SIGNATURE PAGE

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CLINICAL STUDY PROTOCOL

STUDY CODE No.: CLI-10067AA1-02

EUCT/IND number: 2024-514246-37-00/161904

A Phase IIb, multicentre, randomised, double-blind, placebo-controlled, three-arm parallel-group study to evaluate the efficacy, safety, and tolerability at Week 24 of 2 doses of CHF10067 (zampilimab) in participants with idiopathic pulmonary fibrosis
ZAPPHIRE
A study to find an efficacious and safe dose of CHF10067 (zampilimab) in participants with idiopathic pulmonary fibrosis

Version No.: 5.0
Version Date: 14 May 2026

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GENERAL INFORMATION

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VERSION HISTORY

Version	Date	Change History
1.0	13 OCT 2025	First version
2.0	27 OCT 2025	Adjudication Committee removal
3.0 Argentina, Australia, Brazil, Chile, South Korea, Japan, Turkey, UK, and USA	18 FEB 2026	FDA requested changes on the protocol (regarding the optional Extension Part B and some inclusion/exclusion criteria).
4.0 EU	01 APR 2026	EU member states requested changes on the protocol as per EU CTR Part I RFIs issued in Mar 2026.
5.0	14 MAY 2026	Removal of the optional Part B (Extension Study Phase), incorporation of EU CTR Part I Assessment Report issued in Apr 2026, and integration of Versions 3 and 4 into a harmonised global protocol.

SUMMARY OF CHANGES

Amendment 4: 14 May 2026
Global

Overall Rationale for the Changes

Removal of the optional Part B (Extension Study Phase), incorporation of EU CTR Part I Assessment Report received in Apr 2026, and integration of Versions 3 and 4 into a harmonised global protocol.

Section # and name	Description of change	Change rationale
Changes applicable globally		
Cover Page; Protocol Outline; Section 3 Study Design; Section 4.1 Participant Recruitment; Section 4.2 Inclusion Criteria; Section 4.3 Exclusion Criteria; Section 4.5 Discontinuation From Study; Section 6 Treatments; Section 7.1 Study Schedule; Section 7.2 Study Assessments And Procedures; Section 12.3 Statistical Analysis; and Section 15 Informed Consent	Removal of Part B from study title and all relevant protocol sections; correspondingly, removal of reference to Part A (Main study phase) and optional Part B (Extension study phase).	Removed Part B, as per Food and Drug Administration (FDA) Information Request (IR) #1 issued in Jan 2026; removed Part B to minimise the procedural and visit burden on participants, and to limit the duration of placebo use, as per EU CTR Part I Request for Information (RFI) issued in Mar 2026.
Protocol Outline; Section 4.2 Inclusion Criteria; Section 7.1 Study Schedule/Table 5, Footnote 3; and Section 7.1.2 Visit 1 (Screening)	Text aligned for consistency and clarified that multiple inclusion criteria may be reassessed once, latest at Visit 2.	Text was clarified and aligned across sections for consistency.
Protocol Outline; Section 12.3.3 Primary Efficacy Variables; and Section 12.3.4 Secondary Efficacy Variables	Clarified that, for the statistical models, a broader geographic region variable may be used instead of country.	Given the potentially large number of countries involved in the study, country-level effects may lead to sparse data within categories. Therefore, a broader geographic region variable may be used instead of country.
Protocol Outline and Section 12.3.5 Safety, Immunogenicity, and Pharmacokinetic Variables	Text on adverse event aligned for consistency.	Text was clarified and aligned across sections for consistency.
Section 6 Treatments; Section 6.7 Drug storage; and Section 6.1.2.3 Administration	Infusion Manual added.	Additional information can be found in the Pharmacy Manual and the Infusion Manual.
Section 6.1.2.3 Administration and Section 7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions	Revised the duration for completing study treatment administration from 8 to 10 hours from the start of the preparation of the study treatment.	Based on available compatibility data, the extension of the overall study treatment duration from 8 hours to 10 hours is considered scientifically justified and operationally appropriate, with no impact on the quality, safety, or efficacy of the IMP.
Section 7.1 Study Schedule/Table 5, Footnote 12; Section 7.1.6 Follow-Up Visit 10 Or Early Termination Visit; and Section 7.1.7 Follow-up Visit 11	Removal of the interactive response technology system from Visits 10 and 11.	The interactive response technology system will not be used at Visits 10 and 11.
Section 7.2.1 Pulmonary Function Test (Spirometry)	Reported spirometry values are corrected without any additional input from the Investigator (or delegate)	Text was clarified to ensure consistency with spirometry manual, e.g. no body temperature needs to be measured by the Investigator (or delegate).

Section # and name	Description of change	Change rationale
Section 7.2.7 Vital Signs	Added instructions for peripheral oxygen saturation measurements, oxygen saturation will be measured according to the standard processes at the site. Corresponding removal of Section 7.2.11 (Peripheral Capillary Oxygen Saturation).	Added peripheral oxygen saturation measurements and corresponding instructions to vital signs, as per FDA IR#1 issued in Jan 2026.
Section 7.2.4.6 Immunogenicity	Amended the regulatory framework governing the analytical process.	Clarified that the International Conference on Harmonisation guideline M10 on bioanalytical method validation and study sample analysis will be followed.
Section 7.2.5 Nasosorption and Section 7.2.6 Exhaled Breath Condensate	Assessment-specific manuals were replaced by Laboratory Manual.	Details on nasosorption and exhaled breath condensate samples are incorporated in the Laboratory Manual.
Section 10.3 Intensity of Adverse Events	Abnormal laboratory values shall be judged based on the ranges provided in that laboratory report.	Abnormal laboratory values shall be judged based on the ranges provided in that laboratory report and not based on local ranges.
Section 12.3.3 Primary Efficacy Variables	Introduced a rationale for not adjusting for multiplicity to control the study-wise Type I error, despite the presence of multiple pairwise treatment comparisons.	Text was clarified as per EU CTR Part I Assessment Report issued in Apr 2026.
Section 12.3.4 Secondary Efficacy Variables	Clarified the model planned for the analysis of relative change from baseline in percent predicted forced vital capacity (ppFVC).	Text was expanded as per EU CTR Part I Assessment Report issued in Apr 2026.
List of abbreviations and definition of terms	Added definition of terms.	Definition was added as per EU CTR Part I Assessment Report issued in Apr 2026.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.
Changes applicable to Argentina, Australia, Brazil, Chile, South Korea, Japan, Turkey, UK, USA, and Macedonia		
Protocol Outline and Section 4.2 Inclusion Criteria	Clarified inclusion criterion 2, that sex assigned at birth, inclusive of all gender identities, is to be considered for eligibility.	Text was clarified to facilitate screening as per EU CTR Part I RFIs issued in Mar 2026.
Protocol Outline; Section 7.1.1 Visit 0 (Prescreening Visit); and Section 15 Informed Consent	Removed references to the participant's legal representative.	Incapacitated individuals should not be enrolled to the study; text was clarified as per EU CTR Part I RFIs issued in Mar 2026.
Protocol Outline; Section 10.13 Safety Advisory Committee; and Section 23 Premature Termination of the Study	Clarified the role of the Safety Advisory Committee and aligned text across section.	Text was clarified and aligned across sections for consistency as per EU CTR Part I RFIs issued in Mar 2026.
Protocol Outline; Section 8.4 Other Investigations; Section 9.1 Safety and Immunogenicity Variables; Section 9.2 Pharmacokinetic Variables; Section 12.3.5.1 Safety and, Immunogenicity Variables; and Section 12.3.5.2 Pharmacokinetic Variables	Added text to facilitate the link between objectives and variables and corresponding statistical analyses. Analyses of physical examinations was clarified.	Text was clarified as per EU CTR Part I RFIs issued in Mar 2026.
Protocol Outline; Section 12.1 Sample Size	Clarified how the half-width of the two-sided 90% confidence interval of 1.5% for the treatment difference was derived and that assumptions are the same for all treatment group comparisons.	Text was clarified to justify the derivation of the half-width based on sample size assumptions and to specify that a common standard deviation across treatment groups is assumed as per EU CTR Part I RFIs issued in Mar 2026. Note: The description and rationale for this change, as described in Protocol Version 4.0, is rephrased for accuracy.
Section 1.2 Study Rationale	Added a justification for using placebo.	Text was added as per EU CTR Part I RFIs issued in Mar 2026.

Section # and name	Description of change	Change rationale
Table 5 Schedule of Assessments and Section 7.1.7 Follow-Up Visit 11	Added pregnancy testing at follow-up Visit 11.	Pregnancy testing should be conducted until the end of relevant systemic exposure (5 half-lives); text was clarified as per EU CTR Part I RFIs issued in Mar 2026.
Section 10.15 Data Monitoring Committee and Section 23 Premature Termination of the Study	Added text that Data Monitoring Committee charter will also include specific rules to inform about study continuation, modification, or termination due to safety concerns.	Text was clarified and aligned across sections for consistency, as per EU CTR Part I RFIs issued in Mar 2026.
Section 12.3.3 Primary Efficacy Variables	Clarified that main comparison of interest will be the 2 dose strengths of CHF10067 versus placebo. Added that pairwise comparison of the 2 dose strengths of CHF10067 will also be explored	Text was clarified as per EU CTR Part I RFIs issued in Mar 2026.
Protocol Outline; List of abbreviations and definition of terms; and Section 7.2.4.8 Exploratory Biomarkers, Including Tg2	Added definition of abbreviations in text and List of Abbreviations.	Definition was added as per EU CTR Part I RFIs issued in Mar 2026.
General Information	Update of Sponsor's medical expert.	Administrative update.
Changes applicable to the EU and Macedonia		
Protocol Outline; and Section 4.2 Inclusion Criteria; and Section 7.2.7 Vital Signs	Updated inclusion criterion 9.	Allow use of reservoir nasal cannula to collect peripheral oxygen saturation measurements
Protocol Outline and Section 4.2 Inclusion Criteria	Updated inclusion criterion 11.	Specified that a male vasectomy must be >6 months prior to enrolment and azoospermia has been documented.
Protocol Outline and Section 4.3 Exclusion Criteria	Updated exclusion criteria 6 and 8 and added exclusion criterion 9.	Excluded participants with non-idiopathic pulmonary fibrosis (IPF) pulmonary diagnoses, as per FDA IR#1 issued in Jan 2026.
Protocol Outline and Section 4.3 Exclusion Criteria	Updated exclusion criterion 18.	Excluded participants who currently smoke marijuana.
Protocol Outline; Section 4.3 Exclusion Criteria; Section 7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions; Section 10.2 Expectedness Section 10.3 Intensity of Adverse Event; Section 10.9 Reporting Serious Adverse Events to the Sponsor; and Section 12.3.5.1 Safety and Immunogenicity Variables	Updated severity grading system to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v6.0.	Changed severity grading system to NCI CTCAE v6.0, as per FDA IR#1 issued in Jan 2026.
Protocol Outline and Section 5.1 Permitted Concomitant Medications	Updated permitted concomitant medications.	Clarified when inhaled corticosteroids, bronchodilators, and intra-articular steroid injections (systemic steroids) are permitted, as per FDA IR#1 issued in Jan 2026.
Protocol Outline and Section 5.2 Non-Permitted Concomitant Medications	Clarified non-permitted concomitant medications for locally approved IPF therapy in combination.	Clarified the non-permitted use of locally approved IPF therapy in combination, as per FDA IR#2 issued in Jan 2026. Note: This change was implemented in Protocol Version 3.0 but was at that time not described in the summary of changes.

Section # and name	Description of change	Change rationale
Protocol Outline; Section 7.1 Study Schedule; Section 7.2.7 Vital Signs; Section 9.1 Safety and Immunogenicity Variables; and Section 12.3.5.1 Safety and Immunogenicity Variables.	Amended vital sign measurements	Added peripheral oxygen saturation measurements, as per FDA IR#1 issued in Jan 2026.
Protocol Outline; Section 12.3.3 Primary Efficacy Variables; and Section 12.3.4 Secondary Efficacy Variables	Updated text to reclassify the former sensitivity analyses of the primary estimand as “alternative” estimands instead, with no practical changes to the study analytical plan. Updated text that full analysis set (FAS) will be used as main analysis set, and per protocol (PP) as supportive set	Minor statistical clarifications as per FDA IR#2 issued in Jan 2026. The Agency’s feedback indicated that: i) sensitivity analysis #1 should not have been labelled as a “sensitivity” analysis of the primary estimand, as it effectively reflects a different hypothetical scenario for handling some intercurrent event; ii) sensitivity analysis #2 should not have been labelled as a “sensitivity” analysis of the primary estimand, as the only difference lies in the choice of the analysis population; iii) supplementary analysis to be labelled as sensitivity analysis of the primary estimand, considering its deviation from the assumption underlying the estimation of the population-level summary. The Agency recommend to prespecify whether the primary analysis is based on the FAS or PP set. .Note: The description and rationale for this change as described in Protocol Version 3.0 is expanded for transparency.
Section 7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions	Included specific criteria that qualify a participant for premedication.	Removed the use of premedication for the whole study population and updated its use only for participants who had previously experienced a non-serious infusion-related reaction CTCAE Grade ≥2, as per FDA IR#1 issued in Jan 2026.
Changes applicable to Macedonia		
Section 15 Informed Consent	Clarified that participants who cannot read will have an impartial witness to read and sign the informed consent form.	A sentence regarding the exclusion of participants who cannot read or write was not deleted as intended, as per Protocol Administrative Clarification letter in Nov 2025.

PROTOCOL OUTLINE

Study title	A Phase IIb, multicentre, randomised, double-blind, placebo-controlled, three-arm parallel-group study to evaluate the efficacy, safety, and tolerability at Week 24 of 2 doses of CHF10067 (zampilimab) in participants with idiopathic pulmonary fibrosis
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the product	CHF10067: Zampilimab (a recombinant humanised monoclonal antibody, full-length immunoglobulin [Ig] G_4, that binds to human transglutaminase 2)
Site(s)	Approximately 150 investigational sites in North and Latin America, Europe, Asia, and Oceania
Indication	Idiopathic pulmonary fibrosis (IPF)
Study design	Randomised, double-blind, placebo-controlled, parallel-group design. Randomisation will be stratified based on concomitant (or no concomitant) locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening
Study phase	Phase IIb
Objectives	**Primary objective** To evaluate the efficacy of 2 dose strengths of CHF10067 in terms of change from baseline in percent predicted forced vital capacity (ppFVC) at Week 24 compared to placebo in the entire study population. **Secondary objectives:** To evaluate the effect of CHF10067 on other lung function parameters, participant's health status, safety, and tolerability. To evaluate pharmacokinetic (PK) variables after repeated doses. **Exploratory objectives:** To evaluate the effect of CHF10067 on a panel of biomarkers. To evaluate disease progression via changes in lung structure using high-resolution computed tomography (HRCT; optional)
Treatment duration	6 weeks of Screening Period (including prescreening), 21 weeks of Treatment Period (with evaluation of primary variable at Week 24), 9 weeks of follow-up after the last dose or the discontinuation of study treatment.
Test product dose/route/regimen	• Test Dose 1: 1000 mg CHF10067 every 3 weeks intravenously (IV) administered • Test Dose 2: 3000 mg CHF10067 every 3 weeks IV administered

Reference product dose/route/regimen	Placebo (0.9% sodium chloride aqueous solution, no active component) every 3 weeks IV administered
Number of participants	A total of 240 participants will be randomised to ensure approximately 210 participants completing the 24 weeks of the double-blind period, considering a 12% drop-out rate. A maximum of 72 participants with IPF not receiving locally approved IPF monotherapy for any reason (including treatment naïve participants or participants with previous use of locally approved IPF monotherapy that has been stopped at least 4 weeks before randomisation) will be enrolled.
Study population	Adult participants diagnosed with IPF who: • are receiving a stable dose of locally approved IPF monotherapy for at least 8 weeks prior to screening, or • are not receiving locally approved IPF monotherapy (e.g., treatment naïve, have discontinued locally approved IPF monotherapy for any reason at least 4 weeks before randomisation).
Inclusion/Exclusion criteria	**Inclusion criteria:** 1. **Informed consent:** Participant's written informed consent obtained prior to any study-related procedure. 2. **Sex and age:** Male or female (sex assigned at birth, inclusive of all gender identities), of any race and ethnicity, aged ≥40 years with a **life expectancy** of at least 1 year at screening in the opinion of the Investigator. 3. **Body mass index (BMI)** between 18.5 and 35.0 kg/m^2, inclusive. 4. **Body weight** ≥45 kg. 5. **Diagnosis of IPF:** Diagnosis as defined by the 2018 and 2022 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society Guidelines for a maximum 8 years before screening. The most recent HRCT ≤6 months prior to screening, reviewed by central reading, should be used to confirm the diagnosis. If not available, a new HRCT should be performed during screening visit and reviewed by central reading. 6. **Stable IPF therapy:** On locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening and it is anticipated the dose will remain unchanged throughout the study, or (naïve) not on locally approved IPF monotherapy (including participants who have discontinued the IPF monotherapy for any reason at least 4 weeks before randomisation). 7. **Lung function:** Forced vital capacity (FVC) ≥45% of predicted normal value and a ratio of forced expiratory volume in the first second/FVC ≥0.7 at screening.

8. **Diffusing capacity of the lung for carbon monoxide** (DLCO) corrected for haemoglobin ≥25% of predicted normal at screening.
9. **Oxygen saturation** measured by pulse oximetry (peripheral capillary oxygen saturation [SpO_2]) >90% at rest when the maximum oxygen flow is 4 L/min by standard nasal cannula or the equivalent oxygen delivery via reservoir nasal cannula (≤2 L/min).
10. **Ability** to perform the study procedures.
11. **Female** participants:
    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, provided he is her sole sexual partner, he is vasectomised (>6 months prior to enrolment), and he has received medical assessment of the surgical success (documented azoospermia),

       or

    b. Female participants of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e., postmenopausal or permanently sterile). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per the Investigator's request, postmenopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

    Males fulfilling 1 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 participants: Contraception is not required in this case, provided he is vasectomised (>6 months prior to enrolment) and he has received medical assessment of the surgical success (documented azoospermia), or
    c. Males with partner not of childbearing potential: Contraception is not required in this case.

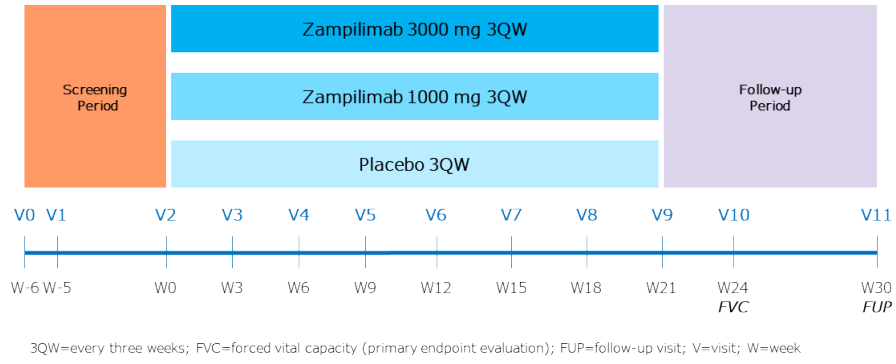
If any of the inclusion criteria #7 (Lung function), #8 (DLCO), or #9 (Oxygen saturation) are not met at screening, they may be reassessed once prior to, or at, Visit 2 (randomisation visit).

Inclusion criteria #3 (BMI), #4 (Body weight), #6 (Stable IPF therapy), and #11 (Female participants) must be rechecked at Visit 2 (randomisation visit).

Exclusion criteria:

1. Participant with a documented diagnosis of **coeliac disease**.
2. **Low respiratory tract infection:** Documented low respiratory tract infection in the last 4 weeks prior to screening or documented acute exacerbation of IPF (defined as acute worsening or development of dyspnoea typically <1 month duration; computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern and deterioration not fully explained by cardiac failure or fluid overload) within 3 months prior to screening, to be rechecked at randomisation.
3. **Surgery:** Any surgery already planned during the study or history of lung volume resection.
4. **Lung cancer:** Active diagnosis or history of lung cancer.
5. **Cancer or history of cancer (other than lung):** Documented active cancer or a history of cancer (other than lung cancer) with less than 5 years disease free survival time (with or without evidence of local recurrence or metastases). Localised carcinoma (e.g., appropriately treated localised non-melanomatous skin cancers, "under surveillance" prostate cancer, in situ carcinoma of uterine cervix, localised bladder cancer, and others discussed on a case-by-case basis) is acceptable.
6. **Emphysema:** HRCT (refer to inclusion criterion #5 [Diagnosis of IPF]), reviewed by central reading, shows the presence of emphysema ≥20% or that the extent of emphysema is greater than the extent of fibrosis.
7. **Organ transplantation:** End-stage fibrotic disease expected to require organ transplantation within 6 months from screening.
8. **Other medical conditions:** Clinically relevant and uncontrolled pulmonary (including any non-IPF pulmonary diagnosis), cardiac, hepatic, gastrointestinal, renal, endocrine, metabolic, neurologic, psychiatric disorders, active or untreated latent tuberculosis/tuberculosis infection that may interfere with the participant's ability to complete this study according to the Investigator's judgement.
9. **Any other comorbid non-IPF pulmonary condition** that may impact FVC according to the Investigator's judgement. Emphysema is allowed, unless it meets exclusion criterion #6.
10. **Cardiovascular diseases:** Chronic heart failure categorised 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 ≥Grade 3 pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the participant's participation in the study or is specified as prohibited concomitant medications (e.g., daily use of phosphodiesterase inhibitors). 11. **Participant currently treated, or been treated** with cytotoxic and immunosuppressant/modulator drugs, e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, tetrathiomolybdate, hydroxychloroquine, interferon gamma-1b, tyrosine kinase inhibitors, monoclonal antibodies with immune-suppressant activity, which require special screening for latent tuberculosis infection for prescription (including, but not limited to, infliximab, etanercept, adalimumab, secukinumab, golimumab, and abatacept), vasodilator therapies for pulmonary hypertension, unapproved treatments for IPF or IPF combination therapy within 4 weeks prior to screening; monoclonal antibodies targeting B cells (including, but not limited to rituximab), within 48 weeks prior to screening. Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of >10 mg/day used for >10 days. 12. **Participation in investigational study**: Participant who received CHF10067 (active arm) or an investigational drug within 3 months or 5 half-lives (whichever is longer) before the randomisation visit (a longer and more appropriate time could be considered by the Investigator based on the elimination half-life and/or long-term effects of the previous investigational drug) or is currently participating in another investigational study. 13. **Hypersensitivity:** Known intolerance and/or hypersensitivity to any of the excipients contained in the formulation or any other substance used in the study. 14. History of **allergic or anaphylactic reaction** to human, humanised, chimeric immunoglobulins (Ig), or murine monoclonal antibodies. 15. History of ≥Grade 3 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. 16. **Mastocytosis:** Confirmed or suspected diagnosis of mastocytosis. 17. **Abnormal laboratory values:** Clinically relevant abnormal laboratory values at screening suggesting an unknown disease and requiring further clinical investigation or which may impact the safety of the participant or the evaluation of the study results according to the Investigator's judgement. Note: In case of abnormal laboratory values that could indicate a temporary condition, the test can be repeated once before randomisation.

	18. **Smoking status:** Current smoker, including and not limited to tobacco, marijuana, and e-cigarettes. Ex-smokers who stopped smoking ≤6 months prior to screening. 19. **Unsuitable veins** for repeated venipuncture. 20. **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. Serum pregnancy test to be performed at screening and urine pregnancy test to be performed prior to randomisation. *Exclusion criteria #2 (Low respiratory tract infection), #11 (Past and current therapies), and #20 (Pregnant or lactating women) must be rechecked at Visit 2 (randomisation visit). Exclusion criterion #17 (Abnormal laboratory values) may be rechecked at Visit 2 (randomisation visit), if applicable.*
Study plan	 3QW=every three weeks; FVC=forced vital capacity (primary endpoint evaluation); FUP=follow-up visit; V=visit; W=week A total of 12 clinic visits (Visit 0 to Visit 11) will be performed: • A prescreening visit (Visit 0) will be carried out to fully explain the study to potential participants, to obtain the written informed consent from the participant, and instruct the participant on screening visit procedures (e.g., medication or procedure-related restrictions). If feasible, the prescreening visit may be combined with the screening visit (Visit 1). • A screening visit (Visit 1) will be carried out to identify eligible participants for inclusion in the study. This visit will be followed by a Screening Period of 3 to 35 days (duration based on participant's availability, and on time for getting the laboratory results, the overreading feedback for spirometry and HRCT assessments). • Participants will be assessed and study treatment will be administered at Weeks 0, 3, 6, 9, 12, 15, 18, and 21 (21 weeks of treatment from Visit 2 to Visit 9) at clinic/hospital. • After last study treatment administration (Visit 9/Week 21), a Visit 10 will be conducted to assess the primary, secondary, and exploratory outcomes, and Visit 11/Week 30 will be conducted

	for follow-up (9 weeks after the last study treatment administration). • Adverse events (AEs) and serious adverse events (SAEs) will be monitored throughout the study. • Only for participants that had an HRCT scan performed at screening, or ≤3 months prior to screening, the Investigator may request for an additional HRCT scan at Week 24. Total duration: Up to 36 weeks. During the course of the study, the following assessments will be performed: • Written informed consent, inclusion/exclusion criteria, demographics, medical history, concomitant medications, and AE/SAE assessment • Living with Pulmonary Fibrosis (L-PF) questionnaire • Vital signs • 12-lead electrocardiogram (ECG) • DLCO • SpO_2 • Pulmonary function test (spirometry) • Physical examination and body weight and height • Blood sampling • Pregnancy test • Nasosorption • Exhaled breath condensate • HRCT • Study treatment administration **SAC Subgroup Analysis** A Safety Advisory Committee (SAC) will review the data of approximately the first 30 randomised participants (SAC subgroup) in a blinded fashion once the last participant of this group has been enrolled and the relevant data up to Week 15 (Visit 7, predose) have been collected (after they have reached the steady state [~ fifth dose]). The aim of this single evaluation is to carefully monitor any safety issue or trend as well as the PK profile after repeated administrations of CHF10067 before treating the entire study population. While the SAC will review the data, the recruitment will continue, and additional participants will be screened, enrolled, and treated.

Most relevant allowed concomitant treatments	• Background treatment with locally approved IPF monotherapy is permitted in the study, as long as the dose has been stable for at least 8 weeks prior to screening. • The participants who enter the study on locally approved IPF monotherapy are expected to stay on stable IPF standard-of-care treatment for the duration of the study. • In case of acute exacerbation (defined as acute worsening or development of dyspnoea typically <1 month duration; computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern and deterioration not fully explained by cardiac failure or fluid overload), any treatments could be freely initiated or increased as deemed appropriate by the Investigator and according to local guidelines to preserve the well-being of study participants. • Any approved vaccine during the study (1 week should elapse from vaccination and the subsequent study treatment administration) will be permitted if it does not interfere with the study evaluations; vaccine type, date, dosage, administration site, and vaccination-related AEs should be reported. • Inhaled corticosteroids (ICS) and bronchodilators are only allowed if the dose/regimen has been stable for at least 8 weeks prior to screening and if wash-out periods are respected prior to pulmonary function test (spirometry), DLCO, nasosorption, and exhaled breath condensate testing as follows: o ICS: 12 hours o Bronchodilators: ▪ Short-acting beta-agonist (e.g., albuterol, salbutamol): 6 hours ▪ Short-acting muscarinic agonist (e.g., ipratropium bromide): 12 hours ▪ Long-acting beta-agonist (e.g., salmeterol, formoterol): 24 hours ▪ Ultra-long-acting beta-agonist (e.g., indacaterol, vilanterol, olodaterol): 36 hours ▪ Long-acting muscarinic agonist: 48 hours • Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of ≤10 mg/day. Intermittent use for non-IPF conditions (e.g., allergies) is allowed as needed during the study, with allowed >10 mg/day use for a maximum of 10 days.

	• Intra-articular steroid injections to treat acute issues are permitted; however, regular use is prohibited due to systemic effects of intra-articular injections. • N-Acetylcysteine, up to 1800 mg daily.
Most relevant forbidden concomitant treatments	• Use of locally approved IPF therapy in combination. In the case of nerandomilast use, for example, this means that participants receiving nerandomilast in combination with any other locally approved IPF therapy (e.g., pirfenidone) will be excluded from the study. If, during the study, treatment with locally approved IPF therapies in combination becomes necessary according to the treating physician, the participant will be discontinued from the study. Use of a single, locally approved IPF monotherapy is permitted. • Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of >10 mg/day used for >10 days. • Cytotoxic and immunosuppressant/modulator drugs, e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, tetrathiomolybdate, hydroxychloroquine, interferon gamma-1b, tyrosine kinase inhibitors, monoclonal antibodies with immune-suppressant activity, which require special screening for latent tuberculosis infection for prescription (including, but not limited to, infliximab, etanercept, adalimumab, secukinumab, golimumab, and abatacept); monoclonal antibodies targeting B cells (including, but not limited to, rituximab). • Daily use of sildenafil, vardenafil, tadalafil, and avanafil. Intermittent use of these oral drugs for the treatment of erectile dysfunction is allowed as needed during the study. • Use of any investigational drug and/or medical device.
Efficacy variables (and PK variables)	**<u>Primary variable:</u>** Absolute change from baseline in ppFVC at Week 24. **<u>Secondary variables:</u>** • Pulmonary function tests: o Absolute change from baseline in ppFVC at Weeks 6, 12, 18, and 30 o Relative change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30 o Categorical absolute change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -10%, -5%, 0%, 5%, and 10%)

	○ Categorical relative change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -10%, -5%, 0%, 5%, and 10%) ○ Rate of decline in ppFVC over 24 weeks ○ Absolute and relative change from baseline in FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30 ○ Categorical absolute change from baseline in FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -200 mL, -100 mL, 0 mL, 100 mL, and 200 mL) ○ Rate of decline in FVC (mL) over 24 weeks • Patient-reported outcome measures: ○ Change from baseline in the L-PF questionnaire at Week 12 and at Week 24 ○ Change from baseline in specific modules of the L-PF questionnaire (symptoms and impacts) and within the symptom modules of specific domains (shortness of breath, cough, and fatigue) at Week 12 and at Week 24 • PK variables: ○ CHF10067 serum concentrations over time (from Week 0 to Week 21). No non-compartmental analysis is foreseen.
Safety variables	• AEs and adverse drug reactions (ADRs). • Vital signs: Systolic (SBP) and diastolic blood pressure (DBP), heart rate, respiratory rate, SpO_2, and body temperature. • 12-lead ECG parameters (heart rate, PR, QRS, and QT interval corrected for heart rate using Fridericia's formula [QTcF]). • Clinical laboratory evaluations: Haematology, blood chemistry, and urinalysis. • Physical examinations. • Screening and confirmed antidrug antibody (ADA) and neutralising antibody (nAb) (for positive ADA participants at confirmation test). Confirmed ADA will be tested for the presence of CHF10067 IgE. Isotype characterisation may be performed. • Systemic markers for the evaluation of immediate hypersensitivity reactions to a biological at baseline for all participants with postdose measurement as needed, i.e., in case of immediate hypersensitivity reactions: Tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-10, mast cell tryptase, complement markers (C3a, C5a, CH50, and sC5b-9) and CHF10073 IgE.

Exploratory variables	• Biomarkers: o Changes from baseline to Weeks 6, 12, 18, and 24 in serum Cancer Antigen 19-9 (CA-19-9), Cancer Antigen 125/Mucin 16 (CA-125/MUC16), Chemokine Ligand 18/Pulmonary and Activation-Regulated Chemokine (CCL18/PARC), C-X-C Motif Chemokine Ligand 13/B Lymphocyte Chemoattractant (CXCL13/BLC), Cytokeratin 19 fragment (CYFRA 21-1), soluble Intercellular Adhesion Molecule-1 (sICAM-1), Matrix Metalloproteinase 7 (MMP-7), Krebs von den Lungen-6/Mucin 1 (KL-6/MUC-1), Plasminogen Activator Inhibitor 1 (PAI-1), Surfactant Protein D (SP-D), and Tenascin C (TN-C) levels o Rate of change in serum CA-19-9, CA-125/MUC16, CCL18/PARC, CXCL13/BLC, CYFRA 21-1, sICAM-1, MMP-7, KL-6/MUC-1, PAI-1, SP-D, and TN-C levels over 24 weeks o Plasma transglutaminase 2 levels at baseline, and at Weeks 12 and 24 • Fibrotic changes on the HRCT from baseline to Week 24 will be evaluated by a radiologist. This will be a descriptive review without quantitative assessment.
Other investigations	Optional sample collection will be proposed to the participants, depending on the feasibility of sample collection at the site. This includes whole blood for genomics (deoxyribonucleic acid [DNA]), transcriptomics (ribonucleic acid [RNA]), additional blood, serum, and plasma samples (including volume for proteomics), nasosorption samples, and exhaled breath condensate samples. These samples will be collected and archived for post-hoc investigations. HRCT scans may be performed at Week 24 to evaluate disease progression.
Sample size calculation	A total of 240 participants (80 participants per treatment arm) will be randomised in a 1:1:1 ratio. This sample size, not based on a formal power calculation, is in line with the size of several recent Phase II studies in participants with IPF and it is considered sufficient for evaluating the dose-related efficacy and safety of CHF10067. It is anticipated that the minimal statistically detectable difference (i.e., the minimal difference reaching statistical significance) between CHF10067 (any dose) and placebo in mean absolute change from baseline in ppFVC at Week 24 is approximately 1.5%, assuming 70 evaluable participants per group at this time point (i.e., a drop-out rate of 12%), a common standard deviation of 5.5%, and a two-sided significance level of 0.1. Under the assumptions above, the evaluable participants per group at Week 24 will ensure a distance from mean difference to the 90% confidence interval (CI) limits of 1.5% (i.e., half-width of the

two-sided 90% CI, derived from the standard error of the mean difference between groups and the corresponding critical value for the specified confidence level).

The following table provides some scenarios of varying hypothesised treatment differences, the corresponding attainable 90% CIs, and estimated powers, with all other assumptions kept stable.

CHF10067 versus placebo mean absolute CFB in ppFVC at Week 24	**90% CI**	**Estimated Power**
1.5%	(0.0%-3.0%)	49%
1.8%	(0.3%-3.3%)	61%
2.0%	(0.5%-3.5%)	69%
2.3%	(0.8%-3.8%)	79%
2.7%	(1.2%-4.2%)	89%
2.8%	(1.3%-4.3%)	91%

CFB=change from baseline; CI=confidence interval; ppFVC=percent predicted forced vital capacity.
Note: The hypotheses considered for the calculations are as follows: 70 evaluable participants per group in 1:1 ratio, common standard deviation of 5.5%, two-sided significance level of 0.1.

Statistical methods

Efficacy variables

Primary efficacy variable

Absolute change from baseline to Week 24 in ppFVC will be analysed using a linear mixed model for repeated measures (MMRM) including treatment, country (or region), visit, treatment by visit interaction, locally approved IPF monotherapy as fixed effects, as well as baseline value (collected at Visit 2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment arm, the adjusted mean difference between treatments, and their 95% CIs at Week 24 will be estimated by the model.

The primary efficacy analysis will be based on the data collected up to Week 24 using full analysis set (FAS) as main analysis set, and per protocol (PP) as supportive set. Details of this analysis will be provided in the Statistical Analysis Plan (SAP).

Primary estimand

Target population: Adult participants with IPF, aged ≥40 years with a life expectancy of at least 1 year at screening: IPF diagnosis for a maximum 8 years before screening. Stable locally approved IPF monotherapy for at least 8 weeks prior to screening; or (naïve) not on locally approved IPF therapy (including participants who have discontinued locally approved IPF monotherapy for any reason at least 4 weeks before randomisation).

Treatment: CHF10067 1000 mg or CHF10067 3000 mg or placebo administered every 3 weeks by IV infusion.

Variable: Absolute change from baseline to Week 24 in ppFVC

Strategy for events leading to missing data:

- Treatment discontinuation for any reason (including lack of efficacy, AE, or death): Hypothetical strategy, assuming that participants adhered to their randomised treatment up to Week 21 (missing at random [MAR] imputation of off-treatment data)

Intercurrent events strategy:

- All other intercurrent events (including use of rescue medication, prohibited concomitant medications, use of locally approved IPF monotherapy in participants not on locally approved IPF monotherapy prior to screening, wrong study treatment administration, and any other important protocol deviations): treatment policy strategy (data included in the analysis regardless of whether or not the intercurrent event occurred)

Population-level summary: Adjusted mean difference in the change from baseline to Week 24 in ppFVC comparing CHF10067 1000 mg versus placebo, and CHF10067 3000 mg versus placebo

Sensitivity analysis

To assess the impact of the presence of outliers (specific to the IPF disease, participants may have large variability that can impact analysis results) in the response variable, a sensitivity analysis will be performed on the primary estimand by means of a robust linear regression model. The main purpose of this model is to provide stable estimates of means in the presence of outliers (i.e., non-normality) of the response variable. This model limits the influence of outliers through a process known as iteratively reweighted least squares; conceptually, the iterative process detects unusual observations and assigns them with a smaller contribution in estimating means.

Robust linear regression will be implemented using M-estimation and the bisquare weighting function. The model will include change from baseline value as response variable using treatment, country (or region), locally approved IPF monotherapy as fixed effects, as well as baseline as covariate.

Missing data will be imputed using multiple imputation with MAR assumption, in line with the main analysis of the primary estimand.

Alternative Estimands

Alternative estimands will be defined and analysed as described below to investigate the potential impact of missing data on the treatment effect. The analyses of primary estimand assume that any missing data are MAR, meaning that the probability of a value being missing, conditional on the observed data and factors in the statistical model, is

	random, and not dependent on the unknown value of the missing data point. Full details of the analyses of alternative estimands will be provided in the SAP. <u>Alternative Estimand #1</u> A different hypothetical scenario for post-treatment discontinuation will be assessed: • Treatment discontinuation due to safety reasons, lack of efficacy, AE, or death: Copy-reference multiple imputation, i.e., imputation of data after study discontinuation in all treatment arms will be based on the data distribution of the placebo group. Multiple imputation with missingness not at random (MNAR) assumption. • Treatment discontinuation for any other reason: Multiple imputation with MAR assumption. Absolute change from baseline in ppFVC will be analysed using an analysis of covariance (ANCOVA) model, including treatment, country (or region), locally approved IPF monotherapy as fixed effects, as well as baseline as covariate. MMRM accounts for missing data under the MAR assumption, whereas ANCOVA does not. However, after imputing missing data under different MNAR assumptions, both models yield similar results when analysing complete data at a single timepoint. Given this equivalence, the simpler ANCOVA model is preferred for its ease of interpretation and implementation, avoiding the additional complexity and computational burden of MMRM. <u>Alternative Estimand #2</u> A second alternative estimand will be defined and analysed to assess the treatment effect under continued treatment up to Week 24 in participants who are able to complete the planned Treatment Period. The analysis will be performed, including only participants with measurements of ppFVC available both at baseline and at Week 24 (participants with missing ppFVC measurements between baseline and Week 24 will be included), by means of the same model as for the main analysis of the primary estimand. **<u>Secondary efficacy variables</u>** The intercurrent event strategy for secondary efficacy variables will be the same as for the main analysis of the primary estimand. The secondary analysis will be using FAS as main analysis set, and PP as supportive set. No sensitivity analyses will be performed. Details of these analyses will be provided in the SAP.

- For absolute change from baseline in ppFVC, the adjusted means in each treatment arm and the adjusted mean differences between treatments at Weeks 6, 12, 18, and 30 will be estimated with their 95% CIs by the same model used for the primary efficacy analysis.
- For relative change from baseline in ppFVC, the adjusted means in each treatment arm and the adjusted mean differences between treatments at Week 24 and at Weeks 6, 12, 18, and 30 will be estimated with their 95% CIs by the same model used for the primary efficacy analysis. Similar analyses will be performed for change from baseline in FVC (mL) and L-PF questionnaire (at Week 12 and Week 24, including specific modules [symptoms and impact] and, within the symptom modules, of specific domains [shortness of breath, cough, and fatigue]).
- Categorical absolute and relative change from baseline in ppFVC, and categorical absolute change from baseline FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30 will be compared between treatment arms using a logistic model including treatment, country (or region), locally approved IPF monotherapy as factors and the baseline value as a covariate. Separate analyses will be conducted based on each of the dichotomous threshold used (-10%, -5%, 0%, 5%, and 10% for ppFVC; -200 mL, -100 mL, 0 mL, 100 mL, and 200 mL for FVC).
- The analysis of the rate of decline in ppFVC and FVC (mL) over 24 weeks will be based on a linear mixed model including treatment, country (or region), locally approved IPF monotherapy, time, and treatment by time interaction as fixed effects and participant-specific random intercept and slope, assuming an unstructured covariance matrix for random effects. The baseline value will be part of the response vector, so it will not be included in the model as a covariate.

PK variables

At each timepoint serum concentrations will be summarised by study treatment using descriptive statistics.

Serum concentration/time curves will be presented in linear/linear scale. Plots will be presented by study treatment, based on arithmetic means, and by participant, by showing the individual curves grouped by study treatment (1 plot for each study treatment) and ADA positivity/negativity (using different colours). No non-compartmental analysis is foreseen.

PK data will be submitted for population PK modelling, which will be described in a separate analysis plan. The results will be summarised in a separate report which will not be part of the Clinical Study Report (CSR).

Safety and immunogenicity variables

For all safety and immunogenicity variables, baseline is the Visit 2 predose, with exception of the systemic markers for immediate hypersensitivity reactions, which will be collected at predose for each visit (Week 0 to Week 21).

Safety and immunogenicity variables will be presented for the whole population, and for participants on locally approved IPF monotherapy and not on locally approved IPF monotherapy prior to screening. Details of these analyses will be provided in the SAP.

Adverse events

The number of events and the number and percentage of participants experiencing treatment-emergent adverse events (TEAEs), treatment-emergent ADRs, serious TEAEs, non-serious TEAEs, serious treatment-emergent ADRs, TEAEs by Common Terminology Criteria for Adverse Events grade, ≥Grade 3 TEAEs, TEAEs leading to discontinuation of study treatment, and TEAEs leading to death will be presented overall and by treatment arm. The aforementioned categories of AEs will be also summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities.

Vital signs

At screening, at baseline, and at each postbaseline (with or without dosing) time point, the following statistics will be presented by treatment arm for each parameter (SBP, DBP heart rate, respiratory rate, SpO_2, and body temperature):

- mean absolute value with its 95% CI
- mean change from baseline with its 95% CI
- mean change from predose with its 95% CI

In addition, the number and percentage of participants with

- SBP change from baseline >20 mmHg
- DBP change from baseline >10 mmHg
- Heart rate:
  - <50 bpm or >100 bpm
  - Increase >20 bpm from baseline
  - Decrease >15 bpm from baseline
- Respiratory rate:
  - <10 breaths/min or >20 breaths/min
  - Increase >5 breaths/min from baseline
  - Decrease <5 breaths/min from baseline

- Body temperature
  - ≥38.0 °C
  - Increase ≥1.0 °C from baseline

will be presented at each postbaseline time point postdose and at any postbaseline time point by treatment arm.

12-lead ECG

At baseline and at each postbaseline (with or without dosing) time point, the following statistics will be presented by treatment arm for 12-lead ECG parameters (heart rate, PR, QRS, and QTcF):

- mean absolute value with its 95% CI
- mean change from baseline with its 90% CI (for postbaseline time points with or without dosing)
- mean change from predose with its 90% CI (for postbaseline time points with dosing only)

Laboratory data

At screening, at baseline, and at each postbaseline (with or without dosing) time point, quantitative laboratory parameters (complete blood count with differential cell count, blood chemistry panel, liver function test panel, and urinalysis) will be summarised. For continuous laboratory parameters, the laboratory values and the change from baseline will be summarised at each visit by treatment arm using descriptive statistics and 95% CIs. For categorical laboratory parameters, a frequency table of results will be produced at each visit by treatment arm.

Shift tables from baseline to each postbaseline visit, with regards to normal range, will be presented by treatment arm.

Physical Examinations

Abnormal physical examination findings will be listed.

Immediate hypersensitivity reaction markers

Cytokine markers (TNF-α, IL-1β, IL-6, and IL-10), mast cell tryptase, and complement markers (C3a, C5a, CH50, and sC5b-9), CHF10067 IgE will be presented by participant and by visit for each postdose timepoint as absolute value and change from baseline.

Immunogenicity data

The number and percentage of participants who fulfil the below criteria will be presented by treatment arm.

- ADA-positive at baseline
- ADA-positive at any visit, including baseline and all postbaseline measurements (ADA prevalence)

- CHF10067 IgE-positive at baseline and at any visit, including baseline and all postbaseline measurements (for ADA-positive samples only)
- ADA incidence
  - Treatment-induced ADA (positive ADA any time postbaseline in participant with ADA-negative at baseline).
    - Persistently positive ADA
      Treatment-induced ADA detected at 2 or more sampling time points during the treatment (including Follow-up Period), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer,
      or
      treatment-induced ADA incidence in the last available assessment (including Follow-up Period)
    - Transiently positive ADA
      Treatment-induced ADA not fulfilling the above condition for persistently positive
  - Treatment-boosted ADA (baseline positive ADA titre that was boosted to a 4-fold or higher level following study treatment administration)
  - nAb positive at any visit, including baseline and all postbaseline measurements

All immunogenicity data will be listed.

Only if immunogenicity data will allow the effect of immunogenicity on efficacy, PK, and safety will be evaluated:

- Efficacy: The analysis of the primary efficacy variable will be performed by participant ADA status (i.e., ADA-positive or ADA-negative).
- PK: Serum concentration/time curves will be presented in linear/linear scale. Plots will be presented by dose level and participant ADA status (i.e., ADA-positive or ADA-negative) based on arithmetic means.
- Safety: The number and percentage of participants with TEAEs will be summarised by participant ADA status (i.e., ADA-positive or ADA-negative).

Exploratory variables

At baseline and at each postbaseline (with or without dosing), quantitative biomarker parameters will be summarised. For continuous biomarker parameters, the absolute biomarker values, the mean change (absolute and percentage) from baseline will be summarised at each visit by treatment arm using descriptive statistics and 95% CIs.

For categorical biomarker parameters, a frequency table of results will be produced at each visit by treatment arm.

Fibrotic changes on the HRCT from baseline to Week 24 will be evaluated by a radiologist. This will be a descriptive review without quantitative assessment.

Other investigations

Post-hoc investigations might be performed to analyse the optional samples (whole blood for genomics (DNA), transcriptomics (RNA), additional blood, serum, and plasma samples (including volume for proteomics), nasosorption samples, and exhaled breath condensate samples) and HRCT scans. The outcome variables and their analyses will be described in a separate post-hoc statistical plan. The results will not be included in the CSR.

Examination of subgroups

The primary and secondary efficacy variables, except for PK variables, as well as safety and immunogenicity variables will also be analysed in the 2 subgroups defined as per stratification factor:

- On concomitant locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening
- Not on concomitant locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening

No adjustment of the significance level for testing will be made, since all these subgroup analyses will be considered exploratory and may only be supportive of the analyses of the primary and secondary variables.

SAC subgroup analysis

An SAC will review blinded data of the SAC subgroup. The safety parameters that will be reviewed will be specified in the SAC charter and include but are not limited to:

- TEAEs
- Vital signs
- 12-lead ECG (heart rate, PR, QRS, and QT interval corrected for heart rate using Fridericia's formula)
- Pulmonary function test (spirometry)
- Clinical laboratory parameters (haematology, blood chemistry, and urinalysis)
- Available PK and ADA data up to Week 15 (Visit 7, predose)

No specific analyses performed for the evaluation of the SAC subgroup will be included in the CSR.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Antidrug antibody
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ALAT	Latin American Thoracic Association
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
BMI	Body mass index
CA-125/MUC16	Cancer Antigen 125/Mucin 16
CA-19-9	Cancer Antigen 19-9
CCL18/PARC	Chemokine Ligand 18/Pulmonary and Activation-Regulated Chemokine
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL13/BLC	C-X-C Motif Chemokine Ligand 13/B Lymphocyte Chemoattractant
CYFRA 21-1	Cytokeratin 19 fragment
DBP	Diastolic blood pressure
DLCO	Diffusing capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPO	Data protection officer
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ERS	European Respiratory Society
ETD	Early treatment discontinuation
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

FEV1	Forced expiratory volume in the first second
FIH	First-in-human
FVC	Forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practices
HRCT	High-resolution computed tomography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICON	Name of the Contract Research Organisation contracted by the Sponsor
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
ILD	Interstitial lung disease
IMP	Investigational medicinal product
IND	Investigational new drug
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous(ly)
JRS	Japanese Respiratory Society
KL-6/MUC-1	Krebs von den Lungen-6/Mucin 1
L-PF	Living with Pulmonary Fibrosis
LTBI	Latent tuberculosis infection
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMP-7	Matrix Metalloproteinase 7
MMRM	Mixed model for repeated measures
MNAR	Missingness not at random
nAb	Neutralising antibody
PAI-1	Plasminogen Activator Inhibitor 1
PD	Pharmacodynamic

PK	Pharmacokinetic
PP	Per protocol
ppFVC	Percent predicted forced vital capacity
PR	The time measured from the onset of the P wave to the beginning of the QRS complex
QRS	The time taken from the onset of the Q wave (or the beginning of the QRS complex) to the end of the S wave
QT	The time measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAC	Safety Advisory Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
[redacted]	
sICAM-1	Soluble Intercellular Adhesion Molecule-1
SP-D	Surfactant Protein D
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse events
TG2	Transglutaminase 2
TN-C	Tenascin C
TNF-α	Tumour necrosis factor-α
WOCBP	Women of childbearing potential

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1. INTRODUCTION

1.1 BACKGROUND INFORMATION

Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic, fibrosing interstitial lung disease (ILD) characterised by decline in lung function and worsening dyspnoea [1]. IPF is the most common ILD and carries a poor prognosis, with a median postdiagnosis survival in untreated participants 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 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 (also identified as zampilimab) is a recombinant, humanised, full-length immunoglobulin (Ig) G4 inhibitory monoclonal antibody with high affinity for human TG2. [redacted]

Clinical experience with CHF10067 consists of 2 completed Phase I studies in healthy participants investigating [redacted] doses of [redacted] (Study UP0029) and [redacted] doses (at a [redacted] than the UP0029 Study) of [redacted] (Study UP0105). CHF10067 was found to be well tolerated at [redacted] doses up to [redacted] (at [redacted]) and [redacted] doses up to [redacted] in healthy participants. A Phase Ib study in participants with IPF was also completed with [redacted] of [redacted] doses from [redacted] at a [redacted] of [redacted] and CHF10067 was found to be safe and well tolerated. In addition, a Phase I/II study in adult kidney transplant recipients with chronic allograft injury associated with moderate-to-severe fibrosis and declining renal function (Study CAI001) was started, then prematurely interrupted due to poor recruitment. No new safety concerns were identified in the 3 participants treated with repeated administrations of CHF10067.

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

1.2 STUDY RATIONALE

The development of novel therapies for the treatment of IPF, a progressive and fatal chronic 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 efficacy data of 2 dose strengths of CHF10067 in terms of change from baseline in percent predicted forced vital capacity (ppFVC) at Week 24. CHF10067 will be administered IV as doses of either 1000 or 3000 mg every 3 weeks for a duration of 21 weeks to participants with IPF.

The expected study results, together with the pharmacokinetic (PK) and immunogenicity data, will help establish the doses suitable for future studies in participants. The effect of CHF10067 on biomarkers levels will also be investigated as an exploratory variable.

Based upon the preclinical and clinical data and the potential of antidrug antibody (ADA) response, the 21-week Treatment Period is considered adequate to achieve the study objectives, i.e., to provide a statistically significant and clinical meaningful increase in FVC in adult participants with IPF.

The study is designed as 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 or variability. The study design is ethically appropriate as participants are not denied effective treatment, as they may continue receiving approved standard-of-care therapies (e.g., antifibrotic treatments) during the study.

[redacted] were tolerated up to a dose of [redacted] and [redacted] were tolerated up to a dose of [redacted] therefore, [redacted] is the maximum dose to be tested also in this study. In addition, the IV administration is the intended clinical route of administration. Refer to Section 6.1.2.1 for details.

1.3 RISK/BENEFIT ASSESSMENT

1.3.1 RISK EVALUATION

The proposed study has been designed to confirm the efficacy and safety of CHF10067 (1000 or 3000 mg every 3 weeks) in participants with IPF.

No studies evaluating efficacy as primary variable have been conducted so far.

The safety experience is limited to [redacted] administration of CHF10067 in healthy study participants in the first-in-human (FIH) and Phase I PK/pharmacodynamic (PD) studies (Study UP0105 and UP0029) and to 3 participants affected by chronic allograft injury enrolled in the CAI001 Phase I/II study (Study CAI001).

No treatment-emergent adverse events (TEAEs) considered related to CHF10067 by the Investigator were reported in the completed Study UP0105 in healthy participants.

In Study UP0029 in healthy participants, TEAEs considered related to investigational medicinal product (IMP) by the Investigator and reported by >1 participant in the CHF10067 total group were headache (4 participants [6.9%]), [redacted], nasal congestion, and hot flush (2 participants [3.4%], each). Notably, headache was also reported in the placebo total group (2 participants [10.0%]).

TEAEs considered related to IMP per Investigator assessment and reported by >1 participant, by preferred term, in the CHF10067 [redacted] and headache (2 participants [5.7%], each), and in the CHF10067 [redacted] were headache and hot flush (2 participants [8.7%], each).

In Study CAI001 in participants with chronic allograft injury, [redacted] happened during the up-titration period; 1 was mild in intensity on [redacted] CHF10067 [redacted] and 1 of moderate intensity following CHF10067 [redacted] on [redacted]. These TEAEs were non-serious, did not lead to

discontinuation of IMP, nor to change in dose, and were considered resolved by [redacted], respectively.

The limited clinical data available to date and the study population (healthy study participants) must be considered when interpreting these data at this stage of clinical development.

Infusion-related reactions, hypersensitivity and anaphylactic reactions, local reactions, wound healing delayed/impaired healing, and immunogenicity are known risks associated to the class of drugs to which CHF10067 belongs (monoclonal antibodies), and/or AEs that may be predicted to occur based on the physical, chemical, pharmaceutical, pharmacological, and toxicological properties of CHF10067 even if not yet observed with CHF10067 in humans.

As with any therapeutic protein products, administration of CHF10067 may be associated with development of ADA. [redacted]

The incidence of ADA, following administration of CHF10067 either [redacted], occurred in 20 study participants (36.4%) in the FIH (Study UP0029). Some baseline reactivity was also observed. There was no treatment-emergent ADA detected in the placebo group. Due to analytical method limitations, no conclusion could be drawn with these results.

After optimisation of analytical method according to the current industry guidelines, the incidence of ADA, following [redacted] of CHF10067, occurred in only 1 study participant (8.3%) in the Phase I PK/PD (Study UP0105) and 1 study participant (5.6%) in the Phase Ib study in participants with IPF (Study CLI-10067AA1-01). The latter also showed positivity to the neutralising antibody (nAb) assay.

In Study CAI001 it was planned that ADA would be measured using a 3-tiered assay approach (screening assay, confirmatory assay, and titration assay). However, ADAs were not analysed for the 3 participants in this study randomised to CHF10067, due to the low number of samples collected and the inability to update the bioanalytical method with the matrix effect for the chronic allograft injury.

The characterisations of ADA to CHF10067 and subsequent clinical consequences have yet to be determined due to limited data and duration of exposure. In this current study, blood samples will be collected during clinical studies to detect the presence of ADA. Study participants will be closely observed for evidence of clinical events, e.g., infusion-related reaction/cytokine release syndrome that may originate from response due to immunogenicity.

The potential for infusion-related reaction or allergic reactions, including anaphylaxis, is known following administration of any protein in human study participants.

Two (5.7%) study participants reported mild-to-moderate treatment-related AEs suggestive of infusion-related reaction in FIH (Study UP0029). In 1 study participant, the event was serious and led to premature stopping of the infusion. This study participant remained in the study and events resolved with conservative treatment. It is suspected that this infusion-related reaction may have resulted from the high concentration of IMP administered and the speed of the infusion. No AEs suggestive of infusion-related reactions were reported in the placebo groups.

To reduce the risk of infusion-related reactions, in Phase I PK/PD, Phase I/II in participants with CAI, and Phase Ib in participants with IPF, CHF10067 infusion solution was administered at a [redacted] concentration and [redacted] of time compared with the FIH study (Study UP0029).

One case of immediate hypersensitivity reaction was reported in 1 study participant (5.6%) in the Phase Ib study (Study CLI-10067AA1-01). The event was of moderate intensity and fully resolved on the day after the onset. As a precaution, the infusion scheme to be used for the next study participants was modified with progressive increase of infusion rate to reach [redacted]

No TEAEs suggestive of infusion-related reactions were reported in the completed Phase I PK/PD study (Study UP0105) and the completed Study CAI001.

Due to the absence of embryofoetal and developmental studies, CHF10067 is contraindicated in pregnant or breastfeeding women.

CHF10067 is contraindicated in study participants with known hypersensitivity to the active substance or any of the excipients. Participants already dosed with CHF10067 are excluded from this study.

1.3.2 BENEFIT EVALUATION

It is anticipated that the minimal statistically detectable difference (i.e., the minimal difference reaching statistical significance) between CHF10067 (any dose) and placebo in mean absolute change from baseline in percent predicted FVC (ppFVC) at Week 24 is approximately 1.5%.

Data from previous studies with CHF10067 in healthy volunteers and the Phase Ib study in patients with IPF, demonstrated an acceptable safety profile and that it was well tolerated in when administered at doses of [redacted]

1.3.3 CONCLUSIONS

Considering the safety profile of CHF10067, the measures in place to assure the participants' 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 [14].

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of 2 dose strengths of CHF10067 in terms of change from baseline in ppFVC at Week 24 compared to placebo in the entire study population.

The primary estimand associated with the primary objective is defined by the attributes in Table 1.

Table 1: Primary Estimand Associated With the Primary Objective

Target population	Adult participants with IPF, aged ≥40 years with a life expectancy of at least 1 year at screening: IPF diagnosis for a maximum 8 years before screening. Stable locally approved IPF monotherapy for at least 8 weeks prior to screening; or (naïve) not on locally approved IPF therapy (including participants who have discontinued locally approved IPF monotherapy for any reason at least 4 weeks before randomisation)
Treatment	CHF10067 1000 mg or CHF10067 3000 mg or placebo administered every 3 weeks by IV infusion
Variable	Absolute change from baseline to Week 24 in ppFVC

Strategy for intercurrent events and events leading to missing data	**Treatment discontinuation for any reason** (including lack of efficacy, AE, or death): **Hypothetical strategy**, assuming that participants adhered to their randomised treatment up to Week 21 (MAR imputation of off-treatment data). **All other intercurrent events** (including use of rescue medication or prohibited concomitant medications, use of locally approved IPF monotherapy in participants not on locally approved IPF monotherapy prior to screening, wrong study treatment administration, and any other important protocol deviations): **Treatment policy strategy** (data included in the analysis regardless of whether or not the intercurrent event occurred)
Population-level summary	Adjusted mean difference in the change from baseline to Week 24 in ppFVC comparing CHF10067 1000 mg versus placebo, and CHF10067 3000 mg versus placebo

AE=adverse event; IPF=Idiopathic pulmonary fibrosis; IV=intravenous(ly); MAR=missing at random; ppFVC=percent predicted forced vital capacity

2.2 SECONDARY OBJECTIVES

The secondary objectives are the following:

- to evaluate the effect of CHF10067 on other lung function parameters, participant's health status, safety, and tolerability
- to evaluate PK variables after repeated doses

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are the following:

- to evaluate the effect of CHF10067 on a panel of biomarkers
- to evaluate disease progression via changes in lung structure using high-resolution computed tomography (HRCT; optional)

2.4 OTHER INVESTIGATIONS

Other investigations include the following:

- the exploration of biomarkers analysed in optionally collected blood, nasal, and breath condensate samples
- the exploration of quantitative changes in lung structure using HRCT (optional)

3. STUDY DESIGN

This is a Phase IIb, randomised, double-blind, placebo-controlled, multinational, multicentre, three-arm parallel-group, 24-week study evaluating the efficacy and safety of 2 doses of CHF10067 (Figure 1).

A total of 240 participants with IPF will be randomised in approximately 150 investigational sites in North and Latin America, Europe, Asia, and Oceania.

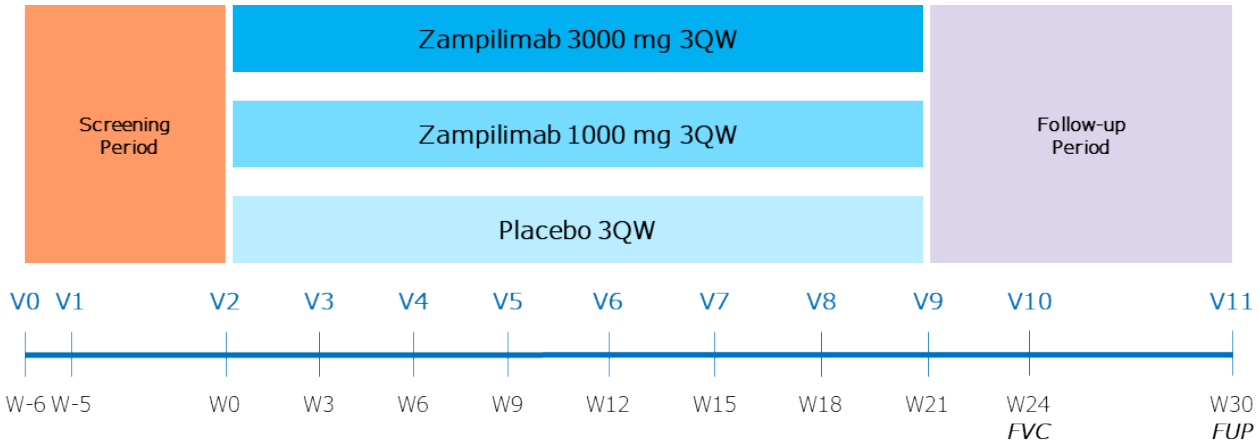
A maximum of 72 participants with IPF not receiving locally approved IPF monotherapy for any reason (including treatment naïve participants or participants with previous use of locally approved IPF monotherapy that has been stopped at least 4 weeks before randomisation) will be enrolled.

Randomisation will be stratified based on concomitant (or no concomitant) locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening.

A subgroup consisting of approximately the first 30 randomised participants (Safety Advisory Committee [SAC] subgroup) will be involved in the evaluations of safety, immunogenicity, and available PK across the 3 treatment arms. Data collected will be reviewed during the study by an SAC according to the procedure described in Section 10.13, to confirm the safety and tolerability profile of the 1000 and 3000 mg doses of study treatment after multiple administration cycles.

The study will include a Screening Period of 6 weeks (including prescreening), a Treatment Period of 21 weeks (with evaluation of primary variable at Week 24), and a Follow-up Period of 9 weeks after the last dose or the discontinuation of study treatment.

Figure 1: Study Scheme



3QW=every three weeks; FVC=forced vital capacity (primary endpoint evaluation); FUP=follow-up visit; V=visit; W=week

The end of the study is defined as the last visit of the last participant.

4. PARTICIPANT SELECTION CRITERIA

The Investigator will evaluate each participant on the selection criteria below and will make the final decision on eligibility.

4.1 PARTICIPANT RECRUITMENT

A total of 240 participants will be randomised to ensure approximately 210 participants completing the 24 weeks of double-blind period, considering a 12% drop-out rate.

Advertisements to support recruitment may be used following applicable local laws and regulations.

4.2 INCLUSION CRITERIA

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

1. **Informed consent:** Participant's written informed consent obtained prior to any study-related procedure.
2. **Sex and age:** Male or female (sex assigned at birth, inclusive of all gender identities), of any race and ethnicity, aged ≥40 years with a **life expectancy** of at least 1 year at screening in the opinion of the Investigator.

3. **Body mass index (BMI)** between 18.5 and 35.0 kg/m^2, inclusive.
4. **Body weight** ≥45 kg.
5. **Diagnosis of IPF:** Diagnosis as defined by the 2018 and 2022 ATS/ERS/JRS/ALAT Guidelines for a maximum 8 years before screening. The most recent HRCT ≤6 months prior to screening, reviewed by central reading, should be used to confirm the diagnosis. If not available, a new HRCT should be performed during screening visit and reviewed by central reading.
6. **Stable IPF therapy:** On locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening and it is anticipated the dose will remain unchanged throughout the study, or (naïve) not on locally approved IPF monotherapy (including participants who have discontinued the IPF monotherapy for any reason at least 4 weeks before randomisation).
7. **Lung function:** FVC ≥45% of predicted normal value and a ratio of forced expiratory volume in the first second (FEV1)/FVC ≥0.7 at screening.
8. **Diffusing capacity of the lung for carbon monoxide** (DLCO) corrected for haemoglobin ≥25% of predicted normal at screening.
9. **Oxygen saturation** measured by pulse oximetry (peripheral capillary oxygen saturation [SpO_2]) >90% at rest when the maximum oxygen flow is 4 L/min by standard nasal cannula or the equivalent oxygen delivery via reservoir nasal cannula (≤2 L/min).
10. **Ability** to perform the study procedures.
11. **Female participants**:

a. Women of childbearing potential (WOCBP, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile) 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. Highly effective contraceptive methods are defined as follows: Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, and true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), whereas periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception, or

   ii. WOCBP with non-fertile male partners: Contraception is not required in this case, provided he is her sole sexual partner, he is vasectomised (>6 months prior to enrolment), and he has received medical assessment of the surgical success (documented azoospermia),

or

b. Female participants of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e., postmenopausal or permanently sterile). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per the Investigator's request, postmenopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

1. **Males** fulfilling 1 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 participants: Contraception is not required in this case, provided he is vasectomised (>6 months prior to enrolment) and he has received medical assessment of the surgical success (documented azoospermia), 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 I.

If any of the inclusion criteria #7 (Lung function), #8 (DLCO), or #9 (Oxygen saturation) are not met at screening, they may be reassessed once prior to, or at, Visit 2 (randomisation visit).

Inclusion criteria #3 (BMI), #4 (Body weight), #6 (Stable IPF therapy), and #11 (Female participants) must be rechecked at Visit 2 (randomisation visit).

4.3 EXCLUSION CRITERIA

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

1. Participant with a documented diagnosis of **coeliac disease**.
2. **Low respiratory tract infection:** Documented low respiratory tract infection in the last 4 weeks prior to screening or documented acute exacerbation of IPF (defined as acute worsening or development of dyspnoea typically <1 month duration; computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern and deterioration not fully explained by cardiac failure or fluid overload [15]) within 3 months prior to screening, to be rechecked at randomisation.
3. **Surgery:** Any surgery already planned during the study or history of lung volume resection.
4. **Lung cancer:** Active diagnosis or history of lung cancer.
5. **Cancer or history of cancer (other than lung):** Documented active cancer or a history of cancer (other than lung cancer) with less than 5 years disease free survival time (with or without evidence of local recurrence or metastases). Localised carcinoma (e.g., appropriately treated localised non-melanomatous skin cancers, “under surveillance” prostate cancer, in situ carcinoma of uterine cervix, localised bladder cancer, and others discussed on a case-by-case basis) is acceptable.
6. **Emphysema:** HRCT (refer to inclusion criterion #5 [Diagnosis of IPF]), reviewed by central reading, shows the presence of emphysema ≥20% or that the extent of emphysema is greater than the extent of fibrosis.
7. **Organ transplantation:** End-stage fibrotic disease expected to require organ transplantation within 6 months from screening.
8. **Other medical conditions:** Clinically relevant and uncontrolled pulmonary (including any non-IPF pulmonary diagnosis), cardiac, hepatic, gastrointestinal, renal, endocrine, metabolic, neurologic, psychiatric disorders, active or untreated latent tuberculosis/tuberculosis infection that may interfere with the participant’s ability to complete this study according to the Investigator’s judgement.
9. **Any other comorbid non-IPF pulmonary condition** that may impact FVC according to the Investigator’s judgement. Emphysema is allowed, unless it meets exclusion criterion #6.

10. **Cardiovascular diseases:** Chronic heart failure categorised 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 ≥Grade 3 pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the participant's participation in the study or is specified as prohibited concomitant medications (e.g., daily use of phosphodiesterase inhibitors).
11. **Participant currently treated, or been treated** with cytotoxic and immunosuppressant/modulator drugs, e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, tetrathiomolybdate, hydroxychloroquine, interferon gamma-1b, tyrosine kinase inhibitors, monoclonal antibodies with immune-suppressant activity, which require special screening for latent tuberculosis infection for prescription (including, but not limited to, infliximab, etanercept, adalimumab, secukinumab, golimumab, and abatacept), vasodilator therapies for pulmonary hypertension, unapproved treatments for IPF or IPF combination therapy within 4 weeks prior to screening; monoclonal antibodies targeting B cells (including, but not limited to rituximab), within 48 weeks prior to screening. Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of >10 mg/day used for >10 days.
12. **Participation in investigational study:** Participant who received CHF10067 (active arm) or an investigational drug within 3 months or 5 half-lives (whichever is longer) before the randomisation visit (a longer and more appropriate time could be considered by the Investigator based on the elimination half-life and/or long-term effects of the previous investigational drug) or is currently participating in another investigational study.
13. **Hypersensitivity:** Known intolerance and/or hypersensitivity to any of the excipients contained in the formulation or any other substance used in the study.
14. History of **allergic or anaphylactic reaction** to human, humanised, chimeric Igs, or murine monoclonal antibodies.
15. History of ≥Grade 3 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.
16. **Mastocytosis:** Confirmed or suspected diagnosis of mastocytosis.
17. **Abnormal laboratory values:** Clinically relevant abnormal laboratory values at screening suggesting an unknown disease and requiring further clinical investigation or which may impact the safety of the participant or the evaluation of the study results according to the Investigator's judgement. Note: In case of abnormal laboratory values that could indicate a temporary condition, the test can be repeated once before randomisation.
18. **Smoking status:** Current smoker, including and not limited to tobacco, marijuana, and e-cigarettes. Ex-smokers who stopped smoking ≤6 months prior to screening.
19. **Unsuitable veins** for repeated venipuncture.
20. **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. Serum pregnancy test to be performed at screening and urine pregnancy test to be performed prior to randomisation.

Exclusion criteria #2 (Low respiratory tract infection), #11 (Past and current therapies), and #20 (Pregnant or lactating women) must be rechecked at Visit 2 (randomisation visit). Exclusion

criterion #17 (Abnormal laboratory values) may be rechecked at Visit 2 (randomisation visit), if applicable.

4.4 STUDY RESTRICTIONS

During this study, participants are asked to:

- Refrain from consumption of dairy products before blood collection for clinical laboratory tests (e.g., during breakfast).
- Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final PK sample on the same visit.
- Abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

4.5 DISCONTINUATION FROM STUDY

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

- An AE occurs that, in the opinion of the Investigator, makes it unsafe for the participant to continue in the study. In this case, the appropriate measures will be taken.
- The participants miss 3 sequential infusions or more than 1 instance of 2 sequential infusions. If a participant misses more than 2 infusions in a 12week period throughout the study, or 2 sequential infusions, the Sponsor Medical Monitor and ICON Medical Monitor should be notified, and allowance to continue the study will be decided on a case-by-case basis.
- The participant is lost to follow-up (Section 4.6).
- The participant withdraws consent.
- The participant's safety is affected by a violation of inclusion or exclusion criteria or by the use of non-permitted concomitant medication.
- The participant, in the opinion of the Investigator, is unwilling or unable to adhere to the study requirements (e.g., non-compliance).
- The Sponsor, the regulatory authorities, or the Ethics Committee(s) (ECs) terminates the entire study, or terminates the study for this study site or for this particular participant.
- The study treatment assigned to the participant is unblinded by the Investigator.
- Occurrence of pregnancy.

It is understood by all concerned that an excessive rate of discontinuations can render a study uninterpretable; therefore, every effort should be made to avoid discontinuation from the study. The Sponsor Medical Monitor and ICON Medical Monitor should be contacted prior to or as soon as possible after a discontinuation occurs.

Discontinued participants should return to the clinic as soon as possible to perform the assessments planned, depending on the time point of withdrawal:

- A participant who discontinues the study should attend Visit 10/ETD visit and Visit 11.
- The Investigator is responsible for ensuring that participant who discontinue the study are subsequently prescribed the optimal treatment. Post-treatment medications are to be recorded in the electronic case report form (eCRF).

If a participant withdraws consent and cannot or is unwilling to attend any further visit(s) (e.g., ETD visit), further visits will not be carried out and no data can be collected after withdrawal.

In case of discontinuation from the study, the Investigator must fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal and must update the participant's status in the interactive response technology (IRT) system.

The assigned participant number of an individual who is withdrawn or drops out of the study is not to be reassigned to another participant.

4.6 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator (or designee) must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's printed or eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.7 SCREEN FAILURES

Screen failures are defined as potential participants who sign the informed consent form (ICF) but who do not meet 1 or more criteria required for participation and are subsequently not treated with the study treatment.

Rescreened participants should sign a new ICF, be assigned a new participant number. The rescreening procedure can be done only once.

5. CONCOMITANT MEDICATIONS

5.1 PERMITTED CONCOMITANT MEDICATIONS

- Background treatment with locally approved IPF monotherapy is permitted in the study, as long as the dose has been stable for at least 8 weeks prior to screening.
- The participants who enter the study on locally approved IPF monotherapy are expected to stay on stable IPF standard-of-care treatment for the duration of the study.
- In case of acute exacerbation (defined as acute worsening or development of dyspnoea typically <1 month duration; computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern and deterioration not fully explained by cardiac failure or fluid overload [15]), any treatments could be freely initiated or increased as deemed appropriate by the Investigator and according to local guidelines to preserve the well-being of study participants.

- Any approved vaccine during the study (1 week should elapse from vaccination and the subsequent study treatment administration) if it does not interfere with the study evaluations. Vaccine type, date, dosage, administration site, and vaccination-related AEs should be reported.
- Inhaled corticosteroids (ICS) and bronchodilators are only allowed if the dose/regimen has been stable for at least 8 weeks prior to screening and if wash-out periods are respected prior to the pulmonary function test (spirometry), DLCO, nasosorption, and exhaled breath condensate testing as follows:
  - ICS: 12 hours
  - Bronchodilators:
    - Short-acting beta-agonist (e.g., albuterol, salbutamol): 6 hours
    - Short-acting muscarinic agonist (e.g., ipratropium bromide): 12 hours
    - Long-acting beta-agonist (e.g., salmeterol, formoterol): 24 hours
    - Ultra-long-acting beta-agonist (e.g., indacaterol, vilanterol, olodaterol): 36 hours
    - Long-acting muscarinic agonist: 48 hours
- Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of ≤10 mg/day. Intermittent use for non-IPF conditions (e.g., allergies) is allowed as needed during the study, with allowed >10 mg/day use for a maximum of 10 days.
- Intra-articular steroid injections to treat acute issues are permitted; however, regular use is prohibited due to systemic effects of intra-articular injections.
- N-Acetylcysteine, up to 1800 mg daily.

5.2 NON-PERMITTED CONCOMITANT MEDICATIONS

The following concomitant medications are not permitted during the study:

1. Use of locally approved IPF therapy in combination. In the case of nerandomilast use, for example, this means that participants receiving nerandomilast in combination with any other locally approved IPF therapy (e.g., pirfenidone) will be excluded from the study. If, during the study, treatment with locally approved IPF therapies in combination becomes necessary according to the treating physician, the participant will be discontinued from the study. Use of a single, locally approved IPF monotherapy is permitted.
2. Systemic (IV, intramuscular, or oral) corticosteroids prednisone-equivalent dose of >10 mg/day used for >10 days.
3. Cytotoxic and immunosuppressant/modulator drugs, e.g., azathioprine, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, tetrathiomolybdate, hydroxychloroquine, interferon gamma-1b, tyrosine kinase inhibitors, monoclonal antibodies with immune-suppressant activity, which require special screening for latent tuberculosis infection for prescription (including, but not limited to, infliximab, etanercept, adalimumab, secukinumab, golimumab, and abatacept); monoclonal antibodies targeting B cells (including, but not limited to, rituximab).
4. Daily use of sildenafil, vardenafil, tadalafil, and avanafil. Intermittent use of these oral drugs for the treatment of erectile dysfunction is allowed as needed during the study.
5. Use of any investigational drug and/or medical device.

6. TREATMENTS

CHF10067 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. The commercially sourced 0.9% sodium chloride aqueous solution for IV infusion as well as suitable ancillaries for preparation, administration, and blinding will also be supplied by the Sponsor as described within the Pharmacy Manual and the Infusion Manual. Refer to Table 2 for more details.

To maintain the study blind at the site, personnel are required to be strictly classified into 1 of the 2 categories, blinded or unblinded personnel. The handling, storage of the kits and related activities together with preparation of the infusion bags will be performed by the unblinded pharmacist (or designee), while the study treatment administration will be performed by a blinded Investigator or nurse. A site-specific Blinding Plan will be developed for each participating site to outline the details of how the blind will be maintained during the course of the study.

Table 2: Treatment Plan

IMPs	Description	Authorisation status and indication if it is used in the study in accordance with the Marketing Authorisation		Sourcing
		Authorised	Not authorised	
CHF10067 (Test product)	100 mg/mL CHF10067 sterile, preservative-free solution for IV infusion	No	Yes	Centrally provided to the site by the Sponsor
0.9% sodium chloride aqueous solution (Placebo)	0.9% sodium chloride aqueous solution for IV infusion	Yes	No	Centrally provided to the site by the Sponsor.

IMP=investigational medicinal product; IV=intravenous(ly)

- For treatment arm A (CHF10067 1000 mg [Test Dose 1]) and treatment arm B (CHF10067 3000 mg [Test Dose 2]), 0.9% sodium chloride aqueous solution will be used to dilute CHF10067.
- For treatment arm C (placebo), the infusion bag will only contain 0.9% sodium chloride aqueous solution. For more details, please refer to the Pharmacy Manual and the Infusion Manual.

6.1 TREATMENTS BEING INVESTIGATED

6.1.1 APPEARANCE AND CONTENT

The appearance and content of the treatments is described in Table 3.

Table 3: Appearance and Content of CHF10067 (Test Product)

	CHF10067 (1000 mg)	CHF10067 (3000 mg)
Active ingredient	100 mg/mL CHF10067 sterile, preservative-free solution for IV infusion	
Excipients	[redacted]	
Presentation	Clear to opalescent solution supplied in 6 mL glass vial containing not less than 4.3 mL extractable volume	

IV=intravenous(ly)

6.1.2 DOSAGE AND ADMINISTRATION

6.1.2.1 Rationale for Dose Selection

The starting point for dose selection was based on PK/PD modelling, which allowed us to predict the relationship between drug exposure and the expected PD effect. For the PD input, TG2 Target Occupancy % (TO%) data obtained from skin biopsies in healthy volunteers (Study UP0029) were used, while PK data from both healthy participants and participants with IPF were used. From this modelling, a concentration threshold of approximately [redacted] was determined, corresponding to the EC_{90} (i.e., the concentration at which 90% of the maximum effect is expected), and would be required to achieve a therapeutic effect.

Based on these simulations, a dose of 3000 mg every 3 weeks was identified as the most likely therapeutic dose. At this dose, it is anticipated that approximately 80% of participants will maintain C_{trough} concentrations (minimum concentration at the steady state) above the minimum threshold throughout the Treatment Period, ensuring the desired level of TO%.

Additionally, a secondary dose of 1000 mg every 3 weeks was selected. At this dose, C_{trough} concentrations are expected to hover around the EC_{50}, which represents the concentration at which 50% of the maximum effect is achieved. Although this dose is expected to show a significant difference from the 3000 mg dose in terms of both PK and effect, it should still produce a minimal PD response.

Both doses have been previously tested as single administrations both in healthy volunteers and in participants with IPF and were confirmed to be safe and well tolerated.

6.1.2.2 Dosage

The dosage during the randomised Treatment Period:

- Treatment arm A: 1000 mg CHF10067 (Test Dose 1) every 3 weeks IV administered
- Treatment arm B: 3000 mg CHF10067 (Test Dose 2) every 3 weeks IV administered
- Treatment arm C: Placebo (0.9% sodium chloride aqueous solution) every 3 weeks IV administered

6.1.2.3 ADMINISTRATION

For study restriction refer to Section 4.4.

Study treatment administration must be completed within 10 hours from the start of the preparation of the study treatment.

A dose of 1000 or 3000 mg CHF10067 or placebo will be administered as an IV infusion.

The study treatment administration will take place at the clinical site on Visit 2 and every 3 weeks thereafter during the Treatment Period, under the supervision of the Investigator (or designee). Administration will be documented in the source documents and reported in the eCRF.

Infusion will be performed at a maximum rate of 120 mL/h reached with a scheme detailed in the Pharmacy Manual and the Infusion Manual. The infusion rate may be slowed or temporarily stopped based on participant status and Investigator evaluation.

A physician (or designee) must be immediately available during the study treatment administration and observation period for each participant.

A postinfusion observation of minimum of 3 hours for the first 3 infusions is required. Blood pressure, respiration rate, and heart rate should be recorded at the end of the infusion (±10 minutes), 30 minutes (±10 minutes) and 1 hour (±10 minutes) after the end of infusion, and every hour thereafter (±30 minutes).

The postinfusion observation can be reduced to a minimum of 1 hour from the fourth infusion based on the Investigator's evaluation (e.g., no previous immediate hypersensitivity reactions). Blood pressure, respiration rate, and heart rate should be recorded at the end of the infusion (±10 minutes), 30 minutes (±10 minutes) after the end of infusion, and right before discharge.

Overnight stays at the facility or alternative accommodation may occur for logistical reasons or based on site/participant preference. Such stays are not considered formal hospital admissions and therefore do not qualify as SAEs. However, if an overnight stay is required due to immediate infusion-related reactions, hypersensitivity reactions, any other clinical reason, it will be classified as an SAE. Refer to Section 7.2.4.7 for details.

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

6.2 PACKAGING

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

CHF10067 will be supplied as a sterile, preservative-free solution for infusion in a 6 mL glass vial containing not less than 4.3 mL extractable volume. 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 with all the ancillary materials required for the preparation, administration, and blinding of the study treatment. The list of these components will be detailed in the Pharmacy Manual. Only in exceptional circumstances, the sites could use their ancillary materials after Sponsor's authorisation.

The 0.9% sodium chloride aqueous solution will be supplied from an approved commercial source.

The composition of the CHF10067 treatment kits is detailed in Table 4.

Table 4: CHF10067 Treatment Kits

	Primary packaging	Secondary packaging
CHF10067 treatment kit	6 mL labelled glass vial containing not less than 4.3 mL extractable volume	Labelled box containing 4 labelled glass vials
CHF10067 replacement kit	6 mL labelled glass vial containing not less than 4.3 mL extractable volume	Labelled box containing 1 labelled glass vial

Depending on the participant's treatment arm, the following kits will be dispensed:

- Treatment arm A: 1000 mg CHF10067 (Test Dose 1): 1 CHF10067 treatment kit
- Treatment arm B: 3000 mg CHF10067 (Test Dose 2): 2 CHF10067 treatment kits

The CHF10067 replacement kit will only be dispensed if needed; for more details refer to the Pharmacy Manual.

6.3 LABELLING

All labelling will be in the local language, according to local law and regulatory requirements, and will be compliant with Annex VI of EU Regulation 536/2014, 21 Code of Federal Regulations (CFR) 312.6 "Labelling of an Investigational New Drug" for US trials and any other local requirements

The kit number is assigned by the IRT system, which will allow the full traceability of essential details, e.g., site identification, Investigator's name, visit number, and randomisation number. Therefore, these details are omitted from the labels. Furthermore, Investigator's name (main contact), address, and phone number are omitted from labels, since a card with these details will be provided to the participants.

Refer to the Pharmacy Manual for additional information (e.g., tear-off labels).

6.4 TREATMENT ALLOCATION

A balanced block stratified randomisation scheme will be generated by the IRT system provider, using a 21 CFR Part 11 validated system. At Visit 2, the participants will be centrally assigned to 1 of the 3 treatment arms with a 1:1:1 ratio through an IRT system (using the lowest available randomisation number). The randomisation list will be stratified by use of locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening (yes/no).

During the prescreening Visit 0 and once the participant has consented to participate to the study, a unique participant screening number will be assigned to each participant through the IRT system. The participant screening numbers will consist of a 9-digit number:

- The first 6 digits correspond to the site number (first 3 digits for the country number corresponding to the International Organization for Standardization [ISO] country codes and last 3 progressives for the site).
- The last 3 digits correspond to the screening number (allocated in a chronological way in each site).

The IRT system will also be used by the Investigator to screen at Visit 1 and to randomise participants at Visit 2.

6.5 TREATMENT CODE

Study treatment will be packaged and uniquely numbered. The IRT will be used to assign kits to individual participants in order to have an inventory control and participant dosing tracking. The IRT will also maintain quantities, kit numbers, drug types, batch/code numbers, and expiration dates. The IRT will monitor inventory levels and expiration dates at all sites and manage the study treatment resupply.

The randomisation list will be provided to the labelling facility and to the PK/biomarkers/immunogenicity laboratory, as applicable, but will not be available to the participants, Investigators, employees of the site, Sponsor and Contract Research Organisation (CRO; ICON) clinical team 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 designee) involved in IMP (also referred to as "study treatment") preparation, dispensing, accountability, and identified in the appropriate delegation log
- Unblinded monitor(s) who review(s) the IMP-related documentation
- Unblinded Sponsor Clinical Study Manager and Clinical Supplies representative, unblinded ICON Clinical Study Manager.

In case of emergency, where the Investigator considers it essential to know what study treatment the participant was taking, unblinding of the treatment code will be done through IRT and the treatment arm will be disclosed. The IRT will generate a confirmation. The IRT will also promptly notify the Sponsor and the ICON Medical Monitor when emergency unblinding is performed.

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

6.6 TREATMENT COMPLIANCE

For each participant, details of study treatment administration will be recorded in the eCRF.

Any change from the dosing schedule, dose interruptions, and dose discontinuations will be recorded in the eCRF. Treatment compliance will be ensured by reconciliation of site drug accountability logs.

Details on evaluation of exposure and compliance will be provided in the Statistical Analysis Plan (SAP).

Every attempt should be made to complete all the study visits within defined windows (Table 5). If a study treatment administration is delayed (i.e., outside the visit window), the next dose should be administered as soon as possible, so that the dosing interval is close to 3 weeks. No participant should receive more than 1 infusions in any 14-day period. If a participant misses more than 2 infusions in a 12-week period throughout the study, or 2 sequential infusions, the Sponsor Medical Monitor and ICON Medical Monitor should be notified, and allowance to continue the study will be decided on a case-by-case basis. Participants who miss 3 sequential infusions or more than 1 instance of 2 sequential infusions will not be allowed to continue in the study and will be terminated early. See Section 4.5 for details.

6.7 DRUG STORAGE

The unblinded pharmacist (or designee) will be responsible for the safe storage of study treatments. The study treatments are to be stored in a locked, secure storage facility with access limited to those

individuals authorised to dispense them. They are to be maintained within the appropriate ranges of temperature.

All CHF10067 kits will be stored at refrigerated temperatures at 2°C to 8°C. Sodium chloride will be stored at room temperature according to the storage conditions indicated on the commercial label. The Pharmacy Manual will contain additional information for temperature condition before and after the preparation.

In the event that a missing or damaged kit was already allocated for dispensing to a participant, the unblinded pharmacist (or designee) should use the "Kit replacement" transaction to replace the missing/damaged kit with a new kit and contact ICON unblinded monitor to report the issue.

Damaged kits should be stored separately from usable kits and should be marked accordingly to prevent dispensing.

For the study treatments, the maximum cumulated hold time from the start of the preparation to the end of infusion is 10 hours.

In case the study treatment is exposed to temperatures outside the required temperature range, the Sponsor (or designee) shall issue the assessment of its usability, which shall either release the quarantined study treatment or declare its permanent non-usability.

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

6.8 TREATMENT ACCOUNTABILITY AT SITE

The Investigator (or designee) is responsible for the management of all the study treatments to be used for the study.

An inventory will be maintained by the unblinded pharmacist (or designee) 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 unblinded pharmacist (or designee) shall conduct and document a final inventory of the drug supply (used and unused). An explanation will be given for any discrepancies.

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

6.9 PROVISION OF ADDITIONAL CARE

At completion of a participant's study participation, it is the Investigator's responsibility to prescribe another appropriate treatment, or to restore the initial therapy, or to refer the participant to his/her general practitioner.

7. STUDY PLAN

7.1 STUDY SCHEDULE

The schedule of assessments is provided in Table 5.

Table 5: Schedule of Assessments

	Pre-screening [1]	Screening	Treatment Period								Follow-up [2]	
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ ETD**	**V11**
Time (weeks)	**W-6**	**W-5**	**W0**	**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W30**
Window (days)	**7 d**	**3 to 35 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**
Informed consent form	X											
Demographic data	X											
Medical history/ Previous medications		X	X									
Concomitant medications/ procedures		X	X	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria [3]		X	X									
Adverse event assessment [4]		X	X	X	X	X	X	X	X	X	X	X
Physical examination		X	X								X	X
Focused physical examination				X	X	X	X	X	X	X		
Height (screening only), weight, BMI		X	X		X		X		X		X	X
Vital signs pre/postdose		X	X	X	X	X	X	X	X	X	X	X
HRCT [5]		X									X	
12-lead ECG (predose)		X	X	X	X	X	X	X	X	X	X	X
PFT (spirometry)		X	X		X		X		X		X	X
DLCO		X										
SpO_2		X	X	X	X	X	X	X	X	X	X	X
L-PF questionnaire			X				X				X	X
Haematology and blood chemistry		X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X
Cotinine urine test		X										
Tuberculosis test		X										
Markers of immediate hypersensitivity reaction [6]			X	X	X	X	X	X	X	X		
ADA and nAb (in case of positive ADA) [7]			X	X	X	X	X	X	X	X	X	X
Pregnancy test [8]		X	X	X	X	X	X	X	X	X	X	X
TG2 levels			X				X				X	
Pharmacokinetics [9]			X	X	X	X	X	X	X	X		
Exploratory biomarkers - serum and plasma			X		X		X		X		X	
Optional – blood, serum, plasma for long-term storage [10]			X		X		X		X		X	
Optional –			X				X				X	

	Pre-screening [1]	Screening	Treatment Period								Follow-up [2]	
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ ETD**	**V11**
Time (weeks)	**W-6**	**W-5**	**W0**	**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W30**
Window (days)	**7 d**	**3 to 35 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**
transcriptomics RNA [11]												
Optional - genomics DNA [11]			X									
Optional – nasosorption [10]			X								X	
Optional - exhaled breath condensate [10]			X				X				X	
IRT [12]	X	X	X	X	X	X	X	X	X	X		
Study treatment administration [13]			X	X	X	X	X	X	X	X		

ADA=antidrug antibody; AE=adverse event; BMI=body mass index; d=Day; DLCO=diffusing capacity of the lung for carbon monoxide; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eCRF=electronic case report form; ETD=early treatment discontinuation; HRCT=high-resolution computed tomography; ICF=informed consent form; IPF=idiopathic pulmonary fibrosis; IRT=interactive response technology; L-PF=Living with Pulmonary Fibrosis; nAb=neutralising antibody; PFT=pulmonary function test; RNA=ribonucleic acid; SAE=serious adverse event; SpO_2=peripheral capillary oxygen saturation; TG2=transglutaminase 2; V=visit; W=week; WOCBP=women of childbearing potential

Footnotes for Evaluation Schedule:

1. If feasible, the V0 may be combined with V1.
2. After last study treatment administration, V10 will be conducted to assess the primary, secondary, and exploratory outcomes. Participants will attend the last visit (V11), 9 weeks after the last study treatment administration.
3. If any of the inclusion criteria #7 (Lung function), #8 (DLCO), or #9 (Oxygen saturation) are not met, they may be reassessed once prior to, or at, Visit 2 (randomisation visit). Specific inclusion and exclusion criteria will also be rechecked at randomisation (V2) before the first dosing for confirmatory purposes: Inclusion criteria #3 (BMI), #4 (Body weight), #6 (Stable IPF therapy), and #11 (Female participants); exclusion criteria #2 (Low respiratory tract infection), #11 (Past and current therapies), and #20 (Pregnant or lactating women). Exclusion criterion #17 (Abnormal laboratory values) may be rechecked, if applicable.
4. At randomisation (V2): The occurrence of any AE since ICF signature will be recorded, including verification of exclusion criterion #2 (Low respiratory tract infection). In case of any clinically significant abnormality revealed during the screening procedures, it will be recorded in the participants' medical history in the eCRF, unless its onset date is after the ICF signature date and it is not due to a pre-existing condition. In this case it will be recorded as an AE in the eCRF. At subsequent visit: The occurrence of any new AE since the previous visit will be recorded; the status of ongoing AEs will be checked and updated in the eCRF if applicable.
5. Participants will undergo HRCT scan during the Screening Period only if the most recent HRCT (≤6 months) is not available for any reasons or judged of low quality by central reading. The HRCT scans will be reviewed by central reading for pattern confirmation according to the procedure described in Section 7.2.3. Only for participants who had an HRCT scan performed at screening, or ≤3 months prior to screening, the Investigator may request for an additional HRCT scan at Week 24.
6. Blood sample will be collected predose for all participants for markers of immediate hypersensitivity reaction. In case of immediate hypersensitivity reaction blood sample will be collected 1 hour [±30 minutes] and 2 hours [±30 minutes] after the onset of the event; refer to Section 7.2.4.7 for more details.
7. ADA will be measured predose for all participants at all visits; refer to Section 7.2.4.6 for more details.
8. Only for WOCBP: Pregnancy test (serum β-human chorionic gonadotropin) will be performed at screening (V1) and urine pregnancy tests will be performed prior to randomisation (V2) and at subsequent visits; refer to Section 7.2.4.4.
9. Pharmacokinetic samples will be collected at predose at all applicable visits and at the end of the infusion at V2, V6, and V9.
10. Optional consent is required.
11. Optional and additional ICF required for genetic data.
12. The IRT system will be used by the Investigator at V0 to allocate a unique participant number, at V1 to screen participants, at V2 to randomise participants, and from V0 to V9 to record participant visits, screening failures, treatment dispensation, and discontinuations from the study treatment and study, if applicable. The IRT system will generate an electronic confirmation after every IRT system transaction is performed.
13. A physician (or designee) must be immediately available during the study treatment administration and observation period for each participant. A postinfusion observation of minimum of 3 hours for the first 3 infusions is required. Blood pressure, respiration rate, and heart rate should be recorded at the end of the infusion (±10 minutes), 30 minutes (±10 minutes) and 1 hour (±10 minutes) after the end of infusion, and every hour thereafter (±30 minutes). The postinfusion observation can be reduced to a minimum of 1 hour from the fourth infusion based on the Investigator's evaluation (e.g., no previous immediate hypersensitivity reactions). Blood pressure, respiration rate, and heart rate should be recorded at the end of the infusion

(±10 minutes), 30 minutes (±10 minutes) after the end of infusion, and right before discharge. Overnight stays at the facility or alternative accommodation may occur for logistical reasons or based on site/participant preference. Such stays are not considered formal hospital admissions and therefore do not qualify as SAEs. However, if an overnight stay is required due to immediate infusion-related reactions, hypersensitivity reactions, any other clinical reason, it will be classified as an SAE. Refer to Section 7.2.4.7 for details.
Last dose will be given at V9.

A total of 12 clinic visits (Visit 0 to Visit 11) will be performed.

7.1.1 VISIT 0 (PRESCREENING VISIT)

If feasible, the prescreening visit may be combined with the screening visit (Visit 1).

A prescreening visit will be carried out to fully explain the study to the potential participant. The Investigator (or designee) must provide the participant with ample time and opportunity to inquire about details of the study and to decide whether to participate or not.

If the participant agrees to participate, signed and dated informed consent must be obtained before any study-related procedures are performed. See Section 15.

The following procedures will take place:

- Demographic data including sex at birth, race, date of birth (full date or only year depending on country privacy restrictions), and childbearing potential status (for female only) will be recorded.
- As soon as the informed consent is signed, the Investigator (or designee) will connect to IRT to allocate a unique participant number. This number will be sequentially assigned.

An appointment for Visit 1 will be scheduled. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible.

Before discharge:

- A participant card with, at least, the site's contact details will be handed out to the participants.
- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4.
  - To respect the wash-out period of non-permitted medications prior to Visit 1 as mentioned in Section 5.1.
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit.

7.1.2 VISIT 1 (SCREENING)

A screening visit will be carried out to identify eligible consenting participants for the study.

In case the wash-out of medications has not been respected (see Section 5.1), the visit will be rescheduled within the Screening Period. Only 1 reschedule is allowed.

The following procedures will take place:

- Medical history/previous medications: Recording of participant's health history and previous medications, including verification of inclusion criterion #6 (Stable IPF therapy).
- Concomitant medications/procedures: Recording of participant's concomitant medications and procedures, including verification of inclusion criterion #6 (Stable IPF therapy) and exclusion criterion #11 (Past and current therapies). Intake of non-permitted medication constitutes a non--eligibility criterion for enrolment in the study.

- Adverse event (AE) assessment: The occurrence of any AE since ICF signature will be recorded, including verification of exclusion criterion #2 (Low respiratory tract infection). In case of any clinically significant abnormality revealed during the screening procedures, it will be recorded in the participants' medical history in the eCRF, unless its onset date is after the ICF signature date and it is not due to a pre-existing condition. In this case it will be recorded as an AE in the eCRF.
- Physical examination: A comprehensive physical examination will be performed according to Section 7.2.9.
- Vital signs: Measurement of systolic (SBP) and diastolic blood pressure (DBP), heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead electrocardiogram (ECG): A triplicate 12-lead ECG will be recorded according to Section 7.2.8.
- Participant selection: Inclusion/Exclusion criteria will be checked, including the assessment of the following:
  - Weight, height, and the calculation of BMI.
  - HRCT: A scan during the Screening Period will be performed only if the most recent HRCT (≤6 months) is not available for any reasons or judged of low quality by central reading. The HRCT scans will be reviewed by central reading for pattern confirmation; refer to Section 7.2.3.
  - Pulmonary function test (spirometry) will be assessed according to Section 7.2.1.
  - Diffusing capacity: DLCO will be assessed according to Section 7.2.2.
- Blood samples for standard haematology and blood chemistry will be collected and analysed according to Section 7.2.4.1.
- Urine will be collected for standard urinalysis according to Section 7.2.4.1 and a cotinine test according to Section 7.2.4.2.
- Pregnancy test: A serum pregnancy test will be assessed only for WOCBP according to Section 7.2.4.4.
- IRT system:
  - The Investigator (or designee) will connect to IRT to record the Visit 1 date.
  - If the participant is not eligible, the Investigator will record the participant as a screening failure.

This visit will be followed by a Screening Period of 3 to 35 days (duration based on participant's availability, and on time for getting the laboratory results, the overreading feedback for spirometry and HRCT assessments).

If any of the inclusion criteria #7 (Lung function), #8 (DLCO), or #9 (Oxygen saturation) are not met, they may be reassessed once prior to, or at, Visit 2 (randomisation visit).

Before discharge:

An appointment for Visit 2 will be scheduled after the period allowed for screening is fully covered and once the participant is deemed eligible for Visit 2. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible;

- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4
  - To respect the wash-out period of non-permitted medications prior to Visit 2 as mentioned in Section 5.1
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit

7.1.3 VISIT 2 (RANDOMISATION)

In case the wash-out of medications has not been respected (see Section 5.1), the visit will be rescheduled within 2 days. Only 1 reschedule is allowed.

The following procedures, including the verification of participants' eligibility, will take place:

- Medical history/previous medications: Recording of participant's health history and previous medications, including verification of inclusion criterion #6 (Stable IPF therapy).
- Concomitant medications/procedures: Recording of participant's concomitant medications and procedures, including verification of inclusion criterion #6 (Stable IPF therapy) and exclusion criterion #11 (Past and current therapies). Intake of non-permitted medication constitutes a non-eligibility criterion for enrolment in the study.
- AE assessment: The occurrence of any AE since ICF signature will be recorded, including verification of exclusion criterion #2 (Low respiratory tract infection). In case of any clinically significant abnormality revealed during the screening procedures, it will be recorded in the participants' medical history in the eCRF, unless its onset date is after the ICF signature date and it is not due to a pre-existing condition. In this case it will be recorded as an AE in the eCRF.
- The Living with Pulmonary Fibrosis (L-PF) questionnaire will be completed according to Section 7.2.10.
- Physical examination will be performed according to Section 7.2.9.
- Weight and the calculation of BMI: Including verification of inclusion criteria #3 (BMI) and #4 (Body weight).
- Vital signs predose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead ECG predose: A single 12-lead ECG will be recorded according to Section 7.2.8.
- Pulmonary function test (spirometry) will be assessed via according to Section 7.2.1.
- Blood samples will be collected according to Section 7.2.4, before study treatment administration, if applicable, for the assessments of the following:
  - Standard haematology and blood chemistry
  - Markers of immediate hypersensitivity reaction (predose for all participants). In case of immediate hypersensitivity reaction: 1 hour [±30 minutes] and 2 hours [±30 minutes] after the onset of the event
  - Immunogenicity
  - PK samples
  - Exploratory biomarkers, including TG2

- Genomics and transcriptomics (optional)
- Long-term storage (optional)

- Urine will be collected for standard urinalysis according to Section 7.2.4.1.
- Pregnancy test: A urine pregnancy test will be performed only for WOCBP according to Section 7.2.4.4, including verification of inclusion criterion #11 (Female participants).
- Nasosorption (optional): Mucosal samples will be collected according to Section 7.2.5.
- Exhaled breath condensate (optional): Breath condensate will be collected according to Section 7.2.6.
- IRT system:
  - The Investigator (or designee) will connect to IRT to record the Visit 2 date.
  - Eligible participants will be randomised, the kit number will be obtained, and treatment dispensation will be recorded.
  - If the participant is not eligible, the Investigator will record the participant as a screening failure.
- Study treatment administration: Participants will be administered a single IV dose of CHF10067 or placebo. For details on study treatment administration and the postdose observation period refer to Section 6.1.2.3.
- Blood samples will be collected after study treatment administration for the assessments of PK samples. Please refer to Section 7.2.4.5.
- Vital signs postdose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 6.1.2.3 and Section 7.2.7.

Before discharge:

An appointment for Visit 3 will be scheduled. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible;

- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit

7.1.4 VISIT 3, VISIT 5, VISIT 7, AND VISIT 9

In case the wash-out of medications has not been respected (see Section 5.1), the visits will be rescheduled within 2 days. Only 1 reschedule is allowed.

The following procedures will take place:

- Concomitant medications/procedures: The Investigator (or designee) will verify the use of non-permitted medication since the previous visit (see Section 5.1). Any change of concomitant medications/procedures will be recorded.
- AE assessment: The occurrence of any new AE since the previous visit will be recorded; the status of ongoing AEs will be checked and updated in the eCRF if applicable.

- Focused physical examination: A focused physical examination will be performed according to Section 7.2.9.
- Vital signs predose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead ECG predose: A single 12-lead ECG will be recorded according to Section 7.2.8.
- Blood samples will be collected according to Section 7.2.4, before study treatment administration, if applicable, for the assessments of the following:
  - Standard haematology and blood chemistry.
  - Markers of immediate hypersensitivity reaction (predose for all participants). In case of immediate hypersensitivity reaction: 1 hour [±30 minutes] and 2 hours [±30 minutes] after the onset of the event.
  - Immunogenicity.
  - PK samples.
- Urine will be collected for standard urinalysis according to Section 7.2.4.1.
- Pregnancy test: A urine pregnancy test will be assessed only for WOCBP according to Section 7.2.4.4.
- IRT system: The Investigator will access the IRT system to record the visit date, to obtain the kit number, and to record treatment dispensation.
- Study treatment administration: Participants will be administered a single IV dose of CHF10067 or placebo. For details on study treatment administration and the postdose observation period refer to Section 6.1.2.3.
- For Visit 9 only: Blood samples will be collected according to Section 7.2.4, after study treatment administration for the assessments of PK samples. Please refer to Section 7.2.4.5.
- Vital signs postdose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 6.1.2.3 and Section 7.2.7.

Before discharge:

An appointment for the next visit will be scheduled. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible;

- For Visit 9 only: An appointment for Visit 10 will be scheduled
- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4
  - For Visit 5 and Visit 9 only: To respect the wash-out period of non-permitted medications prior to Visit 6 and Visit 10 as mentioned in Section 5.1
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit

7.1.5 VISIT 4, VISIT 6, AND VISIT 8

In case the wash-out of medications has not been respected (see Section 5.1), the visit will be rescheduled within 2 days. Only 1 reschedule is allowed.

The following procedures will take place:

- Concomitant medications/procedures: The Investigator (or designee) will verify the use of non-permitted medication since the previous visit (see Section 5.1). Any change of concomitant medications/procedures will be recorded.
- AE assessment: The occurrence of any new AE since the previous visit will be recorded; the status of ongoing AEs will be checked and updated in the eCRF if applicable.
- For Visit 6 only: The L-PF questionnaire will be completed according to Section 7.2.10.
- Focused physical examination including the measurement of weight: A focused physical examination will be performed according to Section 7.2.9.
- Vital signs predose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead ECG predose: A single 12-lead ECG will be recorded according to Section 7.2.8.
- Pulmonary function test (spirometry) will be assessed according to Section 7.2.1.
- Blood samples will be collected according to Section 7.2.4, before study treatment administration, if applicable, for the assessments of the following:
  - Standard haematology and blood chemistry
  - Markers of immediate hypersensitivity reaction (predose for all participants). In case of immediate hypersensitivity reaction: 1 hour [±30 minutes] and 2 hours [±30 minutes] after the onset of the event
  - Immunogenicity
  - PK samples
  - Exploratory biomarkers, including TG2 (Visit 6 only)
  - Transcriptomics at Visit 6 only (optional)
  - Long-term storage (optional)
- Urine will be collected for standard urinalysis according to Section 7.2.4.1.
- Pregnancy test: A urine pregnancy test will be assessed only for WOCBP according to Section 7.2.4.4.
- For Visit 6 only: Exhaled breath condensate (optional): Breath condensate will be collected according to Section 7.2.6.
- IRT system: The Investigator (or designee) will access the IRT system to record the visit date, to obtain the kit number, and to record treatment dispensation.
- Study treatment administration: Participants will be administered a single IV dose of CHF10067 or placebo. For details on study treatment administration and the postdose observation period refer to Section 6.1.2.3.
- For Visit 6 only: Blood samples will be collected after study treatment administration for the assessments of PK samples. Please refer to Section 7.2.4.5.
- Vital signs postdose: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 6.1.2.3 and Section 7.2.7.

Before discharge:

An appointment for the next visit will be scheduled. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible;

- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit

7.1.6 FOLLOW-UP VISIT 10 OR EARLY TERMINATION VISIT

In case the wash-out of medications has not been respected (see Section 5.1), the visit will be rescheduled within 2 days. Only 1 reschedule is allowed.

The following procedures will take place:

- Concomitant medications/procedures: The Investigator (or designee) will verify the use of non-permitted medication since the previous visit (see Section 5.1). Any change of concomitant medications/procedures will be recorded.
- AE assessment: The occurrence of any new AE since the previous visit will be recorded; the status of ongoing AEs will be checked and updated in the eCRF if applicable.
- The L-PF questionnaire will be completed according to Section 7.2.10.
- Physical examination including the measurement of weight: A comprehensive physical examination will be performed according to Section 7.2.9.
- Vital signs: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead ECG: A single 12-lead ECG will be recorded according to Section 7.2.8.
- Pulmonary function test (spirometry) will be assessed via according to Section 7.2.1.
- Blood samples will be collected according to Section 7.2.4 for the assessments of the following:
  - Standard haematology and blood chemistry
  - Immunogenicity
  - Exploratory biomarkers, including TG2
  - Transcriptomics (optional)
  - Long-term storage (optional)
- Urine will be collected for standard urinalysis according to Section 7.2.4.1.
- Pregnancy test: A urine pregnancy test will be assessed only for WOCBP according to Section 7.2.4.4.
- Nasosorption (optional): Mucosal samples will be collected according to Section 7.2.5.
- Exhaled breath condensate (optional): Breath condensate will be collected according to Section 7.2.6.
- HRCT scan if requested by the Investigator will be performed according to Section 7.2.3.

Before discharge:

An appointment for the next visit will be scheduled. It is recommended to schedule the visit always at the same time of the day throughout the study, if possible;

- Participants will be instructed for the next visit:
  - To adhere to the study restrictions as outlined in Section 4.4
  - To bring the usual therapy and all other concomitant medications they are taking to the next visit

7.1.7 FOLLOW-UP VISIT 11

In case the wash-out of medications has not been respected (see Section 5.1), the visit will be rescheduled within 2 days. Only 1 reschedule is allowed.

The following procedures will take place:

- Concomitant medications/procedures: The Investigator (or designee) will verify the use of non-permitted medication since the previous visit (see Section 5.1). Any change of concomitant medications/procedures will be recorded.
- AE assessment: The occurrence of any new AE since the previous visit will be recorded; the status of ongoing AEs will be checked and updated in the eCRF if applicable.
- The L-PF questionnaire will be completed according to Section 7.2.10.
- Physical examination including the measurement of weight: A comprehensive physical examination will be performed according to Section 7.2.9.
- Vital signs: Measurement of SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature according to Section 7.2.7.
- 12-lead ECG: A single 12-lead ECG will be recorded according to Section 7.2.8.
- Pulmonary function test (spirometry) will be assessed via according to Section 7.2.1.
- Blood samples will be collected according to Section 7.2.5 after an overnight fasting for the assessments of the following:
  - Standard haematology and blood chemistry
  - Immunogenicity
- Urine will be collected for standard urinalysis according to Section 7.2.4.1.
- Pregnancy test: A urine pregnancy test will be assessed only for WOCBP according to Section 7.2.4.4.

7.2 STUDY ASSESSMENTS AND PROCEDURES

Study assessments will be performed according to the schedule of assessments (Table 5).

It is recommended to perform the following assessment in this specific order:

- Written informed consent, inclusion/exclusion criteria, demographics, medical history/previous medications, concomitant medications/procedures, and AE/SAE assessment (refer to Section 10.8)
- L-PF questionnaire

- Vital signs
- 12-lead ECG
- DLCO
- SpO_2
- Pulmonary function test (spirometry)
- Blood sampling
- Pregnancy test
- Nasosorption
- Exhaled breath condensate
- Physical examination and body weight and height
- HRCT
- Study treatment administration (refer to Section 6.1.2)

7.2.1 PULMONARY FUNCTION TEST (SPIROMETRY)

Spirometry will be assessed centrally. The specific procedures for centralised spirometry will be provided to the Investigator by the vendor. The Investigator will confirm that the participants adhered to assessment-related restrictions as specified in Section 5.1. The same brand and model of spirometer will be provided by the vendor for all measurements and adjusted for the ATS/ERS standards [16]. Lung function measurements will be done with participants sitting with the nose clipped after resting for ≥10 minutes. The values reported by the spirometer are corrected for BTPS (body temperature and pressure, saturated) conditions without any additional input from the Investigator (or delegate).

The following parameters (but not limited to) will be recorded: FEV1, FVC, ppFEV1%, ppFVC %, and FEV1/FVC ratio.

Predicted values of FEV1 will be calculated according to formulas reported by Quanjer et al. [17].

For details refer to the Spirometry Manual.

For inclusion criterion #7 (Lung function), if the criterion is not met at screening, or the quality per ATS guidelines (grade A or grade B) are not met, the participant may repeat the test once during the Screening Period.

7.2.2 DIFFUSING CAPACITY (DLCO)

DLCO will be assessed locally, per local practice, using the device available at each site. The devices used should be in accordance with current requirements issued by ERS/ATS in 2017 [18]. The test will be performed with participants in a sitting position and nose clipped. Participants should avoid exercise on the day of the test.

The following parameters (but not limited to) will be reported: DLCO (unadjusted), DLCO % predicted, DLCO corrected for haemoglobin, DLCO corrected for haemoglobin % predicted, the rate of alveolar capillary blood carbon monoxide uptake, and alveolar volume.

The reported DLCO will be corrected for the current haemoglobin level, using reference equations.

For inclusion criterion #8 (DLCO), if the criterion is not met at screening, the participant may repeat the test once during the Screening Period.

7.2.3 HIGH-RESOLUTION COMPUTED TOMOGRAPHY

HRCT will be assessed centrally including the ones performed prior to screening. The specific procedures for centralised reading will be provided to the Investigator by the vendor. The Investigator will confirm that participants adhered to assessment-related restrictions as specified in Section 5.1.

Participants that had an HRCT scan performed at screening, or ≤3 months prior to screening may undergo additional HRCT scans according to the schedule of assessments if requested by the Investigator.

A radiologist of the vendor will assess any qualitative changes in pulmonary fibrosis patterns on HRCT imaging from participants. The qualitative assessment will be categorised as improved, stable, or worsened in terms of overall fibrotic pattern, including features, e.g., honeycombing, reticulation, and ground-glass opacities.

Individual patient reports will be prepared and included in the Clinical Study Report (CSR). No data will be entered in the eCRF.

For details refer to the HRCT Manual.

7.2.4 LABORATORY TESTS

Blood sampling will be done for haematology and blood chemistry (Section 7.2.4.1), for tuberculosis testing (Section 7.2.4.3), pregnancy testing (Section 7.2.4.4) for PK evaluation (Section 7.2.4.5), for immunogenicity evaluation (Section 7.2.4.6), for biomarkers including TG2 (Section 7.2.4.7), and for possible post-hoc investigations (Section 7.2.4.9). Urine will be collected for urinalysis (Section 7.2.4.1) and cotinine testing (Section 7.2.4.2).

Samples may be stored for a maximum of 20 years (or according to local regulations) following the last participant's final visit for the study at a facility selected by the Sponsor to enable further bioanalytical investigations or research activities.

7.2.4.1 STANDARD HAEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS

The collection will always be done before study treatment administration and after spirometry.

The following parameters will be assessed by a central laboratory:

- *Blood Chemistry*: Creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, sodium, potassium, calcium, and chloride electrolytes (Na, K, Ca, and Cl)
- *Haematology*: Red blood cell count, white blood cell count, and differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils) (% and values), total haemoglobin (Hb), haematocrit (Hct), and platelets count
- *Urinalysis*: pH, glucose, ketones, bilirubin, urobilinogen, blood, leucocytes, nitrites and protein

Blood and urine collection and sample preparation will be performed according to procedures provided by the central laboratory, who will be responsible for transmitting the results to the Investigator.

After Visit 1, in case of non-interpretable data, another blood/urine sampling and laboratory analysis must be performed as soon as possible and prior to the randomisation visit (Visit 2/Week 0). Results must be available for randomisation of the participant.

CS abnormalities in laboratory tests, as judged by the Investigator, will be reported as AEs in the eCRF unless they are due to a pre-existing condition or the changes from the pre-existing values are not CS.

If the participant is discontinued from treatment during a scheduled visit on site, blood samples for standard haematology and blood chemistry will be collected as far as the participants agrees.

7.2.4.2 Cotinine Test

At screening, a urine cotinine test will be performed.

Participants identified as active/current smokers will not be eligible for the study.

Urine sample preparation will be performed according to procedures provided by the central laboratory, who will be responsible for transmitting the results to the Investigator. For details refer to the Laboratory Manual.

7.2.4.3 Tuberculosis Test

At screening, an interferon gamma release assay (IGRA) for latent tuberculosis infection will be performed.

Participants with a positive IGRA or untreated latent tuberculosis infection (LTBI) are not eligible for the study.

Evidence of active or untreated LTBI:

a) Positive IGRA and evidence of symptoms suggesting active tuberculosis.

b) Positive IGRA, or repeated indeterminate IGRAs, no evidence of active tuberculosis and untreated for LTBI, unable to be treated for, or declines treatment for LTBI.

c) Participants newly diagnosed with LTBI on initial screening could be considered for rescreening if they complete a full course of treatment for LTBI in accordance with recommended treatment guidelines prior to screening. In this situation, repeat IGRA test is not required after completion of treatment for LTBI.

d) Participants with an indeterminate IGRA could undergo a repeat test and if still indeterminate may be enrolled only after being treated for LTBI.

QuantiFERON®-TB Gold Plus In-tube test will be used for the tuberculosis infection detection. Blood sample preparation will be performed according to procedures provided by the central laboratory, who will be responsible for transmitting the results to the Investigator. For details refer to the Laboratory Manual.

7.2.4.4 Pregnancy Test

Only for WOCBP, pregnancy tests will be performed.

At screening, a serum β-human chorionic gonadotropin test will be performed and assessed by a central laboratory.

Blood sample preparation will be performed according to procedures provided by the central laboratory, who will be responsible for transmitting the results to the Investigator.

Prior to randomisation (V2) and at subsequent visits, a urine pregnancy test will be performed.

7.2.4.5 Blood Collection for Pharmacokinetic Evaluation

PK blood sample collection will be performed in all participants.

7.2.4.5.1 Sample Collection for Pharmacokinetic Evaluation and Sample Preparation

Blood sample preparation will be performed according to procedures provided by the central laboratory.

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 CSR.

7.2.4.5.2 Determination of CHF10067

Blood samples (1 sample=2 mL) for determination of serum CHF10067 concentrations will be collected at the following timepoints:

- At Visit 2 to Visit 9: At predose: Within 75 minutes before start of infusion
- At Visit 2, Visit 6, and Visit 9: Within end of infusion +15 minutes

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

7.2.4.6 Immunogenicity

A blood sample for immunogenicity assessments (serum non-isotype ADAs) and nAb (in case of ADA-positive result) and another sample for possible IgE evaluation will be collected predose.

The analytical procedures will be described in a separate analytical protocol and will be performed in accordance with the ICH guideline M10 on bioanalytical method validation and study sample analysis. Validation data and details of the analytical procedures will be gathered in an analytical report that will be included in the CSR. The processing, storage, and shipment of samples are detailed in the Laboratory Manual.

Samples will be screened for antibodies binding to CHF10067, and the titre 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. Full isotype characterisation may also be performed.

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

7.2.4.7 Immediate Infusion-Related Reactions and Hypersensitivity Reactions

Participants will be monitored for up to 3 hours postdose for immediate infusion-related reactions and hypersensitivity reactions and will be discharged if no symptoms are reported.

Predose samples will be collected from all participants, postdose samples only from participants with immediate hypersensitivity reactions (1 hour [±30 minutes] and 2 hours [±30 minutes] after the onset of the event, or as soon the clinical situation of the participant allows for this procedure to be

performed) and thus having both pre- and postdose evaluations. The classification of an event as an infusion-related reaction or hypersensitivity reaction will be at the discretion of the Investigator based on the clinical presentation and available information. Management of such events should be performed in accordance with local standard-of-care.

Blood samples will be analysed only in case of infusion-related reactions and immediate hypersensitivity reactions and include following markers:

- Markers of cytokine release syndrome: Tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL6, IL-10
- Mast cell tryptase
- Complement markers (C3a, C5a, CH50, and sC5b-9)
- 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 participant safety and operational activities.

7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions

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

Immediate infusion-related reactions and hypersensitivity reactions [19] 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 infusion-related reactions or hypersensitivity reaction 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, pruritus, 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.

When an anaphylactic reaction is suspected, CHF10067 should be discontinued immediately and appropriate therapy as per standard-of-care including but not limited to epinephrine, diphenhydramine, corticosteroids, oxygen, and volume expansion should be administered.

Clinical criteria to diagnose anaphylaxis are summarised below [20]:

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, pruritus, 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, pruritus, 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 participant'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 participant (minutes to several hours):
    a. SBP of <90 mmHg,
    or
    b. Drop in SBP >30% decrease from that participant's baseline

Participants experiencing severe immediate infusion-related reactions or hypersensitivity reactions or satisfying the diagnostic criteria for anaphylaxis (detailed above) should not be re-exposed to the IMP and should discontinue the study (refer to Section 4.5).

For participants experiencing a Grade 1 or Grade 2, as per Common Terminology Criteria for Adverse Events (CTCAE), immediate infusion-related reaction and hypersensitivity reaction, the subsequent dosing of a participant should be discussed with the Sponsor Medical Monitor (or designee).

Premedication will only be permitted for participants who have previously experienced a non-serious, ≥Grade 2 infusion-related reaction. If the Investigator wishes to use premedication (e.g., antihistamines, systemic steroids, other drugs), this should be discussed with the Sponsor Medical Monitor (or designee).

Reduction of the maximum infusion rate (120 mL/h) is allowed as long as the total infusion duration does not last more than 5 hours, and infusion is completed within 10 hours from the start of the preparation of the study treatment.

7.2.4.8 Exploratory Biomarkers, Including TG2

Blood samples for biomarker assessment will be collected before study treatment administration, if applicable. The levels of Cancer Antigen 19-9 (CA-19-9), Cancer Antigen 125/Mucin 16 (CA-125/MUC16), Chemokine Ligand 18/Pulmonary and Activation-Regulated Chemokine (CCL18/PARC), C-X-C Motif Chemokine Ligand 13/B Lymphocyte Chemoattractant (CXCL13/BLC), Cytokeratin 19 fragment (CYFRA 21-1), soluble Intercellular Adhesion Molecule-1 (sICAM-1), Matrix Metalloproteinase 7 (MMP-7), Krebs von den Lungen-6/Mucin 1 (KL-6/MUC-1), Plasminogen Activator Inhibitor 1 (PAI-1), Surfactant Protein D (SP-D), and Tenascin C (TN-C) will be measured.

Blood samples for TG2 evaluation in plasma will be collected before study treatment administration, if applicable.

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

7.2.4.9 Whole Blood, Serum, and Plasma (for Possible Other Investigations)

Blood samples, including whole blood for genomics (deoxyribonucleic acid [DNA]), transcriptomics (ribonucleic acid [RNA]), and additional whole blood, serum, and plasma samples (including volume for proteomics) will be collected before study treatment administration, if applicable. The processing, storage, and shipment of samples will be detailed in the Laboratory Manual.

The samples will be retained for up to 20 years to be used for possible post-hoc investigations. These tests could include analysis of various biomarkers to characterise groups of participants with different levels of biomarkers or with different responses to the study treatments as well as to evaluate the biological effect of the study treatments.

Only if participants have signed a separate ICF, whole blood will be stored for genetic analyses including genomics (DNA) and transcriptomics (RNA).

Results will not be part of the current statistical analysis and will not be included in the CSR.

7.2.5 NASOSORPTION

Two mucosal samples (1 from each nostril) will be collected before study treatment administration, if applicable. Nasosorption is a non-invasive procedure using a synthetic absorptive matrix swab to absorb mucosal lining fluid from the mucosa within the nose.

For details on the procedure processing, storage, and shipment of samples refer to the Laboratory Manual.

The mucosal samples will be retained for up to 20 years for possible post-hoc investigations. These tests could include analysis of various biomarkers (e.g. proteins and/or metabolites) to characterise groups of participants with different levels of biomarkers or with different responses to the study treatments as well as to evaluate the biological effect of the study treatments. The future research will not include genetic analysis.

Results will not be part of the current statistical analysis and will not be included in the CSR.

7.2.6 EXHALED BREATH CONDENSATE

Condensates of exhaled breath will be collected before study treatment administration, if applicable. The collection of breath is a non-invasive procedure.

For details on the procedure processing, storage, and shipment of samples refer to the Laboratory Manual.

The exhaled breath condensate samples will be retained for up to 20 years for possible post-hoc investigations. These tests could include analysis of various biomarkers (e.g. proteins and/or metabolites) to characterise groups of participants with different levels of biomarkers or with different responses to the study treatments as well as to evaluate the biological effect of the study treatments. The future research will not include genetic analysis.

Results will not be part of the current statistical analysis and will not be included in the CSR.

7.2.7 VITAL SIGNS

Vital signs (SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature) will be evaluated at each postbaseline visit predose and postdose, if applicable.

Blood pressure will be measured in duplicate, after resting for ≥10 minutes in the supine position. The single values of duplicate blood pressure measurements will be reported in eCRF.

Oxygen saturation (SpO_2) will be measured according to the standard processes at the site by pulse oximetry when the maximum oxygen flow is 4 L/min by standard nasal cannula using the device available at each site or the equivalent oxygen delivery via reservoir nasal cannula (≤2 L/min).

For inclusion criterion #9 (Oxygen saturation), if the criterion is not met at screening, the participant may repeat the test once during the Screening Period.

7.2.8 12-LEAD ELECTROCARDIOGRAM

12-lead ECG will be assessed locally using the device available at each site.

At screening, a triplicate ECG will be performed. Thereafter a single ECG will be performed prior to each dosing, unless a QTc measurement from the single reading is >450 msec. In that case a triplicate ECG will be performed and single values will be reported in the eCRF. Postdose ECGs will not be performed unless clinically indicated, based on the Investigator's judgement and/or in the event of hypersensitivity reaction.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The ECG tracing should include the date and time of the assessment and the signature of the person who made the interpretation; the tracing will be archived at the study site.

Before ECG recording, participants should be in a quiet supervised setting with minimal stimulation (e.g., no television, loud music, computer games) and in a resting position for ≥10 minutes before ECG. The ECG must be performed in supine position before blood sampling.

QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

Heart rate, PR, and QRS values will be also evaluated from ECG.

ECGs are considered normal if

- 45≤heart rate ≤110 bpm

- 120 ms ≤PR ≤210 ms
- QRS ≤120 ms
- QTcF<450 ms for male participants and <470 ms for female participants

The Investigator (or designee) will review the ECG tracing and provide interpretation in the eCRF.

Clinically significant abnormalities evaluated by the Investigator at Visit 2 not due to a pre-existing condition or clinically significant changes at subsequent visits, in the medical opinion of the Investigator, will be reported as AEs in the eCRF.

7.2.9 PHYSICAL EXAMINATION AND BODY WEIGHT AND HEIGHT

The full comprehensive physical examination will include the usual assessment of the body systems:

- Cardiac
- Ear and labyrinth
- Endocrine and lymph
- Head and eye
- Mouth, throat, and gastrointestinal
- Musculoskeletal and connective tissue
- Nervous system
- Respiratory, thoracic, and mediastinal
- Skin and SC tissue
- Vascular

Other body system assessments can be collected in case of abnormalities or symptoms of concern are detected.

A focused physical examination will be a symptom-directed physical assessment.

Any newly revealed clinically significant abnormality since the last visit will be recorded as an AE.

Clinically significant findings will be reported and participant study treatments should be discontinued in case of any potential suicidal behaviour.

Body weight must be assessed preferably using the same weight scale for the same participant. Height will be measured at screening only. BMI will be automatically calculated.

7.2.10 LIVING WITH PULMONARY FIBROSIS QUESTIONNAIRE

The L-PF questionnaire was developed to assess multiple aspects of health-related quality of life in participants with progressive fibrosing ILD [21].

The L-PF questionnaire comprises 2 distinct modules, the L-PF symptoms (23 items) and the L-PF impacts (21 items). The symptoms module assesses shortness of breath, cough, and fatigue in the past 24 hours. The impacts module assesses multiple aspects of health-related quality of life with a recall period of 1 week.

These will be made available electronically to the participant (available web-based and as an application for tablet or mobile phone), unless otherwise specified. The L-PF questionnaire should be completed by the participant during the visits before study treatment administration.

The Investigator (or designee) will verify the L-PF questionnaire was completed.

Training and instructions will be provided to Investigators (and designee) and participants.

8. EFFICACY ASSESSMENTS

8.1 PRIMARY VARIABLE

- Absolute change from baseline in ppFVC at Week 24.

8.2 SECONDARY VARIABLES

- Pulmonary function tests:
  - Absolute change from baseline in ppFVC at Weeks 6, 12, 18, and 30
  - Relative change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30
  - Categorical absolute change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -10%, -5%, 0%, 5%, and 10%)
  - Categorical relative change from baseline in ppFVC at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -10%, -5%, 0%, 5%, and 10%)
  - Rate of decline in ppFVC over 24 weeks
  - Absolute and relative change from baseline in FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30
  - Categorical absolute change from baseline in FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30 (5 dichotomous thresholds: -200 mL, -100 mL, 0 mL, 100 mL, and 200 mL)
  - Rate of decline in FVC (mL) over 24 weeks
- Patient-reported outcome measures:
  - Change from baseline in the L-PF questionnaire at Weeks 12, 24, and 30
  - Change from baseline in specific modules of the L-PF questionnaire (symptoms and impact) and within the symptom modules of specific domains (shortness of breath, cough, and fatigue) at Week 12 and at Week 24

8.3 EXPLORATORY VARIABLES

- Biomarkers:
  - Changes from baseline to Weeks 6, 12, 18, and 24 in serum CA-19-9, CA-125/MUC16, CCL18/PARC, CXCL13/BLC, CYFRA 21-1, sICAM-1, MMP-7, KL-6/MUC-1, PAI-1, SP-D, and TN-C levels
  - Rate of change in serum CA-19-9, CA-125/MUC16, CCL18/PARC, CXCL13/BLC, CYFRA 21-1, sICAM-1, MMP-7, KL-6/MUC-1, PAI-1, SP-D, and TN-C levels over 24 weeks
  - Plasma TG2 levels at baseline, and at Weeks 12 and 24
- Fibrotic changes on the HRCT from baseline to Week 24 will be evaluated by a radiologist. This will be a descriptive review without quantitative assessment.

8.4 OTHER INVESTIGATIONS

Optional sample collection will be proposed to the participants, depending on the feasibility of sample collection at the site. This includes whole blood for genomics (DNA), transcriptomics (RNA), additional blood, serum, and plasma samples (including volume for proteomics), nasosorption samples, and exhaled breath condensate samples. These samples will be collected and archived for post-hoc investigations.

HRCT scans may be performed at Week 24 and Week 48 to evaluate disease progression.

The outcome variables and their analyses will be described in a separate post-hoc statistical plan, whose results will not be included in the CSR.

9. SAFETY, IMMUNOGENICITY, AND PHARMACOKINETIC ASSESSMENTS

9.1 SAFETY AND IMMUNOGENICITY VARIABLES

The definitions of the variables related to the below listed assessments are reported and detailed in Section 12.3.5.1:

- AEs and ADRs.
- Vital signs: SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature.
- 12-lead ECG parameters (heart rate, PR, QRS, and QTcF).
- Clinical laboratory evaluations: Haematology, blood chemistry, and urinalysis.
- Physical examinations.
- Screening and confirmed ADA and nAb (for positive ADA participants at confirmation test). Confirmed ADA will be tested for the presence of CHF10067 IgE. Isotype characterisation may be performed.
- Systemic markers for the evaluation of immediate hypersensitivity reactions to a biological at baseline for all participants with postdose measurement as needed (refer to Section 7.2.4.7):
  - Markers of cytokine release syndrome: TNF-α, IL-1β, IL-6, and IL-10
  - Mast cell tryptase
  - Complement markers (C3a, C5a, CH50, and sC5b-9)
  - CHF10067 IgE

9.2 PHARMACOKINETIC VARIABLES

- CHF10067 serum concentrations over time (from Week 0 to Week 21). No non-compartmental analysis is foreseen.

10. ADVERSE EVENT REPORTING

10.1 DEFINITIONS

An **AE** is any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding [e.g., blood chemistry, haematology, and urinalysis abnormalities]), symptom, or disease temporally associated with the use of a medicinal product, whether, or not considered related to the medicinal product.

An **ADR** is a noxious and unintended response to an IMP-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.

Adverse reactions could derive from medication errors and uses outside what is foreseen in the protocol in relation to the IMP, including misuse, and abuse of the product.

An **SAE/Serious ADR** is any untoward medical occurrence/noxious and unintended response to an IMP that at any dose falls into 1 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 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 participant was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, anaphylaxis). The term does not refer to an event that 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 24 hour hospitalisation or 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 participant's physical or psychological well-being to the extent that the participant is unable to function normally.

- Is a congenital anomaly or birth defect
- Is a medically significant AE

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

Medical and scientific judgement should be exercised in deciding whether an event is "serious" in accordance with these criteria.

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.

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

A **Non-serious AE/Non-serious ADR** is an AE or ADR that does not meet the criteria listed above for an SAE/serious ADR.

10.2 EXPECTEDNESS

An unexpected serious adverse reaction means a serious adverse reaction, the nature, CTCAE Grade, or outcome of which is not consistent with the applicable reference safety information (included in Section 7.4 of the IB for CHF10067; and in Section 4.8 of the summary of product characteristics for 0.9% sodium chloride aqueous solution [Placebo]).

Reports which add significant information on specificity, increase of occurrence, or CTCAE Grade 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

Each adverse event will be graded by severity using CTCAE Version 6.0.

If an AE is not listed in the CTCAE criteria, a corresponding grading is to be provided by the Investigator based on his/her best medical judgement as follows:

- Mild (Grade 1): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): Minimal, local, or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)*
- Severe (Grade 3): Medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting self-care ADL**
- Life-threatening (Grade 4): Life-threatening consequences; urgent intervention indicated
- Death (Grade 5): Death related to an adverse event

*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 CTCAE Grade), 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 and the AE CTCAE Grade will be judged by the Investigator based on the ranges provided in that laboratory report.

Taking into consideration the diseased 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 CTCAE Grade remains the responsibility of the Investigator.

10.4 CAUSALITY ASSESSMENT

In determining whether an AE is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the IMP (also referred to as “study drug”), to be intended as both the tested product and the reference product, based on an analysis of available evidence.

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

Is there a reasonable possibility of relatedness to study treatment?

- Yes

- No

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 treatment administration 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 treatment
- Class effects
- Other treatments (prior or concomitant)
- Withdrawal of study treatment(s)
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study treatments (or concomitant medication)
- Protocol-related process

10.5 ACTION TAKEN WITH THE STUDY TREATMENT DUE TO AN AE

- Dose not changed
- Drug permanently withdrawn
- Drug temporarily interrupted
- Total infusion volume not administered
- Infusion 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 the following:

- 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 be completed as well.

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) whether collected through participants' spontaneous, unsolicited reports, by observation, or by routine open questionings.

Clinically significant abnormal laboratory findings (e.g., blood chemistry, haematology, and urinalysis abnormalities) or other abnormal assessments 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. Vice-versa, no AE should be recorded if the abnormal result is assessed to be non-clinically significant.

A diagnosis, if known, or clinical signs, and symptoms if diagnosis is unknown, rather than the clinically significant abnormal 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.

The window for recording AEs in the eCRF is the period starting from the informed consent signature until the participant's study participation ends. All AEs must be followed and recorded in the eCRF until this date.

10.9 REPORTING SERIOUS ADVERSE EVENTS TO THE SPONSOR

The Investigator must report all SAEs to the ICON Safety Contact listed below (Table 6) without undue delay but not later than within 24 hours of awareness. The information is to be sent by providing the completed SAE form. At a later date, the ICON Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager, and the Clinical Research Physician.

Table 6: ICON and Sponsor Safety Contact Information

Safety contacts	Telephone no.	Fax no.	E-mail
ICON Drug Safety Centre EAPA	[redacted]		
ICON Drug Safety Centre Americas			
Chiesi Safety Contact Global Pharmacovigilance			

- Reporting of SAEs by the Investigator is from the time of the participant's signature of informed consent until the participant's study participation ends. No active monitoring of SAEs by the Investigator is required after this date, but SAEs with a suspected causal relationship to the IMP must be reported without **UNDUE** delay, if the Investigator becomes aware of them.
- Up to the closure of the site, all SAE reports (both initial and follow-up) are to be reported to the ICON Safety Contact. After the site is closed, SAE reports are to be reported directly to the Sponsor Safety Contact.
- For pharmacovigilance purposes, all SAEs must be followed up until all queries have been resolved, clinical recovery is complete, laboratory results have returned to normal, a stable

condition has been reached, or the participant has been lost to follow-up. This is necessary in order to elucidate the nature and/or causality of the SAEs as completely as possible. Follow-up may therefore continue after a participant has left the study. For related SAEs, the follow-up will continue with no timelines, 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), CTCAE Grade, and medical significance of the event.

10.10 REPORTING SERIOUS ADVERSE EVENTS AND OTHER SAFETY ISSUES TO REGULATORY AUTHORITIES/ETHICS COMMITTEES/INSTITUTIONAL REVIEW BOARDS

All reportable SAEs/SUSARs that occur with the IMPs within or outside the concerned clinical study, if required, will be reported by Chiesi Global Pharmacovigilance to the Medicine and Healthcare products Regulatory Agency (MHRA) through the MHRA Individual Case Safety Report Submission portal and to the European Medicines Agency via Eudravigilance in compliance with the timelines and standards for reporting SUSARs set out in EU Clinical Trial Regulation 536/2014 or according to local requirements (as applicable). Investigators and ECs will be informed about any safety profile changes and will receive SUSARs via Council for International Organizations of Medical Sciences (CIOMS) I form or by periodic line-listings produced by Chiesi Global Pharmacovigilance.

Any other reportable SAE will be reported according to local reporting requirements.

With regard to regulations in force for pharmacovigilance, Investigators must fulfil their obligations according to the law in force in their country.

In addition to SUSARs, all unexpected events that might materially influence the benefit-risk assessment of the medicinal product will be notified as set out in EU Clinical Trial Regulation 536/2014.

All SUSARs/investigational new drug (IND) safety reports that occur with the IMPs within or outside the concerned clinical study, if required, will be reported in compliance with the timelines and standards for reporting SUSARs/IND safety reports set out in 21CFR Part 312.32 IND Safety Reporting and linked Food and Drug Administration (FDA) guidance (Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies). The SUSAR/IND safety report will be reported using the CIOMS I form or the FDA Form 3500 A, or in an electronic format acceptable to the FDA. The FDA will be informed through transmission of the report to the Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research review division that has responsibility for review of the IND.

The involved IRBs and the Investigators will also receive copies of the report.

10.11 REPORTING ANNUAL SAFETY REPORTS

Annual safety reports will be prepared and submitted in accordance with EU Clinical Trial Regulation 536/2014, ICH E2F, and any local applicable requirements.

A single annual safety report on the tested IMP will be submitted, which will also address relevant safety information on the reference product.

10.12 GENERAL NOTES

- In case of death, a comprehensive narrative report of the case must be prepared by the Investigator and sent to the ICON Safety Contact within the SAE form.

- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the ICON Safety Contact as soon as available, retaining a copy on site.
- All documents provided by the Investigator or site staff to the ICON Safety Contact must be carefully checked for respect of confidentiality. All personal data that could identify a participant must be redacted.
- In case of pregnancy, the participant will be immediately withdrawn from the study and will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and until the child reaches 1 year of age, in order 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 ICON Safety Contact using the paper Pregnancy Report Form. The ICON Safety Contact will inform the Sponsor of the pregnancy within 1 working day of being notified.
- The first 2 pages of the Pregnancy Report Form are to be completed by the Investigator with all the available information and sent to the ICON Safety Contact. Some of the sections in this form may be completed only if the participant/participant's partner has signed the separate consent form to permit the pregnancy to be followed. 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 the outcome meets the criteria for immediate classification of an SAE (e.g., spontaneous, or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, or birth defect), the Investigator must follow the procedure for reporting SAEs.
- If a male participant's partner becomes pregnant during the study, the participant is not to be discontinued from the study, but the same reporting procedure is to be followed and the Pregnancy Report Form is to be completed as described above.
- Pregnancies that occur at any time during the study must be reported.
- If a pregnancy is discovered before a participant has taken the first dose of study treatment medication, the participant must be immediately withdrawn from the study, but the pregnancy does not need to be reported.
- Any ADR occurring with a concomitant medication during the study must be reported by the Investigator to the National Competent Authority of the country where the reaction occurred, according to the applicable laws, or to the marketing authorisation holder of the medicinal product suspected to have caused the ADR. (It should not be reported to both, to avoid duplicate submission of individual case safety reports.) Additionally, conditions of use outside the marketing authorisation of the medicinal product (e.g., off-label use, overdose, misuse, abuse, and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breastfeeding exposure, and lack of efficacy, are to be reported.

10.13 SAFETY ADVISORY COMMITTEE

An SAC will review the data of approximately the first 30 randomised participants (SAC subgroup, see definition in Section 12.2) in a blinded fashion once the last participant of this group has been enrolled and the relevant data up to Week 15 (Visit 7, predose) have been collected (after they have reached the steady state [~ fifth dose]). The aim of this single evaluation is to carefully monitor any safety issue or trend as well as the PK profile after repeated administrations of CHF10067 before treating the entire study population.

The safety parameters that will be reviewed will be specified in the SAC charter and include but are not limited to:

- TEAEs
- Vital signs
- 12-lead ECG
- Pulmonary function test (spirometry)
- Clinical laboratory parameters (haematology, blood chemistry, and urinalysis)
- Available PK and ADA data up to Week 15 (Visit 7, predose)

Members of the SAC will be at least the ICON Project Manager and Medical Monitor, the Sponsor Clinical Project Manager, Clinical Research Physician, Clinical Pharmacologist, and the Coordinating Investigator. Other members may be included. The SAC members, their roles, and the review process will be described in the SAC charter. The SAC has no authority to make decisions regarding study continuation, modification, or termination. Its role is limited to review, recommending risk mitigation procedures, and alerting in the event of any significant safety findings. The SAC, as per charter, will promptly inform the independent Data Monitoring Committee (DMC) in the event of any significant safety findings.

While the SAC will review the data, the recruitment will continue, and additional participants will be screened, enrolled, and treated.

Refer to the SAC charter for details.

10.14 STEERING COMMITTEE

The Steering Committee will be established to provide overall supervision and strategy for the study.

The Steering Committee members, their roles, and the review process will be described in the Steering Committee charter. There will be separate written operating procedures for the Steering Committee.

10.15 DATA MONITORING COMMITTEE

The DMC will be established to ensure external objective medical and/or statistical review of safety data to protect the ethical and safety interests of participants and to protect the scientific validity of the study.

The DMC will be composed of independent Clinicians and 1 independent Biostatistician.

The DMC members, their roles, and the review process will be described in the DMC charter. There will be separate written operating procedures for the DMC. The DMC charter will also include specific rules to inform about study continuation, modification, temporary interruption, or termination due to safety concerns. Reasons for modifying, temporary interrupting, or stopping the study will include, but are not limited to:

1. Unacceptable Risk-Benefit Profile: Accumulative Safety data indicates that treatment-related toxicity is disproportionate to the anticipated therapeutic benefit.
2. Occurrence of SUSARs that result in a significantly altered CHF10067 safety profile.
3. Important new safety information from other studies involving CHF10067 that becomes available during the study and which implies a significant negative impact on participant safety.

The DMC will have periodical face-to-face and video/telephone meetings, as appropriate, and a Safety Assessment Report will be issued after each meeting.

All relevant listings will be transmitted for evaluation to the DMC according to the agreed timelines.

The Sponsor (and other study personnel) may be involved in some parts of the DMC meetings; however, they will never have access to unblinded data and/or unblinded/coded comparisons.

All DMC members will keep as confidential all information and data deriving from their activity, without disclosing them to other parties.

11. DATA MANAGEMENT

Participant data will be collected using the Sponsor electronic data capture (EDC) system (eCRF) and external systems (e.g., spirometry, laboratory, and L-PF questionnaire).

Data on all participants who sign the ICF will be included in the study data package.

All screen failed participants will be included in the database with a collection of a minimal set of information to ensure transparent reporting and to respond to queries from regulatory authorities. Minimal information includes date of informed consent signed, visit date, demography, screen failure details, eligibility criteria, and any AE/SAE and concomitant medications/procedures related to SAE only.

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

The eCRF will be filled in by the Investigator and/or designee based on source documents.

External data (HRCT, spirometry, laboratory, and L-PF questionnaire) will be processed centrally and sent to ICON for inclusion in the study data package.

Samples collected for possible post-hoc investigations (including genomics [DNA], transcriptomics [RNA], additional blood, serum, and plasma samples (including volume for proteomics), nasosorption, and condensates of exhaled breath) will be processed externally, and only sample collection information will be sent to ICON and reconciled with the corresponding information recorded in the eCRF. Data from the analysis of samples collected for possible post-hoc investigations will not be included in the study data package that is extracted from all electronic systems used for data collection (e.g., EDC, spirometry).

To ensure data consistency and completeness, data will be cleaned by front-end edit checks running at the time of data collection and by back-end checks used by the Data Manager.

External data will be also reconciled with the corresponding information recorded in the eCRF to avoid discrepancies. Unnecessary transcription steps between the source record and the data acquisition tool should be avoided.

Medical history, AEs, and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification.

After data collection, cleaning, and coding have been completed, a review meeting will be held to finalise the list of important protocol deviations and to define the analysis sets. 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. Any updates to the study data must be authorised by the Sponsor.

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

12. STATISTICAL METHODS

12.1 SAMPLE SIZE

A total of 240 participants (80 participants per treatment arm) will be randomised in a 1:1:1 ratio.

This sample size, not based on a formal power calculation, is in line with the size of several recent Phase II studies in participants with IPF and it is considered sufficient for evaluating the dose-related efficacy and safety of CHF10067.

It is anticipated that the minimal statistically detectable difference (i.e., the minimal difference reaching statistical significance) between CHF10067 (any dose) and placebo in mean absolute change from baseline in ppFVC at Week 24 is approximately 1.5%, assuming 70 evaluable participants per group at this time point (i.e., a drop-out rate of 12%), a common standard deviation of 5.5%, and a two-sided significance level of 0.1.

Under the assumptions above, the evaluable participants per group at Week 24 will ensure a distance from mean difference to the 90% confidence interval (CI) limits of 1.5% (i.e., half-width of the two-sided 90% CI, derived from the standard error of the mean difference between groups and the corresponding critical value for the specified confidence level).

Table 7 provides scenarios of varying hypothesised treatment differences, and the corresponding attainable 90% CIs and estimated powers, with all other assumptions kept stable.

Table 7: Scenarios of Hypothesised Treatment Differences, the Corresponding Attainable 90% Confidence Intervals, and Estimated Powers

CHF10067 versus placebo mean absolute CFB in ppFVC at Week 24	90% CI	Estimated power
1.5%	(0.0%-3.0%)	49%
1.8%	(0.3%-3.3%)	61%
2.0%	(0.5%-3.5%)	69%
2.3%	(0.8%-3.8%)	79%
2.7%	(1.2%-4.2%)	89%
2.8%	(1.3%-4.3%)	91%

CFB=change from baseline; CI=confidence interval; ppFVC=percent predicted forced vital capacity
Note: The hypotheses considered for the calculations are as follows: 70 evaluable participants per group in 1:1 ratio, common standard deviation of 5.5%, two-sided significance level of 0.1.

12.2 ANALYSIS SETS

- **Safety set:** All randomised participants who receive at least 1 dose of study treatment.
- **Full analysis set (FAS):** All randomised participants who receive at least 1 dose of the study treatment and who have at least 1 postbaseline evaluation of efficacy. The primary efficacy analysis will be carried out using the FAS.
- **Per protocol set (PP):** All participants from the FAS without any important protocol deviations leading to participant exclusion (e.g., wrong inclusions, poor compliance, non-permitted medications).

- **PK set:** All participants from the Safety set excluding participants receiving placebo and participants without any valid PK measurement or with important protocol deviations significantly affecting PK, for example, non-compliance. Exact definitions of important protocol deviations concerning PK will be discussed by the clinical team and described in a specific document before bioanalytical data are disclosed.
- **SAC subgroup:** A subgroup consisting of approximately the first 30 randomised participants having received 5 consecutive dosing cycles of the study treatment. The SAC subgroup will serve as an initial safety and PK sentinel cohort, enabling the SAC to evaluate potential safety signals and the PK profile of CHF10067 after repeated dosing before proceeding with treatment of the full study population (see Section 10.13).

For the efficacy analyses based on the FAS and PP, participants will be analysed according to the treatment arm to which they are randomised. For the safety and PK analyses, participants will be analysed based on the treatment actually received.

12.3 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP will be finalised prior to database lock.

12.3.1 IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or well-being. Important protocol deviations will be assessed during monitoring activities and derived programmatically from the clinical database. They will include but are not limited to:

- Informed consent issues
- Eligibility criteria not met
- Intake of non-permitted concomitant medications
- Unsatisfactory compliance to study treatments
- Non-compliance with study protocol procedures
- Study treatment not discontinued despite withdrawal criteria met
- Safety reporting time frame not respected

Prior to database lock, the list of important protocol deviations and their potential impact on the statistical analysis will be finalised. All important protocol deviations will be summarised using descriptive statistics and presented in the CSR.

12.3.2 PARTICIPANT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic characteristics, medical history and concomitant diseases, prior and concomitant medications, and efficacy and safety parameters at screening and/or baseline will be summarised using the FAS (and the Safety and PP sets, if relevant) by treatment arm and overall using descriptive statistics.

12.3.3 PRIMARY EFFICACY VARIABLES

The primary efficacy variable of this study is the absolute change from baseline in ppFVC at Week 24.

Absolute change from baseline to Week 24 in ppFVC will be analysed using a linear mixed model for repeated measures (MMRM) including treatment, country (or region), visit, treatment by visit interaction, locally approved IPF monotherapy (the stratification factor) as fixed effects, as well as baseline value (collected at Visit 2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment arm, the adjusted mean difference between treatments, and their 95% CIs at Week 24 will be estimated by the model.

The primary analysis will be based on the data collected up to Week 24 using FAS as main analysis set, and PP as supportive set. The main comparisons of interest will be CHF10067 1000 mg and CHF10067 3000 mg versus placebo. Considering the nature of the study, being designed to estimate the dose-response relationship rather than testing, with a sample size not based on a formal power calculation, there will be no adjustment for multiplicity to control the study-wise Type I error α=0.05. The remaining pairwise comparison (i.e., CHF10067 3000 mg vs. CHF10067 1000 mg) will be explored.

Given the potentially large number of countries involved in the study, country-level effects may lead to sparse data within categories. Therefore, a broader geographic region variable may be used instead of country. The definition and categorisation of regions will be specified in the SAP.

Estimands:

The attributes of the primary and alternative estimands in terms of target population, treatments, variable, strategies for intercurrent events, and population-level summary are provided in Table 8.

Table 8: Attributes of the Primary and Alternative Estimands

	Primary Estimand - Main Analysis	Primary Estimand - Sensitivity Analysis	Alternative Estimand #1	Alternative Estimand #2
Target population	Adult participants with IPF, aged ≥40 years with a life expectancy of at least 1 year at screening: IPF diagnosis for a maximum 8 years before screening. Stable locally approved IPF monotherapy for at least 8 weeks prior to screening; or (naïve) not on locally approved IPF therapy (including participants who have discontinued locally approved IPF monotherapy for any reason at least 4 weeks before randomisation)			Subgroup of the target population for primary estimand including only participants with measurements of ppFVC available both at baseline and at Week 24 (participants with missing ppFVC measurements between baseline and Week 24 will be included)
Treatment	CHF10067 1000 mg or CHF10067 3000 mg or placebo administered every 3 weeks by IV infusion			
Variable	Absolute change from baseline to Week 24 in ppFVC			

	Primary Estimand - Main Analysis	Primary Estimand - Sensitivity Analysis	Alternative Estimand #1	Alternative Estimand #2
Strategy for intercurrent events and events leading to missing data	**Treatment discontinuation for any reason** (including lack of efficacy, AE, or death): **Hypothetical strategy,** assuming that participants adhered to their randomised treatment up to Week 21 (MAR imputation of off-treatment data).		**Treatment discontinuation due to safety reasons, lack of efficacy, AE, or death: Hypothetical strategy,** assuming post-discontinuation outcomes follow the same trajectory as those remaining on placebo (MNAR imputation of off-treatment data by means of copy-reference imputation). **Treatment discontinuation for other reasons: Hypothetical strategy,** assuming that participants adhered to their randomised treatment up to Week 21 (MAR imputation of off-treatment data).	Same as per main analysis of primary estimand
	All other intercurrent events (including use of rescue medication or prohibited concomitant medications, use of locally approved IPF monotherapy in participants not on locally approved IPF monotherapy prior to screening, wrong study treatment administration, and any other important protocol deviations): **Treatment policy strategy** (data included in the analysis regardless of whether or not the intercurrent event occurred)			
Population-level summary	Adjusted mean difference in the change from baseline to Week 24 in ppFVC comparing CHF10067 1000 mg versus placebo, and CHF10067 3000 mg versus placebo; estimated by means of a MMRM	Adjusted mean difference in the change from baseline to Week 24 in ppFVC comparing CHF10067 1000 mg versus placebo, and CHF10067 3000 mg versus placebo; estimated by means of a robust linear regression model	Adjusted mean difference in the change from baseline to Week 24 in ppFVC comparing CHF10067 1000 mg versus placebo, and CHF10067 3000 mg versus placebo; estimated by means of ANCOVA model	Same as per main analysis of primary estimand

AE=adverse event; ANCOVA=analysis of covariance; IPF=idiopathic pulmonary fibrosis; IV=intravenous(ly); MAR=missing at random; MMRM=mixed model for repeated measures; MNAR=missing not at random; ppFVC=percent predicted forced vital capacity

Sensitivity Analysis

To assess the impact of the presence of outliers (specific to the IPF disease, participants may have large variability that can impact analysis results) in the response variable, a sensitivity analysis will be performed on the primary estimand by means of a robust linear regression model. The main

purpose of this model is to provide stable estimates of means in the presence of outliers (i.e., non-normality) of the response variable. This model limits the influence of outliers through a process known as iteratively reweighted least squares; conceptually, the iterative process detects unusual observations and assigns them with a smaller contribution in estimating means.

Robust linear regression will be implemented using M-estimation and the bisquare weighting function. The model will include change from baseline value as response variable using treatment, country (or region, see Section 12.3.3), locally approved IPF monotherapy as fixed effects, as well as baseline as covariate.

Missing data will be imputed using multiple imputation with missing at random (MAR) assumption, in line with the main analysis of the primary estimand.

Alternative Estimands:

Alternative estimands will be defined and analysed as described below to investigate the potential impact of missing data on the treatment effect. The analyses of the primary estimand assume that any missing data are MAR, meaning that the probability of a value being missing, conditional on the observed data and factors in the statistical model, is random, and not dependent on the unknown value of the missing data point.

Full details of the analyses of alternative estimands will be provided in the SAP.

Alternative Estimand #1

A different hypothetical scenario for post-treatment discontinuation data will be assessed:

- Treatment discontinuation due to safety reasons, lack of efficacy, AE, or death: Copy-reference multiple imputation, i.e., imputation of data after study discontinuation in all treatment arms will be based on the data distribution of the placebo group. Multiple imputation with missingness not at random (MNAR) assumption.
- Treatment discontinuation for any other reason: Multiple imputation with MAR assumption.

The analysis of alternative estimand #1 assumes that missing data arising from treatment discontinuation due to safety reasons, lack of efficacy, AE, or death are MNAR, meaning that, even after conditioning on the observed data and covariates included in the statistical model, the probability of missingness may depend on the unobserved (missing) values themselves.

Absolute change from baseline in ppFVC will be analysed using an analysis of covariance (ANCOVA) model, including treatment, country (or region, see Section 12.3.3), locally approved IPF monotherapy as fixed effects, as well as baseline as covariate.

MMRM accounts for missing data under the MAR assumption, whereas ANCOVA does not. However, after imputing missing data under different MNAR assumptions, both models yield similar results when analysing complete data at a single timepoint. Given this equivalence, the simpler ANCOVA model is preferred for its ease of interpretation and implementation, avoiding the additional complexity and computational burden of MMRM.

Alternative Estimand #2

A second alternative estimand will be defined and analysed to assess the treatment effect under continued treatment up to Week 24 in participants who are able to complete the planned Treatment Period. The analysis will be performed, including only participants with measurements of ppFVC available both at baseline and at Week 24 (participants with missing ppFVC measurements between baseline and Week 24 will be included), by means of the same model as for the main analysis of the primary estimand.

12.3.4 SECONDARY EFFICACY VARIABLES

The intercurrent event strategy for secondary efficacy variables will be the same as for the main analysis of the primary estimand. No sensitivity analyses will be performed. Analyses will be performed on FAS as main analysis set, and PP as supportive set.

- For absolute change from baseline in ppFVC, the adjusted means in each treatment arm and the adjusted mean differences between treatments at Weeks 6, 12, 18, and 30 will be estimated with their 95% CIs by the same model used for the primary efficacy analysis.
- For relative change from baseline in ppFVC, the adjusted means in each treatment arm and the adjusted mean differences between treatments at Week 24 and at Weeks 6, 12, 18, and 30 will be estimated with their 95% CIs by the same model used for the primary efficacy analysis. Relative change from baseline in ppFVC at the given visit will be calculated as $\text{ppFVC relative change} = \frac{\text{ppFVC at visit} - \text{baseline ppFVC}}{\text{baseline ppFVC}}$, and analysed using a linear MMRM including treatment, country (or region, see Section 12.3.3), visit, treatment by visit interaction, locally approved IPF monotherapy as fixed effects, as well as ppFVC baseline value (collected at Visit 2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. Similar analyses will be performed for change from baseline in FVC (mL), and L-PF questionnaire (at Week 12 and Week 24, including specific modules [symptoms and impact] and, within the symptom modules, of specific domains [shortness of breath, cough, and fatigue]).
- Categorical absolute and relative change from baseline in ppFVC, and categorical absolute change from baseline FVC (mL) at Week 24 and at Weeks 6, 12, 18, and 30 will be compared between treatment arms using a logistic model including treatment, country (or region, see Section 12.3.3), locally approved IPF monotherapy as factors and the baseline value as a covariate. Separate analyses will be conducted based on each of the dichotomous threshold used (-10%, -5%, 0%, 5%, and 10% for ppFVC; -200 mL, -100 mL, 0 mL, 100 mL, and 200 mL for FVC).
- The analysis of the rate of decline in ppFVC and FVC (mL) over 24 weeks will be based on a linear mixed model including treatment, country (or region, see Section 12.3.3), locally approved IPF monotherapy, time, and treatment by time interaction as fixed effects and participant-specific random intercept and slope, assuming an unstructured covariance matrix for random effects. The baseline value will be part of the response vector, so it will not be included in the model as a covariate.

12.3.5 SAFETY, IMMUNOGENICITY, AND PHARMACOKINETIC VARIABLES

12.3.5.1 Safety and Immunogenicity Variables

For all safety and immunogenicity variables, baseline is the Visit 2 predose, with exception of the systemic markers for immediate hypersensitivity reactions, which will be collected at predose each visit (Week 0 to Week 21).

Safety and immunogenicity variables will be presented for the whole population, and for participants on locally approved IPF monotherapy and not on locally approved IPF monotherapy for at least 8 weeks prior to screening.

Adverse Events

All AEs starting on or after the time of first study treatment administration will be classified as TEAEs. Any AEs started after the informed consent signature and before the time of first study treatment administration will be classified as pretreatment AEs.

The number of events and the number and percentage of participants experiencing TEAEs, treatment-emergent ADRs, serious TEAEs, non-serious TEAEs, serious treatment-emergent ADRs, TEAEs by CTCAE grade, ≥Grade 3 TEAEs, TEAEs leading to discontinuation of study treatment, and TEAEs leading to death will be presented overall and by treatment arm. The aforementioned categories of AEs will be also summarised by system organ class and preferred term using the MedDRA.

All AEs will be listed.

Pretreatment AEs will be listed.

12-lead ECG

At baseline and at each postbaseline (with or without dosing) time point, the following statistics will be presented by treatment arm for 12-lead ECG parameters (heart rate, PR, QRS, and QTcF):

- Mean absolute value with its 95% CI
- Mean change from baseline with its 90% CI (for postbaseline time points with or without dosing)
- Mean change from predose with its 90% CI (for postbaseline time points with dosing only)

Time profile plots of mean values by treatment arm will be presented for change from baseline.

The number and percentage of participants with QTcF:

- In the intervals >450 and ≤480 ms, >480 and ≤500 ms, or >500 ms for males and >470 and ≤500 ms, or >500 ms for females
- Change from baseline in the intervals >30 and ≤60 ms, or >60 ms (for postbaseline timepoints with or without dosing)

will be presented at each postbaseline time point postdose and at any postbaseline time point by treatment arm.

Vital Signs

At screening, at baseline, and at each postbaseline (with or without dosing) time point, the following statistics will be presented by treatment arm for each parameter (SBP, DBP, heart rate, respiratory rate, SpO_2, and body temperature):

- Mean absolute value with its 95% CI
- Mean change from baseline with its 95% CI (for postbaseline timepoints with or without dosing)
- Mean change from predose with its 95% CI (for postbaseline timepoints with dosing only).

Time profile plots of mean values by treatment arm will be presented for change from baseline.

In addition, the number and percentage of participants with

- SBP change from baseline >20 mmHg
- DBP change from baseline >10 mmHg
- Heart rate:
  - <50 bpm or >100 bpm
  - Increase >20 bpm from baseline
  - Decrease >15 bpm from baseline

- Respiratory rate:
  - <10 breaths/min or >20 breaths/min
  - Increase >5 breaths/min from baseline
  - Decrease <5 breaths/min from baseline
- Body temperature
  - ≥38.0 °C
  - Increase ≥1.0 °C from baseline

will be presented at each postbaseline time point postdose and at any postbaseline time point by treatment arm.

Laboratory Data

At screening, at baseline, and at each postbaseline (with or without dosing) time point, quantitative laboratory parameters (complete blood count with differential cell count, blood chemistry panel, liver function test panel, and urinalysis) will be summarised. For continuous laboratory parameters, the laboratory values and the change from baseline will be summarised at each visit by treatment arm using descriptive statistics and 95% CIs. For categorical laboratory parameters, a frequency table of results will be produced at each visit by treatment arm.

Shift tables from baseline to each postbaseline visit with reference to normal ranges will be provided by treatment arm. All laboratory data will be listed with abnormal values flagged.

Physical Examinations

Abnormal physical examination findings will be listed.

Immediate Hypersensitivity Reaction Markers

Markers of cytokine release syndrome (TNF-α, IL-1 β, IL-6, and IL-10), mast cell tryptase, complement markers (C3a, C5a, CH50, and sC5b-9) and CHF10067 IgE will be presented by participant and by visit for each postdose timepoint as absolute value and change from baseline.

Immunogenicity Data

The number and percentage of participants who fulfil the below criteria will be presented by treatment arm.

- ADA-positive at baseline
- ADA-positive at any visit, including baseline and all postbaseline measurements (ADA prevalence)
- CHF10067 IgE-positive at baseline and at any visit, including baseline and all postbaseline measurements (for ADA-positive samples only)
- ADA incidence
  - Treatment-induced ADA (positive ADA any time postbaseline in participant with ADA-negative at baseline)
    - Persistently positive ADA
      Treatment-induced ADA detected at 2 or more sampling time points during the treatment (including Follow-up Period), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer,

or
treatment-induced ADA incidence in the last available assessment (including Follow-up Period)

- Transiently positive ADA
  Treatment-induced ADA not fulfilling the above condition for persistently positive

- Treatment-boosted ADA (baseline positive ADA titre that was boosted to a 4-fold or higher level following study treatment administration)
- nAb positive at any visit, including baseline and all postbaseline measurements

All immunogenicity data will be listed.

Only if immunogenicity data will allow the effect of immunogenicity on efficacy, PK, and safety will be evaluated:

- Efficacy: The analysis of the primary efficacy variable will be performed by participant ADA status (i.e., ADA-positive or ADA-negative).
- PK: Serum concentration/time curves will be presented in linear/linear scale. Plots will be presented by dose level and participant ADA status (i.e., ADA-positive or ADA-negative) based on arithmetic means.
- Safety: The number and percentage of participants with TEAEs will be summarised by participant ADA status (i.e., ADA-positive or ADA-negative).

12.3.5.2 PHARMACOKINETIC VARIABLES

Serum concentration/time curves will be presented in linear/linear scale. Plots will be presented by study treatment, based on arithmetic means, and by participant, by showing the individual curves grouped by study treatment (1 plot for each study treatment) and ADA positivity/negativity (using different colours). No non-compartmental analysis is foreseen.

In addition, PK data will be submitted for population PK modelling, which will be described in a separate analysis plan. The results will be summarised in a separate report, which will not be part of the CSR.

12.3.6 EXPLORATORY VARIABLES

At baseline and at each postbaseline visit (with or without dosing), quantitative biomarker parameters will be summarised. For continuous biomarker parameters, the absolute biomarker values, the mean change (absolute and percentage) from baseline will be summarised at each visit by treatment arm using descriptive statistics and 95% CIs. For categorical biomarker parameters, a frequency table of results will be produced at each visit by treatment arm.

Fibrotic changes on the HRCT from baseline to Week 24 will be evaluated by a radiologist. This will be a descriptive review without quantitative assessment.

12.3.7 OTHER INVESTIGATIONS

Post-hoc investigations might be performed to analyse the optional samples (whole blood for genomics (DNA), transcriptomics (RNA), additional blood, serum, and plasma samples (including volume for proteomics), nasosorption samples, and exhaled breath condensate samples) and HRCT scans. The outcome variables and their analyses will be described in a separate post-hoc statistical plan. The results will not be included in the CSR.

12.3.8 EXAMINATION OF SUBGROUPS

The primary and secondary efficacy variables, except for PK variables, as well as safety and immunogenicity variables will also be analysed in the 2 subgroups defined as per stratification factor:

- On concomitant locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening
- Not on concomitant locally approved IPF monotherapy at a stable dose for at least 8 weeks prior to screening

No adjustment of the significance level for testing will be made, since all these subgroup analyses will be considered exploratory and may only be supportive of the analyses of the primary and secondary variables.

SAC Subgroup Analysis

An SAC will review blinded data of the SAC subgroup. The safety parameters that will be reviewed will be specified in the SAC charter and include but are not limited to:

- TEAEs
- Vital signs
- 12-lead ECG (heart rate, PR, QRS, and QTcF)
- Pulmonary function test (spirometry)
- Clinical laboratory parameters (haematology, blood chemistry, and urinalysis)
- Available PK and ADA data up to Week 15 (Visit 7, predose)

While the SAC will review the data, the recruitment will continue and additional participants will be screened, enrolled, and treated. For more details refer to Section 10.13.

No specific analyses performed for the evaluation of the SAC subgroup will be included in the CSR.

12.3.9 INTERIM ANALYSIS

No interim analysis is planned.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study application will be submitted to the EC/IRB in accordance with the requirements of each country.

The EC/IRB 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/IRB will be provided to the Sponsor.

The Investigator is to provide written reports to the EC/IRB, annually or more frequently if requested by the EC/IRB, on any changes that significantly affect the conduct of the study and/or that increase risk to the participants (according to the requirements of each country).

14. REGULATORY AND COMPLIANCE REQUIREMENTS

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

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

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2)/Integrated Addendum E6 (R3); US FDA CFR (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Regulation 536/2014; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

15. INFORMED CONSENT

Prior to any study-related procedures taking place, it is the responsibility of the Investigator (or designee) to obtain written consent from each participant, by using the latest EC/IRB approved version of the document.

The Investigator (or designee) will explain the purpose and nature of the study as well as possible benefits, risks, and adverse effects to the participant in a manner that facilitates their understanding and answer all questions regarding the study. The Declaration of Helsinki does not only require that the information is provided, but also that the Investigator needs to make sure that the potential participant has understood the information (Art. 26).

The processing of participants' data as well as participant inclusion in the study is based on participant explicit consent as pointed out within the informed consent.

Adequate time shall be given to the participant to ask the Investigator (or designee) about any clarification needed and to consider his/her decision to participate in the study.

Consent must be documented by the participant, with a dated signature. The signature confirms that the individual has understood the information provided. The Investigator (or designee) must sign and date the ICF as well. One copy is to be given to the participant and the other is retained by the site.

If a participant is unable to read, informed consent will be obtained in the presence of an impartial witness who will read the ICF and the written information. The witness shall sign and date the informed consent document.

Each participant's signed ICF on paper format must be kept on file by the Investigator. One copy of written version must be given to the participant, and the other is retained by the site.

Participants who are rescreened will be required to sign a new ICF. A link to the prior participant number will be recorded in the eCRF.

A female participant or the female partner of a male participant who becomes pregnant during the study will be asked to sign a specific ICF to provide permission to the Sponsor to collect information about her pregnancy, its outcome, and the health of the child up to the age of 1 year. If the female participant or female partner and/or her legal representative is unable to read, the consent for pregnancy follow-up will be obtained in the presence of an impartial witness who will read the ICF and the written information. The witness shall sign and date the informed consent document.

Provision of separate informed consent is mandatory for the genetic research. The participants will be informed about its purpose, confidentiality of test results, and will be asked for their authorisation to perform the test. If the participant does not consent to the blood sample for genetic testing, they may still participate in the study but will not have a blood sample taken for the genetic testing.

16. SOURCE DOCUMENTS/DATA

16.1 RECORDING OF SOURCE DATA

The Investigator should define what is considered to be a source record(s), the methods of data capture, and their location prior to starting the study and should update this definition when needed.

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG, computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

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 that the source data are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

The Investigator should review and endorse the reported data at important milestones agreed upon with the Sponsor (e.g., SAC subgroup analyses).

Data entered in the eCRF derived from source documents must be consistent with the data recorded on the source documents.

No data are to be recorded directly on eCRFs.

16.2 DIRECT ACCESS TO SOURCE DOCUMENT/DATA

All source documents from this study are to be maintained by the Investigator and made available for inspection by authorised persons. The Investigator (or designee) must permit study-related monitoring, audits, EC/IRB review or regulatory inspection, providing direct access to source data/documents. The Sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, EC/IRB review, and regulatory inspection.

17. STUDY MONITORING

Monitoring is a principal quality control activity. Monitoring will be performed by ICON who have been designated by the Sponsor.

Monitoring will include on-site, off-site monitoring, and risk-based monitoring (with centralised and/or statistical monitoring). The Study Monitors will comprise of blinded and unblinded staff with roles and responsibilities outlined in the functional plans.

The dedicated functional plans for the study must provide monitoring details describing strategy, including definition of study-critical data and processes (e.g., risk-based initiatives in operations and quality, e.g., risk management and mitigation strategies, and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring). The list of impacted functional plans can be found in the Integrated Quality Risk Management plan of the study.

It is understood that the monitor(s) will contact and/or visit the Investigator/site before the study begins, regularly throughout the study, and after the study has been completed, and that they will be permitted to inspect the various study records (eCRF, Investigator study files, and source data), provided that participant confidentiality is respected, and clinical study supplies (dispensing and storage areas). Whenever needed (e.g., in case of emergency or sanitary situations), ICON and the

Sponsor may agree to convert planned on-site visits into telephone or video visits, or to postpone, or completely cancel planned visits.

The purposes of these visits are the following:

- To verify that the safety and rights of participants are being protected
- To assess the progress of the study
- To review the compliance with the currently approved study protocol
- To verify that the study is being conducted in accordance with ICH GCP, and all applicable regulatory requirements
- To discuss any emergent problem
- To validate that data entered in the eCRFs by authorised site personnel are accurate, complete, and verifiable from the source documents (source data verification and source data review)
- To assess the status of drug storage, dispensing, and retrieval
- To check the accuracy of PK sample collection, handling, management, and storage

Prior to each monitoring activity and upon prior notification by the monitoring activity, the Investigator or authorised staff will record all data generated since the last visit in the eCRFs. For on-site visits, 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. Similarly, in case of remote monitoring, the Investigator and/or study staff will be expected to be available for a remote contact with the monitor 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/or after the study has been completed.

To ensure oversight and data (clinical and operational) reliability, the monitoring methodology for source data verification and reviewing could be a combination of the following:

- On-site monitoring (blinded and unblinded)
- Remote monitoring
- Central monitoring (if applicable)

The extent and nature of the monitoring will be determined on the basis of an assessment that considers the characteristics of the study, including the level of intervention of the study, its objectives, and methodology, as well as the degree of the deviation of the interventions from normal clinical practice. The assessment is (regularly) reviewed (whenever an anticipated significant risk emerges).

Where appropriate, quality control activities may also be applied to facilities outside of Investigator sites (e.g., central image reading facilities).

18. QUALITY ASSURANCE

The Sponsor will implement processes to manage quality and oversight throughout all stages and activities of the study, based on data and processes identified as critical for the participants' rights and safety as well as on data reliability and robustness.

Quality management will include system tools and procedures for data collection and processing, as well as the collection of information essential to decision-making.

The quality management system will use a risk-based approach as described in ICH E6, with:

- Critical Process and Data Identification
- Risk Identification/Evaluation/Control/Communication and Review
- Risk Reporting

Quality tolerance limits (QTLs) are predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR. The specifications for QTLs are documented in the Integrated Quality Risk Management plan of the study.

The R&D Quality Assurance Department of the Sponsor 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 currently approved protocol and is conducted in a manner that is proportionate to the risks associated with the conduct of the study.

19. INVESTIGATOR RESPONSIBILITIES

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. The Sponsor staff or an authorised representative will evaluate and approve all Investigators, who in turn will select their staff.

The Investigator must ensure that all staff assisting with the study are adequately informed about the protocol, amendments, and study treatments, as well as all study-related duties and functions, including obligations of confidentiality of the Sponsor information.

The Investigator is to maintain a list of Subinvestigators and other appropriately qualified staff members or parties to whom he/she has delegated significant study-related duties. Also, the Investigator must ensure qualification of the service and integrity of any data generated.

The Investigator is responsible for keeping a record of all participants who sign an ICF/assent form and are screened for entry into the study. Participants who fail screening must have the reason(s) recorded in their source documents.

The Investigator (or designee) must be available during monitoring visits to review data, resolve queries, and allow direct access to participant records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The Investigator must notify the EC/IRB of SAEs or other significant safety findings as required by EC/IRB procedures.

The Investigator and his/her study staff are responsible for keeping the confidentiality of the information contained in the protocol and amendments (with the exception of the information provided by the Sponsor on public registry websites). The protocol, any protocol amendments, and IB information are not to be made publicly available (for example, on the Investigator's or institution's website) without express written approval by the Sponsor.

The Investigator should not implement any deviation or changes to the protocol without agreement from the Sponsor and prior review and approval from the EC/IRB of an appropriate protocol amendment, except where necessary to eliminate an immediate hazard to a study participant, or, in accordance with applicable regulatory requirements, when the change involves only logistical or administrative aspects of the study. The Sponsor should take prompt action to address immediate hazards to participants. The Sponsor should determine the causes of the hazard and based on this,

take appropriate remedial actions. The Sponsor should consider whether the protocol requires amendment in response to an immediate hazard. The information on the immediate hazard, if required, and any subsequent protocol amendment should be submitted to the EC/IRB and/or regulatory authorities by the Investigator/institution or Sponsor (in accordance with applicable regulatory requirements).

The Investigator's responsibilities about records and documents retention are described in Section 27.

The Investigator must have oversight of the conduct of the study at the site and must adhere to the requirements of ICH guidelines, the EC/IRB, 21 CFR (where applicable), EU Regulation 536/2014 for clinical studies, and all other applicable local regulations.

20. INSURANCE AND INDEMNITY

The Sponsor holds and will maintain an adequate insurance policy covering damages arising out of its sponsored clinical research studies.

The Sponsor will indemnify the Investigators and hold them harmless for claims for damages arising out of the study, in excess of those covered by their own professional liability insurance, providing that the drug was administered under their supervision (or that of a deputy) and in strict accordance with accepted medical practice and with the study protocol.

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

21. CONFIDENTIALITY

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

The Investigator must assure that participants' anonymity will be maintained. The Investigator will keep a separate list with at least each participant's initials, study number, name, addresses, e-mail address, 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 the Sponsor.

22. PERSONAL DATA AND DATA SECURITY

As an EU-based Sponsor, Chiesi will collect and process participants' data in accordance with the European General Data Protection Regulation (GDPR), and any applicable data protection laws and regulations. The personal data involved in the study will be processed in a pseudonymised form, in compliance with both GCP and data protection laws and regulations.

The Sponsor is committed to abiding by all requirements foreseen by the applicable data protection laws and regulations, including processing participants' data in compliance with data minimisation, transparency, and purpose limitation principles, and by implementing adequate technical and organisational safeguards, to ensure data security as provided under Article 32 of the GDPR. More specifically, all the Sponsor's employees are bound by confidentiality obligations set out in their employment contracts and the specific data processing instructions and training programmes provided by the Sponsor. Therefore, the Sponsor's employees will not disclose or permit the disclosure of any of the information, including participants' data, and any other confidential, non-public, or proprietary information related to the clinical study protocol.

Access to participants' data will be granted to the Sponsor's appointed employees through their personal credentials, solely for the purposes herein described and, on a need-to-know basis in

compliance with the principles of purpose limitation and data minimisation. All study information, including participants' personal data, will be processed and stored in an encrypted form to prevent its identification by non-authorised persons.

The Sponsor has implemented adequate cybersecurity measures, including best practices, software, hardware, and physical means to protect participant data and prevent any unexpected disclosure or threat that may affect the data. The Sponsor will also conduct periodical cybersecurity assessments, e.g., penetration tests, to ensure that its systems are in line with the required security standards.

In compliance with the GDPR, the Sponsor has in place a dedicated data breach management process to detect, mitigate, and, where applicable, notify the competent data protection authority of a data security breach affecting participant data. The process is coordinated by the Sponsor's data protection functions, including the appointed data protection officer (the DPO Office), which must be notified as soon as a data incident has been detected. After being notified, the DPO Office convenes a working group together with the cybersecurity function as well as with the business functions potentially affected by the incident. The working group, coordinated by the DPO Office, is responsible for assessing the impact of the incident, and carries out activities necessary to mitigate any resulting problems. Based on the result of the evaluation of risks of the breach, the working group will determine whether it is necessary to notify the data protection authority and will proceed in compliance with the legal terms provided under Article 33 of the GDPR. In any case, the DPO Office keeps track of all the notified data incidents in a dedicated register.

The data breach management process described above will be initiated by the Sponsor upon notification by any parties involved in the study with whom the Sponsor has entered into specific data processing agreements (e.g., CROs).

23. PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. The SAC, as per charter, will promptly inform the independent DMC in the event of any significant safety findings. The DMC will inform the Sponsor about study continuation, modification, temporary interruption, or termination due to safety concerns. Should termination of the study be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

Reasons for the early closure of a study site by the Sponsor or an Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.
- Unacceptable Risk-Benefit Profile
  Accumulative Safety data indicates that treatment-related toxicity is disproportionate to the anticipated therapeutic benefit.
- Occurrence of SUSARs that result in a significantly altered CHF10067 safety profile.
- Important new safety information from other studies involving CHF10067 that becomes available during the study and which implies a significant negative impact on participant safety.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the EC/IRB or local Health Authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- The total number of participants has been included in the study earlier than expected

If the study is prematurely terminated or suspended for any reason, the Investigator/site personnel should promptly inform the study participants and should ensure appropriate therapy and follow-up for the participants.

The Sponsor must submit a written notification to the concerned Regulatory Authority and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the site personnel/institution, where applicable. The Investigator/site personnel should promptly inform the Sponsor and the EC/IRB. The Investigator/site personnel should also provide the Sponsor and the EC/IRB a detailed documented explanation of the termination or suspension.

24. CLINICAL STUDY REPORT

The CSR, including the statistical and clinical evaluations, shall be prepared and sent for agreement and signature to the Coordinating Investigator, when applicable.

The distribution of the CSR or CSR synopsis to all ECs/IRBs and to the Competent Authority will follow local regulations.

At the end of the study, the CSR synopsis will be provided to all Investigators.

25. DISSEMINATION OF CLINICAL STUDY DATA

In accordance with local legislative and applicable requirements on clinical studies, the Sponsor will disclose protocol- and study-related information and the summary results of this clinical study in public registries (*https://euclinicaltrials.eu/search-for-clinical-trials*) in a timely manner.

In accordance with the Sponsor commitments on Clinical Trial Transparency (i.e., clinical study registration and posting of summary results, sharing the CSR synopsis, publication in scientific literature journals, and sharing of Lay Summary results), study information will be also publicly disclosed on a voluntary basis.

The Sponsor website www.chiesi.com contains the commitments on Clinical Trial Transparency and all the study information publicly disclosed.

25.1 SUMMARY OF RESULTS FOR STUDIES (TRIALS) CONDUCTED IN EU MEMBER STATES

The Sponsor will submit to the EU database a summary of the results of the clinical study as well as a summary for a layperson.

26. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If a publication is presented by the Investigator, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Data from individual study sites must not be published separately. The Sponsor furthermore reserves the right to use such data for industrial purposes.

27. RECORD RETENTION

ICH E6 GCP guidelines require that essential documents of a clinical study be retained for at least 2 years after the final marketing approval in an ICH region, and until there are no pending or contemplated marketing applications in that region or until 2 years have elapsed since the formal interruption of the clinical development of the product under study.

Documents must be retained for a longer period if required by the applicable regulatory requirement(s).

The Sponsor and the Investigator shall archive the content of the clinical Trial Master File for at least 25 years after the end of the clinical study in the EU. This period can be extended if another EU law (e.g., applicable to the marketing authorisation applicant or holder) requires the Sponsor to archive for a longer period.

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. In addition, all participants' medical records and other source documentation will be kept for the maximum time permitted by the institution and in accordance with national laws.

No records may be destroyed at a clinical study site during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor is responsible for informing the Investigator in writing of the requirements for the retention of essential records and should notify the Investigator(s)/institution(s) and Service Providers, when appropriate, in writing when these documents need no longer be retained, in accordance with the applicable regulatory requirements.

The Sponsor may transfer, or the Investigator may delegate, some or all their tasks, duties, or activities, but they retain overall responsibility for their respective activities. If an Investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. The Investigator/institution should keep the Sponsor informed of the name of the person responsible for maintaining the essential records during the retention period. Notice of transfer must be made to and agreed by the Sponsor. The Sponsor should also inform the Investigator if sponsorship of the study changes.

28. REFERENCES

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APPENDIX I - RECOMMENDATIONS RELATED TO CONTRACEPTION

Definition of women 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 postmenopausal 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 postmenopausal 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 the following:

- Combined (oestrogen 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[1]
- Intrauterine device (IUD)[1]
- Intrauterine hormone-releasing system (IUS)[1]
- Bilateral tubal occlusion[1]
- Vasectomised partner[1,2]
- Sexual abstinence[3]

Source: CTCG Clinical Trials Coordination Group: Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.2, 07 March 2024

[1] Method of low user dependency
[2] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[3] 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 trial and the preferred and usual lifestyle of the participant.

APPENDIX II – PROTOCOL CHANGES HISTORY

Amendment 3: 01 Apr 2026

EU specific

Section # and name	Description of change	Change rationale
Section 1.2 Study Rationale	Added a justification for using placebo.	Text was added as per EU CTR Part I RFIs in Mar 2026.
Cover Page; Protocol Outline; Section 7.1 Study Schedule; Section 7.1.2 Part B (Extension Study Phase); and 12.3 Statistical Analysis	Added a note to specify Part B is only applicable to Macedonia.	Removed Part B, to minimise the procedural and visit burden on participants and to limit the duration of placebo use; as per EU CTR Part I RFIs in Mar 2026.
Protocol Outline; Section 12.1 Sample Size	Clarified how the group difference of 1.5% was derived and that assumptions are the same for all group comparisons.	Text was clarified to ensure consistency with the primary objective: to assess the efficacy of 2 dose strengths of CHF10067 compared to placebo; as per EU CTR Part I RFIs in Mar 2026.
Protocol Outline; Section 10.13 Safety Advisory Committee; and Section 23 Premature Termination of the Study	Clarified the role of the Safety Advisory Committee, aligned text across section.	Text was clarified and aligned across sections for consistency; as per EU CTR Part I RFIs in Mar 2026.
Section 10.15 Data Monitoring Committee; and Section 23 Premature Termination of the Study	Added text that Data Monitoring Committee charter will also include specific rules to inform about study continuation, modification, or termination due to safety concerns.	Text was clarified and aligned across sections for consistency; as per EU CTR Part I RFIs in Mar 2026.
Protocol Outline; Section 8.4 Other Investigations; Section 9.1 Safety and Immunogenicity Variables; Section 9.2 Pharmacokinetic Variables; Section 12.3.5.1 Safety and, Immunogenicity Variables; and Section 12.3.5.2 Pharmacokinetic Variables	Added text to facilitate the link between objectives and variables and corresponding statistical analyses. Analyses of physical examinations was clarified.	Text was clarified as per EU CTR Part I RFIs in Mar 2026.
Table 5 Schedule of Assessments Part A; Table 6 Schedule of Assessments Optional Part B; Section 7.1.1.7 Follow-Up Visit 11; and Section 7.1.2.5 Follow-Up Visit 19	Added pregnancy testing at follow-up Visit 11 and 19.	Pregnancy testing should be conducted until the end of relevant systemic exposure (5 half-lives), text was clarified as per EU CTR Part I RFIs in Mar 2026.
Protocol Outline and Section 4.2 Inclusion criteria	Clarified inclusion criterion #2, that sex assigned at birth, inclusive of all gender identities, is to be considered for eligibility.	Text was clarified to facilitate screening, as per EU CTR Part I RFIs in Mar 2026.
Section 15 Informed Consent	Clarified that participants who cannot read will have an impartial witness to read and sign the informed consent form.	A sentence regarding the exclusion of participants who cannot read was not deleted as intended, as per Protocol Administrative Clarification letter in Nov 2025; text was clarified as per EU CTR Part I RFIs in Mar 2026.
Protocol Outline; Section 7.1.1.1 Visit 0 (Prescreening visit); and Section 15 Informed Consent	Removed references to the participant's legal representative.	Incapacitated individuals should not be enrolled to the study; text was clarified as per EU CTR Part I RFIs in Mar 2026.
Section 12.3.3 Primary Efficacy Variables	Clarified that main comparison of interest will be the 2 dose strengths of CHF10067 versus to placebo. Added that pairwise comparison the 2 dose strengths of CHF10067 will be explored.	Text was clarified as per EU CTR Part I RFIs in Mar 2026.

Section # and name	Description of change	Change rationale
Protocol Outline; List of abbreviations and definition of terms; and Section 7.2.4.8 Exploratory Biomarkers, Including Tg2	Added definition of abbreviations in text and List of Abbreviations.	Text was clarified as per EU CTR Part I RFIs in Mar 2026.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.

Amendment 2: 18 Feb 2026

Argentina, Australia, Brazil, Chile, South Korea, Japan, Turkey, UK, and USA; Country specific

Section # and name	Description of change	Change rationale
Cover Page; Protocol Outline; Section 7.1 Study Schedule; and Section 7.1.2 Part B (Extension Study Phase)	Added a note to specify Part B is only applicable to the EU and Macedonia.	Removed Part B, as per FDA IR#1 in Jan 2026.
Protocol Outline and Section 4.3 Exclusion Criteria	Updated exclusion criteria 6 and 8 and added exclusion criterion 9.	Excluded participants with non-IPF pulmonary diagnoses, as per FDA IR#1 in Jan 2026.
Protocol Outline and Section 5.1 Permitted Concomitant Medications	Updated permitted concomitant medications.	Clarified when inhaled corticosteroids and bronchodilators are permitted, as per FDA IR#1 in Jan 2026.
Protocol Outline and Section 7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions	Included specific criteria that qualify a participant for premedication.	Removed the use of premedication for the whole study population and updated its use only for participants who had previously experienced a non-serious infusion-related reaction CTCAE Grade ≥2, as per FDA IR#1 in Jan 2026.
Protocol Outline; Section 7.1 Study Schedule; Section 7.1.1 Part A (Main Study Phase) (excluding Visit 0); Section 7.1.2 Part B (Extension Study Phase); Section 7.2.7 Vital Signs; Section 9.1 Safety and Immunogenicity Variables; and Section 12.3.5.1 Safety and Immunogenicity Variables	Amended vital sign measurements.	Added peripheral oxygen saturation measurements, as per FDA IR#1 in Jan 2026.
Section 15 Informed Consent	Clarified that participants and/or their legal representative who cannot read or write will have an impartial witness to read and sign the ICF.	A sentence regarding the exclusion of participants who cannot read or write was not deleted as intended, as per Protocol Administrative Clarification letter in Nov 2025.
Protocol Outline; Section 4.2 Inclusion Criteria; and Section 7.2.11 Peripheral Capillary Oxygen Saturation	Updated inclusion criterion 9.	Allow use of reservoir nasal cannula to collect peripheral oxygen saturation measurements.
Protocol Outline and Section 4.2 Inclusion Criteria	Updated inclusion criterion 11.	Specified that a male vasectomy must be >6 months prior to enrolment and azoospermia has been documented.
Protocol Outline and Section 4.3 Exclusion Criteria	Updated exclusion criterion 18.	Excluded participants who currently smoke marijuana.

Section # and name	Description of change	Change rationale
Protocol Outline; Section 4.3 Exclusion Criteria; Section 7.2.4.7.1 Management and Documenting of Immediate Infusion-Related Reactions and Hypersensitivity Reactions; and Section 10.3 Intensity of Adverse Event; and Section 12.3.5.1 Safety and Immunogenicity Variables	Updated severity grading system to NCI CTCAE v6.0.	Changed severity grading system to NCI CTCAE v6.0.
Protocol Outline; Section 12.3.3 Primary Efficacy Variables; and Section 12.3.4 Second Efficacy Variables	Updated text.	Minor statistical clarifications.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.

Amendment 1: 27 Oct 2025

This change was considered non-substantial based on the criteria set forth in regulation (EU) No 536/2014.

Overall Rationale for the Changes

Removal of Section 10.14 Adjudication Committee as it was mistakenly left in the body text of Protocol Version 1.0.

Section # and name	Description of change	Change rationale
List of abbreviations and definitions of terms	Deleted first line	Deleted definition for AC – adjudication committee
Index	Updated for Section 10.14	Section 10.14 removed
10.14 Adjudication Committee	Removed entire section	As per Steering Committee decision in Feb 2025 this section should have been removed but was left by mistake in body text

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Status**
Amendment 4 Global	V5.0	14 May 2026	Effective (derived from V4.0 EU specific and V3.0 Argentina, Australia, Brazil, Chile, South Korea, Japan, Turkey, UK, and USA Country specific)
Amendment 3 EU specific	V4.0	01 Apr 2026	Superseded, replaced by V5.0
Amendment 2/Argentina, Australia, Brazil, Chile, South Korea, Japan, Turkey, UK, and USA Country specific	V3.0	18 Feb 2026	Superseded, replaced by V5.0
Amendment 1 Global	V2.0	27 Oct 2025	Superseded, replaced by V5.0
Original Protocol Global	V1.0	13 Oct 2025	Superseded, replaced by V2.0