawley rats. The high-dose of pirfenidone was reduced from 1000 mg/kg to 875 mg/kg early in the study due to marked clinical signs similar to those described previously for this compound. Toxicokinetic analysis revealed that exposure to LYT-100 at a dose of 750 mg/kg was similar to the exposure to the same dose of pirfenidone.

Mortalities were observed in both the LYT-100 and pirfenidone-treated groups, but these were not considered test-article-related due to the lack of dose dependency and the sporadic timing of the early deaths, which was consistent with gavage error / reflux findings as an unintended complication of oral gavage. There were no LYT-100- or pirfenidone-related ophthalmic, group mean body weight changes, clinical pathology, or gross pathology findings. Non-adverse LYT-100- and pirfenidone-related changes were observed in clinical observations, body weight gain, feed consumption, organ weights, and histopathology. Test article-related organ weight changes included increased mean liver weights in males and females (LYT-100 250, 500, and 750 mg/kg; pirfenidone 750 and 875 mg/kg); and increased mean kidney weights in males (LYT-100 500 and 750 mg/kg; pirfenidone 750 and 875 mg/kg). Increased liver weight was correlated histopathologically with centrilobular hepatocyte hypertrophy (believed to be an adaptive change associated with drug metabolizing enzyme induction), and the kidney weight changes were possibly caused by hyaline droplet accumulation in the renal tubules (considered specific to the male rat). These findings were not considered adverse and were correlated with LYT-100 C_{max} of up to 187476.1 ng/mL (female) and 135080.3 ng/mL (male) on Day 1.

7.2.1.4. Carcinogenesis

The carcinogenic potential of pirfenidone was evaluated in a 24-month carcinogenicity study in B6C3F1 mice and a 24-month carcinogenicity study in Fisher rats. In these studies pirfenidone caused increases in hepatocellular adenoma and carcinoma (rats and mice), hepatoblastoma (mice), and uterine adenocarcinoma and adenoma (rats). The relevance of these findings in rodents to humans is unknown.

7.2.2. Clinical Studies

Administration of LYT-100 in a fed state was tested in a Phase 1, randomized, double-blind, single dose crossover study to compare the PK, safety, and tolerability of LYT-100 with pirfenidone in 24 healthy volunteers (LYT-100-2020-01-US). The objectives of the study were to compare the PK of LYT-100 and pirfenidone and to evaluate and compare the safety and tolerability of a single dose of LYT-100 and pirfenidone. Subjects received single 801 mg oral doses of LYT-100 and pirfenidone in a random sequence, separated by a washout period of at

least 7 days. Overall, single doses of LYT-100 and pirfenidone were well tolerated and had a comparable safety profile. A total of 44 treatment-emergent adverse events (TEAEs) were reported during the study by 14 (58%) of the 24 subjects enrolled. Most of these events were mild in severity and there were no events rated as severe. There were no deaths, serious adverse events (SAEs), or AEs leading to withdrawal of study drug reported during the study. No significant differences were observed between the two treatments in terms of incidence, type, severity, relationship, or frequency of TEAEs. The most common AE following either treatment was headache, reported by 21% of subjects during each treatment. No significant changes in laboratory parameters, vital signs, or ECGs were observed following either treatment.

Deuteration of pirfenidone resulted in an approximately 25% higher C_{max} and 35% higher overall exposure relative to the non-deuterated form. The C_{max} and overall exposure were not associated with an appreciable difference in elimination $t_{½}$ (2.67 vs. 2.39 hours for LYT-100 and pirfenidone, respectively). Increased systemic exposure of deuterated pirfenidone was associated with a corresponding decrease in C_{max} and overall exposure of the most abundant circulating metabolite (5-carboxy metabolite).

LYT-100 was also tested in a Phase 1 multiple ascending dose study to ascertain the safety, tolerability, steady state PK, and food effect of LYT-100. Part 1 assessed multiple ascending doses of LYT-100 100, 250, 500, 750, and 1000 mg BID given over 5 days without titration. Part 2 assessed the effects of food versus fasting on the pharmacokinetic profile resulting from a single 500 mg dose of LYT-100. All doses through 1000 mg were well tolerated with adverse events being mild and transient. Exposure was slightly lower in the fed condition. LYT-100 was well tolerated and demonstrated a dose-proportional PK profile. The ratio of parent to major metabolite concentration is higher than previously reported with pirfenidone, which is consistent with an effect of deuteration on metabolism. No maximum tolerated dose was identified through 1000 mg twice-daily dosing.

The safety of pirfenidone has been evaluated in over 1500 healthy volunteers and patients with IPF, including four Phase 3 multicenter, double-blind, placebo-controlled, randomized studies. Three multinational studies (CAPACITY 004 and CAPACITY 006, N = 779 patients; ASCEND, N=555 patients) included a total of 1334 patients (King et al., 2014; Noble et al., 2011). A study conducted in Japan included 275 patients (Taniguchi et al., 2010).

Following treatment for up to 72 weeks with either pirfenidone 801 mg TID (three times a day), 399 mg TID, or placebo, the majority of patients (98%) in both the CAPACITY 004 and 006 studies (Noble et al., 2011), experienced at least one treatment-emergent AE. The most common AEs in the pooled pirfenidone 801 mg TID group, with at least a 1.5-times increased incidence relative to placebo, were GI events (nausea, dyspepsia, vomiting, and anorexia), skin-related events (rash, photosensitivity), and dizziness; a dose-response in frequency was noted. Most AEs were assessed as mild to moderate in severity. SAEs were reported in 33% of the pooled pirfenidone group and 31% of the pooled placebo group. The incidence of patients discontinuing pirfenidone due to AEs was low (15% of pooled pirfenidone group; 9% of pooled placebo group).

In the ASCEND study (King et al., 2014), gastrointestinal and skin-related events were more common in the pirfenidone group than in the placebo group; most AEs were assessed as mild to moderate in severity. The incidence of patients discontinuing pirfenidone due to AEs was low (14% of the pirfenidone group; 11% of the placebo group). Excluding patients with worsening

fibrosis, serious AEs were reported in 18.7% of patients in the pirfenidone group and 20.2% of patients in the placebo group.

In the Japanese study (Taniguchi et al., 2010), photosensitivity, anorexia, dizziness, and elevated γ-glutamyl-transpeptidase were significantly more common (≥ 5%; $p < 0.05$) in the high-dose (600 mg TID) group than in the placebo group. Skin-related (photosensitivity, asteatotic eczema) and gastrointestinal AEs (abdominal discomfort) as well as decrease in white blood cells were more common in the low-dose (400 mg TID) group than in the placebo group. Photosensitivity was the major AE observed in 51% of the patients in the high-dose group and 53% in the low-dose group. Of the patients who developed photosensitivity, most had mild events (70% in the high-dose group and 80% in the low-dose group), and the remainder had moderate events. Most of the AEs resolved after decreasing the pirfenidone dose or temporarily withholding the pirfenidone. The incidence of subjects discontinuing pirfenidone due to AEs was low in both dose groups (18% of the high-dose pirfenidone group, 20% of the low-dose pirfenidone group, 13% of the placebo group).

Overall, pirfenidone was well tolerated in the Phase 3 studies. The most common AEs were gastrointestinal AEs (e.g., nausea, dyspepsia, diarrhea, vomiting), fatigue, anorexia, dizziness, rash, and photosensitivity reactions. Serious AEs occurred infrequently and with similar incidence for pirfenidone and placebo subjects. AEs leading to discontinuation of study treatment were infrequent and included nausea, rash, and photosensitivity reactions.

Further information on clinical experience with LYT-100 and pirfenidone is provided in the Investigator's Brochure.

7.3. Summary of Potential Risks and Benefits

In nonclinical studies to date, no meaningful differences have been observed in the *in vivo* pharmacology and toxicology profiles of LYT-100 when compared with pirfenidone. In humans, LYT-100 is expected to have an AE profile similar to that of pirfenidone when subjects achieve comparable systemic exposure. Therefore, AEs associated with the use of pirfenidone are considered expected with use of LYT-100 and prescribing recommendations for pirfenidone are expected to be applicable for LYT-100.

7.4. Dosage and Treatment Periods

Dosage and treatment periods are summarized in Table 7. This study is a placebo-controlled assessment of safety and efficacy signals in the target patient population.

Patients will be randomized in a 1:1 ratio to double-blind treatment with either LYT-100 or matching placebo.

Table 7. Dose and Dosing Regimen

Study Design	Placebo (N)	LYT-100 (N)	LYT-100 dose	Treatment Duration (Days)
N = 50	25	25	LYT-100 BID** (titrate to 750 mg) or matching placebo**	182

** Patients will be administered LYT-100 study medication, or placebo, orally with food with approximately 10 to 12 hours between the two daily doses (BID).

7.4.1. Rationale for Selection of Dose

Pirfenidone has been approved for use at a recommended dose of 801 mg TID (2403 mg per day), achieved by weekly titration from a starting dose of 267 mg TID. Preclinical studies have shown that LYT-100 and pirfenidone exhibit similar pharmacology at similar concentrations and that the toxicity of LYT-100 is not different from that of pirfenidone. Furthermore, the PK on LYT-100 and pirfenidone in humans have been shown to be comparable. It is therefore expected that 750 mg LYT-100 BID will give exposure lower than that observed with 267 mg pirfenidone TID, which has been shown in clinical practice to be a safe dose of pirfenidone with limited pharmacological efficacy.

The dose to be used and instructions to take with food was determined from previous clinical trials performed by the Sponsor. The LYT-100 dose level selected was 750 mg BID. If safety or tolerability issues arise for patients while receiving their study medication, the dose may be reduced. In addition, the dose will be titrated over 3 days unless safety or tolerability issues are noted with initiation of treatment in patients.

7.5. Patient Population

This study will be conducted in breast carcinoma patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy with or without radiation.

Women of childbearing potential (WOCBP) will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow-up period (see Section 10.4.3). WOCBP must demonstrate negative pregnancy testing at Screening and prior to study drug administration on Day 1 and be willing to have additional pregnancy tests as required throughout the study. This is in line with regulatory Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (FDA 2006).

7.6. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). The conduct of the study will be in accordance with the ICH Integrated Addendum to E6(R1): Guideline for GCP ICH E6(R2).

This study will be conducted under a protocol reviewed and approved by an appropriate IRB/IEC and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

8. TRIAL OBJECTIVES AND PURPOSE

8.1. Objectives

This study will be performed in breast carcinoma patients with secondary mild to moderate lymphedema following axillary node dissection and/or sentinel lymph node biopsy, with or without radiation, dosed with LYT-100 750 mg BID with for 26-weeks.

Primary Objectives

- To evaluate the safety and tolerability of the double-blinded study medication on breast cancer carcinoma patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy.

Secondary Objectives

- To explore efficacy signals of LYT-100 on:
  - Lymphatic obstruction and subsequent edema,
  - Infection (as characterized by cellulitis and/or lymphangitis), and
  - QoL.
- To assess the population PK profile of the double-blinded study medication
  - To describe the association between fibrotic and inflammatory biomarkers, in particular: TGF-β1, and disease progression in mild to moderate lymphedema.

8.2. Endpoints

Primary Endpoints

- AEs, physical examination, vital signs, ECGs, clinical laboratory parameters (hematology, serum chemistry, coagulation, and urinalysis) and concomitant treatments.

Secondary Endpoints

- Efficacy (see Section 17)
  - Limb water content, by BIS
  - Limb volume (truncated cone tape measure and/or perometry)
  - Tissue dielectric constant (MoistureMeterD)
  - Tissue firmness (tonometry/SkinFibroMeter)
  - Visual analog scales for pain, swelling, discomfort, and function
- Health-related QoL
  - LYMPH-Q – Upper Extremity Module (Appendix 2)
  - LYMQOL (Appendix 3)
- Infection

  - Cellulitis
  - Lymphangitis
- Population PK parameters
- Fibrotic and Inflammatory Biomarkers:
  - Fibrotic and inflammatory biomarkers (G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxinα**/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP1)**

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

This study will be a 26-week randomized, double-blind, placebo-controlled assessment of LYT-100 at multiple study centers in patients with secondary lymphedema following axillary node dissection and/or sentinel lymph node biopsy treatment for breast carcinoma.

Informed consent will be obtained prior to each study part. Screening will be performed up to 28 days prior to administration of the first dose of LYT-100. Only patients who meet all of the applicable inclusion and none of the applicable exclusion criteria will be enrolled.

9.1.1. Treatment Period

This is a double-blind, parallel, placebo-controlled study being conducted to evaluate the safety and efficacy of LYT-100 compared to placebo. This study will be conducted across multiple centers in the US and Australia, with approximately 50 patients randomized to receive LYT-100 or placebo at a ratio of 1:1. LYT-100 dosing is to be titrated starting at 500 mg BID during the first 3 days of dosing, followed by 750 mg BID thereafter.

Patients will take double-blind study medication orally with food BID (approximately 10 to 12 hours between the two daily doses) on an outpatient basis for 26 weeks.

Patients with breast cancer-related lymphedema (BCRL) will be assessed for safety, tolerability, clinical endpoints, PK, and biomarkers while receiving LYT-100 or placebo over the 6-month (26-week) dosing period. If a patient is using a standard of care compression sleeve, compression pump therapy, and/or manual lymphatic drainage at least 4 weeks prior to Screening, they must be agreeable to continuing the same routine care throughout the 6-month (26-week) study treatment period and throughout 2 weeks post-study drug discontinuation. If a patient is not using a standard compression sleeve, compression pump therapy, and/or manual lymphatic drainage ≥ 4 weeks prior to Screening and are not planning to be using these prior to the study, they must be agreeable to not using the lymphedema therapy(s) throughout treatment and 2 weeks post-study drug discontinuation.

Following confirmation of study eligibility, patients will be seen in the clinic for their final baseline assessments (Day -1). Patients will begin their BID dosing of study medication on the following morning (Study Day 1) and will continue for 26 weeks, with clinic visits at Weeks 1, , 4, 8, 12, 16, 20, and 26.

All patients will be monitored for safety (including assessment of hematology, serum chemistry, coagulation, and urinalysis parameters, ECGs, vital signs, and AEs). Efficacy assessments will include clinical and QoL measures at time points as delineated in the Schedule of Events (Table 5). Sparse PK samples will be obtained for population PK analysis to determine the variability of LYT-100 drug concentration data in individual patients across multiple clinical sites. Fibrotic and inflammatory biomarkers will be assessed for changes from baseline. With patients using compression sleeves, compression pumps and/or lymphatic drainage as a treatment modality at least 4 weeks prior to and at Screening, they will remain on compression treatments and/or manual lymphatic drainage during the treatment period as noted. Compression sleeves will be removed upon arrival at each study visit and until after the bioimpedance assessment is collected, which should be scheduled at the end of the visit. Time of sleeve

removal will be noted at each study visit. In addition to routine practices such as diet, exercise, or skin care, use or non-use of compression sleeves, compression pumps and/or lymphatic drainage will be recorded in the Patient Diary 1 week prior to each study visit with lymphedema assessments, including frequency of use and the number of hours used on each occasion. Any disruptions in taking study medication as instructed will also be recorded in the Patient Diary.

9.1.2. Follow-Up

Safety and tolerability will be assessed throughout the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis), and review of concomitant treatments/medication use.

Patients will return to the clinic 28 ± 3 days from the last dose of study medication for a safety follow-up visit as delineated in the Schedule of Events (Table 5).

In the event of premature discontinuation from the study, patients will return to the investigative site and complete an early termination visit with assessments as delineated in the Schedule of Events (Table 5). Following the early termination visit, patients will be asked to return to the investigative site for one last safety follow-up visit, approximately 28 days from the last dose of study medication.

9.2. Number of Patients

Approximately 50 patients, randomized to LYT-100 or placebo in a 1:1 ratio, with breast cancer-related upper limb unilateral secondary lymphedema.

9.3. Treatment Assignment

Novotech will prepare a randomization list and will manage the randomization of eligible patients accordingly. A randomization list will be prepared using a statistical software package by a Novotech Biostatistician.

Each patient will be provided with a unique screening number post documentation of informed consent. Once deemed eligible for enrolment in the study, the patient will be assigned a sequential randomization number prior to first dosing. Patients who withdraw from the study during Screening, for any reason, without completing all necessary screening assessments will be considered screen failures. Screen failures will not receive a randomization number; however, source documents may be transcribed onto the electronic Case Report Forms (eCRFs).

Randomization will be stratified by higher risk of lymphedema progression (axillary lymph node dissection) versus lower risk of lymphedema progression (sentinel node biopsy) (Table 8). Patients will be stratified upon enrolment into the standard compression sleeve, compression pump therapy, and/or manual lymphatic drainage stratum compression versus non-compression/non-lymphatic drainage groups stratum.

Table 8. Baseline Randomization Stratification Levels

Compression Sleeve, Compression Pump, and/or Lymphatic Drainage			
Yes		No	
Risk for Progression		***Risk for Progression***	
High (history of axillary lymph node dissection and/or regional lymph node radiation posterior field with or without supraclavicular)	Low (history of sentinel node biopsy or excision/clearance)	High (history of axillary lymph node dissection and/or regional lymph node radiation posterior field with or without supraclavicular)	Low (history of sentinel node biopsy or excision/clearance)

9.4. Safety Review Committee

The study will be subject to oversight by an SRC comprised of the PI, MM, and Sponsor representative as core members and guided by an SRC charter. The SRC will convene to review any safety signals deemed relevant relative to the study conduct i.e., incidence and nature of any AEs, SAEs, vital sign changes, changes in physical findings, ECGs, and laboratory abnormalities.

The SRC will convene after 20% of the patients enrolled on study have completed Week 8 of the Treatment Phase and the double-blind data is available for review**.** If safety or tolerability issues are identified by the MM for patients while receiving LYT-100 versus placebo at *any time*, the SRC may meet to review safety and available population PK data and provide recommendations**.** Options for changes to dosing or protocol assessments may be recommended by the SRC. Ultimate decisions regarding those recommendations remain with the Sponsor

AEs of special interest including elevated liver enzymes (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin elevations), photosensitivity and rash, and gastrointestinal disorder (e.g., nausea, vomiting diarrhea, dyspepsia, gastroesophageal reflux, and abdominal pain) will be reviewed by the MM periodically for changes in IP tolerability throughout the trial and, if warranted, may trigger additional ad hoc SRC meeting(s).

Following each review, the SRC will make the following recommendations:

1. To continue the study as planned.
2. To continue the study with modifications.
3. To temporarily suspend or terminate the study.

If at any time the study is terminated, a written statement fully documenting the reasons for termination will be provided to the relevant IRB/IEC

9.5. Dose Adjustment Criteria

Dose adjustment guidance for non-hematological adverse events are listed below.

Table 9. Non-Hematological Adverse Events Dose Adjustment Guidance

	Grade 1	Grade 2	Grade 3	Grade 4
Abdominal Pain*	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750 mg BID dosing If with dose reduction it does not resolve to ≤ grade 1, stop treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID	Cease treatment until resolved to ≤ grade 1, then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID If the same AE at grade 3 recurs upon re-escalation to 750 mg BID, cease treatment until resolved to ≤ grade 1, then continue with 500mg BID If the same AE recurs at grade 3, permanently discontinue LYT-100 Involve a gastroenterologist if needed as per PI's and medical monitor's judgement	Permanently discontinue LYT-100
Diarrhea	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750 mg BID dosing	Cease treatment until resolved to ≤ grade 1, then re-titrate by administering 500 mg BID over a period of 3 days	Permanently discontinue LYT-100

		If with dose reduction it does not resolve to ≤ grade 1, stop treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID	then escalate to 750 mg BID If the same AE at grade 3 recurs upon re-escalation to 750 mg BID, cease treatment until resolved to ≤ grade 1, then continue with 500 mg BID If the same AE recurs at grade 3, permanently discontinue LYT-100 Involve a gastroenterologist if needed as per PI's and medical monitor's judgement	
Vomiting	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750 mg BID dosing If with dose reduction it does not resolve to ≤ grade 1, stop treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period	Cease treatment until resolved to ≤ grade 1, then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID If the same AE at grade 3 recurs upon re-escalation to 750 mg BID, cease treatment until resolved to ≤ grade 1, then continue with 500 mg BID	Permanently discontinue LYT-100

		of 3 days then escalate to 750 mg BID	If the same AE recurs at grade 3, permanently discontinue LYT-100 Involve a gastroenterologist if needed as per PI's and medical monitor's judgement	
Photosensitivity/Rash**	Maintain LYT-100 dose	Stop treatment until resolved to ≤ grade 1 then resume by titrating with 500 mg BID for 3 days then escalating to 750 mg BID 750 mg BID dosing If the AE recurs at grade 2, stop until resolved to ≤ grade 1, then resume 500 mg BID dosing	Permanently discontinue LYT-100	Permanently discontinue LYT-100
Weight Loss	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750 mg BID dosing If with dose reduction it does not resolve to ≤ grade 1, stop	Cease treatment until resolved to ≤ grade 1 then resume 750 mg BID dosing If with dose reduction it does not resolve to ≤ grade 1 permanently discontinue LYT-100	Permanently discontinue LYT-100

		treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID		
Dyspepsia/ Gastro-esophageal Reflux	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750mg BID dosing If with dose reduction it does not resolve to ≤ grade 1, stop treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID	Cease treatment until resolved to ≤ grade 1, then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID If the same AE at grade 3 recurs upon re-escalation to 750 mg BID, cease treatment until resolved to ≤ grade 1, then continue with 500 mg BID If the same AE recurs at grade 3, permanently discontinue LYT-100	Permanently discontinue LYT-100
Other non-hematological AEs	Maintain LYT-100 dose	Dose reduce to 500 mg BID until resolved to ≤ grade 1 then resume 750mg BID dosing If with dose reduction it	Cease treatment until resolved to ≤ grade 1, then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID	Permanently discontinue LYT-100

		does not resolve to ≤ grade 1, stop treatment until resolved to ≤ grade 1 then re-titrate by administering 500 mg BID over a period of 3 days then escalate to 750 mg BID	If the same AE at grade 3 recurs upon re-escalation to 750 mg BID, cease treatment until resolved to ≤ grade 1, then continue with 500 mg BID If the same AE recurs at grade 3, permanently discontinue LYT-100	

*Includes lower abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort. **Rash includes acneiform and maculo-papular

Dose adjustment guidance for hematological adverse events are listed below.

Table 10. Hematological Adverse Events Dose Adjustment Guidance

	Dose modification
ANC ≥ 1.0 mm3	No dose modification
0.5 < ANC < 1.0 mm3	Stop LYT-100, repeat blood test in 48-72 hrs, or at a clinically indicated time interval, and when resolved to ANC>1.0 then resume at 500mg BID for 3 days followed by 750mg BID If the same AE repeats, stop LYT-100, repeat blood test in 48-72 hrs, or at a clinically indicated time interval, and when resolved to ANC>1.0 then resume at 500mg BID If the same AE repeats, discontinue LYT-100 permanently
ANC < 0.5 mm3	Discontinue LYT-100 permanently
Hgb ≤ 8.5 g/dL	Stop LYT-100, clinically manage as appropriate and when Hgb > 10.0 resume LYT-100 at 500mg BID for 3 days followed by 750MG BID If the same AE repeats, permanently discontinue LYT-100
Platelets > 100,000 mcL	No dose modification

Platelets 50,000-100,000 mcL	Stop LYT-100 until resolved to >100,000 then resume at 500mg BID for 3 days followed by 750mg BID If the same AE repeats, stop LYT-100, repeat blood at a clinically indicated time interval, and when resolved to >100,000 then resume at 500mg BID If the same AE repeats, discontinue LYT-100 permanently
Platelets < 50,000 mcL	Stop LYT-100 until resolved to >100,000 then resume at 500mg BID for 3 days followed by 750mg BID If the same AE repeats, permanently discontinue LYT-100

Hepatic Impairment

No dose modifications are needed for AST and/or ALT elevation ≤ 3 x the upper limit of normal (ULN) without symptoms or hyperbilirubinemia.

If a patient exhibits >3 but ≤5 × the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting LYT-100 therapy:

- Discontinue any potential confounding co-medications, exclude other causes, and monitor the patient closely.
- Repeat liver chemistry tests as clinically indicated.
- Dose reduce to 500 mg BD until resolved to ≤ 3 x upper limit of normal (ULN) ALT and/or AST with subsequent re-titration to the full dosage as tolerated.

If a patient exhibits >3 but ≤5 × ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:

- Permanently discontinue LYT-100. Do not rechallenge patient with LYT-100.

If a patient exhibits >5 × ULN ALT and/or AST:

- Permanently discontinue LYT-100. Do not rechallenge patient with LYT-100.

Renal Impairment

No dose modifications are needed for in patients with mild renal impairment (CLcr 50–80 mL/min).

In patients with moderate renal impairment (CLcr 30–50 mL/min):

Discontinue any potential confounding co-medications, exclude other causes, and monitor the patient closely.

- Repeat renal function tests as clinically indicated.
- Dose reduce to 500 mg BD until resolved to CLcr 50–80 mL/min, with subsequent re-titration to the full dosage as tolerated

Avoid use if eGFR less than 30 mL/minute. Patients with end-stage renal diseases requiring dialysis are not eligible.

9.6. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients in the study. This may be determined by the Sponsor, the Investigator, the SRC, the IRB/IEC, or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IRB/IEC, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during the course of termination or study suspension.

10. SELECTION AND WITHDRAWAL OF PATIENTS

10.1. Patient Inclusion Criteria

To be eligible for this study, patients have to meet ***all*** of the following inclusion criteria:

1. Provides written Ethics Committee approved informed consent prior to any study procedures.
2. Female or male aged ≥ 18 years old at the time of informed consent.
3. At least 6 months and no more than 15 years since the most recent type of surgery related to breast cancer including sentinel lymph node biopsy or excision/clearance, axillary lymph node dissection, or any other type of surgery excluding FNA biopsy at the time of study screening. No intention to have breast reconstructive surgery, nipple reconstruction, and/or tattooing during the course of the study.
4. At least 3 months since completion of any neoadjuvant therapy, adjuvant chemotherapy, intravenous biologic therapy (e.g., trastuzumab and pertuzumab), radiotherapy, and/or any investigational adjuvant therapy at the time of study Screening.
5. At least 3 months since initiation of anti-hormonal oral adjuvant therapy as well as goserelin and/or adjuvant zolendronic acid.
6. Diagnosis of primary breast cancer, and without evidence of local, locoregional and/or distant recurrence of breast cancer for at least 6 months since completion of adjuvant therapy (excluding anti-hormonal therapy regimens), as determined at Screening and Baseline.
7. Documented evidence of pitting edema in one arm for at least 3 months and also at Screening, and <u>at least one</u> of the following:
    a. Increase in relative limb volume of between 10% to 25% as measured by perometry or the truncated cone method of circumferential tape measurement compared to any prior documented measurement or relative to measurement of non-affected arm.
    b. A bioimpedance measure of > 10 at baseline visit or a change from pre-surgical measure of > +6.5 L-Dex at Baseline visit; or
    c. Overt signs of lymphedema in the arm clinically indicating Lymphedema Stage I or II and/or confirmed by asymmetry > 2 via LymphaScan (TDC) in swell spot.
8. Receiving standard of care compression or agreeable to using care compression, i.e., sleeves and/or pumps and/or manual lymphatic drainage, or no compression care and/or no manual lymphatic drainage ≥ 4 weeks prior to Screening and throughout the study.
9. In good general health at Screening and Baseline apart from a history of breast cancer and secondary lymphedema, i.e., free from clinically significant unstable medical, surgical, or psychiatric illness (at the discretion of the Investigator); no acute conditions requiring invasive care or hospitalization; and no conditions or elective procedures requiring invasive intervention within the next 6 months.
10. Vital signs (measured in supine position after 10 minutes rest) at Screening:

a. Systolic blood pressure ≥ 90 and ≤ 140 mmHg;

b. Diastolic blood pressure ≥ 50 and ≤ 90 mmHg;

c. Heart rate ≥ 45 and ≤ 100 bpm;

d. Vital signs may be repeated once, within a minimum of 10 minutes of the completion of the last set of vital signs (while maintaining supine positions until the repeated set of vital signs are collected), if it is suspected that falsely high or low levels have been obtained.

11. Body Mass Index (BMI) ≥ 18 and ≤ 50 kg/m^2 at Screening.
12. HIV, HCV, and HBsAg negative at Screening.
13. Adequate venous access in contralateral, unaffected limb.
14. Willing and able to comply with all study procedures and requirements including adherence to maintaining routine in either using or not using compression sleeve, compression pump, lymphatic drainage therapy/self-manual lymph drainage (MLD). Patient should agree to not making extreme changes to their routine, also including diet, exercise, or skin care.
15. Willing and able to abstain from direct whole body sun exposure from 2 days prior to dosing and until final study procedures have been conducted. Patients should be instructed to avoid or minimize exposure to sunlight (including sunlamps), use an SPF 50 sun block, or higher, wear clothing that protects against sun exposure, and avoid concomitant medications known to cause photosensitivity.
16. WOCBP must be non-pregnant and non-lactating, and must use an acceptable, highly effective double contraception or be abstinent from heterosexual intercourse from Screening until study completion, including the follow-up period (please see Section 10.4.3 for acceptable methods of contraception). WOCBP must have a negative pregnancy test at Screening and Day 1 and be willing to have additional pregnancy tests as required throughout the study. Women not of childbearing potential must be postmenopausal for ≥ 12 months or be surgically sterile, including a hysterectomy with retention of ovary function is permitted. Postmenopausal status will be confirmed through testing of FSH levels ≥ 40 IU/mL at Screening for amenorrhoeic female patients.
17. Male patients must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the patient and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period and an additional 12 weeks after the last dose (please see Section 10.4.3 for acceptable methods of contraception).
18. Males must not donate sperm for at least 90 days after the last dose of study drug.
19. Partners of male patients and female patients will report pregnancy occurring within 90 days from cessation of study medication.

10.2. Patient Exclusion Criteria

To be eligible for this study, patients ***must not meet any*** of the following exclusion criteria:

1. Bilateral lymphedema or history of bilateral axillary lymph node removal (i.e., sentinel lymph node biopsy or axillary lymph node dissection), or primary lymphedema or lymphatic or vascular malformation, determined at Screening.
2. Chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs within 3 months prior to study drug administration; corticosteroids are permitted at the discretion of the PI.
3. Recent history (in the 8 weeks prior to Screening) of cellulitis, lymphangitis, dermatitis, necrotizing fasciitis, or current open wounds or sores in the affected extremity.
4. Fibrotic stranding on affected arm not related to BCRL; history of breast or arm procedures unrelated to axillary node dissection such as non-cancer-related reconstructive or cosmetic breast surgery, Botox for hyperhidrosis, chronic intravenous use, port, pic-line, etc. for medical or recreational reasons, tattoos (excluding pink ribbon tattoo designated to inform health caretaker not to take blood pressure in affected arm), or other extreme body modifications, determined at Screening.
5. Relative limb volume > 25%, stage III secondary lymphedema, or history of clinically diagnosed secondary lymphoedema greater than 4 years, determined at Screening.
6. Initiated use of compression or manual lymphatic drainage or other lymphedema therapies at the start of the study within 4 weeks of the Screening visit. Rescreening is allowed following a course of stable compression regimen of > 4 weeks.
7. Metal implant(s) including implantable cardioverter defibrillators, cardiac resynchronization therapy-defibrillators, and pacemakers that may be affected by assessments used in the trial, e.g., bioimpedance, and/or that may inconsistently affect collection of secondary lymphedema assessments.
8. Presence of malignancy, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma), carcinoma in-situ of the cervix, or unilateral breast cancer history with completed treatment and with no active cancer at the time of Screening or in the preceding 6 months.
9. Evidence of clinically relevant medical history/illness at Screening, as determined by the Investigator, including stroke, uncontrolled hypertension, and other cardiac disease, vascular disease, pulmonary disease, gastrointestinal disease, hepatic disease, renal failure and other kidney disease, rheumatologic disease, coagulopathy or other hematological disease, uncontrolled diabetes and other endocrine disorders, any progressive neurologic disorder, psychiatric disease, dermatological disorder, or surgical history except for orthopedic and reconstructive breast cancer surgery.
10. Clinically significant infection within 28 days of the start of dosing, as determined by the Investigator.

11. Clinically significant surgical procedure/s, including but not limited to breast cancer reconstruction surgery, within 3 months of Screening, or further breast cancer reconstruction surgery planned during the Study.
12. For baseline LFTs, 2.5 × upper normal limit (UNL) or severe hepatic impairment.
13. Positive test for HCV, HBsAg, or HIV antibody at Screening.
14. Currently suffering from clinically significant systemic allergic disease at Screening or Baseline or has a history of significant drug allergies including a history of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
15. Pregnant or lactating at Screening or planning to become pregnant (self or partner) at any time during the study, including the follow-up period.
16. Symptoms of dysphagia or known difficulty in swallowing capsules, determined at Screening.
17. History or presence of cardiac arrhythmia or congenital long QT syndrome determined at Screening.
18. QTcF > 450 msec demonstrated by two ECGs between 30 and 60 minutes apart at Screening.
19. Use of tobacco or nicotine-containing products in the previous 30 days prior to dosing or a positive urine cotinine test at Screening or Baseline.
20. Lack of willingness to abstain from the consumption of tobacco or nicotine-containing products throughout the duration of the study and until completion of the final follow-up visit.
21. Regular alcohol consumption defined as > 21 alcohol units per week (where 1 unit = 284 mL of beer, 25 mL of 40% spirit, or a 125 mL glass of wine), determined at Screening.
22. Positive toxicology Screening panel (urine test including qualitative identification of barbiturates, , amphetamines, , opiates, and cocaine) or alcohol breath or urine test, determined at Screening. Repeat urine toxicology screenings may be conducted.
23. History of substance abuse or dependency or history of recreational IV drug use over the last 2 years, determined at Screening.
24. Use of any over-the-counter medication, herbal supplements, or diet aids within 48 hours prior to dosing, without the prior review and approval of the PI and medical monitor
25. Treated with immunosuppressive or antifibrotic drugs, anti-tumor necrosis factor, immunotherapy, or investigational drugs at Screening or within the preceding 30 days.
26. Use of any of the following drugs within 28 days or 10 half-lives of that drug, whichever is the longer, prior to study drug administration:
    a. Fluvoxamine, enoxacin, ciprofloxacin
    b. Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)

c. Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)

d. Drugs associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol)

27. Use of any investigational drug or device within 28 days or 10 half-lives of the drug, whichever is the longer, prior to start of dosing.
28. Clinically significant blood loss or any blood or blood product donation > 250 mL within 28 days of start of dosing.
29. Any condition (e.g., chronic diarrhea, inflammatory bowel disease, or prior surgery of the gastrointestinal tract) that would interfere with drug absorption or any disease or condition that is likely to affect drug metabolism, or excretion, determined at Screening.
30. History of anaphylactic reaction (particularly reactions to general anesthetic agents); allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
31. As a result of medical review and physical examination at Screening, the Investigator considers the patient unfit for the study**.**

10.3. Patient Withdrawal Criteria

Patients may withdraw their consent to participate in the study at any time. If a patient withdraws consent, the date and reason for consent withdrawal should be documented. Patients will be encouraged to remain in the CRU to complete all necessary assessments and until the Investigator deems that it is safe to be discharged. Patient data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early termination of individual patients can include:

- Protocol deviations or patient non-compliance (must be specified on the appropriate eCRF)
- Serious or severe AEs
- Administrative decision by the Investigator or the Sponsor
- Death
- Other (must be specified).

Wherever possible, the tests and evaluations, including those listed for the final visit, should be performed for all patients who discontinue prior to the completion of the study.

10.4. Diet, Activity, and Other Restrictions

10.4.1. Medication

Patients are required to have completed their treatment for breast cancer (including but not limited to neoadjuvant, radiotherapy, chemotherapy, and immunotherapy) at least 3 months before Screening, with the exception of adjuvant treatment with hormonal or anti-HER2 therapy (which must be stable for at least 3 months prior to Screening, with no planned changes during the study). If a patient is using a standard of care compression sleeve, compression pump, and/or manual lymphatic drainage for at least 4 weeks prior to Screening, they must be agreeable to continuing the same care throughout treatment and through 2 weeks post-study drug discontinuation. If a patient is not using a standard compression sleeve, compression pump, and/or was using manual lymphatic drainage for at least 4 weeks prior to Screening, they must be agreeable to not using these routine lymphatic therapy(s) throughout treatment and through 2 weeks post-study drug discontinuation.

Immunosuppressants or other immune-modifying drugs are not permitted, except for corticosteroids at the discretion of the Investigator. Chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs must be discontinued at least 30 days prior to study drug administration.

Use of any over-the-counter medication (OTC), herbal supplements, or diet aids should be discontinued at least 48 hours prior to dosing, unless approved by the PI and MM. These may be resumed on study, however the following OTC/supplements are not allowed on study:

- Preparations containing a mixture of more than one of the following: kola nut, grape seed extract, or green tea extract
- Goldenseal
- St. John’s wort
- Curcumin

Treatment with immunosuppressive or antifibrotic drugs, anti-tumor necrosis factor, immunotherapy, or investigational drugs is not permitted during the study, and must be discontinued at least 30 days prior to Screening.

The following drugs are not permitted during the study, and they must be discontinued at least 28 days or 10 half-lives (whichever is the longer) prior to study drug dosing:

- Fluvoxamine, enoxacin, ciprofloxacin
- Other inhibitors of CYP1A2 (including but not limited to methoxsalen or mexiletine)
- Inducers of CYP1A2 (such as phenytoin), CYP2C9 or 2C19 (including but not limited to carbamazepine or rifampin)
- Any drug associated with ***substantial risk for prolongation of the QTc interval*** (including but not limited to moxifloxacin, quinidine, procainamide, amiodarone, sotalol)

Use of investigational drugs or devices is not permitted and must be discontinued at least 28 days or 10 half-lives (whichever is the longer) prior to start of dosing.

10.4.2. Smoking

All patients are required to abstain from tobacco or nicotine-containing products in the 30 days prior to dosing and for the duration of the study until completion of the final follow-up visit.

10.4.3. Contraception

No estrogen preparations (e.g., oestradiol, ethinyloestradiol) are to be used throughout the trial for contraception, hormone replacement therapy, or menopausal replacement therapy.

Acceptable, highly effective double contraception is defined as a condom AND one other form of the following:

- Established hormonal contraception (oral contraceptive pills [OCPs], long-acting implantable hormones, injectable hormones) except for preparations containing oestradiol, ethinyloestradiol
- A vaginal ring or an intrauterine device (IUD)
- Documented evidence of surgical sterilization at least 6 months prior to Screening (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy for women or vasectomy for men [with appropriate post-vasectomy documentation of the absence of sperm in semen] provided the male partner is a sole partner).

Women not of childbearing potential must be postmenopausal for ≥ 12 months. Postmenopausal status will be confirmed through testing of FSH levels ≥ 40 IU/mL at Screening for amenorrhoeic female patients. Females who are abstinent from heterosexual intercourse will also be eligible.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered highly effective methods of birth control. Patient complete abstinence for the duration of the study and for 1 month after the last study treatment is acceptable.

Female patients who are in same sex relationships are not required to use contraception.

Males must be surgically sterile (> 30 days since vasectomy with no viable sperm), abstinent, or if engaged in sexual relations with a WOCBP, the patient and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period. Acceptable methods of contraception include the use of condoms and the use of an effective contraceptive for the female partner that includes: OCPs, long-acting implantable hormones, injectable -hormones, a vaginal ring, or an IUD. Patients with same sex partners (abstinence from penile-vaginal intercourse) are eligible when this is their preferred and usual lifestyle.

10.4.4. Food

Patients are required to take study medication with food.

10.4.5. Other Restrictions

All patients must be willing to abstain from direct whole body sun exposure from 2 days prior to dosing and until final study procedures have been conducted. Patients should be instructed to avoid or minimize exposure to sunlight (including sunlamps), use an SPF 50 sun block, or higher, wear clothing that protects against sun exposure, and avoid concomitant medications known to cause photosensitivity.

All patients must refrain from blood or blood product donation > 250 mL within 28 days of Screening, and blood or blood products donation is not permitted from Screening until the final visit.

11. TREATMENT OF PATIENTS

11.1. Description of Study Drug

The LYT-100 drug product and matching placebo are presented as follows:

- LYT-100, 250 mg and matching placebo – Size 0 or 1, Swedish orange opaque, hard-gelatin capsules.

The capsules are packaged in high-density polyethylene (HDPE) bottles and a white, polypropylene screw cap with an induction sealed aluminum inner seal. The IPs should be stored at a controlled room temperature of 15°C to 25°C.

11.2. Prior and Concomitant Medications

11.2.1. Prior Medications

All medications, including over-the-counter (OTC) medications, vitamins, and herbal supplements, taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the Investigator to determine whether the patient is suitable for inclusion in the study.

11.2.2. Concomitant Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken by patients during the course of the study will be recorded in the eCRF and coded using the most current World Health Organization (WHO) drug dictionary available at Novotech. Prior and concomitant medications will be listed by patient and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (PT).

11.3. Treatment Compliance

Patients will be provided with enough LYT-100 study medication bottles to cover the prescribed daily dose until their next study visit. The number of capsules dispensed at each study visit will be recorded in the patient's source documents. Patients will be instructed to retain and return all emptied and non-emptied bottles to each study visit. Study drug capsule counts returned at each visit will be totaled and recorded in the patient's source document record. The difference in the number of capsules dispensed and number of capsules returned will be reconciled against the anticipated number of capsules administered to account for all dosing intervals since the last study visit to determine study drug medication compliance.

A phone application to provide medication reminders will be used to assist the patient with medication adherence during the study treatment phase of the trial.

11.4. Blinding

The study will be double blinded to patients, research staff, the Sponsor and CRO, with the exception of one unblinded statistician who will provide the randomization. There will be specific unblinded members at the site (pharmacist), CRO, and Sponsor to ensure study drug accountability/management is performed accurately and for medical oversite of patient safety.

The Sponsor, Investigator, MM, study personnel, and patients are not to make any effort to determine which study drug therapy is being received. Unblinded pharmacy (or other qualified site) personnel will be used in this study to prepare the study drug.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, the Investigator may unblind a patient's treatment assignment. Please see Section 16.7 for details of the procedure to be followed for randomization code breaking.

As soon as possible, and without revealing the patient's study treatment assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding.

In the event that the Investigator considers an AE to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, the Investigator may break the study code for that patient.

All unblinding events must be reported to the Sponsor, MM, and Novotech promptly.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Study Supplies

The Sponsor will supply the study drug to the investigational site. The study drug provided for this study was manufactured under current Good Manufacturing Practices and will be suitable for human use.

12.2. Study Drug Packaging and Labeling

The Sponsor is responsible for the preparation and labeling of the study drug and for providing details of batch numbers, safety, and stability data.

The study drug is labeled in accordance with local regulatory requirements and will be shipped at a temperature of 15°C to 25°C.

12.3. Study Drug Storage

Upon receipt, the study drug must be stored at 15°C to 25°C.

The Investigator will be fully responsible for the security, accessibility, and storage of the study drug while it is at the investigational facility.

12.4. Study Drug Preparation

Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

12.5. Administration

The Investigator is responsible for the education of study staff and patients as to the correct administration of the study drug.

12.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record given to the study monitor.

12.7. Study Drug Handling and Disposal

On completion of the study, any surplus study drug supplies will be destroyed upon receipt of written approval from the Sponsor and evidence of destruction supplied to the study monitor. If no supplies remain, this will be documented in the dispensing record.

13. STUDY SCHEDULE

Please see Table 5 for Schedules of Event.

Where possible, assessments should be conducted in order of least invasive to most invasive.

13.1. Screening (Visit 1), Day -28 to Day -2

Prior to enrolling in the study, and before performance of any procedures, potential patients will attend a Screening session at which time they will be provided with full information concerning details of the study assessments and procedures. They will also be provided with an Informed Consent Form (ICF). Prior to being asked to sign the ICF, patients will be given time to review study information and ask any questions.

After the consent form is signed, Screening assessments will be carried out as follows:

- Eligibility assessment
- Review of medications, medical/surgical history (including breast cancer, surgical, radiation, and chemotherapy history, and inclusion/exclusion criteria)
- Recording of demographic information
- 12-lead ECG (after patient has been resting in a supine position for at least 5 minutes and prior to blood draws and assessment of vital signs)
- Complete physical examination
- Vital signs (body temperature, heart rate [HR], blood pressure [BP], respiratory rate [RR])
- Height, weight, and BMI
- Pre-treatment AEs and concomitant medication, including name, indication, dose, route, start and end dates. Pre-treatment concomitant medication will include all medications 30 days prior to Screening visit
- Urine pregnancy test: Not required for amenorrhoeic female patients (see below); if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
- FSH test: Amenorrhoeic female patients only; postmenopausal status will be confirmed through testing of FSH levels (≥ 40 IU/mL)
- Blood hematology (complete blood counts and leukocyte differential counts)
- Serum chemistry: including glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, total CO_2], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), ALT or AST, alkaline phosphatase (ALP), creatinine, blood urea nitrogen, and creatine phosphokinase (CPK). LFTs will be collected at each visit and includes bilirubin (total, direct), ALT or AST, and ALP
- Coagulation: INR, prothrombin time, activated partial thromboplastin time (APTT)
- Urinalysis (dipstick – microscopy if abnormal)
- Urine drug screen (including cotinine test) and alcohol breath test

- Patients will be asked to participate in interviews to discuss their Breast Cancer related Lymphedema to help further research. Subjects will either be asked to participate in interviews as part of screening or as part of the post-blinded treatment follow up Visit (week 30)

13.2. Baseline (Visit 2), Day -1

The following assessments will be performed:

- Visual analog scales
- LYMPH-Q—Upper Extremity Module
- LYMQOL
- Eligibility assessment
- Vital signs (Body Temperature, HR, BP, RR)
- Weight and BMI
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Study drug dispensing
- Urine pregnancy test: Not required for amenorrhoeic female patients; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
- Genotyping, for CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Patients are required to provide consent for genotyping.
- Urinalysis (dipstick – microscopy if abnormal)
- Urine drug screen (including cotinine test) and alcohol breath test
- Inflammatory biomarkers: G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxin-α/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP-1
-

Following completion of all baseline assessments, and assuming patients still meet all eligibility criteria, patients will be randomized to study treatment. Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 3. Study drug self-administration begins on Day 1.

13.3. Visit 3 (Week 1, +2 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- Concomitant medication
- AE monitoring
- Review patient diary
- 12-lead ECG (QTcF), to collected 2.5 (+/- 15 minutes) after the morning study drug dose
- Symptom directed physical exam
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse PK blood sample collection
- Blood hematology
- Serum chemistry
- Coagulation
- Urinalysis
- Inflammatory biomarkers

Patients will then be provided with a quantity of study medication sufficient for self-administration BID until Visit 4.

13.4. Telephone Visit (Week 2, ± 3 days)

Phone call made with patients to assess ongoing study medication compliance, AEs, concomitant medications, and reminder to complete the Patient Diary 1 week prior to Visit 4 (Week 4).

13.5. Visit 4 (Week 4, ± 3 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse PK blood samples
- Blood hematology
- Serum chemistry (including LFT panel)
- Coagulation
- Urinalysis

Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 5.

13.6. Visit 5 (Week 8, ± 3 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter

- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse PK blood samples
- Serum chemistry (including LFT panel)
- Inflammatory biomarkers

Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 6.

13.7. Visit 6 (Week 12, ± 3 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- 12-lead ECG (QTcF), to be collected 2.5 (+/- 15 minutes) after the morning study drug dose
- Symptom directed physical exam
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse PK blood samples
- Urine pregnancy test: Not required for amenorrhoeic female patients; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Blood hematology
- Serum chemistry (including LFT panel)
- Coagulation
- Urinalysis

Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 7.

13.8. Visit 7 (Week 16, ± 3 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse PK blood samples
- Serum chemistry (including LFT panel)
- Inflammatory biomarkers

Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 8.

13.9. Visit 8 (Week 20, ± 3 days)

Patients will attend an onsite visit at the CRU. The following assessments will be performed:

- Visual analog scales
- LYMPH-Q
- LYMQOL
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume

- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (weight, BMI, body temperature, HR, BP, RR)
- Study drug dispensing and drug accountability
- Sparse pharmacokinetic blood samples
- Serum chemistry (including LFT panel)

Patients will be provided with a quantity of study medication sufficient for self-administration BID until Visit 9.

13.10. Telephone Visit (Week 23, ± 3 days)

Phone call made with patients to assess ongoing compliance, AEs, concomitant medications, and reminder to take study medication through the morning of their Week 26 visit and to complete the Patient Diary 1 week prior to Visit 9 (the Week 26 clinic visit).

13.11. Visit 9 (Week 26 ± 3 days) or Early Termination

Patients will attend an onsite visit at the CRU. This visit marks the conclusion of the study treatment. The following assessments will be performed:

- Visual Analog Scales
- LYMPH-Q
- LYMQOL
- 12-lead ECG (QTcF)
- Symptom directed physical exam
- Concomitant medication
- Adverse events
- Review patient diary
- Bioimpedance
- Limb volume
- MoistureMeterD
- Tonometry/Skin FibroMeter
- Vital signs (BMI, weight, body temperature, HR, BP, RR)
- Study drug accountability only - no further dispensing
- Sparse PK blood samples
- Urine pregnancy test: Not required for amenorrhoeic female patients; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test

- Blood hematology
- Serum chemistry
- Coagulation
- Urinalysis
- Urine drug screen (including cotinine test) and alcohol breath test
- Inflammatory biomarkers

13.12. Visit 10 (Final Safety Visit), 28 ± 3 Days After Termination of Study Treatment

Patients will attend an onsite visit at the CRU. Every effort should be made to conduct this final safety visit for both completers and patients who terminated early from study treatment. The following assessments will be performed:

- 12-lead ECG (QTcF)
- Symptom directed physical exam
- Concomitant medication
- Adverse events
- Vital signs (BMI, weight, body temperature, HR, BP, RR)
- Blood hematology
- Serum chemistry
- Coagulation
- Urinalysis
- Patients will be asked to participate in qualitative interviews about their Breast Cancer-related Lymphedema. Subjects will either be asked to participate in interviews as part of screening or as part of the post-blinded treatment follow-up Visit (week 30)

14. PHARMACOKINETIC AND FIBROTIC AND INFLAMMATORY BIOMARKER ASSESSMENTS

14.1. Blood and Urine Sample Collection

Blood samples (for PK and fibrotic and inflammatory biomarker analysis) and urine samples (for Screening and safety evaluations) will be obtained at the time points delineated in the Schedule of Events (Table 5). The actual collection time of each sample must be recorded in the source data documentation, on the collection tube, and in the eCRF.

All blood and urine samples will be collected in accordance with the site's standard operating procedures and will be processed according to instructions provided in the Laboratory Manual at the time points delineated in the Schedule of Assessments.

The total volumes of blood to be taken from each patient is detailed in Appendix 1. Blood samples will be drawn from the opposite arm from the site of axillary dissection and sentinel node biopsy.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

14.1.1. Pharmacokinetics

Blood samples (4 mL each) for population PK will be collected at specified times at any on-treatment visit from Week 1 to Week 26 of the study. Throughout the course of the study, each patient will provide up to a minimum of 1 sample at each timepoint in reference to dosing: Pre-dose, 1 to < 2 hours, 2 to < 4 hours, 4 to < 8 hours, 8 to 12 hours. The following is an example of blood collection options:

- Week 1(**4 to < 8 hours** sample collected)
- Week 2 (**pre-dose** sample collected; *note, the patient should bring medication with them to the visit to take it following the PK blood collection*)
- Week 4 (**1 to < 2 hours**, **2 to < 4 hours** samples collected; *note, the site can collect two timepoints at the same visit if the patient plans to be at the site for an extended period of time*)
- Week 20 (**8 to 12 hours** sample collected; *note, again, the patient should bring medication with them to the visit if next dose is due shortly after the blood collection*).

For trough or later timepoint intervals such as 8 to 12 hours, the patient should be instructed to hold their next study medication dose and bring it with them to their study visit(s) to accommodate the longer time intervals required from their last dose taken.

14.1.2. Fibrotic and Inflammatory Biomarkers

Blood samples will be collected for assessment at the time points delineated in the Schedule of Events (Table 5):

- Fibrotic and inflammatory biomarkers (G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxin-α/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, MCP-1).

Of these, the TGF-β1 biomarker is of primary interest.

These data may be reported separately in a supplementary report to the main Clinical Study Report.

14.1.3. Quality of Life

The following will be assessed at Day -1, Weeks 1, 12, and 26 (or early termination), and during follow-up post end of treatment (Weeks 28):

- LYMPH-Q (Appendix 2)
- LYMQOL (Appendix 3)

14.2. Sample Analysis

Plasma PK and fibrotic and inflammatory biomarker sample analysis will be performed using validated procedures and methods as outlined in the Laboratory Manual. The methods used for PK analysis and TGF-β1 will be appropriately validated. Methods for other biomarkers will not be validated, as these biomarkers are exploratory only.

15. ASSESSMENT OF SAFETY

Safety and tolerability will be assessed throughout all parts of the study by monitoring AEs, physical examination, vital signs, 12-lead ECGs, clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis), and review of concomitant treatments/medication use.

15.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 5). However, if a patient is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

15.1.1. Demographic/Medical History

Medical history (including alcohol and smoking status), date of birth, age (calculated), sex, ethnicity, and race will be recorded at Screening.

15.1.2. Vital Signs

Vital signs (body temperature, BP, HR, RR) will be measured at the time points specified in the Schedule of Assessments with patients resting for at least 5 minutes in a supine position. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible while ensuring the blood draw is within the window specified in the protocol.

Additional vital signs may be performed at other times if deemed necessary.

15.1.3. Weight and Height

Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the Schedule of Assessments and will be used to calculate BMI. BMI is calculated by dividing the patient's body weight in kilograms by the patient's height in meters squared (kg/m^2). Body weight and height will be obtained with the patient's shoes and jacket or coat removed.

15.1.4. Physical Examination

Complete and directed physical examinations will be performed by a licensed physician at the time points specified in the Schedule of Assessments.

Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.

Directed physical examinations may include head, ears, eyes, nose, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, lymph nodes, and any pertinent system based on any prior findings, at the discretion of the Investigator.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

15.1.5. Electrocardiogram

A 12-lead ECG will be taken at the time points delineated in the Schedule of Assessments. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with patients in a supine position. Patients must be in this position for at least 5 minutes before the reading is taken.

All ECG tracings will be reviewed by the PI or designee.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

15.1.6. Laboratory Assessments

Safety laboratory tests (hematology, serum chemistry, coagulation, and urinalysis) will be performed at the time points specified in the Schedule of Assessments. Additional clinical laboratory tests may be performed at other times if deemed necessary based on the patient's clinical condition.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

A blood sample will be taken from each patient for hematology, coagulation, and serum chemistry analyses at the time points delineated in the study schedules.

15.1.6.1. Hematology

Hematology parameters to be tested are:

- Hemoglobin (HGB)
- Hematocrit (HCT)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes with differential — including Eosinophils (ESN), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM), and Reticulocytes (RETI)

15.1.6.2. Serum Chemistry

Serum chemistry parameters to be tested are:

- C-reactive protein (CRP)
- Urea (U)
- Creatinine (CREAT)
- Total Bilirubin (BILI) and Direct Bilirubin (BILIDIR)
- Urate (URATE)
- Albumin (ALB)

- Globulin (GLOBUL)
- Alkaline Phosphatase (ALP)
- Creatine phosphokinase (CPK)
- Troponin 1 (TROP1)
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Gamma- glutamyl transpeptidase (GGT)
- Glucose (GLU) (fasting labs only)
- Sodium (NA)
- Potassium (K)
- Calcium (CA)
- Chloride (CL)
- Phosphate (PHOS)
- Bicarbonate (BICARB)

15.1.6.3. Coagulation

Coagulation parameters to be tested are:

- INR
- Prothrombin time
- APTT

15.1.6.4. Urinalysis

A urinalysis test (dipstick) will be performed for each patient. Urinary analysis will be performed at Screening and other times according to the study schedule. If abnormality is noted for protein, blood, nitrite, or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of RBC, white blood cells, bacteria, and casts will be performed.

Macroscopic urinalysis parameters to be tested are:

- pH (PH)
- Specific Gravity (SPGRAV)
- Creatinine (CREATININE)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)

- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

15.1.6.5. Urine Drug Screen

A urine drug screen will be performed at the time points outlined in the Schedule of Assessments and will include Screening for:

- Amphetamines (AMP)
- Methamphetamines (MET)
- Methadone (MTD)
- Barbiturates (BAR)
- Cocaine (COC)
- Opiates (OPI)
- Methylenedioxymethamphetamine (MDMA)
- Phencyclidine (PCP)
- Cotinine (as indicated)

15.1.6.6. Alcohol Breath Test

An alcohol breath test will be performed at the time point indicated in the Schedule of Assessments.

15.1.6.7. Pregnancy Testing

A urine pregnancy test will be performed at the time points indicated in the Schedule of Assessments for WOCBP only. If a urine test is positive, a serum test will be performed immediately for confirmation.

15.1.6.8. Follicle-Stimulating Hormone Test

Postmenopausal status will be confirmed and documented through confirmation of FSH levels (≥ 40 IU/mL) at Screening for amenorrhoeic female patients, as applicable.

15.1.6.9. Genotyping

CYP1A2, CYP2C9, CYP2C19, and CYP2D6 genotyping is conducted prior to study entry as indicated in the Schedule of Assessments; patients are required to provide consent for genotyping.

16. ADVERSE AND SERIOUS ADVERSE EVENTS

In this study, AEs will be reported for all patients from the time of consent until the completion of the follow-up/EOS visit. AEs reported prior to the first dose will be denoted as pre-treatment. SAEs will be reported for all patients (enrolled and not enrolled) from the time of consent. AEs reported from the time of consent to confinement on Day -1 will be recorded as pre-treatment AEs. Treatment-emergent AEs will be evaluated from the first administration of study drug until the EOS visit. AEs that are ongoing at the final onsite visit will be marked as Not Recovered/Not Resolved on the AE eCRF page (see Section 16.1.4).

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the patient's medical records and the eCRF.

Infection due to cellulitis and lymphangitis will be reported as an AE. When noted, the Australian Lymphology Association's Infection/ Cellulitis Form will also be completed (see Appendix 4).

16.1. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition;
- New conditions detected or diagnosed after study drug administration that occur during the reporting periods, even though it may have been present prior to the start of the study;
- Signs, symptoms, or the clinical sequelae of a suspected interaction;
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or concomitant medications (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE;
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Causality/relation to study treatment
- Action taken regarding study drug
- Outcome

16.1.1. Severity of an Adverse Event

Severity of AEs will be graded by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0) or as follows:

- **Mild (Grade 1):** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2):** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.
- **Severe (Grade 3):** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4):** A type of AE that places the patient at immediate risk of death.
- **Death (Grade 5):** Events that result in death.

16.1.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the patient's environment or clinical state, therapeutic interventions or concomitant drugs administered to the patient. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Possible:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the patient's clinical state, other therapeutic interventions, or concomitant drugs administered to the patient.
- **Probable:** The event follows a reasonable temporal sequence from the time of study drug administration and follows a known response to the study drug and cannot be

reasonably explained by other factors such as the patient's clinical state, other therapeutic interventions, or concomitant drugs administered to the patient.

16.1.3. Action Taken with Investigational Products

Should the Investigator need to alter the administration of the study drug from the procedure described in the protocol due to the well-being and safety of the patient then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

16.1.4. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved or attributable to other (defined) cause
- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving, up to a 30-day follow-up period for treatment-related AEs
- Fatal
- Unknown (or patient lost to follow-up after 4 attempts at contact over a period of 30 days)

16.2. Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the study drug (active or placebo), that fulfills one or more of the following:

- Results in death.
- It is immediately life-threatening.
- It requires in-patient hospitalization or prolongation of existing hospitalization.
- It results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the patient, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered "life-threatening" if, in the opinion of either the Investigator or the Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

16.2.1. Notification of a Serious Adverse Event

All SAEs regardless of relationship to the IP during the period starting from the time of informed consent through the follow-up visit, will be recorded in the eCRF. Once the Investigator becomes aware of an SAE, they must report the SAE to the Clinical Research Organization (CRO) Safety Department within 24 hours of knowledge of the event.

A written SAE report must include a full description of the event including the below parameters (include any protocol specific requirements):

- Diagnosis or description of event
- Onset date
- Severity assessment
- Causal relationship to the IP
- Assessment of seriousness of the event
- Corrective treatment administered for the SAE
- Action taken related to IP including the following: dose interruption, dose delay, dose reduction, or IP discontinuation
- Outcome of event and end date

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the CRO Safety Department as soon as information is available.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, scanned, and emailed to the address at the bottom of the report form.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the patient's medical records and in the eCRF.

16.3. Clinical Laboratory Abnormalities and other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., hematology, serum chemistry, coagulation, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as

an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the patient and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

16.4. Recording Adverse Events

AEs spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and SAEs will be collected from the time of consent until the end of the study. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study. AEs that occur during the study must be documented in the patient's medical record, on the AE eCRF, and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 16.2. An AE of severe intensity may not be considered serious.

Pregnancy itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

16.5. Reporting Adverse Events

Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor and/or the CRO Safety Department within 1 business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to the Sponsor and/or CRO Safety Department.

Additional follow-up information, if required or available, should all be emailed to the Sponsor and/or CRO Safety Department within 1 business day of receipt and this should be completed on a follow-up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB/IEC of all SAEs that occur at their site in accordance with the IRB/IEC SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. The investigational site is responsible for notifying its IRB/IEC of these additional SAEs.

16.6. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related, or probably related to the study drug must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient dies or is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a patient dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

16.7. Randomization Code Break

An electronic Interactive Web Response System (IWRS) will be utilized to perform patient randomization (and stratification) using a master randomization list. Therefore, in the event of an emergency and the identification of an individual patient's treatment must be unblinded, the treatment blind for that specific patient can be broken within the IWRS system and made available to appropriate site personnel immediately. A complete audit trail of unblinding will be available within the IWRS.

17. ASSESSMENT OF EFFICACY

Efficacy will be assessed in an exploratory fashion. In general, efficacy will be based on changes from baseline to each post-baseline visit (through the end of treatment at Week 26). The following parameters will be measured at all study visits (except the Screening visit):

- Limb water content, by Bioelectrical impedance spectroscopy (BIS): Multiple frequency BIS (L-dex) provides accurate relative measures of protein-rich fluid in the upper limb of patients. BIS is a non-invasive technique that involves passing an extremely small electrical current through the body and measuring the impedance (or resistance) to the flow of this current. The electrical current is primarily conducted by the water containing fluids in the body. BIS quantifies the amount of protein-rich fluid in lymphedema by comparison of the affected to the non-affected limb.
- Limb volume (perometry): Relative limb volume is measured by perometry. Perometry is a non-invasive technique involving a Perometer (Pero-System), which uses infrared light to scan a limb and obtain measurements of the limb's circumference. The truncated cone tape measure method can be used as a backup if the Perometer is unavailable, or not working at time of the patient visit.
- Tissue dielectric constant (MoistureMeterD): The TDC measures the local tissue water content under the skin at various depths ranging from skin to subcutis. The results are converted into a 0% to 100% scale to reflect subcutaneous fluid deposition that can occur in early stage lymphedema.
- Tissue firmness (tonometry/SkinFibroMeter): A tonometer device is pressed into the skin to measure the amount of force required to make an indent in the tissue. The resulting measurement gauges the degree of firmness or fibrosis (tissue scarring) under the skin to assess the severity of lymphedema. (*r*) at dorsal surface of arm 10 cm below the elbow.
- Visual analog scales for pain, swelling, discomfort, and function: This graphic scale has a straight line with endpoints of 0 and 10 that is marked by the patient to calibrate to their extreme limits of pain, swelling, discomfort and function, ranging from “not at all” to “as bad as it could be”. The higher marks on the line indicates the worse condition.

Additionally, health-related QoL assessments will be collected to assess the following:

- LYMPH-Q (Appendix 2): This is a patient completed questionnaire that measures the degree of symptoms, function, and psychological impact with patients who have upper extremity lymphedema. Symptoms are rated on a 15-item scale (severe, moderate, mild to none) to measure how the arm feels, the function portion is measured on a 12-item scale (extremely difficult, moderately difficult, a little difficult and not at all difficult) to determine arm function capability, and the psychological portion is measured on a 12-item scale (always, often, sometimes, never) to evaluate how a patient feels having lymphedema.
- LYMQOL (Appendix 3): This is a patient completed questionnaire that assesses upper limb lymphedema and symptoms, and ability to perform common functional

activities in patients with BCRL. It addresses the following four domains – Symptoms, Body Image/Appearance, Function, and Mood. Each item is scored as 1 = Not at all; 2 = A little; 3 = Quite a bit; and 4 = A lot. Total scores for each domain are summed and divided by the total number of completed question responses. The overall QoL item ranges from 1 to 10. Lower scores indicate a higher QoL.

- Patient Interviews: Patients will be asked to participate in the qualitative interviews. The interviews will occur during screening and/or after completion of blinded treatment. The sample size was elected to be in line with best practice recommendations for cognitive debriefing of existing measures to provide evidence of content validity. Participants recruited for qualitative interviews will match the main inclusion and exclusion criteria found in the trial protocol (BCRL patients that have at least 6 months and no more than 15 years since the most recent type of breast cancer related surgery, have unilateral upper arm lymphedema no greater than 4 years).

  The interviews will begin with concept elicitation using a set of open-ended questions that ask the patients to spontaneously identify the BCRL symptoms and daily activity impacts they experience. These data will be compared with the content of the existing instruments to determine whether they are complete and relevant in this target population.

  After the open-ended portion of each interview is completed, interviewers will cognitively debrief the BCRL-specific questionnaires included in the current trial protocol. These questionnaires are LYMPH-Q and LYMPHQOL. Participants will be asked to comment on the content of each questionnaire including the clarity of the instructions and the understandability and relevance of each item and its response options.

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Infection due to cellulitis and lymphangitis will be reported as an AE.

- When noted, the Australian Lymphology Association's Infection/ Cellulitis Form will also be completed (see Appendix 4).

18. STUDY COMPLETION AND DISCONTINUATION

18.1. Patient Withdrawal

In accordance with applicable regulations, a patient has the right to withdraw from the study, at any time and for any reason, without prejudice to his future medical care.

If a patient is withdrawn because of an AE, the Investigator must arrange for the patient to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until the PI and MM determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of patients from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or patient noncompliance.

If a patient asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

18.2. Patient Replacement

Patients enrolled who withdraw consent or discontinue for other reasons will not be replaced.

19. TERMINATION OR SUSPENSION OF THE STUDY

The Sponsor, Investigator, and the IRB/IEC reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant IRC/IEC in writing of the study's completion or early discontinuation.

20. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

20.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

The Sponsor has appointed Novotech to manage and monitor the study so as to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitors and the regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that patient confidentiality is respected.

During the study, the monitor will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

20.2. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF

information is to be filled in by site staff as per the eCRF Completion Guidelines. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

20.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

21. STATISTICS

A statistical analysis plan (SAP) will be written that will describe, in greater detail, the analyses to be performed. The sections below provide a summary of the general approach to the analysis. The analysis is consistent with the study design and objectives. Note that this study is not hypothesis testing but rather hypothesis-generating, and thus conclusions regarding outcomes will not be based on inferential tests but rather descriptive outcomes, magnitude of treatment effects, and a preponderance of evidence regarding the risk-benefit profile of LYT-100.

As this study is hypothesis-generating, we will calculate effect sizes (Cohen's D, a standardized difference between the treatment arms) for efficacy and other endpoints as the data warrant. These values may be used to estimate sample sizes and/or power estimates for future clinical studies of LYT-100 in this population.

21.1. Sample Size

This study will randomize approximately 50 patients with secondary lymphedema, in a 1:1 ratio to LYT-100 or placebo, as part of this early development and exploratory study of LYT-100. Formal sample size calculations were not performed; rather, the sample size selected should be adequate for preliminary evaluation of safety, tolerability, efficacy signaling, PK, and fibrotic and inflammatory biomarker parameters in the target patient population.

21.2. General Statistical Plan

Statistical methods will be further outlined in an SAP and approved by the Sponsor prior to any analysis. Procedures outlined in the SAP will supersede protocol specified statistical methods in the event of divergence.

The baseline value for all variables will be the last measurement obtained prior to the patient receiving the first dose of study treatment.

Patient disposition (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study) will be tabulated by treatment group. Summary statistics for days of exposure and concentration of exposure will be provided by treatment group.

AEs, concomitant medications, clinical laboratory findings, physical examinations, ECGs, and vital signs for each patient will be listed and also summarized in tabular form, as appropriate.

Demographic information will be listed for each patient and summarized. TEAEs and laboratory, vital signs, and ECG parameters will be summarized. In addition, change from baseline will be summarized for laboratory and vital sign parameters. Shift tables will also be provided for clinical laboratory results. ECG results will be classified as normal and abnormal and summarized. ECG results for QTcF will also be classified as < 450 msec, 450 to 500 msec or > 500 msec. Changes in physical exams will be described in the final study report.

In general, descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) will be calculated for continuous valued safety data by specified assessment time point. Frequency summaries (i.e., number and percentage of each observed category) will be provided for categorical and ordinal safety data by treatment and by specified assessment time point.

No formal hypothesis testing will be performed for this study.

21.3. Analysis Populations

Patient inclusion into each population will be determined prior to the final analysis. In general:

Safety Population:

The Safety Population will consist of all patients who received any amount of study drug. The Safety Population will be used for the summaries of all safety assessments as well as efficacy/biomarker outcomes.

Full Analysis Set Population:

The Full Analysis Set (FAS) Population is defined as all randomized patients who received at least one dose of double-blinded study medication and had at least one post-baseline efficacy assessment. All efficacy endpoints will be assessed using this population.

Pharmacokinetic Population:

The Pharmacokinetic Population (PP) is defined as all patients who receive the double-blinded study medication and for whom an evaluable concentration-time profile is available for the determination of at least one PK parameter. Patients with emesis after consuming study medication will be assessed on a case-by-case basis for eligibility for inclusion in the PK population. In general, patients who vomit after at least 2 half-lives of the given medication will be included in the PK population (as C_{max} will presumably be reached by that time).

Fibrotic and Inflammatory Biomarker Population:

The Fibrotic and Inflammatory Biomarker Population is defined as all patients who receive the double-blinded study medication and provide biomarker and lymphedema assessment data.

21.4. Safety and Tolerability

All safety assessments, including prior and concomitant medications, AEs, laboratory evaluations, vital signs, ECGs, and other safety assessments will be analyzed using the Safety Population. Data for all endpoints will be tabulated, displayed graphically, or summarized descriptively, as appropriate. Statistical analyses will be descriptive only, no inferential testing will be performed.

21.4.1. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the most current version of the WHO drug dictionary. Prior and concomitant medications will be listed by patient and summarized by treatment using ATC and PT.

21.4.2. Adverse Events

AEs will be coded using the MedDRA® version 23.0. A by patient AE data listing, including verbatim term, PT, system organ class (SOC), treatment, severity, and relationship to study drug will be provided. The number of patients experiencing TEAEs and the number of individual TEAEs will be provided by treatment as well as by SOC and PT. The severity and the relationship to study drug of TEAEs will be summarized by treatment.

21.4.3. Laboratory Evaluations

Laboratory evaluations (including hematology, serum chemistry, coagulation, and urinalysis) will be listed and summarized by treatment and by protocol specified collection time point. This will be done both for actual observed laboratory values and for changes from baseline.

The abnormal urinalysis results (dipstick and microscopy), if applicable, will be listed only.

21.4.4. Vital Signs

Vital signs will be listed and summarized by treatment and by protocol specified collection time point. This will be done both for actual observed vital sign values and for changes from baseline.

21.4.5. Electrocardiogram Values and Results

ECG values will be listed and summarized by treatment and by protocol specified collection time point. This will be done both for actual observed ECG values and for changes from baseline.

21.4.6. Other Safety Assessments

Findings of the following assessments will be listed by patient:

- Medical history
- Pregnancy test/FSH test
- Urine drug screen (including Cotinine Test)/ alcohol breath test
- Physical examination
- Serology (HIV, Hepatitis B and C screen)

21.5. Pharmacokinetics

Sparse PK sampling will be employed for population PK analysis (as a secondary endpoint) to determine the variability of LYT-100 drug concentration data from individual patients across multiple clinical sites.

PK parameter values will be listed and summarized by treatment and assessment time point.

21.6. Fibrotic and Inflammatory Biomarkers

The association between fibrotic and inflammatory biomarkers (in particular TGF-β1), and disease progression in mild to moderate lymphedema will be examined.

Exploratory analysis of fibrotic and inflammatory biomarkers include: G-CSF, MIG, FGF-2, IL-4, IL-10, lymphotoxin α/TNF-β, leptin, IL-6, IL-1β, TNF-α, TGF-β1, MMP-9, TIMP-1, and MCP-1.

For each biomarker of interest, scatterplots of the recorded biomarker value against each of the disease progression metrics (limb water content, limb volume, TDC, tissue firmness, and visual analog scales; see Section 17 and Section 21.7) will be provided on a single set of axes, (with color used to identify the different disease progression metrics). All patients and all time points at which both biomarker assessment and disease progression assessment are performed will be included on the one plot. This will be repeated considering the change from baseline in the

biomarker values as opposed to actual observed values. Further details of this exploratory biomarker analysis will be provided in the SAP.

21.7. Efficacy Endpoints

Analysis of clinical assessments and potential progression or disease will be explored. Comparisons between LYT-100 and placebo will be based on clinical interpretation of effect, magnitudes of effect, and a preponderance of evidence. Estimates of changes over time from these data may be used to power future clinical studies.

Lymphatic obstructions and subsequent edema will be measured using each of the following metrics:

- Limb water content (BIS)
- Limb volume (truncated cone tape measure and/or perometry)
- Tissue dielectric constant (MoistureMeterD)
- Tissue firmness (tonometry/SkinFibroMeter)

For each of these metrics, use of a mixed model for repeated measures (MMRM) will be used to provide model-based estimates of changes over time in each of these outcomes. Descriptive statistics will also be provided at each time point. Details for the model (including covariates to be included) will be provided in the SAP.

The number of occurrences of cellulitis and lymphangitis within the treatment period will be tabulated.

Visual analog scales for pain, swelling, discomfort, and function, and QoL assessments using the LYMPH-Q (Appendix 2) and LYMQOL (Appendix 3) questionnaires will be provided at baseline and treatment period timepoints. Both an MMRM and descriptive statistics will be used to describe the outcomes over time, considering each of their respective domains as listed in Section 17.

22. ETHICS

22.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written approval to the Sponsor before they can enroll any patient into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug (active). The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

22.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP applicable regulatory requirements and the Sponsor's policy on Bioethics.

22.3. Written Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time without prejudice. The patient should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF.

The patient's signed and dated informed consent must be obtained before conducting any study procedures. The patients will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the patient's medical records, as required by the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2), and the ICF will be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legal representative. The date that informed consent was signed will be recorded on the eCRF.

22.4. Data Protection

Patients will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Patients will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, patients will be identified in such reports only by study identification number, gender, and age. All patient data will be held in strict confidence.

23. REGULATORY REQUIREMENTS

The Sponsor will fulfill the obligations that their role entails. Aside from approval by the IRB/IEC, no other regulatory approval will be required.

The Sponsor will file the protocol to an Investigation New Drug following all US FDA requirements.

24. DATA HANDLING AND RECORDKEEPING

24.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

24.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 15 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, study drug accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include but are not limited to: IRB/IEC correspondence, study drug accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution for 15 years.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, they must notify the Sponsor in writing of the new responsible person and/or the new location.

24.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug, but only to the extent that the claim is not caused by the fault or negligence of the patients or Investigator(s).

25. PUBLICATION POLICY

25.1. Publication of Results

The publication, presentation, or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Patient confidentiality will be maintained by referring to individual patients by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented, or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor, the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation, or other disclosure.

The clinical trial will be posted to the Clinicaltrials.gov registry as required by legal agreement, local law, or regulation.

25.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from their staff and the IRB/IEC. Study documents provided by the Sponsor (Protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

The Investigator must ensure that the patient's anonymity is also maintained. Patients should only be identified by their initials and a patient study number on the eCRFs and other source documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

26. QUALITY CONTROL AND QULAITY ASSURANCE

26.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 20.3 for more details regarding the audit process.

The study will be carried out in accordance with the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), Integrated Addendum to ICH E6(R1): Guideline for GCP ICH E6(R2), and the applicable local regulations.

26.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

27. SPONSOR AND INVESTIGATOR OBLIGATIONS

27.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant IRB/IEC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial patients. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

27.2. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant IRB/IEC (if required) and included in the clinical study report.

28. LIST OF REFERENCES

Center for Drug Evaluation and Research (2014). Esbriet (Pirfenidone). NDA 22-535. Pharmacology/Toxicology NDA Review and Evaluation Addendum.

Cormier, J.N., Askew, R.L., Mungovan, K.S., Xing, Y., Ross, M.I., and Armer, J.M. (2010). Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. Cancer *116*, 5138–5149.

King, T.E.J., Bradford, W.Z., Castro-Bernardini, S., Fagan, E.A., Glaspole, I., Glassberg, M.K., Gorina, E., Hopkins, P.M., Kardatzke, D., Lancaster, L., et al. (2014). A Phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med *370*, 2083–2092.

Noble, P.W., Albera, C., Bradford, W.Z., Costabel, U., Glassberg, M.K., Kardatzke, D., King, T.E.J., Lancaster, L., Sahn, S.A., Szwarcberg, J., et al. (2011). Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet *377*, 1760–1769.

Rafii, R., Juarez, M.M., Albertson, T.E., and Chan, A.L. (2013). A review of current and novel therapies for idiopathic pulmonary fibrosis. J Thorac Dis *5*, 48–73.

Rockson, S.G., Keeley, V., Kilbreath, S., Szuba, A., and Towers, A. (2019). Cancer-associated secondary lymphoedema. Nat Rev Dis Primers *5*, 22.

Taniguchi, H., Ebina, M., Kondoh, Y., Ogura, T., Azuma, A., Suga, M., Taguchi, Y., Takahashi, H., Nakata, K., Sato, A., et al. (2010). Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J *35*, 821–829.

APPENDIX 1: Blood Volumes

Table 11: Estimated Blood Volumes

Test	Per Test Volume	Total Number of Samples	Total Volume
CYP1A2, CYP2C9, CYP2C19, and CYP2D6 genotyping	4 mL	1	4 mL
Pregnancy test and/or FSH (as applicable)	4 mL	1	4 mL
Hematology	3 mL	6	18 mL
Blood chemistry	5 mL	10	50 mL
Coagulation	4 mL	6	24 mL
PK	4 mL	8	32 mL
Fibrotic and inflammatory biomarkers	4 mL	5	20 mL
Overall Blood Volume Collected Per Patient			152 mL

Abbreviations: FSH = Follicle-stimulating hormone; PK = Pharmacokinetics.

APPENDIX 2: LYMPH-Q—Upper Extremity Module

LYMPH-Q UPPER EXTREMITY: SYMPTOMS

How does your arm feel (symptoms)?

NOTE: If your breast cancer surgery affected both of your arms, answer each question thinking about the arm that bothers you the most.

Please answer thinking of the PAST WEEK. Please rate the severity of each of these symptoms:

	Severe	Moderate	Mild	None
1. Pain when your arm is touched?	1	2	3	4
2. Pain when your arm is at rest?	1	2	3	4
3. Arm feeling hotter or colder than normal?	1	2	3	4
4. Arm feeling stiff?	1	2	3	4
5. Arm symptoms disturbing your sleep (eg, pain, swelling)?	1	2	3	4
6. Aching feeling in your arm?				
7. Arm feeling numb?	1	2	3	4
8. Pressure in your arm?	1	2	3	4
9. Pain when you move your arm?	1	2	3	4
10.Clumsiness (eg, dropping or spilling things)?	1	2	3	4
11.Tingling in your arm (ie, pins and needles feeling)?	1	2	3	4
12.Arm feeling tired?	1	2	3	4
13.Arm feeling weak (ie, lack of strength)?	1	2	3	4

14.Arm feeling heavy?	**1**	**2**	**3**	**4**
15.Arm swelling?	**1**	**2**	**3**	**4**

LYMPH-Q UPPER EXTREMITY: FUNCTION

How difficult is it for you to use your arm with lymphedema?

	Extremely difficult	Moderately difficult	A little difficult	Not at all difficult
1. Putting on or taking off clothes?	1	2	3	4
2. Washing your hair?	1	2	3	4
3. Buttoning a shirt or coat?	1	2	3	4
4. Holding a phone to your ear?	1	2	3	4
5. Reaching across yourself (eg, to put on a car seatbelt)?	1	2	3	4
6. Gripping a handle (eg, tennis racket, broom)?	1	2	3	4
7. Holding a book to read?	1	2	3	4
8. Using your hand and fingers (eg, type, write)?	1	2	3	4
9. Reaching for an object overhead?	1	2	3	4
10. Holding a bag of groceries?	1	2	3	4
11. Doing household chores that use your arm (eg, vacuum, make bed)?	1	2	3	4
12. Doing physical activities that involve moving your arm (eg, throw a ball, tennis, gardening)?	1	2	3	4

LYMPH-Q UPPER EXTREMITY: PSYCHOLOGICAL

Does lymphedema in your arm(s) affect how you feel?

Please answer thinking of the PAST WEEK. With your arm lymphedema in mind, how often have you felt:

	Always	Often	Sometimes	Never
1. Desperate?	**1**	**2**	**3**	**4**
2. Hopeless?	**1**	**2**	**3**	**4**
3. Angry?	**1**	**2**	**3**	**4**
4. Depressed?	**1**	**2**	**3**	**4**
5. Stressed?	**1**	**2**	**3**	**4**
6. Afraid?	**1**	**2**	**3**	**4**
7. Anxious?	**1**	**2**	**3**	**4**
8. Fed-up?	**1**	**2**	**3**	**4**
9. Unattractive?	**1**	**2**	**3**	**4**
10. Worried?	**1**	**2**	**3**	**4**
11. Irritated?	**1**	**2**	**3**	**4**
12. Frustrated?	**1**	**2**	**3**	**4**

APPENDIX 3: Lymphedema Quality of Life Tool, Arm (Sample)

The score for the individual responses are given below. If the item is not scored and left blank or not applicable this is scored with a 0. Domain totals are calculated by adding the individual scores and dividing the total by the number of questions answered. (If >50% of questions per domain are not answered this cannot be calculated and =0).
The four domains and their corresponding questions are: Function 1 (a–h), 2, 3;
Appearance 4, 5, 6, 7, 8; Symptoms 9, 10, 11, 12, 13, 14; and Mood 15, 16, 17, 18, 19, 20.
Overall quality of life (Q21) is scored as the value marked by the patient, between 0–10.

(1) How much does your swollen arm affect the following daily activities?	Not at all	A little	Quite a bit	A lot
a) occupation	1	2	3	4
b) housework	1	2	3	4
c) combing hair	1	2	3	4
d) dressing	1	2	3	4
e) writing	1	2	3	4
f) eating	1	2	3	4
g) washing	1	2	3	4
h) cleaning teeth	1	2	3	4

(2) How much does it affect your leisure activities/social life?	1	2	3	4

Please give example(s) of this.

.....

.....

(3) How much do you have to depend on other people?	1	2	3	4
(4) How much do you feel the swelling affects your appearance?	1	2	3	4
(5) How much difficulty do you have finding clothes to fit?	1	2	3	4
(6) How much difficulty do you have finding clothes you would like to wear?	1	2	3	4
(7) Does the swelling affect how you feel about yourself?	1	2	3	4
(8) Does it affect your relationships with other people?	1	2	3	4
(9) Does your lymphoedema cause you pain?	1	2	3	4
(10) Do you have any numbness in your swollen arm?	1	2	3	4
(11) Do you have any feelings of 'pins and needles' or tingling in your swollen arm?	1	2	3	4
(12) Does your swollen arm feel weak?	1	2	3	4
(13) Does your swollen arm feel heavy?	1	2	3	4
(14) Do you feel tired?	1	2	3	4
In the past week	1	2	3	4
(15) Have you had trouble sleeping?	1	2	3	4
(16) Have you had difficulty concentrating on things, e.g. reading?	1	2	3	4
(17) Have you felt tense?	1	2	3	4
(18) Have you felt worried?	1	2	3	4
(19) Have you felt irritable?	1	2	3	4
(20) Have you felt depressed?	1	2	3	4
(21) (24) Overall, how would you rate your quality of life at present? Please mark your score on the following scale:	1	2	3	4

Poor	0	1	2	3	4	5	6	7	8	9	10	Excellent

APPENDIX 4: Infection/Cellulitis Form (Sample)

Infection/Cellulitis Form

Name	
Date of Birth	Phone
Postcode	Ref

INFECTION / CELLULITIS

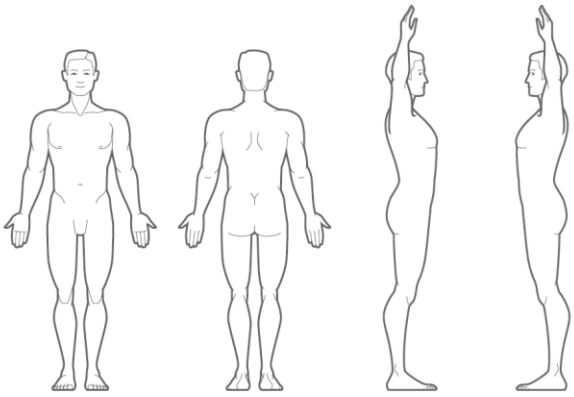
Is the infection/cellulitis most likely to be the cause of lymphoedema?					☐ Yes ☐ No
Is the infection/cellulitis an exacerbating factor of existing L/O?					☐ Yes ☐ No
When was the onset of this episode of infection?			☐ <1 week ago ☐ 1–2 weeks ago ☐ >3 weeks ago		
Cause of infection:	☐ Skin lesion		☐ Insect bite	☐ Fungal	☐ Other:
Site of infection – refer to body diagram					
Extent of infection:					
☐ fingers	☐ hand	☐ forearm	☐ arm	☐ adjacent trunk	☐ breast(s)
☐ toes	☐ foot	☐ calf	☐ thigh	☐ adjacent trunk	☐ genitals
Is the infection active?	☐ Yes ☐ No		Is the infection resolving?		☐ Yes ☐ No
Is this the first episode of infection?	☐ Yes ☐ No		Is this a recurrence?		☐ Yes ☐ No
How many episodes have you had?			☐ 1 ☐ 1–3 ☐ 3–5 ☐ 5–10 ☐ >10		
How frequently has cellulitis occurred?					
Investigations:	Blood culture ☐		Blood count ☐	Swab ☐	Other:
Organism identified:	☐ Yes	☐ No	If yes, describe:		

TREATMENT

Hospitalisation:	☐ Yes	☐ No	Length of stay:	☐ Hospital in the home
Antibiotics:	☐ Oral	☐ Intravenous	☐ Topical	☐ Prophylactic
Other comments/questions:				

DIAGRAM

If completing this form using Acrobat reader, use the sticky note tool to mark diagram.



Signature		Date	

THERAPIST USE

www.lymphoedema.org.au

Australasian Lymphology Association

Excellence in lymphoedema management, research & education