A PHASE 1 STUDY IN HEALTHY VOLUNTEERS TO DETERMINE THE POTENTIAL FOR DRUG-DRUG INTERACTIONS WHEN CO-ADMINISTERING DEUPIRFENIDONE (LYT-100) WITH NINTEDANIB

Protocol Number: LYT-100-2024-03

Authors: PureTech LYT 100, Inc.

Development Phase: Phase 1
Document Version: Protocol Version 2.0

IND Number 153635

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PROTOCOL AUTHORIZATION

Title: A Phase 1 Study in Healthy Volunteers to Determine the Potential for Drug-drug Interactions when Co-administering Deupirfenidone (LYT-100) with Nintedanib

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).

Signed by:
David Golod
Signer Name: David Golod
Signing Reason: I approve this document
Signing Time: 18-Nov-2024 | 09:48 EST
55C56E6C490845BE8B1C4DE585A0BD8F

Printed Name

Signature

Date

INVESTIGATOR'S AGREEMENT

Title: A Phase 1 Study in Healthy Volunteers to Determine the Potential for Drug-drug Interactions when Co-administering Deupirfenidone (LYT-100) with Nintedanib

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), or Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the sponsor and the appropriate ethics committee, except where necessary to avert an immediate hazard to the subjects.

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), in accordance with the current version of International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and in accordance with the current version of National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will also be in accordance with the Integrated Addendum to ICH E6 (R1), Guideline for GCP ICH E6 (R2) and in compliance with regulation EU CTR 536/2014.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 2.0, 18 November 2024 **The following changes are incorporated into Version 2.0 of the protocol:**
Description of change and rationale for change: Increased screening period to 28 days **Section(s) of the protocol affected:** Synopsis, Table 1, Section 3.1

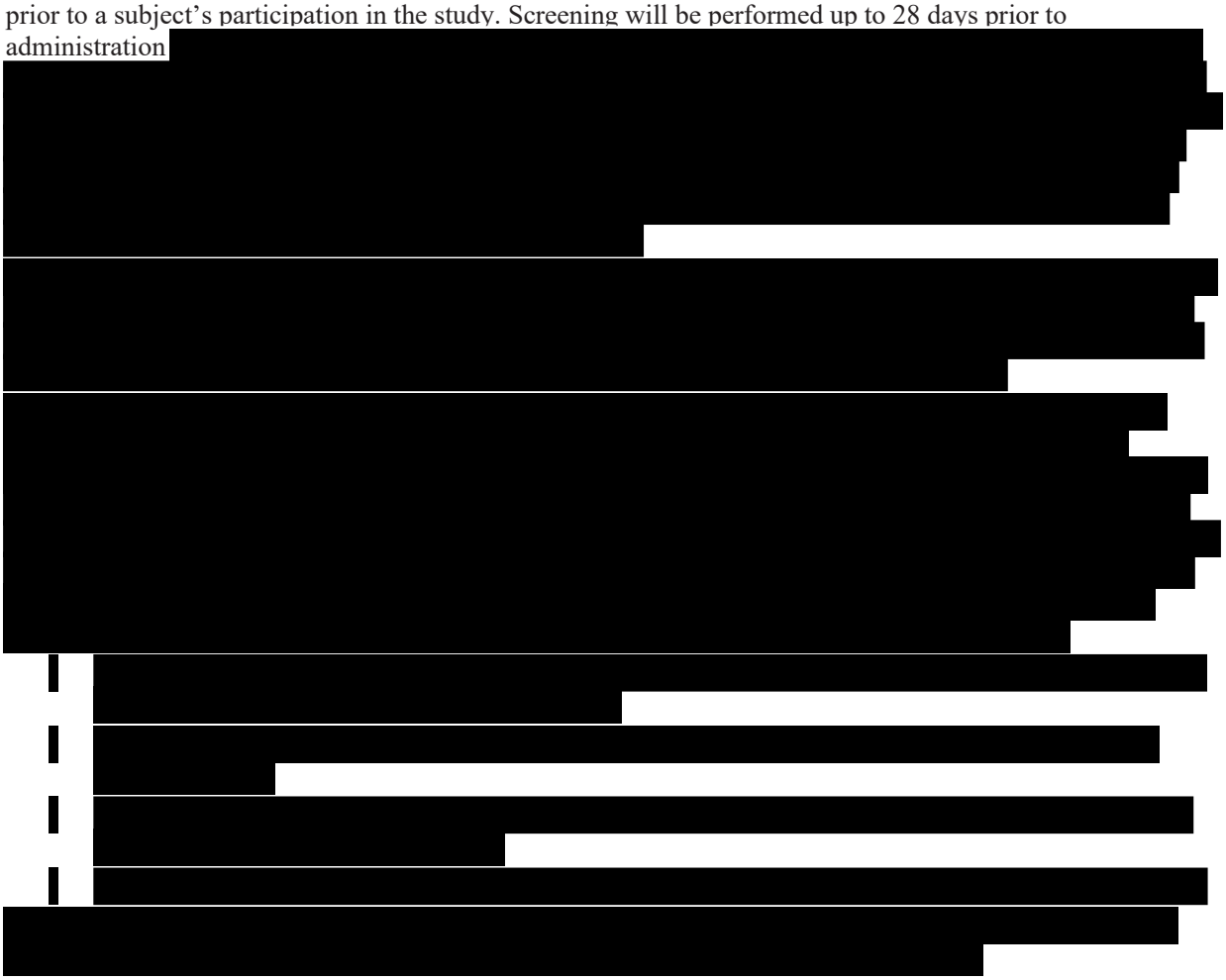
Version 2.0, 18 November 2024 Amendment #1
Version 1.0, 25 October 2024 Initial Creation

SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
PureTech LYT 100, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product:
Deupirfenidone Capsules</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
Deupirfenidone (LYT-100)</td></tr>
<tr><td colspan="2">Protocol Number:
LYT-100-2024-03</td></tr>
<tr><td colspan="2">Title of Study:
A Phase 1 Study in Healthy Volunteers to Determine the Potential for Drug-drug Interactions when Co-administering Deupirfenidone (LYT-100) with Nintedanib</td></tr>
<tr><td colspan="2">Study Center:
Single study centre (Australia)</td></tr>
<tr><td>Subject Duration of Participation:
Estimated date first Subject enrolled: December 2024
Estimated date last Subject completed: February 2025</td><td>Phase of Study:
Phase 1</td></tr>
<tr><td colspan="2">Study Objectives:
Primary objectives
• To assess the effect of deupirfenidone (LYT-100) coadministration on nintedanib pharmacokinetic (PK) parameters at steady state.
• To assess the effect of nintedanib coadministration on LYT-100 PK parameters at steady state.
Secondary objectives
• To evaluate the safety and tolerability of LYT-100 coadministration with nintedanib</td></tr>
</table>

Study Design:

This study will be conducted in healthy subjects at a single study centre. Informed consent will be obtained prior to a subject's participation in the study. Screening will be performed up to 28 days prior to administration



Safety Monitoring and Follow Up

All subjects will be monitored for safety (including assessment of chemistry, hematology, coagulation, and urinalysis parameters, electrocardiograms [ECGs], vital signs and adverse events [AEs]) and samples will be collected for assessment of PK at predefined time points pre- and post-dose as delineated in the Schedule of Events (Table 1).

All subjects will be followed for at least 30 days after the last administered dose of study drug.

Subjects will return to the CRU on an outpatient basis 30 days (± 1 day) following the last administered dose for safety assessments and a final safety follow up visit (Day 60).

In the case of premature discontinuation from the study, subjects will return to the CRU and complete an Early Termination Visit with assessments as delineated in the Schedule of Events (Table 1). Following the early termination visit, subjects will be contacted by telephone by site staff 30 days (± 3 days) post the last administered dose of study drug for a final safety review, at the Investigator's discretion.

The study will be subject to oversight by the Principal Investigator (PI), medical monitor (MM), and Sponsor representative, at a minimum.

Number of Subjects (Planned):

Up to 30, no fewer than 24 healthy female and male adult subjects to obtain 20 subjects that complete the 30-day Treatment Period.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria

1. Provides written Ethics Committee approved informed consent prior to any study procedures.
2. Male or female between 18 and 65 years old (inclusive) at the time of Screening.
3. In good general health at Screening, free from clinically significant unstable and/or acute medical, surgical or psychiatric illness/es and a full physical examination, at the discretion of the Investigator.
4. Clinical laboratory analytes at Screening and Day –1 (including hematology, biochemistry, coagulation, and urinalysis) within normal range as specified by the testing laboratory, unless deemed not clinically significant by the PI.
5. Subjects have a body mass index (BMI) between ≥ 18.0 and ≤ 35.0 kg/m^2 and weigh at least 50 kg at Screening.
6. Vital signs (measured in sitting position after 5 minutes' rest) at Screening and at Day -1:
   a. Systolic blood pressure ≥90 and ≤140 mmHg; and
   b. Diastolic blood pressure ≥40 and ≤ 90 mmHg; and
   c. Heart rate ≥40 and ≤100 beats per minute (bpm).

   Note: If vital signs are out of range, the Investigator may obtain one additional reading, so that up to 2 consecutive assessments are made within 1 hour and with the subject seated quietly during the 5 minutes preceding the assessment.
7. Adequate venous access in the left or right arm to allow collection of multiple blood samples.
8. No relevant dietary restrictions, and willing to consume the entirety of the standard meals provided.
9. Willing to comply with all study procedures and requirements.
10. Willing to abstain from direct whole body sun exposure from 2 days prior to dosing and until EOS/Follow-up Visit.
11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must use acceptable, highly effective contraception or be abstinent from heterosexual intercourse if this is their usual sexual practice from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug. Effective forms of contraception are defined in Section 4.4.4 of the protocol. WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Day -1 and be willing to have additional pregnancy tests as required throughout the study.
12. Women not of childbearing potential must be post-menopausal for ≥12 months (without an alternative medical cause) or be surgically sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Post-menopausal status will be confirmed through testing of follicle stimulating hormone (FSH) levels ≥ 40 IU/L at Screening. Bilateral tubal ligation is acceptable (if completed successfully and done at least one year prior to Screening [verbal

confirmation is permitted]), but condom use by male partner is required until study completion including the follow-up period.

13. Male subjects must be surgically sterile (> 90 days since vasectomy with no viable sperm confirmed by laboratory documentation), abstinent if this is their usual sexual practice, or if engaged in sexual relations with a WOCBP, the subject and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method (See Section 4.4.4 of the protocol) from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug. Male subjects that have undergone a vasectomy must use a condom from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug.
14. Males must not donate sperm and females must not donate ova or oocytes (i.e., human eggs) for at least 90 days after the last dose of study drug.
15. Subjects with same-sex partners (abstinence from penile-vaginal intercourse) or who are abstinent from heterosexual intercourse are not required to use contraception when this is their preferred and usual lifestyle.

Exclusion Criteria

1. Pregnant or lactating at Screening or Day -1 or planning to become pregnant (self or partner) at any time during the study, including the specified follow-up period.
2. History or presence of malignancy at Screening or Day -1, with the exception of adequately treated localised skin cancer (basal cell or squamous cell carcinoma) or carcinoma in-situ of the cervix.
3. History of migraine, whether treated or untreated, within 3 years prior to Screening
4. Clinically significant infection within 28 days of the start of dosing, or infections requiring parenteral antibiotics within the 6 months prior to Screening.
5. Clinically significant surgical procedure within 3 months of Screening, at the discretion of the Investigator, or any planned significant surgical procedure prior to the EOS/Follow-up visit.
6. Family history (biological relatives [i.e., parents, siblings]) of long or short QT syndrome, or Torsades de Pointes.
7. Currently suffering from clinically significant systemic allergic disease at Screening or Day -1 or has a history of significant drug allergies including a history of anaphylactic reaction; allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
8. 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 Investigator). Topical agents are not exclusionary.
9. History or presence at Screening or Day -1 of a condition associated with significant immunosuppression.
10. Positive result of a RT-qPCR diagnostic test for SARS-CoV-2 at Screening or Day -1.
11. Positive test for hepatitis C antibody (HCV), hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) antibody at Screening. Subjects who are positive for HCVAb will be

tested for hepatitis C ribonucleic acid (HCV RNA) by polymerase chain reaction (PCR) and, if HCV RNA PCR is positive, will be excluded.

12. Symptoms of dysphagia at Screening or Day -1 or known difficulty in swallowing capsules.
13. History or presence of gastrointestinal (including a previous episode of pancreatitis), hepatic or renal disease, or any other conditions known to interfere with absorption, distribution, metabolism, or excretion of drugs.
14. Any condition at Screening or Day -1 (e.g., chronic diarrhoea, 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, at the discretion of the Investigator.
15. History or presence at Screening or Day -1 of cardiac arrhythmia or congenital long QT syndrome.
16. QT interval corrected using Fridericia's formula (QTcF) > 450 msec (male) or 470 msec (female) demonstrated by two ECGs 30 to 60 minutes apart at Screening or Day -1 visits. The average of the 2 QTcF intervals should be used to determine the subject's eligibility.
17. Use of smoked tobacco or nicotine containing products in the previous 3 months prior to dosing or use of other tobacco or nicotine containing products in the previous 2 weeks prior to dosing, or a positive urine cotinine test at Screening or Day -1.
18. Lack of willingness to abstain from the consumption of tobacco or nicotine-containing products throughout the duration of the study and until the EOS/Follow-up visit.
19. Lack of willingness to abstain from the use of alcohol throughout the study (Treatment through EOS/Follow-up visit).
20. Positive toxicology screening panel (urine test, including qualitative identification of barbiturates, tetrahydrocannabinol [THC], amphetamines, benzodiazepines, opiates and cocaine) or alcohol breath test at Screening or Day -1, at any time during the Study. One repeat urine toxicology screen may be conducted, within 48 h of the first, if the first is considered by the Investigator to be invalid.
21. History of substance abuse or dependency or history of recreational intravenous (IV) drug use, over the last 2 years.
22. Use of any prescription drugs, over-the-counter (OTC) medication, nonsteroidal anti-inflammatory agents (NSAIDs), herbal remedies, supplements or vitamins within the 14 days prior to dosing or throughout the duration of the study, without prior approval of the Investigator and written approval of the Medical Monitor.
23. Paracetamol/acetaminophen may be utilised, provided that the dose of paracetamol does not exceed 2 g in any 24 h period.
24. Use of any of the any drugs listed in Section 4.4.1 within 28 days or 5 half-lives of that drug, whichever is longer, prior to study drug administration.
25. Vaccination with a live vaccine within the 4 weeks prior to Screening or that is planned prior to the EOS visit, and any non-live vaccination within the 2 weeks prior to Screening or that is planned within 2 weeks of dosing (including those for COVID-19)
26. Exposure to any significantly immune suppressing drug within the 3 months prior to Screening or 5 half-lives, whichever is longer.

27. Use of any investigational drug or device within 3 months prior to Screening.
28. Consumption of soy, grapefruit, grapefruit juice, Seville oranges, Seville orange juice, or any foods containing these ingredients, within 7 days prior to dosing until 24 hours after the final dose of study drug or unwilling to abstain from these throughout the duration of the study, until the EOS visit.
29. Clinically significant blood loss, blood or blood product donation >250 mL within 28 days of Screening.
30. Subject is unwilling to refrain from strenuous exercise which significantly exceeds the subject's usual level of physical activity from 48 h prior to admission to the clinical trial unit and until completion of the final onsite follow-up visit, where strenuous exercise is defined as a significant increase in the Subject's usual level of physical activity or lifting weights or running uphill.
31. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study.

Investigational/Reference Product, Dosage and Mode of Administration:

[redacted]

Duration of Treatment:

[redacted]

Study Endpoints:

Pharmacokinetics:

Blood samples will be collected pre-dose (trough) on all days during the Treatment Period and at the following time points on [redacted]

[redacted]

The following pharmacokinetic (PK) parameters will be determined for [redacted]

- $AUC_{0\text{-}tlast}$
- $AUC_{0\text{-}6h}$ (LYT-100)
- C_{max}
- $AUC_{0\text{-}12h}$
- T_{max}
- other parameters as appropriate

Plasma concentration time data for [redacted] will be analyzed using non-compartmental methods.

Safety:

Safety and tolerability will be assessed throughout the study by monitoring the following parameters:

- AEs (type, severity, and relatedness to study drug)
  - Adverse events of special interest (AESI) defined as severity of Grade 3 or higher per Modified CTCAE:
    - [redacted]
- Physical examination
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory analytes (hematology, serum chemistry, coagulation, and urinalysis)

Statistical Methods:

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.

Sample Size

Up to 30 subjects will be enrolled to obtain 20 completers. [redacted]

[redacted]

General Statistical Plan

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

Subject disposition (including the number and percent of subjects who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study) will be tabulated. Demographic information will be presented for each subject and summarised.

Summary statistics for days of exposure and concentration of exposure will be provided. Treatment-emergent adverse events (including AESIs) and laboratory, vital signs, and ECG parameters will be summarised. In addition, change from baseline will be summarised for laboratory and vital sign parameters. ECG results will be classified as normal and abnormal and summarised. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

Study Populations

Safety Set (SS) is defined as all subjects who have received any study drug.

Pharmacokinetic Population (PP) is defined as all subjects who receive nintedanib and LYT-100 and for whom an evaluable concentration-time profile is available for the determination of at least one PK variable.

[redacted]

Table 1: Schedule of Events

	Screening	Baseline	Treatment Period						EOS (follow-up)/ ET Visit
Study Day	**-28 to -2**	**-1**	**1 to 7**	**8 to 10**	**11 to 13**	**14 to 20**	**21 to 30**	**31**	**60 (± 1 d)**
Informed consent[1]	X								
Admit to CRU		X							
Discharge from Unit								X	
Eligibility	X	X							
Demographics	X								
Medical/ surgical history	X								
Physical exam	X	X							X
Symptom-directed physical exam[2]			X	X	X	X	X		
Height (cm)	X								
Weight (kg)	X	X							X
Body mass index	X	X							X
RT-PCR diagnostic test / SARS-CoV-2	X	X							
Vital signs (BP, PR, RR, tympanic temperature)[3,4]	X	X	X	X	X	X	X		X
Standard 12-lead ECG[2,4]	X		X	X	X	X	X		X
Hematology, coagulation & blood chemistry[3]	X	X	X	X	X	X	X		X
HIV, hepatitis B & C blood screen	X								
Pregnancy test	Serum	Urine[5]							Urine[5]
FSH[6]	X								

1 Informed consent must be documented before any study-specific screening procedures are performed.
2 Symptom-directed physical examinations will be performed, if deemed necessary, prior to dose on Days 2, 7, 9, 13, 15, 20, 22, 26, and 30.
3 [redacted]
4 Subjects should be resting supine for at least 5 minutes before the assessment; exact time of assessment is to be recorded.
5 Not required for amenorrhoeic female subjects (see below); if a urine pregnancy test is positive, a serum pregnancy test must be obtained.
6 Amenorrhoeic female subjects only; post-menopausal status will be confirmed through testing of FSH levels (≥ 40 IU/mL).

	Screening	Baseline	Treatment Period						EOS (follow-up)/ ET Visit
Study Day	**-28 to -2**	**-1**	**1 to 7**	**8 to 10**	**11 to 13**	**14 to 20**	**21 to 30**	**31**	**60 (± 1 d)**
Alcohol breathalyser	X	X							
Urine Cotinine and Drug screen	X	X							
Urinalysis[3]	X	X	X	X	X	X	X		X
Study Drug Admin[7]			[redacted]						
PK blood samples[8]			[redacted]						
Meals and Fluid[9]			X	X	X	X	X		
AE	X	X	X (continuous)						X
Prior & Concomitant medications	X	X	X (continuous)						X

Abbreviations: BP = blood pressure; cm = centimeter; CRU = clinical research unit; d = day; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; kg = kilogram; min = minute; PK = pharmacokinetics; PR = pulse rate; q12h = every 12 hours; RR = respiratory rate; TID = 3 times daily

7 [redacted]

Table 2: Detailed Plasma Pharmacokinetic Schedule

Day	Time Relative to AM Dose	Time Window	Notes
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AM = morning; PM = evening

Notes: Acceptable windows for blood draws are ± 2 minutes during the 0.25- to 4-hour period; ± 5 minutes thereafter. The exact time of each blood draw is to be recorded.

Blood samples will be drawn separately for [redacted] as follows:

[redacted]

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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
ALT	Alanine aminotransferase
AM	Morning
ANCOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
cGMP	Current good manufacturing practice
CI	Confidence interval
C_{max}	Highest concentration of a drug in the blood
CRU	Clinical research unit
ECG	Electrocardiogram
EOS	End of Study
eCRF	Electronic case Report Form
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
IB	Investigators Brochure

Abbreviation or Specialist Term	Explanation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IP	Investigational product
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram
LS	Least-squares
λz	Terminal elimination rate constant
MedDRA®	Medical Dictionary for Regulatory Activities
min	Minute
mg	Milligram
ml	Milliliter
mmHg	Millimeters of mercury
MTD	Maximum tolerated dose
N	Number
ng	Nanogram
NHMRC	National Health and Medical Research Council
NSAID	Non-steroidal anti-inflammatory
OCP	Oral contraceptive pill
OTC	Over the counter
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetics
PM	Evening
PP	Pharmacokinetic Population
PR	Pulse rate
PT	Preferred term
PV	Pharmacovigilance

Abbreviation or Specialist Term	Explanation
q12h	Every 12 hours
QTcF	QT interval corrected using Fridericia's formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-COV-2	COVID-2
SD	Standard deviation
SOC	System organ class
SS	Safety set
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TID	Three times a day
T_{max}	Time to reach maximum drug concentration after administration
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
WHO	World Health Organization
WOCBP	Woman of childbearing potential

PK parameters are defined in Section 14.5.

FACILITIES AND PERSONNEL

A list of personnel, organizations, and facilities associated with the conduct of the study is to be supplied to study sites as part of the Investigator's Study File. The list is to be updated by PureTech LTY 100, Inc. (or delegate) and provided to the study sites, as needed. Novotech has been assigned the contract research organization (CRO) for this study.

1. BACKGROUND AND INTRODUCTION

1.1. Introduction

1.1.1. LYT-100 (Deupirfenidone)

LYT-100 is a selectively deuterated form of pirfenidone. Pirfenidone is an orally active small molecule drug with antifibrotic and anti-inflammatory properties and has been shown in clinical studies to slow the progression of idiopathic pulmonary fibrosis (IPF) (King et al., 2014a; King et al., 2014b; Taniguchi et al., 2010).



Clinical studies have supported the overall safety and PK effect of deuteration (Howland et al., 2015). An example of a commercialized deuterated product that does not substantively alter the pharmacology of a drug but alters the PK profile is Austedo® (deutetrabenazine) which, as a deuterated form of tetrabenazine was approved by the US Food & Drug Administration (FDA) for the treatment of chorea associated with Huntington's disease on April 3, 2017. Importantly, the development program for deutetrabenazine and the 505(b)(2) New Drug Application (NDA) relied, in part, on FDA's prior finding of safety and effectiveness for the reference listed drug tetrabenazine (Austedo Drug Approval Package, 2017).

Both animal models and preclinical toxicology studies have been completed with LYT-100 that demonstrate its biological activity and safety. These were followed by 3 Phase 1 studies; a randomized, double-blind, single-dose crossover study to compare the PK, safety, and tolerability of LYT-100 with pirfenidone in healthy volunteers, a Phase 1b multiple dose safety and PK study and a Phase 1a crossover study in healthy older subjects, evaluating safety and PK with pirfenidone as a comparator. Results of these trials are discussed in Section 1.2.3.1.

PK results demonstrated that the deuteration of pirfenidone within LYT-100 resulted in comparable exposures to pirfenidone but at approximately two thirds of the dose.

Recently, a randomized, double-blind crossover study (LYT-100-2021-103) evaluated the tolerability of LYT-100 550mg 3 times a day (TID) versus pirfenidone 801mg TID in 49 healthy older adults aged 60-79, an age group comparable with that of the IPF patient population. Results showed that there was a 38% reduction in the overall incidence of treatment-emergent adverse events (TEAEs) with LYT-100 vs pirfenidone (30.4% versus 48.9%, respectively). Additionally, approximately 50% fewer subjects experienced GI-related AEs with LYT-100 compared with pirfenidone (17.4% vs 34.0%), most notably nausea (15.2% with LYT-100 vs 29.8% with pirfenidone).

Thus, LYT-100 has the potential to improve efficacy, tolerability, and safety in treatment of the IPF patient population due to equivalent exposure at lower doses without compromising pharmacological activity via deuteration of the parent compound.

1.1.2. Nintedanib (Ofev)

Nintedanib is a small molecule tyrosine kinase inhibitor that binds to growth factor receptors, inhibiting the proliferation of fibroblasts. This action reduces ongoing fibrotic processes and delays the progression to long-lasting damage. Nintedanib is indicated for treating idiopathic pulmonary fibrosis, systemic sclerosis-associated interstitial lung disease, and progressive phenotype interstitial lung disease.

Nintedanib is available in 150mg and 100mg tablets. The recommended dose is 150 mg by mouth twice daily approximately 12 hours apart with food. In the event of adverse reactions, the dose can be reduced to 100 mg twice daily approximately 12 hours apart with food.

The safety and efficacy of nintedanib has been studied extensively in nonclinical and clinical trials that are summarized in the Ofev Summary of Product Characteristics.

The most common adverse reactions (≥5%) are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, and hypertension.

The effect of pirfenidone coadministration on nintedanib AUC and C_{max} was evaluated in a multiple-dose drug-drug interaction study (Richeldi et. al., 2019). Pirfenidone did not have an effect on the exposure of nintedanib. In the two groups, 29 (78.4%) subjects reported one or more adverse events. The most common adverse events were diarrhea, nausea, lower respiratory tract infections, vomiting, headache and dyspepsia. Diarrhea was the most frequently reported adverse event in both groups (group 1 30.0%; group 2 23.5%). Nausea and vomiting were reported with a frequency >10% in each group. All reported adverse events were considered by the investigator to be mild or moderate apart from two cases of severe intensity in group 1.

Concomitant treatment with nintedanib and pirfenidone was also investigated in a separate trial, which was an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks (Vancheri et. al. 2018). Similar nintedanib trough plasma concentrations were observed when comparing patients receiving nintedanib alone with patients receiving nintedanib with add-on pirfenidone. On-treatment gastrointestinal adverse events were reported in 37 patients (69.8%) treated with nintedanib with add-on pirfenidone and 27 patients (52.9%) treated with nintedanib alone. During the randomized treatment period, ALT and/or AST at least three times the ULN was reported in three patients (5.7%) treated with nintedanib with add-on pirfenidone and no patients treated with nintedanib alone. No cases of Hy's law were observed.

1.2. Summary of Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

The nonclinical studies with LYT-100 have been designed to establish a scientific bridge between LYT-100, deuterated pirfenidone, and pirfenidone in order to leverage the nonclinical data generated to support global marketing applications of pirfenidone. Nonclinical data supporting the approval of pirfenidone for IPF included pharmacology, safety pharmacology, ADME, toxicology studies with durations of up to 6 months in rats and 9 months in dogs,

reproductive toxicity, genotoxicity, carcinogenicity in mice and rats, and photo-safety. LYT-100 has been evaluated in pharmacology, PK, metabolism and toxicity studies along with a pirfenidone comparator arm to establish a bridge to pirfenidone.

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

Pharmacology

In vitro and *in vivo* pharmacology studies conducted with LYT-100 have verified that deuteration does not alter the 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 GI effects.

1.2.1.1. Pharmacology

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

LYT-100 (previously known as SD-560) was evaluated in study DRR-2015-004 to confirm that the deuterium substituted form of pirfenidone retains the expected pharmacologic activity by reducing TGF-β-induced collagen (total and soluble) and fibronectin accumulation in primary mouse lung fibroblasts.

Two in vivo models of inflammation and/or fibrosis also demonstrated that LYT-100 retains the desired pharmacologic activity of pirfenidone. Pretreatment of rats with either pirfenidone or LYT-100 resulted in a similar reduction of plasma concentrations of TNF-α and of interleukin 6 (IL-6) induced by lipopolysaccharide injection. In a murine model of NASH, LYT-100 significantly reduced the fibrosis area compared to the vehicle control group.

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

1.2.1.2. 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 IB.



[redacted]

1.2.1.3. Repeat-dose Toxicology

A comparative dose range finding study of a single-dose (male and female rats) or 2 daily oral doses (female rats) of LYT-100 and pirfenidone demonstrated findings consistent with previous reports on pirfenidone and supported dose selection for a subsequent 4-/13-week oral toxicity study in rats, as described briefly below.

The objective of the sub-chronic, repeat-dose study was to evaluate the toxicity of LYT-100 (250, 500, and 750mg/kg/day) or pirfenidone (750mg/kg and 875mg/kg) when administered orally once daily for 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.

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 for both drugs. Increased liver weight was correlated histopathologically with centrilobular hepatocyte hypertrophy (postulated to be an adaptive change associated with drug metabolizing enzyme induction). These findings were not considered adverse and were correlated with LYT-100 C_{max} of up to 187,476 ng/mL (female) and 135,080 ng/mL (male) on Day 1.

[redacted]

1.2.2. Genotoxicity

LYT-100 and pirfenidone were evaluated for their genotoxic potential in an ICH S2 (R1) battery of in vitro and in vivo genotoxicity tests conducted according to Good Laboratory Practice. This includes an in vitro bacterial reverse mutation (Ames) test, an in vitro micronucleus test, and an in vivo micronucleus test. The in vitro studies have been recently completed. In the Ames test, LYT-100 and pirfenidone, the comparator molecule (up to the standard limit dose of 5000 µg/plate) were negative for mutagenic activity in the S. typhimurium strains TA98, TA100, TA1535, and TA1537 and in the E. coli strain WP2 uvrA, with and without metabolic activation. Results of the in vitro micronucleus test demonstrated that neither LYT-100 nor the comparator molecule, pirfenidone, showed clastogenic nor aneugenic genotoxic potential within the in vitro micronucleus assay in CHO-K1 cells.

1.2.3. Clinical Studies

A comprehensive summary of completed, ongoing, and planned LYT-100 clinical studies are detailed in the IB. Clinical studies to support a PK bridge between LYT-100 and pirfenidone are detailed in the following sections.

The PK, safety, tolerability, and food effect of LYT-100 has been evaluated in 3 studies in healthy subjects:

- A Phase 1, randomized, double-blind, single-dose crossover study to compare the PK, safety, and tolerability of LYT-100 (deupirfenidone) with pirfenidone (SD-560-C-22) in healthy volunteers in a fed state
- A Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose design to assess the safety, tolerability, PK, and food effect profile of multiple doses of LYT-100 in healthy volunteers (LYT-100-2020-01)
- A Phase 1, Double-Blind, Randomized, Crossover Study in Older Healthy Subjects to Compare the Safety, Tolerability, and Pharmacokinetics of LYT-100 to pirfenidone (LYT-100-2021-103)

The objective of the completed Phase 1 clinical studies has been the identification of a dose and dose regimen of LYT-100 that provides a daily systemic exposure similar to, or greater than the approved dose of pirfenidone of 801mg TID. Data from multiple completed and ongoing Phase 1 clinical studies have contributed to dose determination.

1.2.3.1. Crossover Study in Healthy Volunteers (SD-560-C-22)

Administration of LYT-100 in a fed state was tested in this Phase 1, randomized, double-blind, single-dose crossover study to compare the PK, safety, and tolerability of LYT-100 (deupirfenidone) with pirfenidone (SD-559) in healthy volunteers. 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. Following Screening, eligible healthy volunteer subjects, N=24, were admitted to a single clinical study site and were randomized to 1 of 2 treatment sequences. Subjects received a comparable single 801mg oral dose of either LYT-100 or pirfenidone following a standardized breakfast in Period 1 and, following washout, crossed over to receive the other treatment in Period 2. Plasma samples were collected over a 48 hour period after dosing for evaluation of PK. Dosing between the 2 periods was separated by a minimum of 7 days. Subjects completed the study upon completion of the 48-hour postdose assessments following dosing in Period 2. Subjects received a single 801mg oral dose of both:

LYT-100 (deupirfenidone) 801mg (267mg capsules × 3), and

Pirfenidone (SD-559) 801mg (267mg capsules × 3)

Results of the Phase 1 single-dose crossover study of LYT-100 and pirfenidone (N=24) showed at an equal single-dose, LYT-100 resulted in an approximately 25% higher C_{max} and 35% higher overall exposure relative to the non-deuterated pirfenidone. Overall, single doses of LYT-100 and pirfenidone were well tolerated and had a comparable safety profile. No clinically significant differences were observed between the 2 treatments in terms of type, severity, or frequency of TEAEs. The most common AE following either treatment was headache. Despite administration of the 801mg dose of LYT-100 resulting in greater drug exposure than the same dose of pirfenidone, the incidence of gastrointestinal and nervous system AEs was comparable with LYT-100. No significant changes in laboratory parameters, vital signs, or electrocardiograms (ECGs) were observed following either treatment.

1.2.3.2. A 5-Part Phase 1b Multiple Ascending Dose Safety and Pharmacokinetics Study #LYT-100-2020-01)

Study LYT-100-2020-01 is a completed study with 5 Parts.

- Part 1: multiple ascending doses (MAD) to assess the safety, tolerability, and PK at doses of LYT-100 at 100mg BID (200mg daily dose), 250mg BID (500mg daily dose), 500mg BID (1000mg daily dose), 750mg BID (1500mg daily dose) and 1000mg BID (2000mg daily dose) in the fed state were assessed. Each cohort consisted of 8 subjects, 6 randomized to active treatment and 2 randomized to placebo. Each subject received the study drug for 5 days.
- Part 2: a double-blind, placebo-controlled study of the food effect on LYT-100 in healthy volunteers, designed to descriptively compare the PK profile and the relative bioavailability of a single-dose of LYT-100 administered at a dose below the maximum tolerated dose (MTD) without food to the equivalent dose with food. The 500mg single daily dose level (250mg × 2) was administered in both the fed and fasted state on 2 days, separated by a minimum 7-day washout period. This was conducted at the same single center as MAD.
- Part 3 is a Phase 2a study in breast cancer related lymphoedema patients to assess safety, tolerability, PK, and exploratory objectives of the effects of LYT-100 on disease progression (this study is ongoing and will not be discussed for the purposes of this protocol).
- [redacted]
- [redacted]

[redacted]



1.2.3.3. Phase 1a Crossover in Older Healthy Subjects -Safety and PK Study (LYT 100-2021-103)

This study is intended to confirm the comparability of exposure and tolerability profile between LYT-100 and pirfenidone in the age group of subjects who are closest to the target IPF patient population.

- Part 1: randomized, double-blinded, 2-period crossover study in older healthy adults comparing the tolerability of LYT-100 850mg twice daily (BID) dosing vs 801mg pirfenidone TID (1:1 ratio)
- Part 2: a randomized, double-blinded, 2-period crossover to compare the tolerability of 3 times daily dosing (TID); 550mg 3 times daily (TID) dosing of LYT-100 vs 801mg pirfenidone TID (1:1 ratio)
- Part 3: randomized, double-blinded, parallel arm, placebo-controlled study in healthy older adults to evaluate the safety and tolerability of a dose of LYT-100 that provides approximately 150% exposure of pirfenidone (but at the nearest equivalent clinical

dose in Part 1 with the healthy older adults) vs placebo. LYT-100 doses were 550mg TID and 824mg TID

In **Part 1**, LYT-100 850mg was administered twice daily (BID) for 3 days (to steady-state [Day 1 to Day 3 and Day 11 to Day 13]) compared to pirfenidone administered TID for 3 days (to steady-state) under fed conditions. A final single-dose of study drug (LYT-100 or pirfenidone) was administered on the morning of the fourth day in each treatment period (Day 4/Day 14) following an overnight fast of at least 8 hours to determine the effect of food on steady-state PK parameters. Subjects were assigned to 1 of 2 cohorts. Sequence A: pirfenidone to LYT-100 or Sequence B: LYT-100 to pirfenidone.

Of the 37 subjects enrolled; 3 subjects (8.1%) did not complete the study. Two subjects discontinued due to an AE (pirfenidone), and 1 subject withdrew consent (LYT-100). Twenty-four subjects (64.9%) experienced at least 1 TEAE. A total of 72 TEAEs were reported; 21 subjects (60.0%) taking LYT-100 850mg BID reported 33 TEAEs, and 18 subjects (48.6%) taking pirfenidone 801mg TID reported 39 TEAEs. The most common TEAEs (incidence ≥10% overall) were nausea (40.5%), somnolence (27.0%), dizziness (27.0%), and headache (n=18.9%). The majority of TEAEs were considered mild. TEAEs leading to study discontinuation were reported by 2 subjects, both while receiving pirfenidone. No SAEs or deaths occurred during the study.

The relatively greater projected C_{max} of LYT-100 at 850mg BID compared to pirfenidone 801mg TID is notable because C_{max} of pirfenidone has been correlated to GI and CNS AEs (Rubino et al., 2009). Therefore, this may provide insight into the AEs observed with LYT-100 850mg BID. Note that LYT-100 was not titrated in Part 1.

Part 2 duplicated the design sequence (A and B) of Part 1 to determine tolerability and PK of LYT-100 administered 550mg TID for 3 days (Period 1 Day 1 to Day 3 or Period 2 Day 11 to Day 13) compared to pirfenidone administered 801mg TID, each under fed conditions.

Forty-nine subjects were enrolled; 24 subjects to Sequence A and 25 subjects to Sequence B. Five subjects (10.2%) did not complete the study; 2 due to an TEAE (1 subject in LYT-100 reported nausea the other in pirfenidone reporting headache and dizziness), 2 due to physician decision and 1 withdrew consent.

Overall, 28 subjects (57.1%) experienced at least 1 TEAE; 14 (30.4%) while taking LYT-100 and 23 (48.9%) while taking pirfenidone. The most common TEAEs (>5% overall) were nausea, headache, dizziness, vomiting, and somnolence. Of the 49 randomized there were 50% fewer subjects who experienced GI-related AEs with LYT-100 550mg TID compared to pirfenidone 801mg TID under fed conditions (17.4% versus 34.0%, respectively). Additionally, there was a 38% reduction in the overall incidence of TEAEs with LYT-100 vs pirfenidone (30.4% versus 48.9%, respectively). The most common TEAE was nausea (LYT-100, 15.2% of subjects; pirfenidone, 29.8% of subjects). There were no deaths or SAEs reported.

Administration of LYT-100 550mg TID substantially reduced incidence of GI and other TEAEs in healthy older adults compared to pirfenidone at doses expected to have comparable daily exposure. The fed-fasted outcomes suggest that better tolerability can be achieved if LYT-100 is given TID with food, thus potentially improving treatment compliance vs pirfenidone.

In Part 3 subjects were administered up to 550mg LYT-100 TID for 3 days (to steady-state [Day 1 to Day 3]) compared to 550mg placebo administered TID for 3 days to steady-state. Day 4 to Day 6, subjects were administered 824mg LYT-100 TID for 3 days compared to 824mg placebo TID for 3 days to steady-state.

Overall, 30 subjects were randomized, 24 subjects to LYT-100 and 6 subjects to placebo. Four subjects discontinued due to a TEAE; 3 subjects in the LYT-100 group and 1 subject in the placebo group. These 4 TEAEs leading to discontinuation were COVID-19 related. Three subjects in the LYT-100 group withdrew consent.

Overall, 9 subjects (30.0%) experienced at least 1 TEAE; 8 (33.3%) while taking LYT-100 and 1 (16.7%) while taking placebo. The most common TEAEs (>5% overall) were Covid-19 and headache. The 4 TEAEs leading to discontinuation were all COVID-19 related. The majority of TEAEs were considered mild.

LYT-100 was very well tolerated in this group of subjects (mean age 65) up to a dose of 824mg TID for 3 days. The only TEAE of note was headache and the vast majority of these events were mild. The supportive adverse event and tolerability profile observed with LYT-100 824mg TID after titration and given with food (Part 3) warrants further investigation of a dose of LYT-100 TID which provides higher systemic exposure than pirfenidone and the potential for a more favorable safety profile for patients with IPF.

Overall Conclusions: LYT-100 and pirfenidone treatment at equivalent exposures exhibit the same characteristics and behave similarly with regards to safety and tolerability. Administration of LYT-100 550mg TID substantially reduced the incidence of GI and other TEAEs in healthy older adults compared to pirfenidone at doses expected to have comparable daily exposure. Additionally, titrating LYT-100 to 824mg TID resulted in a more favorable safety profile compared to dosing LYT-100 BID at doses with comparable daily exposure in previous Phase 1 studies. In addition, the fed-fasted outcomes suggest that better tolerability can also be achieved if LYT-100 is given with food. LYT-100 may offer better tolerability and thus improve treatment compliance vs pirfenidone, potentially offering an improved treatment option for IPF patients.

1.3. Summary of Potential Risks and Benefits of LYT-100 and Nintedanib

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.

Co-administration of LYT-100 and nintedanib is not expected to have any novel AEs reported, but could be expected to have an AE profile similar to the administration of LYT-100 and nintedanib. Based on studies where pirfenidone was co-administered with nintedanib, the incidence of gastrointestinal AEs may be increased.

For a thorough description of potential risks and benefits, please refer to the LYT-100 IB and the Ofev Summary of Product Characteristics.

1.4. Dosage and Treatment Periods

For subjects that meet all eligibility criteria and are admitted to the CRU

- [redacted]

Table 3: Dosing Regimens and Treatment Sequence

Meal	Days 1 to 7	Day 8 to 10	Days 11 to 13	Day 14 to 20	Day 21 to 30
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

1.4.1. Rationale for Selection of Dose

LYT-100 has been shown to be safe and tolerable in humans at doses ranging from 100mg once daily to 2000mg BID. LYT-100 dosed at 550mg TID is projected to have comparable daily exposure (AUC) vs the licensed dose of pirfenidone for the treatment of IPF with a better tolerability profile, as previously outlined in Section 1.2.3.1. LYT-100 dosed at 825mg TID is expected to have comparable tolerability to the approved dosage of pirfenidone based on the projected C_{max} level but with increased exposure (AUC) that may result in greater antifibrotic and anti-inflammatory efficacy, again as outlined in Section 1.2.3.1. Both doses are currently being compared against placebo and pirfenidone 801mg TID in an ongoing Phase 2 study (LYT-100-2022-204) in patients with idiopathic pulmonary fibrosis.

1.5. Subject Population

The purpose of this study is to assess the safety, tolerability, and effects of deupirfenidone (LYT-100) coadministration with nintedanib in healthy subjects. Consistent with that objective, healthy subjects, aged 18 to 65 years will be enrolled in this study.

WOCBP will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow-up period and an additional 90 days after the last dose. 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).

Males must not donate sperm and females must not donate ova or oocytes (i.e., human eggs) for at least 90 days after the last dose of study drug.

1.6. 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 IEC/IRB and investigations will be undertaken by scientifically and medically qualified persons; where the benefits of the study are in proportion to the risks.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Objectives

2.1.1. Primary Objectives

- To assess the effect of deupirfenidone (LYT-100) coadministration on nintedanib PK parameters at steady state.
- To assess the effect of nintedanib coadministration on LYT-100 PK parameters at steady state.

2.1.2. Secondary Objective

- To evaluate the safety and tolerability of LYT-100 coadministration with nintedanib.

2.2. Endpoints

- Pharmacokinetics:
  - The following pharmacokinetic (PK) parameters will be determined for nintedanib, LYT-100, and 5-carboxy-pirfenidone using non-compartmental methods:
    - $AUC_{0\text{-}tlast}$
    - $AUC_{0\text{-}6h}$ (LYT-100)
    - C_{max}
    - $AUC_{0\text{-}12h}$
    - T_{max}
    - other parameters as appropriate
- Safety
  - AEs (type, severity, and relatedness to study drug)
    - Adverse events of special interest (AESI) defined as severity of Grade 3 or higher per Modified CTCAE (Section 21.2):
      - [redacted]
  - Physical examination
  - Vital signs
  - Electrocardiograms (ECGs)
  - Clinical laboratory analytes (hematology, serum chemistry, coagulation, and urinalysis)

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 1 open-label study in healthy volunteers to determine the potential for drug-drug interactions when co-administering deupirfenidone (LYT-100) with nintedanib. Informed consent will be obtained prior to a subject's participation in the study. Screening will be performed up to 28 days prior to administration [redacted]

Planned dosing is outlined in Table 3.

A schematic of the study design is provided in Figure 1.

Timing of Meals Provided

[redacted]

[redacted]

Safety Monitoring and Follow-Up

All subjects will be monitored for safety (including assessment of chemistry, hematology and urinalysis parameters, electrocardiograms [ECGs], vital signs and adverse events [AEs]) and samples will be collected for assessment of PK at predefined time points pre- and post-dose as delineated in the Schedule of Events (Table 1).

All subjects will be followed for at least 30 days after the last administered dose of study drug.

Subjects will return to the CRU on an outpatient basis 30 days (± 1 day) following the last administered dose for safety assessments and a final safety Follow-up Visit (Day 60).

In the case of premature discontinuation from the study, subjects will return to the CRU and complete an Early Termination Visit with assessments as delineated in the Schedule of Events. Following the early termination visit, subjects will be contacted by telephone by site staff 30 days (± 3 days) post the last administered dose of study drug for a final safety review, at the Investigator's discretion.

Figure 1: Study Design



3.2. Number of Subjects

Approximately 30 healthy female and male adult subjects will be enrolled to obtain 20 subjects that complete the study to support the statistical analysis.

3.3. Treatment Assignment

3.3.1. Randomization

This is an open-label study and all subjects will receive active investigational product (LYT-100) and comparator (nintedanib).

Each subject will be provided with a unique Screening number post documentation of informed consent. The subject will maintain their Screening number throughout the study. Screen failures are defined as subjects who consent to participate in the clinical study but fail to meet the eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes screen failure details, eligibility criteria, and any AE/SAE.

Subjects who do not meet the criteria for participation in this study (screen failure) may be re-screened once. Rescreening will be permitted within the recruitment period of the study. Re-screened patients should be assigned a new Screening number.

3.4. Dose Adjustment Criteria

No dose adjustments will be made in this study that deviate from the titration described in Section 1.4 and Table 3.

3.5. Criteria for Study Termination

The study will be completed as planned unless:

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

In the event of a Grade 3 or higher adverse event or laboratory abnormality, or a SAE that is considered possible related to the IP, the Sponsor, MM and Ethics committee (if appropriate) should be notified to discuss whether the IP should be paused or stopped for that subject or all subjects.

If the Sponsor, the IEC/IRB, 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. The PI / Coordinating Investigator should notify the relevant Ethics Committee in writing of the study's completion or early discontinuation.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Subject Inclusion Criteria

To be eligible for this study, subjects ***must meet all*** of the following inclusion criteria:

1. Provides written Ethics Committee approved informed consent prior to any study procedures.
2. Male or female between 18 and 65 years old (inclusive) at the time of Screening.
3. In good general health at Screening, free from clinically significant unstable and/or acute medical, surgical or psychiatric illness/es and a full physical examination, at the discretion of the Investigator.
4. Clinical laboratory values at Screening and Day –1 (including hematology, biochemistry, coagulation, and urinalysis) within normal range as specified by the testing laboratory, unless deemed not clinically significant by the PI.
5. Subjects have a body mass index (BMI) between ≥ 18.0 and ≤ 35.0 kg/m^2 and weigh at least 50 kg at Screening.
6. Vital signs (measured in sitting position after 5 minutes' rest) at Screening and at Day -1:
    a. Systolic blood pressure ≥90 and ≤140 mmHg; and
    b. Diastolic blood pressure ≥40 and ≤ 90 mmHg; and
    c. Heart rate ≥40 and ≤100 beats per minute (bpm)

    Note: If vital signs are out of range, the Investigator may obtain one additional reading, so that up to 2 consecutive assessments are made within 1 hour and with the subject seated quietly during the 5 minutes preceding the assessment.
7. Adequate venous access in the left or right arm to allow collection of multiple blood samples.
8. No relevant dietary restrictions, and willing to consume the entirety of standard meals provided.
9. Willing to comply with all study procedures and requirements.
10. Willing to abstain from direct whole body sun exposure from 2 days prior to dosing and until EOS/Follow-up Visit.
11. Women of childbearing potential (WOCBP) must be non-pregnant and non-lactating, and must use acceptable, highly effective contraception or be abstinent from heterosexual intercourse if this is their usual sexual practice from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug. Effective forms contraception are defined in (Section 4.4.4) of the protocol. WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Day -1 and be willing to have additional pregnancy tests as required throughout the study.
12. Women not of childbearing potential must be post-menopausal for ≥12 months (without an alternative medical cause) or be surgically sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Post-menopausal status will be confirmed through testing of follicle stimulating hormone (FSH) levels ≥ 40 IU/L at Screening. Bilateral tubal ligation is acceptable (if completed

successfully and done at least one year prior to Screening [verbal confirmation is permitted]), but condom use by male partner is required until study completion including the follow-up period.

13. Male subjects must be surgically sterile (> 90 days since vasectomy with no viable sperm confirmed by laboratory documentation), abstinent if this is their usual sexual practice, or if engaged in sexual relations with a WOCBP, the subject and his partner must be surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using an acceptable, highly effective contraceptive method (Section 4.4.4) from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug. Male subjects that have undergone a vasectomy must use a condom from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug.
14. Males must not donate sperm and females must not donate ova or oocytes (i.e., human eggs) for at least 90 days after the last dose of study drug.
15. Subjects with same-sex partners (abstinence from penile-vaginal intercourse) or who are abstinent from heterosexual intercourse are not required to use contraception when this is their preferred and usual lifestyle.

4.2. Subject Exclusion Criteria

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

1. Pregnant or lactating at Screening or Day -1 or planning to become pregnant (self or partner) at any time during the study, including the specified follow-up period.
2. History or presence of malignancy at Screening or Day -1, with the exception of adequately treated localised skin cancer (basal cell or squamous cell carcinoma) or carcinoma in-situ of the cervix.
3. History of migraine, whether treated or untreated, within 3 years prior to Screening
4. Clinically significant infection within 28 days of the start of dosing, or infections requiring parenteral antibiotics within the 6 months prior to Screening.
5. Clinically significant surgical procedure within 3 months of Screening, at the discretion of the Investigator, or any planned significant surgical procedure prior to the EOS/Follow-up visit.
6. Family history (biological relatives [i.e., parents, siblings]) of long or short QT syndrome, or Torsades de Pointes.
7. 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; allergic reaction due to any drug which led to significant morbidity; prior allergic reaction to pirfenidone.
8. 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 Investigator). Topical agents are not exclusionary.
9. History or presence at Screening or Day -1 of a condition associated with significant immunosuppression.

10. Positive result of a RT-qPCR diagnostic test for SARS-CoV-2 at Screening or Day -1.
11. Positive test for hepatitis C antibody (HCV), hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) antibody at Screening. Subjects who are positive for HCVAb will be tested for hepatitis C ribonucleic acid (HCV RNA) by polymerase chain reaction (PCR) and, if HCV RNA PCR is positive, they will be excluded.
12. Symptoms of dysphagia at Screening or Day -1 or known difficulty in swallowing capsules.
13. History or presence of gastrointestinal (including a previous episode of pancreatitis), hepatic or renal disease, or any other conditions known to interfere with absorption, distribution, metabolism, or excretion of drugs.
14. Any condition at Screening or Day -1 (e.g., chronic diarrhoea, 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, at the discretion of the Investigator.
15. History or presence at Screening or Day -1 of cardiac arrhythmia or congenital long QT syndrome.
16. QT interval corrected using Fridericia's formula (QTcF) > 450 msec (male) or 470 msec (female) demonstrated by two ECGs taken 30 to 60 minutes apart at the Screening or Day –1 visits. The average of the 2 QTcF intervals should be used to determine the subject's eligibility.
17. Use of smoked tobacco or any nicotine containing product in the 3 months prior to dosing or use of other tobacco or nicotine containing products in the previous 2 weeks prior to dosing, or a positive urine cotinine test at Screening or Day -1.
18. Lack of willingness to abstain from the consumption of tobacco or nicotine-containing products throughout the duration of the study and until EOS/Follow-up visit.
19. Lack of willingness to abstain from the use of alcohol throughout the study, until the EOS/Follow-up visit
20. Positive toxicology screening panel (urine test, including qualitative identification of barbiturates, tetrahydrocannabinol [THC], amphetamines, benzodiazepines, opiates and cocaine) or alcohol breath test at Screening or Day –1, or at any time during the Study. One repeat urine toxicology screen may be conducted, within 48 h of the first, if the first is considered by the Investigator to be invalid.
21. History of substance abuse or dependency, or history of recreational intravenous (IV) drug use, over the last 2 years.
22. Use of any prescription drugs, over-the-counter (OTC) medication, nonsteroidal anti-inflammatory agents (NSAIDs), herbal remedies, supplements or vitamins within the 14 days prior to dosing and throughout the duration of the study, without prior approval of the Investigator and written approval of the Medical Monitor.
23. Paracetamol/acetaminophen may be utilised, provided that the dose of paracetamol does not exceed 2 g in any 24 h period.
24. Use of any of the any drugs listed in Section 4.4.1 within 28 days or 5 half-lives of that drug, whichever is longer, prior to study drug administration.

25. Vaccination with a live vaccine within the 4 weeks prior to Screening or that is planned prior to the EOS visit, and any non-live vaccination within the 2 weeks prior to Screening or that is planned within 2 weeks of dosing (including those for COVID-19).
26. Exposure to any significantly immune suppressing drug within the 3 months prior to Screening or 5 half-lives, whichever is longer.
27. Use of any investigational drug or device within 3 months prior to Screening.
28. Consumption of soy, grapefruit, grapefruit juice, Seville oranges, Seville orange juice, or any foods containing these ingredients, within 7 days prior to dosing, until 24 hours after the final dose of study drug or unwilling to abstain from these throughout the duration of the study, until the EOS visit.
29. Clinically significant blood loss, blood or blood product donation >250 mL within 28 days of Screening.
30. Subject is unwilling to refrain from strenuous exercise which significantly exceeds the subject's usual level of physical activity from 48 h prior to admission to the clinical trial unit and until completion of the final onsite follow-up visit, where strenuous exercise is defined as a significant increase in the Subject's usual level of physical activity, or lifting weights, or running uphill.
31. Any other reason that, in the opinion of the Investigator, might interfere with the evaluation required by the study.

4.3. Subject Withdrawal Criteria

Subjects may withdraw their consent to participate in the study at any time. If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subjects 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. Subject 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 subjects can include:

- Protocol deviations or subject 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 subjects who discontinue prior to the completion of the study.

4.4. Diet, Activity and Other Restrictions

4.4.1. Prohibited Therapies

[redacted]

4.4.2. Tobacco or Nicotine-Containing Products

[redacted]

[redacted]

4.4.3. Alcohol

Subjects are required to abstain from alcohol beginning 48 hours prior to admission to the CRU and 48 hours prior to study visits until completion of the final Follow-up visit.

4.4.4. Contraception

[redacted]

Women not of childbearing potential must be postmenopausal for ≥12 months (without an alternative medical cause) or be surgically sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Post-menopausal status will be confirmed through testing of follicle stimulating hormone (FSH) levels ≥ 40 IU/L at Screening. Bilateral tubal ligation is acceptable (if completed successfully and done at least one year prior to Screening [verbal confirmation is permitted]), but condom use by male partner is required until study completion including the follow-up period. 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. Complete abstinence for the duration of the study and for 3 months after the last study treatment is acceptable.

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

Males must be surgically sterile (>90 days since vasectomy with no viable sperm confirmed by laboratory documentation), abstinent, or if engaged in sexual relations with a WOCBP, the subject must be using an acceptable, highly effective contraceptive method from Screening until study completion, including the follow-up period. Male subjects that have undergone a vasectomy must use a condom from Screening until study completion, including the follow-up period and an additional 90 days after the last dose of study drug.

Subjects with same sex partners (abstinence from penile-vaginal intercourse) are not required to use contraception.

4.4.5. Food

Subjects should avoid foods that contain poppy seeds prior to Screening and admission to the CPU on Day -1.

Subjects are not permitted to consume soy, grapefruit, grapefruit juice, Seville oranges or Seville orange juice, or any foods containing these ingredients, from 7 days prior to dosing until 24 hours after the final dose of study drug.

Subjects are required to take study drug with food as directed by study personnel.

4.4.6. Activity

Subjects must refrain from strenuous exercise which significantly exceeds the subject's usual level of physical activity from 48 hours prior to admission to the clinical trial unit until completion of the final onsite Follow-up visit, where strenuous exercise is defined as a significant increase in the subject's usual level of physical activity or lifting weights or running uphill.

4.4.7. Other Restrictions

[redacted]

Subjects must not have had major surgery, (e.g., requiring general anesthesia) within 3 months prior to Screening, based on Investigator's discretion, or have surgery planned throughout the study until the final Follow-up visit.

All subjects 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.

5. TREATMENT OF SUBJECTS

5.1. Description of Study Drug

[redacted]

5.1.1. LYT-100 (Deupirfenidone)

The LYT-100 drug product is presented as Swedish orange opaque, hard-gelatin capsules.

The capsules are packaged into cards containing multiple blisters. Each card with be affixed with a study label.

A description of the cards and directions for use will be further detailed in the Pharmacy Manual.

5.1.2. Nintedanib (Ofev)

Nintedanib (Ofev) is provided as brown-coloured, opaque, oblong, soft gelatin capsules imprinted in black on one side with the Boehringer Ingelheim company logo and 150. The capsules contain a bright yellow viscous suspension.

The capsules are packaged into cards containing multiple blisters. Each card with be affixed with a study label.

A description of the cards and directions for use will be further detailed in the Pharmacy Manual

5.2. Prior and Concomitant Medications

5.2.1. Prior Therapy

Prior therapies are defined as those taken within 28 days prior to the first administration of IP.

The use of any IP or investigational medical device within 28 days or 5 half-lives (whichever is shorter) prior to Screening is prohibited. Additional restrictions relating to concomitant medication use are outlined in Section 4.4.1.

All medications, including over-the-counter (OTC) medications, vitamins, and herbal supplements, taken during the 28 days prior to the first study drug administration will be recorded and reviewed by the Investigator to determine whether the subject is suitable for inclusion in the study.

5.2.2. Concomitant Therapy Medications

Concomitant therapies are defined as those taken after the first administration of IP.

All medications, including OTC medications, vitamins, and herbal supplements, taken by subjects 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 subject and summarized by anatomical therapeutic chemical (ATC) and preferred term (PT).

With any medications, including both prescription and non-prescription drugs should be discussed with the PI and Sponsor's MM before the first IP administration, except in the case of necessary treatment of AEs or where appropriate medical care necessitates that therapy should begin before the PI can consult with the CRO MM.

5.3. Treatment Compliance

All doses will be administered at the CRU in the presence of the Investigator or their designee.

The date and time of each dose administered at the site will be recorded in the source documents. The dose of IP and study subject identification will be confirmed at the time of dosing by a member of the site staff other than the person administering the study treatment.

A record of the dose of IP dispensed and administered to each subject must be maintained and reconciled with IP and compliance records. Treatment dates, including dates for treatment delays and/or dose reductions, will also be recorded.

5.4. Blinding

This study will be open-label and no blinding is necessary.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Supplies

The Sponsor will supply the investigational study drug (LYT-100) to the investigational site. The site will procure commercially available nintedanib. The investigational study drug provided for this study was manufactured under current Good Manufacturing Practices (cGMP) and will be suitable for human use.

6.2. Study Drug Packaging and Labeling

The Sponsor is responsible for the preparation and labeling and 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.

6.3. 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.

6.4. Study Drug Preparation

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

6.5. Administration

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

6.6. 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.

6.7. 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.

7. STUDY SCHEDULE

Please see Table 1 for the Schedules of Events and Table 2 for a detailed schedule of plasma PK sampling time points.

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

8. ASSESSMENT OF PHARMACOKINETICS

8.1. Blood Sample Collection

Blood samples (for PK) will be obtained at the time points delineated in the Schedule of Events (Table 1) and further described in the detailed plasma (Table 2) PK schedules. The actual collection time of each sample must be recorded in the source data documentation, on the collection tube, and in the eCRF. Please see footnotes to schedules for permitted time windows for sample collection.

All 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 Events (Table 1).

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

8.2. Sample Analysis

PK sample analysis will be performed using validated procedures and methods as outlined in the Laboratory Manual.

9. ASSESSMENT OF SAFETY

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

9.1. Safety Parameters

Study procedures should be completed as delineated in the Schedules of Events (Table 1) and the detailed plasma (Table 2) PK schedules. However, if a subject is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's Medical Monitor or appropriate designee. Any unscheduled procedures required

for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

9.1.1. Demographics/Medical, Surgical, and Medication History

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

9.1.2. Vital Signs

Vital signs (tympanic body temperature, blood pressure, pulse rate, respiratory rate) will be measured at the time points specified in the study schedule (Table 1) with subjects 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.

Vital Sign Normal Reference Ranges:

- BP Systolic: 90 mmHg - 140 mmHg
- BP Diastolic: 40 mmHg - 90 mmHg
- Heart Rate: 40 bpm - 100 bpm
- Respiration Rate: 10 bpm – 22 bpm
- Temperature: 35.5 °C – 37.5 °C
- SpO_2: ≥ 95%

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

9.1.3. Weight and Height

Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the study schedule (Table 1) and will be used to calculate BMI. BMI is calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (kg/m^2). Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

9.1.4. Physical Examination

Complete and directed physical examinations and symptom-directed physical examinations will be performed by a licensed physician, physician assistant, or nurse practitioner at the time points specified in the study schedule (Table 1).

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.

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

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

9.1.5. Electrocardiogram

A 12-lead ECG will be taken at the time points delineated in the study schedule (Table 1). Additional ECG monitoring may be performed at other times if deemed necessary.

The following ECG measurements will be taken at the time points specified in the study schedules:

- Heart Rate (beats/min)
- QT Interval (msec)
- PR Interval (msec)
- QRS Duration (msec)
- RR Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- ECG Clinical Interpretation

ECGs will be performed after vital signs with subjects in a supine position. Subjects 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.

ECG Normal Reference Ranges:

- Sinus Bradycardia: < 40 bpm
- Sinus Tachycardia: > 100 bpm
- PR Interval: ≥ 120 to ≤ 220 msec
- QRSD: < 120 msec
- QT: < 500 msec
- QT_c: ≤ 450 msec (both genders)

9.1.6. Laboratory Assessments

Safety laboratory tests (hematology, serum chemistry, coagulation, and urinalysis) will be performed at the time points specified in the study schedule (Table 1). Additional clinical laboratory tests may be performed at other times if deemed necessary based on the subject's clinical condition.

When the time of laboratory assessments coincides with vital signs and/or ECGs, blood draws for laboratory assessments will be taken after the scheduled vital signs and ECGs where possible while ensuring the blood draw is within the window specified in the protocol.

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

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

9.1.6.1. 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])

9.1.6.2. 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)

9.1.6.3. Coagulation

Coagulation parameters to be tested are:

- International normalized ratio
- Prothrombin time
- Activated partial thromboplastin time

9.1.6.4. Urinalysis

A urinalysis test (dipstick) will be performed for each subject. Urinary analysis will be performed at Screening and Baseline according to the study schedule (Table 1). If any abnormality is noted for urinalysis parameters (at the discretion of the Investigator) a further examination will be performed.

9.1.6.5. Viral Serology

HBsAg, anti-HCV and HIV antibody testing will be performed at Screening.

9.1.6.6. Urine Drug Screen

A urine drug screen will be performed at Screening and at admission to the CRU in Treatment Period 1 (Day -1). This will include screening for:

- Amphetamines (AMP)
- Methamphetamines (MET)
- Methadone (MTD)
- Barbiturates (BAR)
- Benzodiazepines (BZO)
- Cocaine (COC)
- Opiates (OPI)
- Methylenedioxymethamphetamine (MDMA)
- Phencyclidine (PCP)
- Tetrahydrocannabinol (THC)
- Tricyclic Antidepressants (TCA)

Note: A urine cotinine test will be performed at Screening and at admission to the CRU for the Treatment Period 1 (Day -1).

9.1.6.7. Alcohol Test

An alcohol breath or urine test will be performed at Screening and at admission to the CRU for the Treatment Period 1 (Day -1).

9.1.6.8. Pregnancy Testing

A serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at Day -1, and at the Follow-up/Early Termination Visit for WOCBP only. If a urine test is positive, a serum test will be performed immediately thereafter for confirmation.

9.1.6.9. Follicle-Stimulating Hormone Test

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

10. ADVERSE EVENTS

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

In this study, AEs will be reported for all subjects from the time of consent until the completion of the EOS/Follow-up visit. AEs that occur after the subject signs the ICF, prior to the first dose of study drug will be recorded as pretreatment AEs. SAEs will be reported for all subjects (randomized or not) from the time of consent.

All TEAEs are defined as AEs that occur during or following first dose of study drug and will be evaluated from the first administration of study drug on Day 1 until the EOS/Follow-up visit. AEs that are ongoing at the final visit will be marked as Not Recovered/Not Resolved on the AE eCRF page (Section 10.1.4).

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate eCRF for that visit.

AESIs relate to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, (eg, the potential for AEs based on knowledge from other compounds in the same class).

AESIs as defined in Section 10.2, need to be reported to PureTech Health Pharmacovigilance Department or its designee within the same timeframe that applies to SAEs (see Section 10.6).

10.1. Definition of Adverse Events

An AE is an 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 (eg, 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 (eg, 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

When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., progress notes, laboratory results, diagnostic reports) relevant to the event. The investigator or his/her designee will record all relevant information regarding the event in the eCRF. There may be instances when copies of medical records are requested by the study Sponsor. In these instances, all subject identifiers will be redacted on copies of medical records prior to submission to the Sponsor.

10.1.1. Severity of an Adverse Event

The severity of an event describes the degree of impact upon the subject and/or the need for medical care necessary to treat the event, AEs reported for subjects participating in the study will be graded using the Modified Common Terminology Criteria for Adverse Events (CTCAE) (refer to Section 21.2).

For AEs not included in the Modified CTCAE (Section 21.2), the following should be used as a guideline:

- Mild Grade 1 - Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate Grade 2 - Minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living.
- Severe Grade 3 - Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Life-threatening Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Fatal Grade 5 - Death.

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (as characterized above) whereas seriousness as defined in Section 10.3, defines the requirements for reporting obligations from the Sponsor to applicable regulatory authorities.

10.1.2. Causality Assessment

The investigator will assess the relationship between study drug and the occurrence of each AE or SAE. The investigator’s assessment of the relationship of each AE and SAE 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 classifications should be used when evaluating the relationship of AEs and SAEs to the investigational drug:

- **Not related**: The event is clearly related to other factors such as the subject’s environment or clinical state, therapeutic interventions or concomitant drugs administered to the subject. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Possibly related:** 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 subject’s clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- **Probably related:** The event follows a reasonable temporal sequence from the time of study drugadministration and follows a known response to the study drug and cannot be reasonably explained by other factors such as the subject’s clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

10.1.3. 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 subject then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Drug Interrupted
- Drug Withdrawn
- Not applicable
- Other

10.1.4. Adverse Event Outcomes

AE outcomes will be recorded on the AE eCRF as follows:

- Recovered/Resolved

- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving
- Fatal
- Unknown (or subject lost to follow-up after 3 attempts at contact over a period of 30 days)

10.2. Definition of Adverse Event of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, which requires additional monitoring. Such an event might warrant further investigation to better characterize and understand it.

For this study, the following events will be considered AESIs if the event has a severity of Grade 3 or higher:



Elevations in liver enzymes as well as post marketing reports of drug-induced liver injury have been associated with the parent compound pirfenidone. Therefore, we are monitoring these as AESIs.

10.3. Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject 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 judgement, they are considered clinically significant and may jeopardize the subject, 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 subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

10.3.1. Definition of Terms

Life-threatening: an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the subject providing informed consent, or routine clinical procedures that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened, surgical insertion of central line) need not be considered AEs or SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, inpatient hospital admission refers to an overnight stay in a health care facility over 24 hours for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Exceptions include: rehabilitation facilities, hospice facilities, respite care (e.g., caregiver relief), skilled nursing facilities, nursing homes; all of which do not constitute as hospitalization. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions.

10.3.2. Expectedness of Events

Expectedness of all AEs will be determined according to the LYT-100 IB and Ofev Summary of Product Characteristics.

10.3.3. Suspected Unexpected Serious Adverse Reactions

A suspected, unexpected serious adverse reaction (SUSAR) is an adverse event that is both unexpected (i.e., not listed in the Reference Safety Information for the investigational agent) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Reference Safety Information (i.e., the IB for an investigational agent).

10.3.4. Documenting and Reporting Adverse Events

The investigator will record all observed or volunteered AEs regardless of treatment group or causal relationship to study drug will be recorded on the AE page(s) of the eCRF. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

For all AEs, the investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. For AEs with a causal relationship to the IP, follow-up by the investigator is required until the event resolves or stabilizes at a level acceptable to the investigator and the Sponsor clinical monitor or his/her designated representative.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE, as provided in this protocol. When there is a safety evaluation during the study, the investigator or site staff will be responsible for detecting, documenting, and reporting AEs, as detailed in this section of the protocol. Refer to definitions of an AE, AESI, and SAE in protocol Section 10.

The eCRF should include the following information: start and stop dates, relationship to study drug, action taken, and outcome. AEs should be recorded from the time of informed consent to 30 days following the last dose of study drug regardless of the causal relationship to the study drug. AEs considered related or possibly related to study drug should be recorded at any time regardless of when they occurred.

The investigator will also assess the possible relationship between the AE and any of the study drug s as well as any concomitant medications according to the criteria presented in Section 10.1.2.

10.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (e.g., clinical chemistry, hematology, coagulation, and urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Screening and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

Laboratory measurements that deviate clinically significantly from previous measurements (as determined by the investigator) may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Any action to address subjects with clinically-significant abnormal laboratory values should be discussed with the Sponsor Medical Monitor.

10.5. Recording Adverse Events

AEs spontaneously reported by the subject 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 subject to discontinue the study. AEs that occur during the study must be documented in the subject'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 must be recorded in source and reported in the eCRF. 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. Additional information of reporting SAEs will be provided in the Safety Management Plan.

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 10.1.1. An AE of severe intensity may not be considered serious.

10.5.1. Pregnancy

Pregnancy tests will be performed in all WOCBPs. Where required by local regulations, a serum pregnancy test should be conducted in addition to the urine pregnancy test (i.e., in certain countries, a serum pregnancy test is required at Screening). If a urine pregnancy test is positive, a serum pregnancy test must also be performed as confirmation. Documentation will be made in subject's notes. Where required by local regulations, an appropriate pregnancy test may be performed more frequently than this schedule.

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study intervention and until 30 days after last treatment. If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours (1 calendar day) of learning of the [female subject or female partner of male subject (after obtaining the necessary informed consent from the female partner)] pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. The subject/pregnant female partner will be followed to determine the outcome of the pregnancy.

The investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the Sponsor as described in Section 10.5. While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, he or she may learn of an SAE through spontaneous reporting. Any female subject who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

10.6. Reporting of Serious Adverse Events

10.6.1. Investigator Responsibilities

All SAEs experienced by the subject between the time of the signing of the ICF and the subject's final clinic visit (including Follow-up Visit), must be reported when the site becomes aware of the event(s) by completing the SAE form for the study within 24 hours of first awareness. Follow-up information regarding an SAE also must be reported within 24 hours. Any AESIs or SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in therapy) will be recorded from the time a subject consents to participate in the study.

Subjects will be followed for all SAEs until the final clinic visit (including Follow-up Visit). Thereafter, the event should be reported to PureTech only if the Investigator considered the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. To report initial or follow-up information on an SAE, the investigator or site personnel must complete the paper SAE form and send the completed, signed form via email to PureTech Health Pharmacovigilance Department or its designee at [redacted] within 24 hours of awareness of the event. Reporting Responsibilities

The Sponsor will promptly report SAEs that are unexpected and judged by the investigator or the Sponsor to be related to the study treatment administered (e.g., LYT-100 and/nintedanib), for the purpose of expedited reporting of SUSARs and other applicable SAEs, to the FDA and other appropriate regulatory agencies in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 312.32 (21 CFR 312.32), central institutional review boards (IRBs)/ECs and investigators as required, and local regulatory requirements.

The investigator should also comply with any applicable requirements related to the reporting of SAEs to their local IRB. The Sponsor will provide the final CIOMS-I report to the investigator for further reporting, if applicable.

10.7. Adverse Events and Serious Adverse Events Follow-up

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs/AESI will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

The PI is responsible for ensuring 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 PI perform or arrange for the conduct of supplemental measurements and/or evaluations. If a study subject dies while on study or during a prespecified follow-up period, the Sponsor will be provided with a redacted copy of any postmortem findings, including histopathologic findings.

11. STUDY COMPLETION AND DISCONTINUATION

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

If a subject is withdrawn because of an AE, the Investigator must arrange for the subject 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 Medical Monitor determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of subjects from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or subject noncompliance.

If a subject 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.

A subject is considered lost to follow-up if they did not return to the CPU for the EOS/Follow-Up Visit and multiple attempts to contact the subject were unsuccessful. Three attempts to contact the subject must be documented in the subject's source documents.

12. 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 IRB/IEC in writing of the study's completion or early discontinuation.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a subject 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 regarding 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 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 subject 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 subject'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 subject (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 CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the relevant authority.

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

13.2. 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.

13.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB 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.

14. STATISTICS

A statistical analysis plan (SAP) will be written that will describe, in greater detail, the analyses to be performed. Procedures outlined in the SAP will supersede protocol specified statistical methods in the event of divergence. The sections below provide a summary of the general approach to the analysis. The analysis is consistent with the study design and objectives.

14.1. Sample Size

Up to 30 subjects will be enrolled to obtain 20 completers. A sample size of 20 subjects is based on a one sample design using a multiplicative model for a log-normal mean that will provide 82.2% power to reject both the null hypothesis that the test geometric mean is below 0.7, and the null hypothesis that the test geometric mean is above 1.33.

14.2. General Statistical Plan

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

Subject disposition (including the number and percent of subjects/patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study) will be tabulated. Demographic information will be presented for each subject and summarised.

Summary statistics for days of exposure and concentration of exposure will be provided. Treatment-emergent adverse events (including AESIs) and laboratory, vital signs, and ECG

parameters will be summarised. In addition, change from baseline will be summarised for laboratory and vital sign parameters. ECG results will be classified as normal and abnormal and summarised. ECG results for QTcF will also be classified as <450 msec, 450-500 msec or >500 msec.

14.3. Analysis Populations

Subject inclusion into each population will be determined prior to the final analysis.

14.3.1. Safety Set

Safety Set (SS) is defined as all subjects who have received any study drug.

14.3.2. Pharmacokinetic Population

Pharmacokinetic Population (PP) is defined as all subjects who receive nintedanib and LYT-100 and for whom an evaluable concentration-time profile is available for the determination of at least one PK variable.

14.4. 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.

14.4.1. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the WHO drug dictionary. Prior and concomitant medications will be listed by subject and summarized by treatment using ATC and PT.

14.4.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). A by subject AE data listing, including verbatim term, PT, system organ class (SOC), treatment, severity and relationship to study drug will be provided. The number of subjects experiencing TEAEs and the number of individual TEAEs will be provided by cohort overall, as well as by SOC and PT. The severity and the relationship to study drug of TEAEs will be summarized by cohort.

14.4.3. 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.

14.4.4. 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.

14.4.5. Electrocardiograms

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.

14.4.6. Other Safety Assessments

Findings of the following assessments will be listed by subject:

- Medical History
- Pregnancy Test/FSH Test
- Urine Drug Screen (including Cotinine Test)/ Alcohol Test
- Physical Examination
- Serology (HIV, Hepatitis B and C Screen)

14.5. Pharmacokinetics

Plasma concentration-time data for nintedanib and LYT-100 will be analyzed using noncompartmental methods.

Plasma PK parameters for steady state dosing (Days 7, 13, 20, 30) will include, but are not limited to:

- $AUC_{0\text{-}tlast,ss}$ (area under the time concentration curve from time zero to tau at steady state)
- $AUC_{0\text{-}12,ss}$ (area under the time concentration curve from time zero to 12 hours at steady state)
- $C_{max,ss}$ (maximum concentration in a dosing interval)
- T_{max} (time to maximum concentration, as reported relative to the beginning of a dosing interval in which maximum concentration occurred)
- Other parameters as appropriate

The effect of LYT-100 on nintedanib PK parameters will be evaluated by comparing the PK parameters of nintedanib on Days 7 versus Day 13 as well as Day 7 versus Day 20. Similarly, the effect of nintedanib on LYT-100 will be evaluated by comparing the PK parameters of LYT-100 on Day 20 vs Day 30 per FDA Guidance for Drug Interactions. Determination of steady state for nintedanib and LYT-100 will be performed using Helmert Contrasts and the trough concentrations. Pharmacokinetic parameter values will be listed and summarised by dose. Details of the analysis of drug interaction will be presented in the clinical pharmacology analysis section of the SAP.

15. ETHICS

15.1. 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 IEC/IRB as appropriate. The Investigator must submit written approval to the Sponsor before he or she can consent any subject on study.

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

The Investigator is also responsible for providing the IEC/IRB 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 IEC/IRB according to local regulations and guidelines.

15.2. 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.

15.3. Written Informed Consent

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

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The subjects 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 subject'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 subject 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 subject or legal representative. The date that informed consent was signed will be recorded on the CRF.

15.4. Data Protection

PureTech is compliant with GDPR requirements and takes the privacy and security of individuals and their personal information very seriously. Subjects will be informed that data will be held on file by the Sponsor and that these data may be viewed by internal staff, the study monitor, vendors and/or external auditors on behalf of the Sponsor and appropriate regulatory authorities. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, subjects will be identified in such reports only by study identification number, gender, and age. All subject data will be held in strict confidence and kept only as long as is required by law. Should a data breach occur, PureTech will work with its vendors to recover any stolen data, notify subjects of the potential data leak, and work with vendors to prevent such breaches in the future.

Additionally, PureTech will notify the participating Member States about any serious breaches at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach. For the purposes of this protocol, a 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial. Regulatory Requirements

PureTech Health, LLC will conduct this protocol under an active Investigational New Drug application in accordance with 21 Code of Federal Regulations Part 312.

15.5. Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a patient ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or year of birth may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit the monitor or the Sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (Section 15.3).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected in the eCRF).

Patient study data is collected based on the study procedures outlined in Section 7 and entered into an electronic case report form (iMedidata) stored on an external server. Periodic data transfers of external data (not collected in iMedidata) will be provided on a periodic basis according to vendor data transfer plans. Additional details of the data acquisition tools, the data transmission procedures and database information are provided in the study data management plan.

15.6. Pre-Study Documentation Requirements

The Investigator is responsible for forwarding the following essential documents to the Sponsor for review and approval before study initiation:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of the IRB approval of the protocol, ICF, and subject information sheet (if applicable)
- Curricula vitae of Investigator and all sub-Investigators
- The IRB composition and/or written statement that IRB complies with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Signed study contract
- Completed Form FDA-1572
- Completed Financial Disclosure statements for the PI, all sub-Investigators, and (the disclosure includes financial information of their spouses or (legal partners) and dependent children), as appropriate.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigational sites 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 stock, drug accountability/reconciliation records, subject medical records, study source data, and other records relative to study conduct.

16.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 25 years after the completion of the study. All data will be available for retrospective review or audit.

Source data are original documents, data, and records from which the subject'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 IEC/IRB/HREC correspondence, study drug accountability, 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.

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, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

16.3. 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 subjects or investigator(s).

17. PUBLICATION POLICY

17.1. 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. Authorship will follow the ICMJE (International Committee of Medical Journal Editors) guidelines.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgement will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Subject confidentiality will be maintained by referring to individual subjects by their identifying code used in the study. 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 study 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 study will be posted to 1 or more clinical study registries (including clinicaltrials.gov and the public domain of the Clinical Trials Information System [CTIS] database at https://euclinicaltrials.eu/home) in a timely manner as required by legal agreement, local law, or regulation. As appropriate, this will be accompanied by a summary written in a manner that is understandable to laypersons.

17.2. 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 his/her staff and the local IEC/IRB. 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 subjects who wish to participate in the study.

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

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

The study will be carried out in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans (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.

18.2. Regulatory Inspection

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.

19. SPONSOR AND INVESTIGATOR OBLIGATIONS

19.1. 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 institutional IEC/IRB 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 subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

19.2. 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 IEC/IRB (if required) and included in the clinical study report.

20. LIST OF REFERENCES

Center for Drug Evaluation and Research (CDER). Pharmacology/Toxicology NDA Review and Evaluation Addendum. Esbriet (Pirfenidone) NDA 22535 InterMune. 2014

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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. European Respiratory Journal 35, 821–829.

US Food and Drug Administration (2017). Drug Approval Package: Austedo (deutetrabenazine) NDA # 208082.

US Food and Drug Administration (2014). Drug Approval Package: Esbriet (Pirfenidone) NDA #022535.

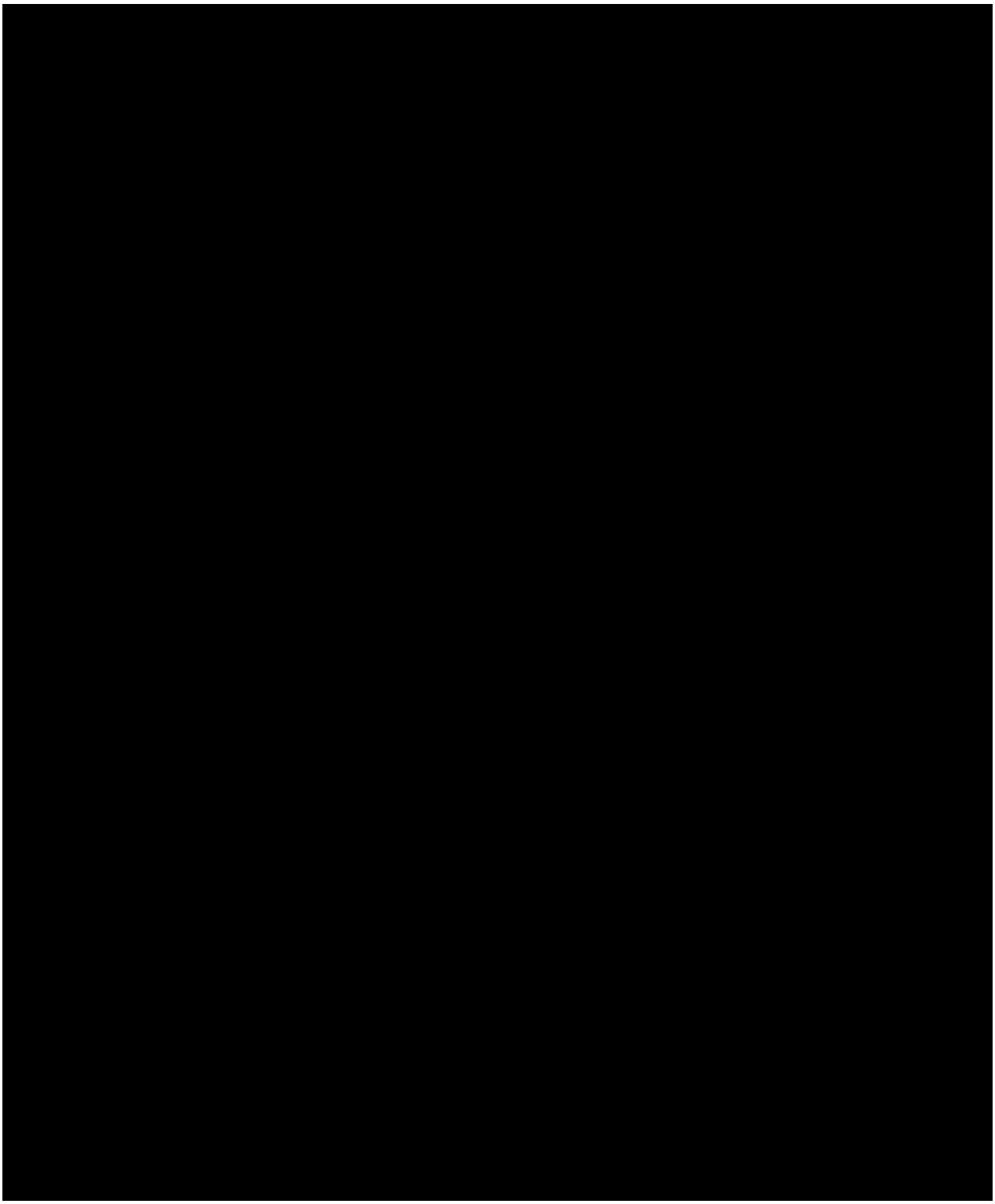
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21. APPENDICES

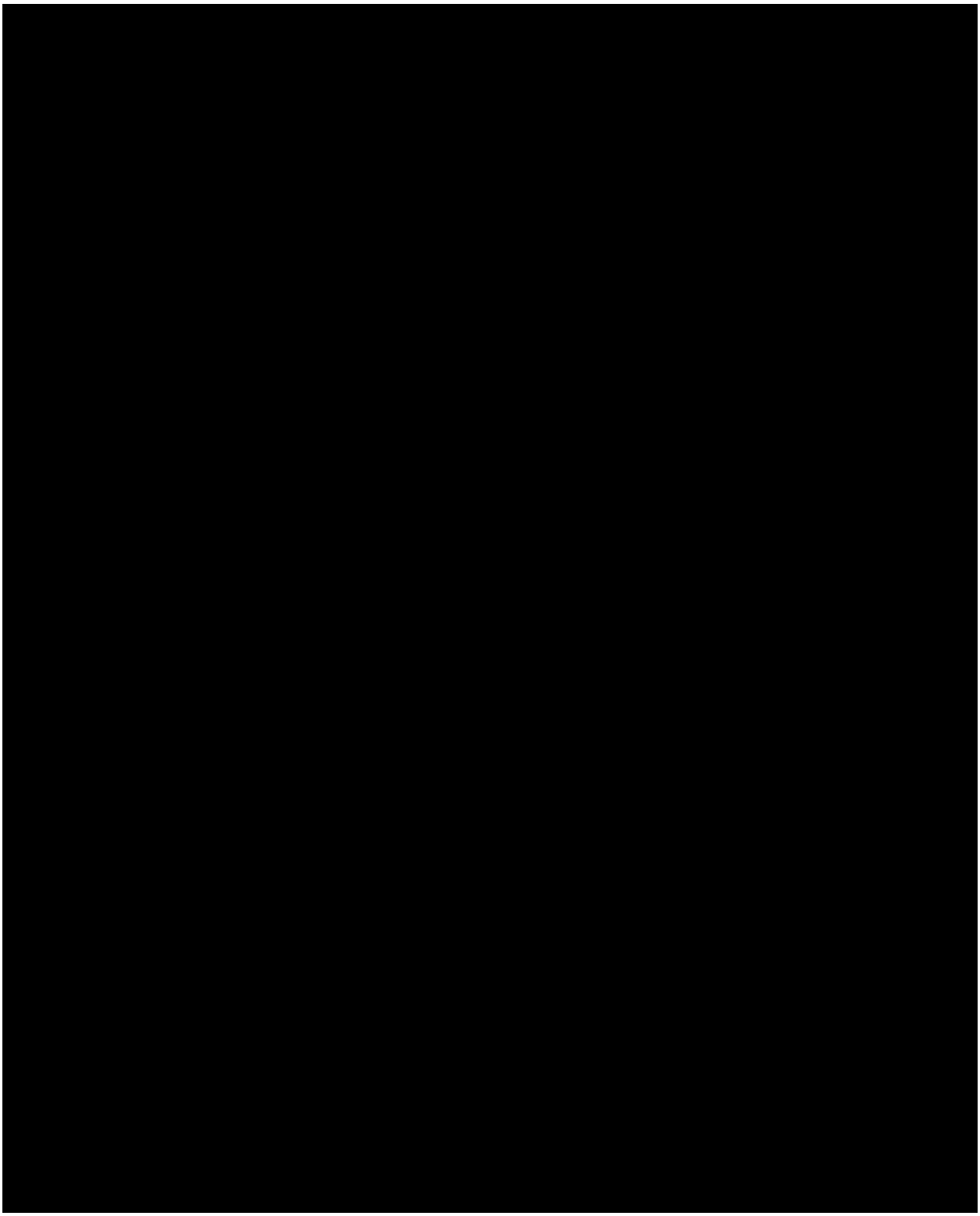
21.1. APPENDIX 1 – Prohibited Medications



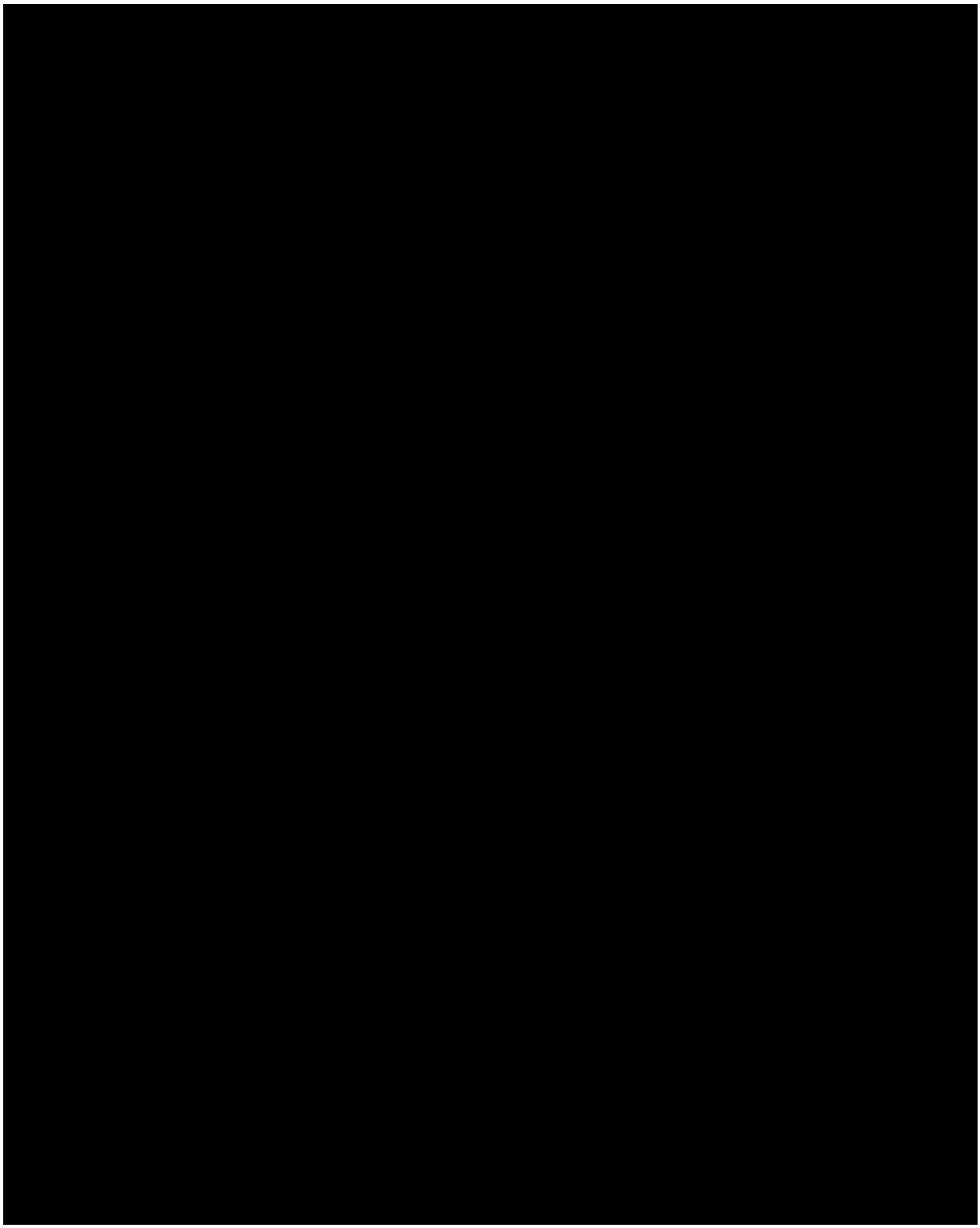
21.2. APPENDIX 2 – MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS



MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)



MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)



MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
CONSTITUTIONAL SYMPTOMS (continued)					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over Baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	severe (e.g., decrease in performance status by >2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 × 109/L Also consider Allergic reaction/ hypersensitivity Note: the temperature measurements listed above are oral or tympanic.	none	38.0–39.0°C (100.4–102.2°F)	39.1–40.0°C (102.3–104.0°F)	>40.0°C (>104.0°F) for <24 hrs	>40.0°C (>104.0°F) for ≥24 hr
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	—	—
Phototoxicity/Photosensitivity	Normal	painless erythema	painful erythema	erythema with desquamation	life threatening, disabling
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	—
Rash/desquamation	none or no change	macular or popular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, popular or vesicular eruption or desquamation covering >50% of body surface area	generalized exfoliative dermatitis or ulcerating dermatitis

MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
DERMATOLOGY/SKIN (continued)					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or corticosteroids for <24 hr	requiring IV medication or corticosteroids for ≥24 hr	—
Wound-infections	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fasciitis
GASTROINTESTINAL					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Diarrhea (patients without colostomy)	none	increase of <4 stools/day over pretreatment	increase of 4–6 stools/day or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	—
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can eat or swallow	painful erythema, edema or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation

MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
GASTROINTESTINAL (continued)					
Vomiting	none	1 episode in 24 hr over pretreatment	2–5 episodes in 24 hr over pretreatment	≥6 episodes in 24 hr over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
HEMORRHAGE					
Hemorrhage – Other (Specify site, _____)	none	mild without transfusion	—	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Liver dysfunction/failure (clinical)	normal	—	—	asterixis	encephalopathy or coma
MUSCULOSKELETAL					
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical examination	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
NEUROLOGY					
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical examination, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
Confusion	Normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization

MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
NEUROLOGY (continued)					
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheaded ness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Mood alteration – anxiety, agitation – depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Neuropathy – cerebellar	none	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotorataxia	cerebellar necrosis
Neuropathy – motor	normal	subjective weakness, but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy–sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
OCULAR/VISUAL					
Ocular/Visual – Other	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)

MODIFIED COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (contd)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
PAIN					
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
RENAL					
Renal failure	none	—	—	requiring dialysis, but reversible	requiring dialysis and irreversible
Proteinuria Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.	normal or <0.15 g/24 hours	1 + or 0.15–1.0 g/24 hours	2+ to 3+ or 1.0–3.5 g/24 hr	4+ or >3.5 g/24 hr	nephrotic syndrome