CLINICAL STUDY PROTOCOL

STUDY CODE No.: CLI-10067AA1-01

EUDRACT No.: 2022-001079-15

NCT05513950

A PHASE IB, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF AN INTRAVENOUS MONOCLONAL ANTIBODY (MAB) AFTER SINGLE ASCENDING DOSES IN SUBJECTS AFFECTED BY IDIOPATHIC PULMONARY FIBROSIS

Version No.: 6.0
Date: 06 July 2023

Chiesi Farmaceutici S.p.A.
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GENERAL INFORMATION

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VERSION HISTORY

Version	Date	Change History
1.0	*03 May 2022*	*First version*
2.0	*25 August 2022*	Protocol version 2.0 (dated 25 August 2022) incorporated the following changes into protocol version 1.0 (dated 03 May 2022) based on Medicines and Healthcare products Regulatory Agency (MHRA) feedback: • Section 6.2.2.1 *Dose escalation* stopping rule was updated: 'Three or more subjects on active drug* experience a severe, possibly drug-related AE lasting for > 24 hours duration' is replaced by 'two or more subjects on active drug* experience a severe, possibly drug-related AE lasting for > 24 hours duration'. • Section 10.3 *Intensity of Adverse Event* was amended so that the Common Terminology Criteria for Adverse Events (CTCAE) would be used as the adverse event severity grading scale rather than a 3-point severity grading scale with CTCAE. • Section 12.3.5.1 *Adverse Events* was amended to change the statistical analysis so that treatment-emergent adverse event data will be summarised by CTCAE grade rather than severe intensity.
3.0	*24 October 2022*	• See the list of substantial changes in the summary of changes dd 24 October 2022.
4.0	*22 May 2023*	Protocol version 4.0 (dated 22 May 2023) removed the bronchoscopy procedure from protocol version 3.0 (dated 24 October 2022) based on MHRA feedback in the following sections: • Section 1.3 *Risk/Benefit Assessment* • Section 4.1 *Subject Recruitment* • Section 7.1 *Study Schedule – All Cohorts* • Section 7.1.2 *Optional Additional Visit for Bronchoscopy*

		• Section 7.2.12 *Optional Bronchoscopy for Bronchoalveolar Lavage and Bronchoabsorption Assessment* • Section 25 *References*
5.0	*16 June 2023*	See the list of the substantial changes in the Summary of Changes dated 16 June 2023.
6.0	*06 July 2023*	Non substantial changes to correct inconsistencies related to the timing of vital signs and oxygen saturation assessments: • Section 7.1 *Footnotes for Evaluation Schedule* • Section 7.2.7.3 *Oxygen Saturation* • Section 7.2.8 *Vital Signs*.

PROTOCOL OUTLINE

Study title	A Phase Ib, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics of an intravenous monoclonal antibody (mAb) after single ascending doses in subjects affected by idiopathic pulmonary fibrosis
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the product	CHF10067
Centre(s)	Multi-centre study (approximately 12 sites)
Indication	Idiopathic pulmonary fibrosis (IPF)
Study design	Randomised, double-blind, placebo-controlled, single-dose escalation
Study phase	Phase Ib
Objectives	The primary objective is to assess the safety and tolerability of single ascending doses of CHF10067 in subjects with IPF. The secondary objectives are: • to evaluate the CHF10067 pharmacokinetic (PK) profile in serum • to evaluate the CHF10067 immunogenicity profile in terms of anti-drug antibody (ADA) and neutralising antibody (nAb). The exploratory objective is to evaluate transglutaminase 2 (TG2) levels in plasma.
Treatment duration	One single dose (CHF10067 or placebo)
Test product dose/route/regimen	A single 1000 mg, anticipated 2000 mg, or anticipated 3000 mg intravenous (IV) dose of CHF10067
Reference product dose/route/regimen	A single dose of placebo [redacted]
Number of subjects	Twenty-four subjects will be studied in 3 cohorts (Cohort A [1000 mg], B [anticipated 2000 mg], and C [anticipated 3000 mg]) consisting of 8 subjects per cohort. In each cohort, 6 subjects will receive CHF10067, and 2 subjects will receive placebo. In each cohort, a minimum of 2 subjects are required to be not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening).
Study population	Subjects with IPF (not receiving antifibrotic treatment [including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening] or receiving standard of care treatments at a stable dose for at least 8 weeks prior to screening [nintedanib or pirfenidone].
Inclusion/exclusion criteria	**Inclusion criteria:** Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:

	1. Subject's written informed consent obtained prior to any study-related procedure. 2. Males or females, of any race, aged ≥ 40 years of age. 3. Body mass index between 18.0 and 35.0 kg/m^2, inclusive. 4. Body weight ≥ 45 kg. 5. Diagnosis of IPF as defined by current American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines (2022), which will include subjects with a usual interstitial pneumonia (UIP) pattern or probable UIP pattern with confirmation of IPF diagnosis based on the Multi-Disciplinary Team Discussion (excluding other possible etiological causes of the high-resolution computed tomography [HRCT] pattern). Where a lung biopsy is available, the computed tomography (CT) pattern and biopsy results must be compatible with a diagnosis of IPF. The diagnosis of IPF must be within the past 5 years prior to enrolment, and in the opinion of the Investigator, has been stable for at least 3 months.[1] 6. Subjects not receiving any IPF treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening) or receiving well-tolerated standard of care approved treatments at a stable dose for at least 8 weeks prior to screening (nintedanib or pirfenidone) and it is anticipated the dose will remain unchanged throughout the study. 7. Oxygen saturation ≥ 92% at rest by pulse oximetry while breathing ambient air at screening **and prior to randomization**. 8. Forced vital capacity (FVC) ≥ 50% of predicted and ratio of forced expiratory volume in the first second (FEV_1)/FVC ≥ 0.7 at screening. 9. Diffusing capacity of the lung for carbon monoxide (D_{LCO}; corrected for haemoglobin) ≥ 35% at screening. 10. Able to understand the study procedures and the risks involved. 11. Female subjects: a. Women of childbearing potential (WOCBP) fulfilling 1 of the following criteria: i. <u>WOCBP with fertile male partners</u>: they and/or their partner must be willing to use a highly effective birth control method preferably with low user dependency from the signature of the informed consent and until the last study visit or ii. <u>WOCBP with non-fertile male partners:</u> contraception is not required in this case. Or b. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e., post-menopausal or permanently sterile). Tubal ligation or partial surgical interventions are not acceptable. If

indicated, as per Investigator's request, post-menopausal status may be confirmed by screening serum follicle-stimulating hormone levels (according to local laboratory ranges).

12. Males fulfilling one of the following criteria:
    a. Males with pregnant or non-pregnant WOCBP partners: they must be willing to use male condom from the signature of the informed consent and until the last study visit or
    b. Non-fertile male subjects: contraception is not required in this case or
    c. Males with partner not of childbearing potential: contraception is not required in this case.

For the definition of WOCBP, fertile men, and the list of highly effective birth control methods with low user dependency see APPENDIX 3 or Section 4.1 of the Clinical Trial Facilitation Group guidance.[16]

The following inclusion criteria should be re-checked at the Day 1 visit (prior to randomisation): 7.

Exclusion criteria:

The presence of any of the following will exclude a subject from study enrolment:

1. History of lower respiratory tract infection within 4 weeks prior to screening and up to Day 1 of the study, which required the use of antibiotics and admission to a clinical facility, or community treated lower respiratory tract infection that in the opinion of the investigator would preclude the subject's participation in the study.
2. History of acute exacerbation of IPF within 3 months prior to screening and up to Day 1 of the study, defined as:
    a. worsening or newly developed dyspnoea as reported by the subject (≤ 30 days)
    b. new bilateral ground-glass opacities on HRCT superimposed on the UIP abnormalities that defined subject eligibility for the study, and
    c. worsening hypoxemia (in the judgment of the Investigator), in the absence of pulmonary infection, heart failure, or other identifiable causes for this finding.
3. Planned surgery during the study.
4. Active diagnosis of lung cancer or a history of lung cancer.
5. Active cancer or a history of cancer (other than lung cancer) with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g., basal cell carcinoma or in situ carcinoma of the cervix adequately treated, etc.) is acceptable.

	6. Infiltrative lung disease other than IPF, including any of the following: a. Other types of idiopathic interstitial pneumonia b. Interstitial lung diseases related to exposure to fibrogenic agents, other environmental toxins, or drugs c. Other types of occupational lung diseases d. Granulomatous lung diseases e. Pulmonary vascular diseases f. Related to systemic diseases (including vasculitis and connective tissue diseases). 7. History of other types of respiratory diseases in the opinion of the Investigator, would impact the endpoints in the protocol or otherwise preclude the subject's participation in the study including diseases or disorders of the airways, lung parenchyma, pleural space, mediastinum, diaphragm, or chest wall. 8. End-stage fibrotic disease expected to require organ transplantation within 6 months. 9. Trauma or surgical procedures requiring hospitalisation within 4 weeks prior to screening visit. 10. Subjects exhibiting unhealed wounds or foot ulcers or have known history of wound healing complications. 11. Clinically relevant and uncontrolled cardiac, hepatic, gastrointestinal, renal, endocrine, metabolic, neurologic, or psychiatric disorders that may interfere with successful completion of this protocol according to the Investigator's judgment. 12. Any abnormal and clinically significant 12-lead electrocardiogram (ECG) that in the Investigator's opinion would affect safety evaluation or place the subjects at risk at screening and prior to randomization. 13. Chronic heart failure categorized as New York Heart Association Class II, III, or IV (this applies to symptoms of chronic heart failure, not IPF); clinical diagnosis of *cor pulmonale* requiring specific treatment; or severe pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study. 14. Currently receiving, or have received, a systemic corticosteroid, immunosuppressant, cytotoxic therapy, vasodilator therapy for pulmonary hypertension, or unapproved or investigational treatment for IPF within 4 weeks prior to screening or prior to randomization. Treatment with pirfenidone or nintedanib, though not both concurrently, is permitted, provided that the subject has been on a well-tolerated stable dose for at least 8 weeks prior to screening and it is anticipated the dose will remain unchanged throughout the study. 15. Participation in another clinical study with an investigational drug in the 1 month or 5 half-lives of that investigational drug

	(whichever is longer) preceding dosing; a longer and more appropriate time could be considered by the Investigator based on the elimination half-life and/or long-term toxicity of the previous investigational drug. 16. Received the coronavirus disease-2019 (COVID-19) vaccine ≤ 7 days before dosing. Any systemic symptoms (e.g., myalgia, fever, chills, fatigue, etc.) after COVID-19 vaccine should subside at least 2 days before the Day 1 visit. 17. Any other drugs which may interfere with the safe completion of the study, according to the Investigator opinion, are also forbidden. 18. Presence of any current infection, or previous infection that resolved less than 7 days prior to screening or before treatment (with the exception of lower respiratory tract infections, for which the exclusion criterion is defined separately: exclusion criterion n. 1). 19. Documented COVID-19 diagnosis within the last 4 weeks or which has not resolved within 7 days prior to screening or before treatment. COVID-19 testing prior to enrolment and during the study will be conducted according to current local guidelines and is not specified in the protocol. 20. Known intolerance and/or hypersensitivity to any of the excipients contained in the formulation or any other substance used in the study. 21. History of allergic or anaphylactic reaction to human, humanised, chimeric, immunoglobulins (Igs), or murine monoclonal antibodies. 22. History of severe episodes of urticaria and angioedema or diagnosis of chronic urticaria and its underlying disorders including, but not limited to acquired angioedema due to C1-inhibitor deficiency, auto-inflammatory disease, hereditary angioedema, or urticarial vasculitis. 23. Confirmed or suspected diagnosis of mastocytosis. 24. Clinically relevant abnormal laboratory values (clinical chemistry and haematology) at screening suggesting an unknown disease and requiring further clinical investigation or which may impact the safety of the subject or the evaluation of the study results according to Investigator judgement. Note: in case of abnormal laboratory values, that could indicate a temporary condition, the test can be repeated twice before randomisation. 25. Positive human immunodeficiency virus (HIV) 1 and/or HIV2 results at screening. 26. Positive hepatitis result that indicates acute or chronic hepatitis B (HB) or hepatitis C (HC) at screening (i.e., positive HB surface antigen, HB core antibody [IgM anti-HB core antibody], or HC antibody).

	27. Blood donation or blood loss (equal or more than 450 mL) within 2 months prior to screening or prior to randomization. 28. History of cigarette (or e-cigarette) smoking or use of nicotine- or tobacco-containing products within 3 months prior to screening or a positive urine test for cotinine at screening. 29. Documented history of alcohol abuse within 12 months prior to screening or a positive alcohol breath test prior to randomization. Note: before randomization, the test can be repeated once, at least 3 days after the last positive test, if the Investigator evaluates that the subject will be compliant to alcohol abstinence during the study. 30. Documented history of drug abuse within 12 months prior to screening or a positive urine drug screen prior to randomization. Note: before randomization, the test can be repeated once at least 15 days after the last positive test, if the Investigator evaluates that the subject will be compliant to drug abstinence during the study. 31. Unsuitable veins for repeated venipuncture. 32. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive serum human chorionic gonadotropin laboratory test. A serum pregnancy test will be performed at screening and urine pregnancy test will be performed prior to randomisation. The following exclusion criteria should be re-checked at the Day 1 visit (prior to randomisation): 1, 2, 12, 14, 18, 19, 27, and 32.
Study plan	The screening visit will take place between 3 to 28 days prior to randomisation and subject eligibility will be assessed according to the inclusion/exclusion criteria. On Day 1, subjects will attend the clinical site for an ambulatory visit. Following confirmation of eligibility, subjects will be randomised to either CHF10067 or placebo and will receive a single IV dose of CHF10067 or placebo. Subjects will be monitored for safety, tolerability, immunogenicity, PK, and TG2 levels for 84 days post-dose and will attend ambulatory visits on Days 2, 5, 7, 14, 28, 56, and 84 (end of study). Even if not mandatory, overnight stay is always possible for logistical reasons or to accomplish site/subject preferences. In each cohort, subjects will be divided into 2 sub-groups, with each sub-group being dosed at least 24 hours apart. The first sub-group will comprise 2 subjects (1 CHF10067; 1 placebo). The second sub-group will comprise 6 subjects (5 CHF10067; 1 placebo). The decision to dose the remaining 6 subjects will be evaluated by at least the Medical Monitor and Sponsor Clinical Research Physician based on the safety data provided by the Investigator(s) where the first sub-group have been dosed and the decision to escalate to the next dose will be made by the Safety Advisory Committee.

Most relevant allowed concomitant treatments	Well-tolerated standard of care treatment of IPF (e.g., nintedanib, pirfenidone) at stable doses for at least 8 weeks prior to screening and not expected to change during the study. Concomitant intake of nintedanib and pirfenidone is not allowed. COVID-19 vaccine at least 7 days before dosing. Note: Any systemic symptoms (e.g., myalgia, fever, chills, fatigue, etc.) after COVID-19 vaccine should subside at least 2 days before the treatment visit. Hormone replacement therapy, oral, implantable, transdermal, injectable, or intravaginal contraceptives.
Most relevant forbidden concomitant treatments	Systemic corticosteroids, immunosuppressants, cytotoxic therapy or vasodilator therapy for pulmonary hypertension, or any other unapproved or investigational treatment for IPF. In case of exacerbations, appropriate medications can be initiated at Investigator's discretion. Any other drug which may interfere with the safe completion of the study, according to the Investigator's opinion, is also forbidden.
Safety and immunogenicity variables	• Adverse events (AEs) and adverse drug reactions • Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) • Oxygen saturation measured via pulse oximetry • 12-lead ECGs (heart rate, PR, QRS, and QT corrected for heart rate by Fridericia's formula) • Physical examinations • Clinical laboratory evaluations: clinical chemistry (including fasting glucose) and haematology • Spirometry (FEV_1, FVC, FEV_1 % of predicted normal and lower limit of normal value, FVC % of predicted normal and lower limit of normal value, and FEV_1/FVC ratio) • Diffusing capacity (D_{LCO} [unadjusted], D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, carbon monoxide transfer coefficient, and alveolar volume) • ADAs and nAb • Analysis of systemic markers* of immediate hypersensitivity reaction pre-dose and post-dose (post-dose only if required): - Markers of cytokine release syndrome (interferon-γ, tumour necrosis factor-α, interleukin [IL]-1 β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), and IL-13) - Mast cell tryptase - Complement markers (C3a, C5a, CH50, and SC5b-9) - CHF10067 IgE *During the study, the markers analysed may be adjusted as required. Any adjustment will be with consideration for subject safety and operational activities.

Pharmacokinetic variables	• Area under the concentration-time curve (AUC) from 0 to the last quantifiable concentration (AUC_{0-t}) • AUC extrapolated to infinity (AUC_{inf}) • Maximum observed concentration (C_{max}) • Time to C_{max} (t_{max}) • Concentration at steady state of infusion (C_{inf}) • Clearance (CL) • Volume of distribution (Vz) • Terminal half-life ($t_{1/2}$).
Other variables	• TG2 level in plasma
Sample size calculation	This study is designed to explore the safety and tolerability of CHF10067 for the first time in subjects affected by IPF, while exposing a minimum number of subjects; therefore, no formal power calculation was performed. A sample size of 24 subjects (8 subjects per cohort; 6 treated with CHF10067 and 2 with placebo) is deemed adequate to assess safety and tolerability of CHF10067. In each cohort, a minimum of 2 subjects are required to be not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening).
Statistical methods	**Safety and Immunogenicity** Safety parameters will be listed and summarised with change from baseline (where applicable) at each post-dose timepoint using descriptive statistics and 95% confidence intervals (CIs; where applicable). Time profile plots will also be presented where relevant. The number of events and the number and percentage of subjects experiencing treatment-emergent AEs will be presented by treatment. **Pharmacokinetics** CHF10067 serum AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, C_{inf}, CL, Vz, and $t_{1/2}$ will be summarised by dose level using descriptive statistics. Serum concentration/time curves will be presented in linear/linear and log/linear scale. Plots will be presented by dose level, based on arithmetic means, and by subject, by showing the individual curves grouped by dose level (1 plot for each dose level) and ADA positivity/negativity (using different colours). Dose proportionality in terms of CHF10067 AUC_{0-t}, AUC_{inf}, and C_{max} will be evaluated using the power model including the log-transformed PK parameters as dependent variables, and the log-transformed CHF10067 dose as a covariate. The slope for log-transformed dose will be estimated with its 90% CI to examine dose proportionality. **Other** At each post-dose timepoint, TG2 levels in plasma will be summarised using descriptive statistics by treatment as absolute value and change from baseline using descriptive statistics and 95% CIs. Time profile plots and boxplots will also be presented.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	anti-drug antibody
ADL	Activities of Daily Living
ADR	adverse drug reaction
AE	adverse event
ALAT	Latin American Thoracic Society
ATS	American Thoracic Society
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from 0 to the last quantifiable concentration
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
BMI	body mass index
CI	confidence interval
C_{inf}	concentration at steady state of infusion
CL	clearance
C_{max}	maximum observed concentration
COVID-19	coronavirus disease-2019
CTCAE	Common Terminology criteria for Adverse Events
CV	coefficient of variation
D_{LCO}	diffusing capacity of the lung for carbon monoxide
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ERS	European Respiratory Society
FEV_1	forced expiratory volume in the first second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HB	hepatitis B
HC	hepatitis C
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IFN-γ	interferon-γ
Ig	immunoglobulin
IL	interleukin
ILD	interstitial lung disease
IMP	investigational medicinal product
IPF	idiopathic pulmonary fibrosis
IRT	interactive responsive technology
IV	intravenous
JRS	Japanese Respiratory Society
KCO	carbon monoxide transfer coefficient
KO	knockout

mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observed values
nAb	neutralising antibody
PR	PR Interval
PK	pharmacokinetic
QRS	QRS Interval
QTcF	QT corrected for heart rate by Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal half-life
TEAE	treatment emergent-adverse events
TG2	transglutaminase 2
t_{max}	time to maximum observed concentration
TNF-α	tumour necrosis factor-α
UIP	usual interstitial pneumonia
VA	alveolar volume
Vz	volume of distribution
WOCBP	women of childbearing potential

CONTENT

1. INTRODUCTION

1.1 Background Information

Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic, fibrosing interstitial lung disease (ILD) characterized by decline in lung function and worsening dyspnea [1]. Idiopathic pulmonary fibrosis is the most common ILD and carries a poor prognosis, with a median post-diagnosis survival in untreated subjects ranging from 2.5 to 3.5 years [2], [3]. Nintedanib and pirfenidone are currently the only drugs registered for the treatment of IPF and recommended in an official American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) clinical practice guideline [4], [5]. Despite the availability of these drugs, the medical need remains high.

Transglutaminase 2 (TG2) is a complex, 4-domain, calcium-dependent multifunctional protein that can act as a transamidase (protein cross-linker) in an extracellular environment, but also as a guanosine/adenosine triphosphatase, protein disulphide isomerase, and protein kinase in an intracellular environment. The role of TG2 in fibrosis is supported by an increasing body of evidence from in vivo interventional studies using experimental animal models of fibrotic disease in multiple organs, in addition to translational data obtained from humans. In these fibrotic diseases, data from knockout (KO) animals and small interfering ribonucleic acid studies in conjunction with human disease expression work have suggested that inhibition of TG2 would affect fibrotic disease progression [6], [7], [8], [9], [10], [11], [12], [13].

CHF10067 (formerly identified as UCB7858 and zampilimab) is a recombinant, humanized, full-length immunoglobulin (Ig) G4 inhibitory monoclonal antibody (mAb) with high affinity for human TG2. Preclinical data generated with CHF10067 provide strong evidence that an inhibitory antibody for TG2 can provide a powerful antifibrotic effect by decelerating the rate of disease progression. [redacted]

Clinical experience with CHF10067 consists of 2 completed Phase I studies in healthy subjects investigating single subcutaneous (SC) and intravenous (IV) doses of [redacted] and IV doses [redacted]. CHF10067 was found to be well tolerated at single IV doses up to [redacted] and single SC doses up to [redacted]. A Phase I/II study in adult kidney transplant recipients with chronic allograft injury associated with moderate-to-severe fibrosis and declining renal function (CAI001) was started, then prematurely interrupted due to poor recruitment (the study is still ongoing in order to monitor enrolled subjects' safety for the required follow-up period).

For detailed information of the preclinical and clinical data, please refer to the Investigator's Brochure (IB) [14].

1.2 Study Rationale

The development of novel therapies for the treatment of IPF, a rapidly progressive and fatal orphan disease, remains a great challenge despite significant unmet medical need. CHF10067 is being developed to meet this unmet need.

The principal aim of this study is to obtain safety and tolerability data when CHF10067 is administered intravenously as single ascending doses to subjects with IPF. This information, together with the pharmacokinetic (PK) and immunogenicity data, will help establish the doses suitable for future studies in subjects. The effect of CHF10067 on TG2 levels will also be investigated as an exploratory endpoint.

A sequential-group, single ascending dose design has been chosen for safety reasons because CHF10067 is in the early stages of clinical development and no data in the IPF population has been collected so far. In addition, sentinel dosing will be used such that 2 subjects (1 CHF10067 and 1 placebo) in each cohort will be dosed at least 24 hours before the remaining 6 subjects.

The study will be double blind and placebo controlled to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the comparison treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

Based upon the preclinical and clinical data and the potential of anti-drug antibody (ADA) response, the planned duration of the treatment period is considered adequate to achieve the study objectives. Subcutaneous doses were tolerated up to a dose of [redacted] and IV doses were tolerated up to a dose of [redacted]; therefore, IV doses have been chosen for this study. [redacted].

1.3 Risk/Benefit Assessment

Subjects in the current study are not expected to experience any health benefit (beyond that of an assessment of their medical status) from participating in the study, since they will be exposed to a single dose of treatment. The risks of participation are primarily those associated with adverse reactions to CHF10067, although there may also be some risks associated with the collection of blood samples and other study procedures. Subjects will be followed at the clinical site and closely monitored throughout the study period. Intravenous doses up to [redacted] have been safely tested in healthy subjects; therefore, a starting dose of 1000 mg is considered appropriate to be tested in the patient population. Considering the safety profile of CHF10067, the measures in place to assure the subjects' safety, and the expected scientific value, the overall risk/benefit assessment can be considered acceptable for the proposed study. More information about the known and expected benefits and risks associated with CHF10067 may be found in the IB.

This study will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), current International Council on Harmonisation (ICH) E6 Good Clinical Practices (GCP), and all other applicable laws and regulations.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the safety and tolerability of single ascending doses of CHF10067 in subjects with IPF.

2.2 Secondary Objectives

The secondary objectives are:

- to evaluate the CHF10067 PK profile in serum
- to evaluate the CHF10067 immunogenicity profile in terms of ADA and neutralising antibody (nAb).

2.3 Exploratory Objective

The exploratory objective is to evaluate TG2 levels in plasma.

3. STUDY DESIGN

This is a Phase Ib, multi-centre, multi-country, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, immunogenicity, and PK of single IV doses of CHF10067 in subjects with IPF. The effect of CHF10067 on TG2 levels will also be investigated as an exploratory endpoint.

Overall, 24 subjects will be studied in 3 cohorts (Cohorts A [1000 mg], B [anticipated 2000 mg], and C [anticipated 3000 mg]) consisting of 8 subjects per cohort. In each cohort, 6 subjects will receive CHF10067, and 2 subjects will receive placebo.

The doses will be administered according to an escalation scheme designed to ensure sufficient safety conditions for subjects. In each cohort, subjects will be divided into 2 sub-groups, with each sub-group being dosed at least 24 hours apart. The first sub-group will comprise 2 subjects, with 1 subject receiving CHF10067 and 1 subject receiving placebo. The second sub-group will comprise 6 subjects, with 5 subjects receiving CHF10067 and 1 subject receiving placebo. Continuation to dose the remaining 6 subjects will be evaluated by at least the Medical Monitor and Sponsor Clinical Research Physician based on the safety data provided by the Investigator(s) where the first-sub-group have been dosed. The decision to escalate to the next dose will be made by the Safety Advisory Committee when safety data until Day 14 have been collected for all subjects at the previous dose level. Pharmacokinetic and immunogenicity data will also be included in the safety evaluation for dose escalation (if available) but are not mandatory to escalate to the next dose. Further details regarding dose escalation are provided in Section 6.2.2.1.

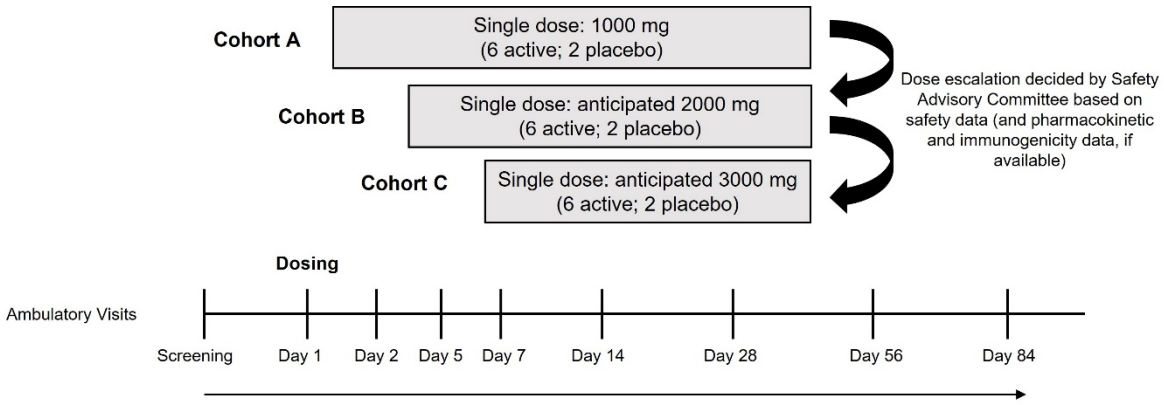
The screening visit will take place between 3 to 28 days prior to randomisation and subject eligibility will be assessed according to the inclusion/exclusion criteria. The signed informed consent form (ICF) will be obtained prior to any study-related procedures.

On Day 1, subjects will attend the clinical site for an ambulatory visit. Following confirmation of eligibility, subjects will be randomised to either CHF10067 or placebo and will receive a single IV dose of CHF10067 or placebo.

Subjects will be monitored for safety, tolerability, immunogenicity, PK, and TG2 levels for 84 days post-dose and will attend ambulatory visits on Days 2, 5, 7, 14, 28, 56, and 84 (end of study). The total duration of participation is expected to last approximately 16 weeks. The end of the study is defined as the last visit of the last subject in the study. Even if not mandatory, overnight stay is always possible for logistical reasons or to accomplish site/subject preferences.

An overview of the study design is shown in Figure 1.

Figure 1: Study Design



4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Overall, 24 subjects will be studied in 3 cohorts (Cohorts A, B, and C), consisting of 8 subjects per cohort. In each cohort, 6 subjects will receive CHF10067, and 2 subjects will receive placebo. In each cohort, a minimum of 2 subjects are required to be not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening).

4.2 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:

1. Subject's written informed consent obtained prior to any study-related procedure.
2. Males or females, of any race, aged ≥ 40 years of age.
3. Body mass index (BMI) between 18.0 and 35.0 kg/m^2, inclusive.
4. Body weight ≥ 45 kg.

5. Diagnosis of IPF as defined by current ATS/ERS/JRS/ALAT guidelines (2022) which will include patients with an usual interstitial pneumonia (UIP) pattern or probable UIP pattern with confirmation of IPF diagnosis based on the Multi-Disciplinary Team Discussion (excluding other possible etiological causes of the high-resolution computed tomography [HRCT] pattern). Where a lung biopsy is available, the computerized tomography (CT) pattern and biopsy results must be compatible with a diagnosis of IPF.[1]

   Diagnosis of IPF must be within the past 5 years prior to enrolment, and in the opinion of the Investigator, has been stable for at least 3 months.

6. Subjects not receiving any IPF treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening) or receiving well-tolerated standard of care approved treatments at a stable dose for at least 8 weeks prior to screening (nintedanib or pirfenidone) and it is anticipated the dose will remain unchanged throughout the study.
7. Oxygen saturation ≥ 92% at rest by pulse oximetry while breathing ambient air at screening **and prior to randomization**.
8. Forced vital capacity (FVC) ≥ 50% of predicted and ratio of forced expiratory volume in the first second (FEV_1)/FVC ≥ 0.7 at screening.
9. Diffusing capacity of the lung for carbon monoxide (D_{LCO}; corrected for haemoglobin) ≥ 35% at screening.
10. Able to understand the study procedures and the risks involved.
11. Female subjects:
    a. Women of childbearing potential (WOCBP) fulfilling 1 of the following criteria:
       i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method preferably with low user dependency from the signature of the informed consent and until the last study visit or
       ii. WOCBP with non-fertile male partners: contraception is not required in this case.

Or

    b. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e., post-menopausal or permanently sterile, as per definitions given in APPENDIX 3). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per Investigator's request, post-menopausal status may be confirmed by screening serum follicle-stimulating hormone levels (according to local laboratory ranges).
12. Males fulfilling one of the following criteria:

a. Males with pregnant or non-pregnant WOCBP partners: they must be willing to use male condom from the signature of the informed consent and until the last study visit or

b. Non-fertile male subjects: contraception is not required in this case or

c. Males with partner not of childbearing potential: contraception is not required in this case.

For the definition of WOCBP, fertile men, and the list of highly effective birth control methods with low user dependency see APPENDIX 3 or Section 4.1 of the Clinical Trial Facilitation Group guidance [16].

The following inclusion criteria should be re-checked at the Day 1 visit (prior to randomisation): 7.

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrolment:

1. History of lower respiratory tract infection within 4 weeks prior to screening and up to Day 1 of the study, which required the use of antibiotics and admission to a clinical facility, or community treated lower respiratory tract infection that in the opinion of the investigator would preclude the subject's participation in the study.
2. History of acute exacerbation of IPF within 3 months prior to screening and up to Day 1 of the study, defined as:
    a. worsening or newly developed dyspnoea as reported by the subject (≤ 30 days)
    b. new bilateral ground-glass opacities on HRCT superimposed on the UIP abnormalities that defined subject eligibility for the study, and
    c. worsening hypoxemia (in the judgment of the Investigator), in the absence of pulmonary infection, heart failure, or other identifiable causes for this finding.
3. Planned surgery during the study.
4. Active diagnosis of lung cancer or a history of lung cancer.
5. Active cancer or a history of cancer (other than lung cancer) with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g., basal cell carcinoma or in situ carcinoma of the cervix adequately treated, etc.) is acceptable.
6. Infiltrative lung disease other than IPF, including any of the following:
    a. Other types of idiopathic interstitial pneumonias [17]
    b. Interstitial lung diseases related to exposure to fibrogenic agents, other environmental toxins, or drugs
    c. Other types of occupational lung diseases

d. Granulomatous lung diseases

e. Pulmonary vascular diseases

f. Related to systemic diseases (including vasculitis and connective tissue diseases).

7. History of other types of respiratory diseases in the opinion of the Investigator, would impact the endpoints in the protocol or otherwise preclude the subject's participation in the study including diseases or disorders of the airways, lung parenchyma, pleural space, mediastinum, diaphragm, or chest wall.
8. End-stage fibrotic disease expected to require organ transplantation within 6 months.
9. Trauma or surgical procedures requiring hospitalisation within 4 weeks prior to screening visit.
10. Subjects exhibiting unhealed wounds or foot ulcers or have known history of wound healing complications.
11. Clinically relevant and uncontrolled cardiac, hepatic, gastrointestinal, renal, endocrine, metabolic, neurologic, or psychiatric disorders that may interfere with successful completion of this protocol according to the Investigator's judgment.
12. Any abnormal and clinically significant 12-lead electrocardiogram (ECG) that in the Investigator's opinion would affect safety evaluation or place the subjects at risk at screening and prior to randomization.
13. Chronic heart failure categorized as New York Heart Association Class II, III, or IV (this applies to symptoms of chronic heart failure, not IPF); clinical diagnosis of *cor pulmonale* requiring specific treatment; or severe pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study.
14. Currently receiving, or have received, a systemic corticosteroid, immunosuppressant, cytotoxic therapy, vasodilator therapy for pulmonary hypertension, or unapproved or investigational treatment for IPF within 4 weeks prior to screening or prior to randomization. Treatment with pirfenidone or nintedanib, though not both concurrently, is permitted, provided that the subject has been on a well-tolerated stable dose for at least 8 weeks prior to screening and it is anticipated the dose will remain unchanged throughout the study.
15. Participation in another clinical study with an investigational drug in the 1 month or 5 half-lives of that investigational drug (whichever is longer) preceding dosing; a longer and more appropriate time could be considered by the Investigator based on the elimination half-life and/or long-term toxicity of the previous investigational drug.
16. Received the coronavirus disease-2019 (COVID-19) vaccine ≤ 7 days before dosing. Any systemic symptoms (e.g., myalgia, fever, chills, fatigue, etc.) after COVID-19 vaccine should subside at least 2 days before the Day 1 visit.
17. Any other drugs which may interfere with the safe completion of the study, according to the Investigator opinion, are also forbidden.

18. Presence of any current infection, or previous infection that resolved less than 7 days prior to screening or before treatment (with the exception of lower respiratory tract infections, for which the exclusion criterion is defined separately: exclusion criterion n. 1).
19. Documented coronavirus disease-2019 (COVID-19) diagnosis within the last 4 weeks or which has not resolved within 7 days prior to screening or before treatment. COVID-19 testing prior to enrolment and during the study will be conducted according to current local guidelines and is not specified in the protocol.
20. Known intolerance and/or hypersensitivity to any of the excipients contained in the formulation or any other substance used in the study.
21. History of allergic or anaphylactic reaction to human, humanised, chimeric, Igs, or murine monoclonal antibodies.
22. History of severe episodes of urticaria and angioedema or diagnosis of chronic urticaria and its underlying disorders including, but not limited to acquired angioedema due to C1-inhibitor deficiency, auto-inflammatory disease, hereditary angioedema, or urticarial vasculitis.
23. Confirmed or suspected diagnosis of mastocytosis.
24. Clinically relevant abnormal laboratory values (clinical chemistry and haematology) at screening suggesting an unknown disease and requiring further clinical investigation or which may impact the safety of the subject or the evaluation of the study results according to Investigator judgement. Note: in case of abnormal laboratory values, that could indicate a temporary condition, the test can be repeated twice before randomisation.
25. Positive human immunodeficiency virus (HIV) 1 and/or HIV2 results at screening.
26. Positive hepatitis result that indicates acute or chronic hepatitis B (HB) or hepatitis C (HC) at screening (i.e., positive HB surface antigen, HB core antibody [IgM anti-HB core antibody], or HC antibody).
27. Blood donation or blood loss (equal or more than 450 mL) within 2 months prior to screening or prior to randomization.
28. History of cigarette (or e-cigarette) smoking or use of nicotine- or tobacco-containing products within 3 months prior to screening or a positive urine test for cotinine at screening.
29. Documented history of alcohol abuse within 12 months prior to screening or a positive alcohol breath test prior to randomization. Note: before randomization, the test can be repeated once, at least 3 days after the last positive test, if the Investigator evaluates that the subject will be compliant to alcohol abstinence during the study.
30. Documented history of drug abuse within 12 months prior to screening or a positive urine drug screen prior to randomization. Note: before randomization, the test can be repeated once at least 15 days after the last positive test, if the Investigator evaluates that the subject will be compliant to drug abstinence during the study.

31. Unsuitable veins for repeated venipuncture.
32. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive serum human chorionic gonadotropin laboratory test. A serum pregnancy test will be performed at screening and urine pregnancy test will be performed prior to randomisation.

The following exclusion criteria should be re-checked at the Day 1 visit (prior to randomisation): 1, 2, 12, 14, 18, 19, 27, and 32.

Re-testing is possible as explicated in the relative notes of the inclusion/exclusion criteria list.

Screening failure subjects due to the presence of a temporary conditions (e.g., lower respiratory tract infections, unhealed wound, etc.) defined in the exclusion criteria list could be re-screened only once if the condition is resolved according to Investigator's opinion.

Rescreened participants should be assigned a new subject number and the rescreening procedure can be done only once.

4.4 Subject Withdrawals

Subjects must be discontinued from the study for any of the following reasons:

- An adverse event (AE) occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the study. In this case, the appropriate measures will be taken.
- The subject meets the individual stopping criteria.
- The subject is lost to follow-up.
- The subject withdraws consent.
- The subject's safety is affected by violation of inclusion or exclusion criteria or use of not-permitted concomitant medication.
- The subject, in the opinion of the investigator, is unwilling or unable to adhere to the study requirements, i.e., non-compliance.
- The Sponsor or the regulatory authorities or the Ethics Committees (ECs), for any reason, terminates the entire study, or terminates the study for this study site or this particular subject.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided. However, should a subject discontinue the study, all efforts will be made to complete the Early Termination procedures and report the observations as thoroughly as possible.

In the event of early termination, if the subject has not withdrawn his/her consent, an Early Termination visit should be scheduled to perform the following safety assessments, as described in section 7.1.3.

In case of withdrawal, the Investigator must fill in the "Study Termination" page in the electronic case report form (eCRF), reporting the main reason for withdrawal. Subjects who discontinue will be replaced in order to ensure that at least 8 evaluable subjects in each dose level complete the Day 14 study assessments. In case the discontinuation is due to safety reasons assessed as related to the study drug, the subject will not be replaced.

If a subject is withdrawn/drops-out of the study after receiving the test treatment, the subject study number and corresponding test treatments should not be reassigned to another subject.

5. CONCOMITANT MEDICATIONS

5.1 Permitted Concomitant Medications

The following concomitant medications are permitted during the study:

1. Well-tolerated standard of care treatment of IPF (nintedanib or pirfenidone) at stable doses for at least 8 weeks prior to screening and not expected to change during the study. Concomitant intake of both nintedanib and pirfenidone is not allowed.
2. COVID-19 vaccine at least 7 days before dosing. Note: Any systemic symptoms (e.g., myalgia, fever, chills, fatigue, etc.) after COVID-19 vaccine should subside at least 2 days before the treatment visit.
3. Hormone replacement therapy, oral, implantable, transdermal, injectable, or intravaginal contraceptives.

5.2 Non-permitted Concomitant Medications

The following concomitant medications are not permitted during the study:

1. Systemic corticosteroids
2. Immunosuppressants
3. Cytotoxic therapy or vasodilator therapy for pulmonary hypertension
4. Any other unapproved or investigational treatment for IPF
5. Any other drug which may interfere with the safe completion of the study, according to the Investigator's opinion, is also forbidden.

In case of exacerbations, appropriate medications can be initiated at Investigator's discretion.

6. TREATMENT(S)

CHF10067 and placebo (study treatments) will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity and Qualified Person release. The placebo solution [redacted] will be supplied by the Sponsor as described within the investigational medicinal product (IMP) Pharmacy Manual.

6.1 Appearance and Content

The appearance and content of the treatments is described in Table 1.

Table 1: Appearance and Content of Study Treatments

	CHF10067 (1000 mg)	CHF10067 (Anticipated 2000 mg)	CHF10067 (Anticipated 3000 mg)	Placebo
Active Ingredient	[redacted]			[redacted]
Excipients	[redacted]			[redacted]
Presentation	[redacted]			[redacted]

6.2 Dosage, Preparation, and Administration

6.2.1 Selection of doses in the study

Intravenous doses [redacted] administered with a slower infusion rate in healthy subjects have been demonstrated to be safe and well tolerated. For a conservative approach and to be more cautious in the IPF population, a dose of 1000 mg is considered as adequate as a starting dose in this study. The IV dose of 3000 mg is the maximum dose to be tested in IPF patients and will not be exceeded, provided that the safety and PK (if available) and immunogenicity data (if available) allow for the dose escalation up to this dose level.

6.2.2 Dosage

To minimize the risk of immediate hypersensitivity reactions (including infusion reactions), the infusion used in this study will have a concentration of [redacted]. As a starting point, all dose levels will be given [redacted], while the duration of the infusion will be adapted accordingly. A decision can be taken by the Safety Advisory Committee during the study to reduce the infusion rate, as described in Section 7.2.2.5.1. All study subjects will be closely observed for potential immediate hypersensitivity reactions, and all dosing will occur in a clinical site with experience in managing AEs.

6.2.2.1 Dose escalation

The doses will be administered according to an escalation scheme designed to ensure sufficient safety conditions for subjects. In each cohort, subjects will be divided into 2 sub-groups, with each sub-group being dosed at least 24 hours apart. The first sub-group will comprise 2 subjects, with 1 subject receiving CHF10067 and 1 subject receiving placebo. The second sub-group will comprise 6 subjects, with 5 subjects receiving CHF10067 and 1 subject receiving placebo.

Continuation to dose the remaining 6 subjects will be evaluated by at least the Medical Monitor and Sponsor Clinical Research Physician based on the safety data (e.g., AE profile) provided by the Investigator(s) where the first sub-group have been dosed. The procedure for communication and initiation of dosing the remaining subjects within each cohort will be clearly detailed in a separate charter.

The decision to escalate to the next dose will be made by the Safety Advisory Committee when safety data until Day 14 have been collected for all subjects at the previous dose level. Pharmacokinetic and immunogenicity data will also be included in the safety evaluation for dose escalation (if available) but are not mandatory to escalate to the next dose.

The Safety Advisory Committee will comprise at least the Coordinating Investigator, Medical Monitor, Sponsor's representatives (these may also include Key Opinion Leaders), and site Investigators identified from some of the enrolling sites. The presence of all site-Investigators is not mandatory. This committee will be governed by a separate charter.

A blinded interim safety report, summarising results from all available safety assessments for each subject, as specified above, will be sent by the Investigator(s) and appropriately blinded PK and immunogenicity data (if available) will be sent by the appropriate parties to the Sponsor and Safety Advisory Committee prior to the start of each successive group. Unblinding during the interim review may occur in certain situations, if necessary to take an informed decision, and will be clearly detailed in a separate charter.

A Safety Advisory Committee meeting will occur prior to each dose escalation. In particular, any clinically significant results will be discussed before dose escalation continues.

The decision to dose-escalate will be a unanimous decision between the Sponsor, Medical Monitor, and the Coordinating Investigator. If either the Sponsor or the Coordinating Investigator considers stopping of dose escalation to be appropriate, dose escalation will be terminated.

Study drug will be discontinued in any individual subject that experiences a drug-related serious AE (SAE) or any other AE that, in the opinion of the Coordinating Investigator or site Investigator, warrants discontinuation of study drug.

Doses will not be further escalated if:

- Two or more subjects on active drug* experience a possibly drug-related SAE
- Two or more subjects on active drug* experience a severe, possibly drug-related AE lasting for > 24 hours duration
- Four or more subjects on active drug* experience at least moderate, possibly drug-related AE in the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class of > 24 hours duration

- Despite the above criteria not being met, a pattern of AEs has emerged that leads the Investigator and/or Safety Advisory Committee to believe that dose escalation is not justifiable on safety grounds.

* Unblinding is possible to take an informed decision before stopping the dose escalation, as detailed in the separate charter.

6.2.2.2 Background medication

Subjects may take permitted concomitant medications allowed by protocol, but these will not be provided by the Sponsor.

6.2.3 Preparation of the study drug

The preparation of the final concentration will be performed in the Laminar Air Flow Bench or other sterile dedicated preparation area using aseptic procedures under unblinded conditions.

The components of the IMP [redacted] and the various items of equipment (infusion bags, lines, syringes, needles, etc.) are all provided in an internally sterile state, in common with such items in routine clinical use. In keeping with best medical practice, the minimum standards that should be applied in the preparation of IMP for administration are those that would be used for the preparation of any other medicinal product for IV administration, to minimise the possibility of pathogenic contamination of the contents and equipment:

- Use of new (previously un-used), freshly-opened materials
- Use of a “sterile” (no-touch) technique
- Preparation and use in a clean, dust-free environment.

In case of any mistakes during the study drug preparation, a new study drug will be prepared using new material.

The list of the components for dose preparation (dilution) and dose administration together with detailed instructions for the preparation and dilution of CHF10067 and placebo are provided in the IMP Pharmacy Manual.

6.2.4 Administration

No fluid or diet restrictions are required prior treatment administration.

Treatment administration must be completed within 10 hours from the removal of the product from the fridge. Doses will be administered as follows:

- Cohort A: Single doses of 1000 mg CHF10067 or placebo will be administered as an IV infusion.

- Cohort B: Single doses of anticipated 2000 mg CHF10067 or placebo will be administered as an IV infusion.
- Cohort C: Single doses of anticipated 3000 mg CHF10067 or placebo will be administered as an IV infusion.

The treatment administration will take place at the clinical site on Day 1 of the treatment period under the supervision of the Investigator or his/her designee. Administration will be documented in the source documents and reported in the eCRF.

Detailed instructions for administration of CHF10067 and placebo are included in the IMP Pharmacy Manual.

6.3 Packaging

All investigational products will be prepared in accordance with Good Manufacturing Practices (GMP) as required by the current ICH E6 GCP.

The study treatments will be prepared at the following dosage strength:

- Test treatment: CHF10067 [redacted]
- Reference treatment: Placebo [redacted]

Throughout the study duration and according to the dose to be tested, CHF10067 will be supplied [redacted] The Type I clear glass vials are closed with a rubber stopper and sealed with an aluminium overseal and flip-off overcap. Separately, the clinical site will be supplied all the ancillary materials required for the preparation and administration of the treatments. The list of these components will be detailed in the IMP Pharmacy Manual. Only in exceptional circumstances, the sites could use their ancillary materials after Sponsor's authorization.

The composition of the treatment kits is detailed in Table 2.

Table 2: Treatment Kits

Treatment	Treatment Kit	Primary Packaging	Secondary Packaging
CHF10067	**Cohort A**	[redacted]	Box containing [redacted] labelled glass vials
CHF10067	**Cohort B**	[redacted]	Box containing [redacted] labelled glass vials
CHF10067	**Cohort C**	[redacted]	Box containing [redacted] labelled glass vials
Placebo	**Cohort A**	[redacted]	Box containing [redacted] labelled plastic ampoules
Placebo	**Cohort B**	[redacted]	Box containing [redacted] labelled plastic ampoules
Placebo	**Cohort C**	[redacted]	Box containing [redacted] labelled plastic ampoules

6.4 Labelling

All labelling will be in local language and according to local law and regulatory requirements and will be compliant with Annex 13 to the Volume 4 of the GMP.

For all the labels, the subject identification is expressed by the kit number. This number is assigned by the interactive response technology (IRT) system which allows the full traceability of essential details such as: site identification, Investigator's name, visit number, randomisation number.

The labels applied on boxes will have an English tear-off part that will be removed and attached to the subjects' specific tracking/dispensing form at the time the box is assigned to the subjects.

6.5 Treatment Allocation

An IRT system will be used for randomisation and assignment to blind treatment (CHF10067 or placebo).

The Investigator, or designee, at the sites will use the IRT system to screen and randomise subjects and to assign treatment kits according to the randomisation list. Subjects will be randomised in a 3:1 ratio within each cohort to receive either CHF10067 or placebo. Randomisation will require a minimum of 2 subjects within each cohort not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening). In each cohort, at least 24 hours must elapse between dosing of the first 2 subjects (1 CHF10067; 1 placebo) and the remaining 6 subjects. The IRT system will be used to coordinate the scheduling of Day 1 visits to be sure that this procedure is followed.

6.6 Treatment Code

Study treatment will be packaged and uniquely numbered. The IRT will be used to assign all kits in order to have an inventory control and subject dosing tracking. The IRT will also maintain quantities, kit numbers, drug types, batch/code numbers, expiration dates, and do not

dispense after these dates. The IRT will monitor inventory levels at all sites and manage the study treatment re-supply.

The randomisation list will be provided to the labelling facility and to the PK/immunogenicity laboratory but will not be available to subjects, Investigators, or employees of the site involved in the management of the study before unblinding of the data (unless in case of emergency) with the following exceptions:

- Unblinded Site Pharmacist(s) or the designated/authorised representative involved in IMP preparation and dispensing and identified in the appropriate delegation log
- Unblinded Monitor(s) who review(s) the IMP-related documentation
- Unblinded bioanalytical laboratory staff involved in the analysis of PK/immunogenicity samples.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomisation list.

In case of emergency, where the Investigator considers essential to know what treatment the subject was taking, unblinding of the treatment code will be done through IRT and the treatment group will be disclosed. The IRT will be designed to send a confirmation (by notification email) to the site for every transaction performed by the Investigators, including unblinding. The IRT will also promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded. The procedure for unblinding before stopping dose escalation will be described in a separate charter.

Users from Chiesi Global Pharmacovigilance will have their own credentials to unblind subjects in case of Suspected Unexpected Serious Adverse Reactions (SUSARs) to be reported to the competent Regulatory Authorities and ECs/Institutional Review Boards.

6.7 Treatment Compliance

For each subject, details of study medication intake will be recorded in the eCRF.

6.8 Drug Storage

The unblinded Pharmacist at the Investigator's site will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access limited to those individuals authorised to dispense the treatment and maintained within the appropriate ranges of temperature.

All CHF10067 kits will be stored at refrigerated temperatures at 2°C to 8°C. Placebo will be stored not above 30°C. The IMP Pharmacy Manual will contain additional information for temperature condition before and after the preparation.

For the study treatments, the maximum cumulated hold time from the removal of product from the fridge to the end of infusion is 10 hours.

A summary of the holding times to be applied will be detailed in the IMP Pharmacy Manual.

6.9 Drug Accountability

The Pharmacist, or the designated/authorised representative, is responsible for the management of all the study treatments to be used for the study. Study treatments should be stored in a locked, secure storage facility with access limited to those individuals authorised to dispense the study treatments.

An inventory will be maintained by the Pharmacist (or other designated individual), to include a signed account of all the study treatments received and dispensed during the study.

At the conclusion or termination of the study, the Investigator or the Pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies.

All the study treatments supplied, used or unused, will be returned to the designated distributor centre to be destroyed centrally. The return of study treatments will occur only after full accountability and reconciliation are completed. The study treatments destruction will not occur until authorised by Chiesi.

6.10 Provision of Additional Care

At completion of subject's study participation, it is under the Investigator's responsibility to prescribe the more appropriate treatment for the subject or to restore the initial therapy or to refer to the General Practitioner.

7. STUDY PLAN

7.1 Study Schedule – All Cohorts

	Screening (Days -28 to -3)	Treatment Period					Early Termination
		Day 1	Day 2	Days 5 and 7 (± 1 day)	Days 14, 28, and 56 (± 2 days)	Day 84 (± 2 days)	
Informed consent	X						
Randomisation		X					
Ambulatory visit	X	X	X	X	X	X	X
Treatment Intake							
CHF10067 or placebo administration [a]		X					
Subject Health Evaluation							
In/Ex criteria	X	X [b]					
Medical history	X						
Demographic data	X						
Height and weight	X						
Alcohol breath test	X						
Physical examination	X	X	X	X			X
Abbreviated physical examination					X	X	
Adverse events recording	X	X	X	X	X	X	X
Restrictions	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X
Safety Assessment in Blood							
Fasting clinical chemistry	X	X (pre-dose)	X	X [h]	X	X	X
Haematology	X	X (pre-dose)	X	X [h]	X	X	X
Fasting glucose	X	X (pre-dose)	X	X [h]	X	X	X
FSH (post-menopausal female subjects) and/or pregnancy test (females of childbearing potential)	X						
Serology	X						
Markers for evaluation of immediate hypersensitivity reactions		X [f]					
ADA and nAb (in case of positive ADA)		X (pre-dose)			X	X	X
Other Assessments							
TG2 levels		X (pre-dose)			X	X	
Naso-absorption samples		X (pre-dose)			X [i]		
Proteomic sample (serum)		X (pre-dose)			X [i]		
Proteomic sample (plasma)		X (pre-dose)					
Optional transcriptomic samples		X (pre-dose)			X [i]		
Assessments in Urine							
Urinalysis	X						
Drug screen	X						

	Screening (Days -28 to -3)	Treatment Period					Early Termination
		Day 1	Day 2	Days 5 and 7 (± 1 day)	Days 14, 28, and 56 (± 2 days)	Day 84 (± 2 days)	
Cotinine	X						
Pregnancy test (females of childbearing potential)		X			X [j]	X	
Pharmacokinetic in Blood [c]							
CHF10067		X	X	X	X	X	
Safety Cardiac Assessments							
Vital signs [d]	X	X	X	X	X	X	X
Local 12-lead ECG [e]	X	X	X	X	X	X	X
Safety Pulmonary Assessments							
Oxygen saturation [g]	X	X	X	X	X	X	X
Spirometry	X			X [k]	X [k]	X	X
Diffusing capacity	X				X [l]	X	X

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; FSH = follicle-stimulating hormone; In/Ex = inclusion/exclusion; nAb = neutralising antibody; TG2 = transglutaminase 2.

Footnotes for Evaluation Schedule:

[a] Special attention will be given to immediate hypersensitivity reactions and monitoring up to 8 hours post-dose is required. If the subject has no symptoms, he/she can be discharged. If the subject has symptoms, he/she may remain overnight. An overnight stay is also permitted for logistical reasons and/or site's/subject's preference.

[b] Specific In/Ex criteria will also be checked pre-dose on Day 1 according to study schedule and In/Ex criteria.

[c] Pharmacokinetic blood samples for serum CHF10067 will be collected at the following timepoints: pre-dose (within 75 minutes from start of infusion), at the end of infusion, and 2, 4, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56 and 84 days post-dose.

[d] Vital signs (blood pressure, pulse rate, respiratory rate, body temperature): systolic and diastolic blood pressure will be evaluated in duplicate after 5 minutes in supine position. Vital signs will be measured at screening and at the following timepoints: pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, and 20 hours after the end of the infusion and 5, 7, 14, 28, 56, and 84 days post-dose.

[e] Local 12-lead ECG: a triplicate ECG will be performed to assess eligibility and a single ECG will be evaluated at all other timepoints. Electrocardiograms will be measured at screening and at the following timepoints: pre-dose on Day 1, and Days 2, 7, 28, and 84.

[f] Markers for evaluation of immediate hypersensitivity reactions: pre-dose for all subjects. If required (based on subject experiencing symptoms of immediate hypersensitivity reactions), blood samples will be collected at 1 and 2 hours after the onset of the event.

[g] Oxygen saturation: will be measured at screening and continuous monitoring will occur from pre-dose to 10 hours post-dose at the following timepoints: pre-dose**,** every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of the infusion and 30 min, 1, 2, 3, 4, 6, 8, hours after the end of infusion. Oxygen saturation will also be measured at 20 hours after the end of infusion, and 5, 7, 14, 28, 56 and 84 days post-dose.

[h] Clinical laboratory evaluations will be conducted on Day 7 only.

[i] Sample(s) will be collected on Day 14 only.

[j] Pregnancy test conducted on Days 28 and 56.

[k] Spirometry conducted on Days 7, 28, and 56 only.

[l] Diffusing capacity conducted on Days 28 and 56 only.

7.1.1 Screening

A screening visit will take place between 3 to 28 days prior to randomisation to identify eligible consenting subjects for the study.

The signed written INFORMED CONSENT by potential eligible subjects will be collected, after the study has been fully explained by the Investigator or designee. The Investigator or his/her designee should provide the subjects ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. If the subject agrees to participate, the signed and dated informed consent must be obtained before any below study related procedures. If the restrictions and/or the fasting are not respected, the visit should be rescheduled.

The following procedures will take place:

- SUBJECT SELECTION: Inclusion/exclusion criteria will be checked.
- MEDICAL/SURGICAL HISTORY AND CONCOMITANT DISEASES: Subject health history will be recorded.
- DEMOGRAPHY DATA COLLECTION: Demographic data including age, sex, and race, will be recorded.
- HEIGHT AND WEIGHT: Will be recorded.
- ALCOHOL BREATH TEST: Will be performed.
- PHYSICAL EXAMINATION: A comprehensive physical examination will be performed according to Section 7.2.10.
- ADVERSE EVENTS RECORDING: Adverse events occurred since the signature of the informed consent will be recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the subject's medical history, unless its start date/time is after the informed consent signature date/time and it is not due to a pre-existing condition. In the latter case, it will be recorded as an AE.
- STUDY RESTRICTIONS: Study restrictions criteria will be checked according to section 7.1.4.
- PRIOR AND CONCOMITANT MEDICATIONS CHECK: Any systemic corticosteroid, immunosuppressant, cytotoxic therapy, vasodilator therapy for pulmonary hypertension, or unapproved or investigational treatment for IPF within 4 weeks prior to screening will be recorded. Any other drug which may interfere with the safe completion of the study will also be recorded. Permitted treatment with pirfenidone or nintedanib will also be recorded.
- BLOOD TESTING: Blood sample collection for safety evaluations (clinical chemistry, haematology, serology, fasting glucose), pregnancy (females of childbearing potential), and FSH (post-menopausal female subjects) testing according to Sections 7.2.2.1 to 7.2.2.3. Subjects have to be in fasting condition from at least 10 hours before clinical chemistry and fasting glucose samples are collected.
- URINE TESTING: Urine sample collection for urinalysis, drug screen and cotinine test will occur according to Section 7.2.6.
- VITAL SIGNS: Measurement of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature according to Section 7.2.8.

- LOCAL ECG: Triplicate 12-lead ECG will be used to measure heart rate, PR, QRS, and QT corrected for heart rate by Fridericia's formula (QTcF) according to Section 7.2.9.
- PULMONARY ASSESSMENTS: Oxygen saturation, Spirometry (FEV_1, FEV_1 % of predicted normal and lower limit of normal value, FVC, FVC% of predicted normal and lower limit of normal value, and FEV_1/FVC), , and diffusing capacity (D_{LCO} [unadjusted], D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, carbon monoxide transfer coefficient [KCO], and alveolar volume [VA]) will be measured according to Section 7.2.7.

7.1.2 Treatment period

The subject will attend ambulatory visits on Days 1, 2, 5, 7, 14, 28, 56, and 84 (end of study).

The following procedures will take place during the treatment period:

- SUBJECT SELECTION (**Day 1 visit**): Inclusion criteria no. 7 and exclusion criteria no. 1, 2, 12, 14, 18, 19, 27, and 32 will be re-checked as requested in Sections 4.2 and 4.3. Subjects not fulfilling the mentioned criteria will be screen failed.
- RANDOMISATION (**Day 1 visit**): Subjects will be randomised to receive a single IV dose of CHF10067 or placebo.
- DOSING (**Day 1 visit**): Subjects will be administered a single IV dose of CHF10067 or placebo.
- PHYSICAL EXAMINATION (**Day 1, 2, 5, and 7 visits**): A full physical examination will be performed according to Section 7.2.10 and any new revealed clinically significant abnormality since the last visit will be recorded as an AE.
- ABBREVIATED PHYSICAL EXAMINATION (**Day 14, 28, 56, and 84 visits**): A symptom-directed physical examination will be performed according to Section 7.2.10 and any new revealed clinically significant abnormality since the last visit will be recorded as an AE.
- ADVERSE EVENTS RECORDING (**all visits**): Any new AE/SAE occurred since the last visit will be checked and recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable. Moreover, during this period in case of any new clinically significant abnormality revealed during the examination or procedures, it will be recorded as an AE.
- STUDY RESTRICTIONS (**all visits**): Study restrictions criteria will be checked according to section 7.1.4.
- CONCOMITANT MEDICATIONS CHECK (**all visits**): Concomitant medications taken by the subject since the last visit will be checked and recorded in the eCRF.
- BLOOD TESTING: Blood sample collection for safety evaluations (clinical chemistry, haematology, fasting glucose [**Day 1 pre-dose, 2, 7, 14, 28, 56, and 84 visits**], immunogenicity [**Day 1 pre-dose, 14, 28, 56, and 84 visits**], and markers for evaluation of immediate hypersensitivity reactions [**Day 1 visit**]) according to Sections 7.2.2.1,

7.2.2.4 and 7.2.2.5. Subjects have to be in fasting condition from at least 10 hours before clinical chemistry and fasting glucose samples are collected.

- URINE TESTING: Urine samples for pregnancy testing (females of childbearing potential [**Day 1, 28, 56, and 84 visits**]) will occur according to Section 7.2.6
- PHARMACOKINETIC INVESTIGATION (**all visits**): Collection of blood for PK assessment according to Section 7.2.1.
- VITAL SIGNS (**all visits**): Measurement of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature according to Section 7.2.8.
- LOCAL ECG (**Day 1, 2, 7, 28, and 84 visits**): Single 12-lead ECG will be used to measure heart rate, PR, QRS, and QTcF according to Section 7.2.9.
- PULMONARY ASSESSMENTS: Oxygen saturation (**all visits**), Spirometry (**Day 7, 28, 56, and 84 visits**); FEV_1, FEV_1 % of predicted normal and lower limit of normal value, FVC, FVC% of predicted normal and lower limit of normal value, FEV_1/FVC, and diffusing capacity (**Day 28, 56, and 84 visits**); D_{LCO} (unadjusted), D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, KCO, and VA) will be measured according to Section 7.2.7.
- TG-2 ASSESSMENT (**Day 1, 14, 28, 56, and 84 visits**): Transglutaminase 2 levels in plasma will be measured according to Section 7.2.3.
- NASO-ABSORPTION SAMPLES (**Day 1 and Day 14 visits**): Two mucosal samples (one from each nostril) will be taken at each timepoint according to Section 7.2.5.
- SERUM PROTEOMIC SAMPLE (**Day 1 and Day 14 visits**): A blood sample for serum proteomic analysis will be taken at each timepoint according to Section 7.2.4.
- PLASMA PROTEOMIC SAMPLE (**Day 1 visit**): A blood sample for plasma proteomic analysis will be taken at each timepoint according to Section 7.2.4.
- OPTIONAL TRANSCRIPTOMIC SAMPLES (**Day 1 and Day 14 visits**): Two blood samples for possible whole blood transcriptomic analysis will be taken at each timepoint according to Section 7.2.11.

7.1.3 Early termination

The following procedures will take place at the early termination visit in case of subject discontinuation/withdrawal:

- PHYSICAL EXAMINATION: A full physical examination will be performed according to Section 7.2.10 and any new revealed clinically significant abnormality since the last visit will be recorded as an AE.
- ADVERSE EVENTS RECORDING: Any new AE/SAE occurred since the last visit will be checked and recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable. Moreover, in case of any new clinically significant abnormality revealed during the examination or procedures, it will be recorded as an AE.
- CONCOMITANT MEDICATIONS CHECK: Concomitant medications taken by the subject since the last visit will be checked and recorded in the eCRF.

- BLOOD TESTING: Blood sample collection for safety evaluations (clinical chemistry, haematology, fasting glucose) and immunogenicity according to Sections 7.2.2.1 and 7.2.2.4.
- VITAL SIGNS: Measurement of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature according to Section 7.2.8.
- LOCAL ECG: Single 12-lead ECG will be used to measure heart rate, PR, QRS, and QTcF according to Section 7.2.9.
- PULMONARY ASSESSMENTS: Oxygen saturation, Spirometry (FEV_1, FEV_1 % of predicted normal and lower limit of normal value, FVC, FVC % of predicted normal and lower limit of normal value, and FEV_1/FVC), and diffusing capacity (D_{LCO} [unadjusted], D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, KCO, and VA) will be measured according to Section 7.2.7.

7.1.4 Study restrictions and standardisation

The following restrictions must be applied and re-checked as appropriate at each visit:

- No smoking cigarettes (or e-cigarettes) or nicotine- or tobacco-containing products during the treatment period
- No strenuous exercise within 24 hours prior to and during each visit
- No caffeine-containing foods and beverages within 10 hours prior to and during each visit
- No intake of beverages or food containing alcohol within 48 hours prior to and during each visit
- No intake of food for at least 10 hours prior to collection of clinical chemistry and fasting glucose.

If these restrictions are not respected, the visit can be rescheduled once and all the information regarding restriction(s) not respected, will be recorded in the eCRF. If the restrictions are again not respected, the visit will be performed anyway and all the information regarding restriction not respected will be recorded in the eCRF.

7.2 Investigations

In case of coinciding investigations, the timepoint for blood collection for PK evaluation takes priority over any other scheduled study activities, e.g., vital signs and oxygen saturation. Where other activities are scheduled together with the PK blood collection, these will be performed in a sequence allowing for blood sampling exactly at the scheduled timepoint. The exact time of each activity will be recorded in the eCRF.

Due to the variability in sampling requirements at different laboratories, the total volume of blood collected from each subject may vary. The approximately blood volume to be withdrawn per subject will be around 250 mL.

7.2.1 Blood collection for pharmacokinetic evaluation

7.2.1.1 Sample collection for PK evaluation and sample preparation

The laboratory analysis will be carried out following GCP.

The analytical procedures will be described in a separate analytical protocol. Validation data and details of the analytical procedures will be gathered in an analytical report that will be included in the Clinical Study Report.

7.2.1.2 Determination of CHF10067

Blood samples (1 sample = 3.5 mL) for determination of serum CHF10067 will be collected at the following timepoints: pre-dose (within 75 minutes from start of infusion), at the end of infusion, 2, 4, 8, and 20 hours after the end of infusion and 5, 7, 14, 28, 56, and 84 days post-dose. The selected timepoints are based on the results obtained after single dose in healthy subjects. Timepoints may be adjusted during the study if the PK profile in IPF patients is significantly different than healthy subjects. In that case, decisions will be taken by the Safety Advisory Committee and appropriately documented. The total number of timepoints is not expected to be modified.

The time deviation window for PK sampling will be:

- ± 5 minutes for timepoints ≤ 2 hours
- ± 15 minutes for timepoints > 2 hours and ≤ 8 hours
- ± 1 hour for the timepoint of 20 hours
- ± 1 day for Days 5 and 7
- ± 2 days for Days 14, 28, 56, and 84.

The processing, storage and shipment of samples are detailed in the Laboratory Manual document.

7.2.2 Blood collection for safety evaluation

Blood collection and sample preparation will be performed according to procedures provided by the local laboratory and central laboratories (where relevant) which will be in charge to transmit the results and the laboratory normal ranges for entry in the eCRF.

7.2.2.1 Clinical laboratory evaluations

The following blood samples will be collected at each visit:

- Blood for serum clinical chemistry testing (creatinine, urea, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, alkaline phosphatase, sodium, potassium, and chlorine), and fasting glucose

- Blood for haematology testing (red blood cells count, white blood cells count and differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils; % and values), total haemoglobin, haematocrit, and platelets count).

For exclusion criteria no. 24, in case clinically relevant abnormal laboratory values are observed at screening that suggest a temporary condition and requiring further clinical investigation, the subject will be asked to return to clinic for a maximum of twice before treatment, to perform again the testing measurement. If at that time no abnormalities are observed, the subject can be included in the study, otherwise the subject will be discharged and recorded as screening failure.

The volume of blood required for these samples may vary between sites.

7.2.2.2 Serology

The following blood sample will be collected at screening:

- Blood for serum serology testing (HIV1, HIV2, Hepatitis B, and Hepatitis C).

The volume of blood required for this sample may vary between sites.

7.2.2.3 Pregnancy and follicle-stimulating hormone testing

The following blood samples will be collected at screening:

- Blood for pregnancy testing (females of childbearing potential)
- Blood for follicle-stimulating hormone testing (post-menopausal subjects only).

The volume of blood required for these samples may vary between sites.

7.2.2.4 Immunogenicity

The following blood samples will be collected pre-dose and Days 14, 28, 56, and 84:

- 5 mL of blood for immunogenicity assessments (serum non-isotype ADAs) and nAb (in case of ADA positive result).

The analytical procedures will be described in a separate analytical protocol. Validation data and details of the analytical procedures will be gathered in an analytical report that will be included in the Clinical Study Report. The processing, storage and shipment of samples are detailed in the Laboratory Manual document.

Antibodies to CHF10067 will be evaluated in blood samples collected from all subjects according to the study schedule (Section 7.1). Additionally, samples should be collected at the early termination visit from subjects who discontinued study drug or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Samples will be screened for antibodies binding to CHF10067, and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterise the immunogenicity of CHF10067. In particular, positive ADA samples will be also evaluated for the presence of IgE CHF10067, to clarify the relationships between this ADA subtype and the presence of adverse reactions.

The detection and characterisation of antibodies to CHF10067 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for CHF10067 concentration, to enable interpretation of the antibody data. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of the study drug. Samples may be stored for a maximum of 20 years (or according to local regulations) following the last subject's final visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to CHF10067.

7.2.2.5 Systemic markers of immediate hypersensitivity reactions

Subjects will be monitored up to 8 hours post-dose for immediate hypersensitivity reactions and will be discharged if no symptoms are reported. If a subject experiences symptoms of an immediate hypersensitivity reactions, they may remain at the clinical site overnight until the resolution of symptoms. Refer to Section 7.2.2.5.1 for recording of immediate hypersensitivity reactions.

The following blood samples will be collected for analysis of systemic markers* of immediate hypersensitivity reactions pre-dose (all subjects) and post-dose (1 and 2 hours after the start of reaction only if required).

- Serum markers of cytokine release syndrome (interferon-γ [IFN-γ], tumour necrosis factor-α [TNF-α], interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 [p70], and IL-13)
- Serum mast cell tryptase
- Complement markers (plasma C3a, plasma C5a, serum CH50, and plasma SC5b-9)
- Serum CHF10067 IgE

*During the study, the markers analysed may be adjusted as required; therefore, due to the potential variability in blood volume, this has not been specified. Any adjustment will be with consideration for subject safety and operational activities.

7.2.2.5.1 Management and documenting of immediate hypersensitivity reactions

Immediate hypersensitivity reactions are known and anticipated reactions occurring with monoclonal antibodies. Standard precautions must be taken for the subjects regarding routine IV infusion complications. Appropriate medical management according to local guidelines and standard operating procedures should be implemented if an immediate hypersensitivity reaction is suspected (e.g., appropriate medical treatment, reducing or stopping the infusion rate, etc.).

Immediate hypersensitivity reactions [15] should be considered in all cases where any symptoms or signs related to the acute/hypersensitivity reactions occur during or within 24 hours from infusion. All efforts should be made to accurately document symptoms, signs, and vital signs to allow accurate characterisation of the reaction.

In case of occurrence of symptoms and signs indicative of the immediate hypersensitivity reactions the Investigator is asked to duly record (but not limited to) the following data:

- Exact time when the reaction started and the duration of the reaction
- Oxygen saturation, respiratory rate, blood pressure, and 12-lead ECG
- Signs or symptoms including, but not limited to:
  - cutaneous and SC involvement: generalised erythema, urticaria, periorbital oedema, angioedema, pruritis, or flushing
  - signs of cardiovascular compromise: cyanosis, arrhythmia, collapse, diaphoresis, or incontinence
  - nervous system involvement: dizziness, confusion, or loss of consciousness
  - gastrointestinal tract involvement: abdominal pain, vomiting, or nausea
  - respiratory involvement: dyspnoea, wheezing-bronchospasm, stridor, chest, or throat tightness.

If any other symptoms/signs, these should be specified. In addition, additional blood samples will be collected as described in Section 7.2.2.5.

The severity grade of the immediate hypersensitivity reactions should be assessed by the Investigator, considering the following grading system [18]:

1. Mild (skin and SC tissues only)
   a. Generalised erythema, urticaria, periorbital oedema, or angioedema.
2. Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal tract involvement)
   a. Dyspnoea, stridor, wheeze, bronchospasm, chest, or throat tightness
   b. Abdominal pain, nausea, or vomiting
   c. Dizziness (presyncope), or diaphoresis.
3. Severe (hypoxia, hypotension, or neurological compromise)
   a. Cyanosis or hypoxemia (oxygen saturation ≤ 92%)
   b. Hypotension (systolic blood pressure < 90 mmHg)
   c. Confusion, collapse, loss of consciousness, or incontinence.

Characterisation of the immediate hypersensitivity reactions will be performed at the end of study after all clinical and biochemical data are available and analysed by Safety Advisory Committee.

Anaphylactic reactions, defined as IgE mediated, are not expected to occur during the first administration. However, when an anaphylactic reaction is suspected, CHF10067 should be discontinued immediately and appropriate therapy as per standard of care including epinephrine, diphenhydramine, corticosteroids, oxygen, and volume expansion should be administered.

Clinical criteria to diagnose anaphylaxis are summarised below [19]:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised urticaria, pruritis, flushing, or angioedema)

   AND at least 1 of the following

   a. Respiratory compromise (e.g., Dyspnoea, wheeze-bronchospasm, stridor, chest tightness, or hypoxemia [oxygen saturation ≤ 92%])

   b. Hypotension (blood pressure < 90 mmHg) or associated symptoms of end-organ dysfunction (e.g., collapse, syncope, or incontinence).

2. **Two or more** of the following that occur after exposure (minutes to several hours):

   a. Involvement of the skin, mucosal tissue, or both (e.g., generalised urticaria, pruritis, flushing, or angioedema)

   b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, chest tightness, or hypoxemia [oxygen saturation ≤ 92%])

   c. Hypotension (blood pressure < 90 mmHg) or drop in blood pressure (> 30% of subject's baseline) or associated symptoms of end-organ dysfunction (e.g., collapse, syncope, or incontinence)

   d. Persistent gastrointestinal symptoms (e.g., abdominal pain, nausea, or vomiting).

3. Reduced blood pressure after exposure to a known allergen for that subject (minutes to several hours):

   a. Systolic blood pressure of < 90mmHg

   OR

   b. Drop in systolic blood pressure > 30% decrease from that subject's baseline.

Additional precautions should be taken for the next subjects to be treated, such as intake of pre-treatment medication or changes in the infusion rate and duration and will be discussed at Safety Advisory Committee level and communicated to all the enrolling sites before the next dosing.

7.2.3 Blood collection for transglutaminase 2 evaluation

The following blood samples will be collected pre-dose and on Days 14, 28, 56, and 84:

- 4 mL of blood for plasma TG2 levels.

Evaluation of TG2 will also include a group of 24 samples obtained from healthy subjects (i.e., from a biobank), in order to allow for a comparison of TG2 levels between healthy volunteers and IPF patients. The analytical procedures will be described in a separate analytical protocol. Validation data and details of the analytical procedures will be gathered in an analytical report that will be included in the Clinical Study Report. The processing, storage, and shipment of samples are detailed in the Laboratory Manual document.

7.2.4 Blood collection for proteomic analysis

The following blood samples will be collected:

- 8.5 mL of blood for serum proteomic analysis (pre-dose on Day 1 and on Day 14).
- 6 mL of blood for plasma proteomic analysis (pre-dose on Day 1).

The processing, storage and shipment of samples are detailed in the Laboratory Manual document. The samples for proteomic analysis will be collected for exploratory purposes and will be retained until up to 20 years to be possibly used for post-hoc analysis and investigations. Results will not be part of the current statistical analysis and will not be included in the Clinical Study Report.

7.2.5 Mucosal sample collection by naso-absorption

Two mucosal samples (1 from each nostril) will be collected pre-dose on Day 1 and on Day 14 via naso-absorption. Naso-absorption is a non-invasive procedure using a synthetic absorptive matrix swab to absorb mucosal lining fluid from the mucosa within the nose. A detailed description of the naso-absorption procedure will be outlined in separate documents.

The processing, storage, and shipment of samples are detailed in the laboratory manual document. The mucosal samples will be collected for exploratory purposes and will be retained until up to 20 years to be possibly used for post-hoc analysis and investigations. Results will not be part of the current statistical analysis and will not be included in the Clinical Study Report.

7.2.6 Urine collection for safety evaluation

The following urine sample will be collected at screening:

- Urine sample for urinalysis – quantitative (proteins) and urinalysis – qualitative (ketones, microscopic examination of the sediment)
- Urine sample for drug test (cannabinoids, opiates, cocaine, benzodiazepines, amphetamines, barbiturates)
- Urine sample for cotinine test.

The following urine samples will be collected on the Day 1, 28, 56, and 84 visit:

- Urine sample for pregnancy test.

Urine collection and sample preparation will be performed according to procedures provided by the local laboratory which will be in charge to transmit the results to the Investigator for entry in the eCRF.

7.2.7 Pulmonary assessments for safety evaluation

7.2.7.1 Spirometry

Spirometry will be assessed at the following timepoints: screening, 7, 28, 56, and 84 days post-dose and in case of early termination visit.

Spirometry will be assessed centrally. The specific procedures for centralized spirometry will be provided to the Investigator by the centralized spirometry company. The same brand and model of spirometer will be provided by the centralised spirometry company for all measurements and adjusted for the ATS/ERS standards [20]. Lung function measurements will be done with subjects sitting with the nose clipped after at least 10 minutes rest. Values will be corrected for body temperature and pressure (saturated) conditions.

The following parameters (but not limited to) will be recorded: FEV_1, FVC, FEV_1% of predicted normal and lower limit of normal value, FVC % of predicted normal and lower limit of normal value, and FEV_1/FVC ratio.

Predicted values of FEV_1 will be calculated according to formulas reported by Quanjer et al. [21].

For FEV_1 and FVC, the highest value from 3 technically satisfactory attempts will be recorded in the eCRF (irrespective of the curve they come from). The chosen value should not exceed the next one by more than 150 mL. If the difference is larger, up to 8 measurements will be made and the largest value be reported. In order to be considered as technically satisfactory attempts, measurements should be free from cough and false-start and meet all the ERS/ATS criteria. The FEV_1/FVC should be taken from the highest FEV_1 and FVC values (even if not coming from the same curve). The acceptability criteria for spirometry assessment will be further specified in separate documents.

For inclusion criterion no. 8 if the criterion is not met at screening, the subject may repeat the tests. If at that time the values fall within the ranges specified, the subject can be included in the study, otherwise the subject will be discharged and recorded as screening failure.

7.2.7.2 Diffusing capacity

Diffusing capacity will be assessed at the following timepoints: screening, 28, 56, and 84 days post-dose and in case of early termination visit.

Diffusing capacity will be assessed locally using the device available at each site. The devices used should be in accordance with current requirements issued by ERS/ATS in 2017 [22]. The test will be performed with subjects in a sitting position and nose clipped. Subjects should avoid exercise and cigarette smoking on the day of the test. All the results will be uploaded to a central database and will be evaluated centrally.

The following parameters (but not limited to) will be reported: D_{LCO} (unadjusted), D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, KCO, and VA.

The reported D_{LCO} will be corrected for the current haemoglobin level, using reference equations.

For inclusion criterion no.9, if the criterion is not met at screening, the subject will repeat the test. If at that time the values fall within the ranges specified, the subject can be included in the study; otherwise, the subject will be discharged and recorded as screening failure.

7.2.7.3 Oxygen saturation

Oxygen saturation will be measured by continuous pulse oximetry at screening and from pre-dose to 10 hours post-dose at the following timepoints: pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of infusion and 30 min, 1, 2, 3, 4, 6, 8 hours after the end of the infusion. Oxygen saturation will also be measured at 20 hours after the end of the infusion, and 5, 7, 14, 28, 56, and 84 days post-dose and in case of early termination visit.

For inclusion criterion no.7, if the criterion is not met at screening or at the Day 1 visit, the subject will repeat the test. If at that time the values fall within the ranges specified, the subject can be included in the study, otherwise the subject will be discharged and recorded as screening failure.

7.2.8 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be evaluated at the following timepoints: screening, pre-dose, every 15 minutes during the infusion (e.g., 15, 30, 45, 60, 75, 90, 105, etc.), at the end of infusion and 30 min, 1, 2, 3, 4, 6, 8 and 20 hours after the end of the infusion and 5, 7, 14, 28, 56, and 84 days post-dose and in case of early termination visit.

Blood pressure will be measured in duplicate, after 5 minutes in the supine position. The single values and the average of duplicate blood pressure measurements will be reported in eCRF, and the average will be used to assess the subject's eligibility.

7.2.9 Local 12-lead electrocardiogram

A triplicate 12-lead ECG will be performed to assess eligibility and a single 12-lead ECG will be evaluated at pre-dose on Day 1, and Days 2, 7, 28, and 84 days post-dose and in case of early termination visit.

The following parameters will be recorded: heart rate, PR, QRS, and QTcF.

7.2.10 Physical examination

A comprehensive full physical examination or abbreviated symptom-directed physical examination will be performed at each visit. Any new revealed clinically significant abnormality since the last visit will be recorded as an AE.

7.2.11 Optional blood collection for transcriptomic analysis

The following blood samples will be collected pre-dose on Day 1 and on Day 14:

- 2 × 2.5 mL of blood for whole blood transcriptomic analysis.

The processing, storage and shipment of samples are detailed in the Laboratory Manual document. The samples for transcriptomic analysis will be collected for exploratory purposes and will be retained until up to 20 years to be possibly used for post-hoc analysis and investigations. Results will not be part of the current statistical analysis and will not be included in the Clinical Study Report. Sample collection and analysis will only be conducted in subjects who have provided a separate and specific informed consent.

8. PHARMACOKINETIC AND OTHER ASSESSMENTS

8.1 Pharmacokinetic Assessments

The following PK parameters will be calculated, whenever possible, for each subject based on the serum concentrations of CHF10067 following a single IV administration:

- Area under the concentration-time curve (AUC) from 0 to the last quantifiable concentration (AUC_{0-t})
- AUC extrapolated to infinity (AUC_{inf})
- Maximum observed concentration (C_{max})
- Time to C_{max} (t_{max})
- Concentration at steady state of infusion (C_{inf})
- Clearance (CL)
- Volume of distribution (Vz)
- Terminal half-life ($t_{1/2}$).

The PK analysis will be performed using WinNonlin Phoenix 6.2 or later (Pharsight Corporation, Palo Alto, CA, USA). Actual elapsed time from dosing will be used to estimate all individual PK parameters. Standard non-compartmental methods will be used for the calculation of the following parameters from the individual serum drug concentrations versus time profile.

8.2 Other Assessments

Levels of TG2 in plasma will be collected for exploratory assessment.

9. SAFETY ASSESSMENTS

9.1 Safety Variables

Safety and tolerability will be assessed through the monitoring of the following:

- AEs and adverse drug reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
- Oxygen saturation measured via pulse oximetry
- 12-lead ECGs (heart rate, PR, QRS, and QTcF)
- Clinical laboratory evaluations: clinical chemistry (including fasting glucose) and haematology
- Physical examinations
- Spirometry (FEV_1, FVC, FEV_1 % of predicted normal and lower limit of normal value, FVC % of predicted normal and lower limit of normal value, and FEV_1/FVC ratio)
- Diffusing capacity (D_{LCO} [unadjusted], D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, D_{LCO} corrected for haemoglobin % predicted, KCO, and VA)
- ADAs and nAb
- Analysis of systemic markers* of immediate hypersensitivity reactions pre-dose and post-dose (post-dose only if required) including:
  - markers of cytokine release syndrome (IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), and IL-13)
  - mast cell tryptase
  - complement markers (C3a, C5a, CH50, and SC5b-9)
  - CHF10067 IgE.

*During the study, the markers analysed may be adjusted as required. Any adjustment will be with consideration for subject safety and operational activities.

9.2 Emergency Situation

In case of health emergency, including COVID-19, the Investigator/site staff must take all necessary precautions to minimise and avoid the risk of transmission and exposure to study subjects and site staff, according to local guidelines. In that particular case:

- a time window for study visits could be allowed when subjects are not able to arrive to the site or to attend the visit
- onsite study visits could be cancelled or replaced by phone calls, or some assessments could be missed.

Special case of COVID-19 outbreak:

Every effort should be made by the site to confirm all suspected incidences of COVID-19 in accordance with local diagnostic guidelines. Documentation of testing and results obtained outside the clinical site, should be collected within 14 days of confirmed diagnosis (or whenever possible) and recorded in the eCRF.

All incidences of COVID-19 as well as the impact on study visits and subject completion must be captured in the eCRF.

Occurrence of SARS-CoV-2 infection and/or COVID-19 disease during the study does not automatically lead to withdrawal of the subject. It will be up to the Investigator's judgement to withdraw the subject from the study if he/she deems that remaining in the study will place the subject and/or the clinical site at undue risk by continuing their participation. All efforts should be made to keep the subject on study drug, if possible.

In case study visits or procedures are modified or missed due to COVID-19, the relevant information will be recorded in the eCRF.

As of the date of this protocol version, there is no specific treatment for COVID-19 and several vaccine therapies have been developed and approved by health authorities with vaccination campaigning being initiated worldwide. For all confirmed cases of COVID-19/SARS-CoV-2 the Investigator must follow the standard of care in accordance with local treatment guidelines. All concomitant treatments must be recorded in the eCRF.

In case of COVID-19 suspect, Investigators are encouraged to perform diagnostic testing locally or obtain results of tests from hospital where the event was diagnosed and/or managed, and every effort should be made to complete the assessments required by the current local guidelines for COVID-19 management (e.g., SARS-CoV-2 test, chest imaging) and to guarantee the appropriate management.

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

Death is not an AE but an outcome. It is the cause of death that should be regarded as the AE. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the AE and "fatal" as its reason for being serious.

- **Is life-threatening**

Life-threatening refers to an event in which the subject was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalisation or prolongation of existing hospitalisation**

Hospitalisation refers to a situation whereby an AE is associated with unplanned formal overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalisation for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits

that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

- **Results in persistent or significant disability or incapacity**

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the subject's physical or psychological well-being to the extent that the subject is unable to function normally.

- **Is a congenital anomaly or birth defect**

- **Is a medically significant adverse event**

This criterion allows for any situations in which important AE/adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the subject's health or may require intervention to prevent one of the above outcomes.

Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A **Non-Serious Adverse Event/Non-Serious Adverse Drug Reaction** is an AE or ADR that does not meet the criteria listed above for an SAE/serious adverse drug reaction.

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (included in the IB for CHF10067) otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the reference safety information would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

For the classification of AEs severity (except for immediate hypersensitivity reactions severity, see below), the Common Terminology Criteria for Adverse Events (CTCAE) [23] will be used:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

In order to guarantee objectivity and consistency in the evaluation of AEs (including classification of severity), the proposed guidance should be followed in alignment with best medical practice.

Laboratory abnormalities and other clinical assessments (e.g., 12-lead ECG) will be reported as AEs if judged by the Investigator as being clinically significant.

In case of laboratory evaluations or other clinical assessments (e.g., 12 -lead ECG) not listed in the CTCAE grading table, the AE severity will be judged by the Investigator based on the local ranges.

Taking into consideration the disease examined in the current study, it should be acknowledged that the guidance may not always be applied. Therefore, although the guidance should be followed, whenever possible, in order to ensure an accurate and objective evaluation of the AEs, the final decision on the severity classification remains the responsibility of the Investigator.

For the specific classification of severity and management of immediate hypersensitivity reactions, refer to Section 7.2.2.5.1.

10.4 Causality Assessment

The following "binary" decision choice will be used by the Investigator to describe the causality assessment:

- Reasonable possibility of a relatedness
- No reasonable possibility of relatedness.

The expression "reasonable possibility of relatedness" is meant to convey, in general, that there are facts (evidence), or arguments meant to suggest a causal relationship.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake and event's onset
- Dechallenge (did the event abate after stopping drug?)
- Rechallenge (did the event reappear after reintroduction?)
- Medical history
- Study treatment(s)
- Mechanism of action of the study drug
- Class effects
- Other treatments-concomitant or previous
- Withdrawal of study treatment
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication (or concomitant)
- Protocol related process.

10.5 Action Taken with the Study Drug due to an Adverse Event

- Dose not changed
- Drug permanently withdrawn
- Drug temporarily interrupted
- Dose reduced
- Dose rate reduced
- Not applicable.

10.6 Other Actions Taken

- Specific therapy/medication
- Concomitant procedure.

10.7 Outcome

Each AE must be rated by choosing among:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown.

10.8 Recording Adverse Events

All AEs occurring during the course of the study must be documented in the AE page of the eCRF. Moreover, if the AE is serious, the SAE Form must also be completed.

It is responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questionings.

The recording period for AEs is the period starting from the informed consent signature until the subject's study participation ends.

Clinically significant abnormalities detected at screening visit not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the Investigator must be reported as AEs in the eCRF.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or until the subject is lost to follow-up. Follow-up may therefore continue after the subject has left the study. In this case, the follow-up will continue with no timelines for related SAEs, while for unrelated SAEs the type and extent of follow-up undertaken will be determined for each individual case and will depend upon the nature (e.g., events with poor prognosis or which do not resolve), severity, and medical significance of the event.

10.9 Reporting Serious Adverse Events to Chiesi

The Investigator must report all SAEs to the Fortrea Safety Contact listed below within 24 hours of awareness. The information must be sent by providing the completed paper SAE form. At a later date, the Fortrea Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager, and the Clinical Research Physician.

Safety Contact	Fax No.	E-mail
Fortrea Safety Contact	+1 609 419 2609	SAEIntake@fortrea.com
Chiesi Safety Contact	+39 0521 1885003	CT_CDS@chiesi.com

- Reporting of SAEs from the Investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be reported if the Investigator becomes aware of them.
- Up to the closure of the site, SAE reports should be reported to the Fortrea Safety Contact. New SAEs occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committee

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical study, if required, will be reported in compliance with the timelines and standards for reporting SUSARs. The Medicines and Healthcare products Regulatory Agency (MHRA) will be informed through MHRA Individual Case Safety Report (ICSR) Submission portal, while other relevant Regulatory Authorities in accordance with local requirements. The ECs and the Investigators will be informed by Council for International Organisations of Medical Sciences I form or by periodic line listings produced by Chiesi Global Pharmacovigilance.

With regard to regulations in force for Pharmacovigilance, the Investigators must fulfil their obligation according to the law in force in their countries.

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Fortrea Safety Contact together with the SAE form, retaining a copy on site.
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Fortrea Safety Contact as soon as available, retaining a copy on site.

- All documents provided by the Investigator or site staff to the Fortrea Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- In case of pregnancy discovered after treatment with study drug, the subject may remain on the study until completion for safety monitoring purposes, if these are considered safe by the Investigator. The subject will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and till the age of one year of the child to detect any congenital anomaly or birth defect. The pregnancy must be reported by the Investigator within 24 hours by fax/e-mail to the Fortrea Safety Contact using the paper Pregnancy Report Form. The Fortrea Safety Contact will inform Chiesi of the pregnancy within 1 working day of being notified.
- The first 2 pages of the Pregnancy Report Form should be completed by the Investigator with all the available information and sent to the Fortrea Safety Contact. Information collected in specific sections relative to the pregnancy will be recorded in the form only upon signature of the specific ICF by the subject/subject's partner. The third page will be completed as soon as the Investigator has knowledge of the pregnancy outcome, together with a follow-up of the first 2 pages, if necessary (e.g., an update in the medications received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.
- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose of study drug, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.
- Any ADR occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority and/or to the relevant Marketing Authorisation Holders of the involved medicinal products according to the applicable laws. Additionally, also conditions of use outside the marketing authorisation of the medicinal products (i.e., off-label, overdose, misuse, abuse, and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy should be reported.

11. DATA MANAGEMENT

An eCRF will be filled in by the Investigator and/or his/her representative designee.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, AEs, and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the World Health Organisation Drug dictionary and Anatomical Therapeutic Chemical classification.

External data (PK, immunogenicity, immediate hypersensitivity reactions systemic markers, spirometry, diffusing capacity, plasma TG2 samples) will be processed centrally, sent to the designated Contract Research Organisation, and reconciled with the corresponding information recorded in the eCRF.

Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

After the completion of data collection and cleaning, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomisation codes will be opened, and the planned statistical analysis will be performed.

If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorised by Chiesi.

At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The Investigators will receive copies of the subject data for retention at the investigational sites.

12. STATISTICAL METHODS

12.1 Sample Size

This study is designed to explore the safety and tolerability of CHF10067 for the first time in subjects affected by IPF, while exposing a minimum number of subjects; therefore, no formal power calculation was performed.

A sample size of 24 subjects (8 subjects per cohort; 6 treated with CHF10067 and 2 with placebo) is deemed adequate to assess safety and tolerability of CHF10067. In each cohort, a minimum of 2 subjects are required to be not receiving antifibrotic treatment (including subjects with previous use of antifibrotic treatment that has been stopped for at least 2 weeks prior to screening).

12.2 Analysis Sets

Safety set: all randomised subjects who receive a dose of study treatment, including partial dose.

PK set: all subjects from the safety population excluding subjects without any valid PK measurement or with important protocol deviations significantly affecting PK, for example, use of non-permitted medications. Exact definition of important protocol deviations significantly affecting PK will be discussed by the clinical team and described in a specific

document before bioanalytical data are disclosed. Subjects will not be excluded on the basis of statistical analysis or for PK reasons, except in the cases defined in the European Medicine Agency guideline [24].

After unblinding, subjects will not be excluded on the basis of statistical or for PK reasons, except in the case of:

- non-zero baseline concentration > 5% of C_{max}
- AUC_{0-t} lower than 5% of the reference medicinal product geometric mean of AUC_{0-t} (calculated without inclusion of data from the outlying subject)
- below the limit of quantification concentration at all timepoints.

Pharmacokinetic variables will be analysed in the PK set. The safety set will be used in the analysis of all safety variables. In case of deviation between randomised treatment and treatment actually received, the treatment actually received will be used (i.e., an as-treated analysis will be performed).

12.3 Statistical Analysis

Detailed statistical analysis will be described in the Statistical Analysis Plan (SAP). The plan will be finalised before breaking the blind.

12.3.1 Descriptive statistics

Descriptive statistics for PK variables (except for t_{max}) will include n (number of observed values), arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. The variable t_{max} will be summarised by using n, median, minimum, and maximum.

All individual concentration data and PK variables will be listed. In addition, a listing of the actual sampling times relative to study treatment administration will be provided. Concentrations will be summarised by treatment and scheduled sampling time by using n, arithmetic mean, SD, CV, median, minimum, and maximum.

Descriptive statistics for the other continuous variables will include n, arithmetic mean, SD, median, minimum, and maximum.

For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented. Missing values will not be used in percentage calculations.

12.3.2 Missing data

Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed during the review of the data. Decisions will be fully documented in the Data Review Report.

12.3.3 Subject demographics and baseline characteristics

The following variables will be summarised using descriptive statistics on the safety population (and on the PK population, if relevant): demographic characteristics (including age, sex, and race), height, weight, BMI, medical history and concomitant diseases, previous and concomitant medications, lung function, diffusing capacity, oxygen saturation, 12-lead ECG, vital signs, laboratories, and other safety parameters at screening and/or at baseline (pre-dose on Day 1).

12.3.4 Pharmacokinetic variables

CHF10067 serum AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, C_{inf}, CL, Vz, and $t_{1/2}$ will be summarised by dose level using descriptive statistics.

Serum concentration/time curves will be presented in linear/linear and log/linear scale. Plots will be presented by dose level, based on arithmetic means, and by subject, by showing the individual curves grouped by dose level (1 plot for each dose level) and ADA positivity/negativity (using different colours).

Dose proportionality in terms of CHF10067 AUC_{0-t}, AUC_{inf}, and C_{max} will be evaluated using the power model, including the log-transformed PK parameters as dependent variables, and the log-transformed CHF10067 dose as a covariate. The slope for log-transformed dose will be estimated with its 90% confidence interval (CI) to examine dose proportionality.

12.3.5 Safety variables

All safety data will be listed. For all safety and immunogenicity variables, baseline is the last available assessment before the dose administration, which is either the screening assessment between Days -28 to -3 or the pre-dose assessment on Day 1.

12.3.5.1 Adverse events

The number of events and the number and percentage of subjects experiencing treatment emergent-adverse events (TEAEs), treatment-emergent ADRs, serious TEAEs, non-serious TEAEs, TEAEs by CTCAE grade, TEAEs leading to discontinuation of study drug and TEAEs leading to death will be presented by treatment. The aforementioned categories of AEs will be also summarised by System Organ Class and Preferred Term using the MedDRA dictionary.

12.3.5.2 Systemic markers for evaluation of immediate hypersensitivity reactions

Cytokine markers (IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), and IL-13), mast cell tryptase, complement markers (C3a, C5a, CH50, and SC5b-9), and CHF10067 IgE will be presented by subject for each post-dose timepoint as absolute value and change from baseline (if collected).

12.3.5.3 Immunogenicity

Anti-drug antibody positive subjects will be defined as described in Section 7.2.2.4.

As a minimum, the following will be prepared:

- A table summarising for each ADA-positive subject:
  - dose administered
  - baseline ADA
  - maximal ADA timepoint
  - maximal ADA value
  - final ADA timepoint
  - final ADA value
  - pre-dose TG2 level
  - TG2 level at maximal ADA timepoint
  - CHF10067 AUC_{inf}.
- A table summarising for ADA-positive subject the ADA and nAb ranges by dose level.

12.3.5.4 Pulmonary assessments

12.3.5.4.1 Spirometry

The FEV_1, FVC, FEV_1/FVC, FEV_1% of predicted and FVC% of predicted, will be summarised by dose level as absolute value, and absolute and relative change from baseline (i.e., the assessment at screening between Days -28 to -3) at each post-dose timepoint using descriptive statistics and 95% CIs. The frequency of subjects with FEV_1% and FVC% below the lower limit of normal at each timepoint will be listed and summarised with descriptive statistics.

Time profile plots by dose level will be presented for mean absolute and relative changes from baseline.

12.3.5.4.2 Diffusing capacity

The D_{LCO} unadjusted, D_{LCO} % predicted, D_{LCO} corrected for haemoglobin, and the other relevant variables collected will be summarised by dose level as absolute value and change from baseline (i.e., the assessment at screening between Days -28 to -3) at each post-dose timepoint using descriptive statistics and 95% CIs.

Time profile plots by dose level will be presented for D_{LCO} corrected for haemoglobin and D_{LCO}% predicted for mean changes from baseline.

12.3.5.4.3 Oxygen saturation

The oxygen saturation will be summarised by dose level as absolute value and change from baseline (i.e., the pre-dose assessment on Day 1) at each post-dose timepoint using descriptive

statistics and 95% CIs. Time profile plots by dose level will be presented for mean changes from baseline.

12.3.5.5 ECG

At each post-dose timepoint, the following statistics will be presented by dose level for 12-lead ECG parameters (heart rate, PR, QRS, QTcF):

- mean absolute value with its 95% CI
- mean change from baseline (i.e., the pre-dose assessment on Day 1) with its 90% CI
- mean placebo-corrected change from baseline with its 90% CI.

Time profile plots, individual and by dose level, will be presented for change from baseline (i.e., the pre-dose assessment on Day 1). Time profile plots of mean difference versus placebo in change from baseline will be presented by dose level for heart rate and QTcF.

The number and percentage of subjects with the following will be presented by dose level at each post-dose timepoint and at any post-dose timepoint:

- Males: QTcF > 450 ms, > 480 ms, and > 500 ms
- Females: QTcF > 470 ms and > 500 ms
- Both sexes: change from baseline in QTcF > 30 ms and > 60 ms.

12.3.5.6 Vital signs

At each post-dose timepoint the following statistics will be presented by dose level for systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature:

- mean absolute value with its 95% CI
- mean change from baseline (i.e., the pre-dose assessment on Day 1) with its 95% CI.

Time profile plots, individual and by dose level, will be presented for change from baseline (i.e., the pre-dose assessment on Day 1).

In addition, the number and percentage of subjects with a change from baseline > 20 mmHg for systolic blood pressure and > 10 mmHg for diastolic blood pressure will be presented by treatment at each post-dose timepoint and at any post-dose timepoint.

12.3.5.7 Safety laboratory data

At each post-dose timepoint quantitative laboratory parameters will be summarised by treatment as absolute value and change from baseline using descriptive statistics and 95% CIs.

Shift tables from baseline to the minimum and the maximum post-dose value, with regards to normal range, will be presented by treatment.

Urinalysis parameters will be presented in the listings.

12.3.6 Other variables

12.3.6.1 TG2 in plasma

At each post-dose timepoint, TG2 levels in plasma will be summarised using descriptive statistics by treatment as absolute value and change from baseline (i.e., the pre-dose assessment on Day 1) using descriptive statistics and 95% CIs.

Time profile plots will be presented by dose level, based on arithmetic means, and by subject, by showing the individual curves grouped by dose level (1 plot for each dose level) and ADA positivity/negativity (using different colours).

The TG2 levels in plasma obtained from healthy subjects will be summarised using descriptive statistics.

Box-plots summarising the pre-dose levels for treated subjects in the study, the healthy subjects' external group, and each post-dose levels for the different doses for treated subjects will be presented.

12.3.7 Interim analysis

Interim analysis not planned.

13. ETHICS COMMITTEE

The study proposal will be submitted to the EC in accordance with the local requirements.

The EC shall give its opinion in writing, clearly identifying the study number, study title and ICF approved, before the clinical study commences.

A copy of all communications with the EC will be provided to the Sponsor.

The Investigator should provide written reports to the EC annually or more frequently if requested on any changes significantly affecting the conduct of the study and/or increasing risk to the subjects (according to the requirements of each country).

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorised by) according to the legal requirements.

Selection of the subjects will not start before the approval of the EC has been obtained and the study notified to Health Authorities (or authorised by).

15. INFORMED CONSENT

Informed consent must be written in a language understandable to the subjects. It is the responsibility of the Investigator to obtain written consent from each subject prior to any study related procedures taking place, by using the latest EC approved version of the document.

Adequate time shall be given to the subject to enquire to the Investigator about any clarification needed and to consider his or her decision to participate to the study.

If the subject is unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read and sign the ICF and the written information for the subject.

Consent must be documented by the subject's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the ICF.

Each subject's signed informed consent must be kept on file by the Investigator. One copy must be given to the subject.

For subjects who agree to the collection of optional samples for transcriptomic analysis, separate informed consent must be obtained and the separate optional ICF signed prior to collection.

Female subjects becoming pregnant during the study and partner of a subject participating to the study becoming pregnant will have to sign a specific informed consent form to provide permission to Chiesi to collect information about the pregnancy, its outcome and the birth and health of the newborn child.

16. SOURCE DOCUMENTS/DATA

16.1 Recording of Source Data

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF transcribed from source documents should be consistent with the data recorded on the source documents.

16.2 Direct Access to Source Document/Data

The Investigators or designee must permit study-related monitoring, audits, EC review, or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by Fortrea who have been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/site before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file, and source data, provided that subject confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study
- to review the compliance with the study protocol
- to discuss any emergent problem
- to check the eCRFs for accuracy and completeness
- to validate the contents of the eCRFs against the source documents
- to assess the status of drug storage, dispensing, and retrieval.

Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GCP and the protocol.

19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.

Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the study treatment was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.

The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, and addresses and telephone numbers (if applicable). The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21. PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

The Sponsor should submit a written notification to the Regulatory Authorities concerned and EC providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

The Clinical Study Report, including the statistical and clinical evaluations, shall be prepared and sent to Coordinating Investigator for agreement and signature.

At the end of the study a summary of the Clinical Study Report will be provided to all EC, to the Competent Authorities and to Investigators.

23. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

Regulations require that essential documents must be retained for at least 2 years after the final marketing approval in an ICH region or until 2 years have elapsed since the formal interruption of the clinical development of the product under study.

It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact Chiesi before destroying any study-related documentation. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the institution.

24. PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical study data to national and international Regulatory Authorities and, if they

fall under the Chiesi commitments on Clinical Trial Transparency, to make them available on www.chiesi.com website.

Chiesi furthermore reserves the right to use such data for industrial purposes.

In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual clinical sites must not be published separately.

25. REFERENCES

[1] Raghu G, Remy-Jardin M, et al. Idiopathic Pulmonary Fibrosis (an Update) and progressive pulmonary fibrosis in adults. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. Vol 205, Iss 9, pp e18-e47, May 1, 2022.

[2] American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161:646–64.

[3] American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.

[4] Thomson CC, Duggal A, Bice T, Lederer DJ, Wilson KC, Raghu G. Clinical practice guideline summary for clinicians: diagnosis of idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2019;16(3):285–90.

[5] Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: Treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19.

[6] Tang J, Huang H, Ji X, Zhu X, Li Y, She M, et al. Involvement of IL 13 and tissue transglutaminase in liver granuloma and fibrosis after schistosoma japonicum infection. Mediators Inflamm. 2014;75348.

[7] Olsen KC, Sapinoro RE, Kottmann RM, Kulkarni AA, Iismaa SE, Johnson GVW, et al. Transglutaminase 2 and its role in pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184:699–707.

[8] Zhao G, Zhang ZQ, Zhang B, Luo M, Sun YW, Wu ZY. Down-regulation of tTG expression by RNAi inhibits HSC proliferation and attenuates liver fibrosis. Int J Clin Exp Pathol. 2011;4(5):513–520.

[9] Huang L, Haylor JL, Hau Z, Jones RA, Vickers ME, Wagner B, et al. Transglutaminase inhibition ameliorates experimental diabetic nephropathy. Kidney Int. 2009;76(4):383–94.

[10] Shweke N, Boulos N, Jouanneau C, Vandermeersch S, Melino G, Dussaule JC, et al. Tissue transglutaminase contributes to interstitial renal fibrosis by favoring accumulation of fibrillar collagen through TGF beta activation and cell infiltration. Am J Pathol. 2008;173(3):631–42.

[11] Johnson TS, Fisher M, Haylor JL, Hau Z, Skill NJ, Jones R, et al. Transglutaminase inhibition reduces fibrosis and preserves function in experimental chronic kidney disease. J Am Soc Nephrol. 2007;18(12):3078–88.

[12] Nardacci R, Iacono OL, Ciccosanti F, Falasca L, Addesso M, Amendola A, et al. Transglutaminase type II plays a protective role in hepatic injury. Am J Pathol. 2003;162(4):1293–303.

[13] Small K, Feng JF, Lorenz J, Donnelly ET, Yu A, Im MJ, et al. Cardiac specific overexpression of transglutaminase II (G(h)) results in a unique hypertrophy phenotype independent of phospholipase C activation. J Biol Chem. 1999;274(30):21291–6.

[14] Chiesi Farmaceutici S.p.A. Investigator's Brochure: CHF10067. 2021.

[15] Bavbek S., Pagani M., Alvarez-Cuesta E, et al., Hypersensitivity reactions to biologicals: An EAACI position paper. Allergy. 2022; 77.39 – 54. https://doi.org/10.1111/all.14984.

[16] Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials (Version 1.1). 2020.

[17] William D Travis, Ulrich Costabel, David M Hansell, Talmadge E King Jr, David A Lynch, Andrew G Nicholson, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. 15. 2013;188(6):733–48.

[18] Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371–6.

[19] Sampson HA, Muñoz-Furlong A, Campbell RL, Jr NFA, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391–7.

[20] Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–88.

[21] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43.

[22] Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49.

[23] Common Terminology Criteria for Adverse Events (CTCAE; Version 5.0). National Cancer Institute; 2017.

[24] European Medicines Agency. Guideline on the Investigation of Bioequivalence (CPMP(EWP/QWP/1401/98 Rev. 1/Corr.) [Internet]. European Medicines Agency; 2010. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

APPENDIX 1 - APPROVAL OF THE PROTOCOL BY COORDINATING CLINICAL INVESTIGATOR

A PHASE IB, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF AN INTRAVENOUS MONOCLONAL ANTIBODY (MAB) AFTER SINGLE ASCENDING DOSES IN SUBJECTS AFFECTED BY IDIOPATHIC PULMONARY FIBROSIS

Product: CHF10067

Pharmaceutical Form: Solution for intravenous infusion

Approval of Clinical Study Protocol by the Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this study will not be initiated without Ethics Committee approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating subjects and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the study will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Coordinating Investigator's Name and Qualifications: _____, _____

Centre No.: _____

_____ _____
Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

Clinical Study Code No.: CLI-10067AA1-01	Version No.: 6.0
EUDRACT No.: 2022-001079-15	Date: 06 July 2023

APPENDIX 2 - APPROVAL OF THE PROTOCOL BY CLINICAL INVESTIGATOR(S)

A PHASE IB, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF AN INTRAVENOUS MONOCLONAL ANTIBODY (MAB) AFTER SINGLE ASCENDING DOSES IN SUBJECTS AFFECTED BY IDIOPATHIC PULMONARY FIBROSIS

Product: CHF10067

Pharmaceutical Form: Solution for intravenous infusion

Approval of Clinical Study Protocol by the Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this study will not be initiated without Ethics Committee approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

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The undersigned agrees that the study will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Investigator's Name and Qualifications: _____, _____

Centre No.: _____

_____ _____
Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

APPENDIX 3 - RECOMMENDATIONS RELATED TO CONTRACEPTION AND PREGNANCY TESTING IN CLINICAL STUDIES

Definition of female of childbearing potential and of fertile men

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Birth control methods, which may be considered as highly effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - ☐ oral
  - ☐ intravaginal
  - ☐ transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - ☐ oral
  - ☐ injectable
  - ☐ implantable [3]
- intrauterine device [3]
- intrauterine hormone-releasing system[3]
- bilateral tubal occlusion [3]
- vasectomised partner [1, 3]
- sexual abstinence [2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP study subject and that the vasectomised partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

[3] Methods with low-user dependency

Clinical Trial Facilitation Group guidance: Recommendations related to contraception and pregnancy testing in clinical trials. Final version 1.1, 21/09/2020.