Clinical Trial Protocol and Statistical Analysis Plan

Title:	**A Phase 2, Multi-Centre, Open-Label, Single-Arm Trial Investigating the Safety, Efficacy and Pharmacokinetics of C21 in Subjects with Idiopathic Pulmonary Fibrosis**
Trial ID:	**VP-C21-005**
NCT No.:	**NCT04533022**
Version:	**7.0**
Date:	**15-Sep-2021**

Clinical Trial Protocol

Title:	**A Phase 2, Multi-Centre, Open-Label, Single-Arm Trial Investigating the Safety, Efficacy and Pharmacokinetics of C21 in Subjects with Idiopathic Pulmonary Fibrosis**
Short Title:	**C21 in IPF**
Sponsor:	**Vicore Pharma AB** **Kronhusgatan 11** **SE-411 05 Göteborg** **Sweden**
Trial ID:	**VP-C21-005**
EudraCT No.:	**2020-000822-24**
Investigational Medicinal Product:	**C21**
Indication:	**Idiopathic Pulmonary Fibrosis (IPF)**
Phase:	**2**
Version:	**7.0**
Date:	**15-Sep-2021**

Sponsor's Approval of Clinical Trial Protocol

This trial protocol was subject to critical review by the Sponsor. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the ethical and scientific principles governing clinical research as set out in the latest version of the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

This trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements.

Sponsor's Medical Responsible: _____ _____

[redacted]

Sponsor's Statistical Expert: _____ _____

[redacted]

VP Clinical Development: _____ _____

[redacted]

Signatory Investigator's Approval of Clinical Trial Protocol

This trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

I confirm, that I agree to conduct this trial in compliance with the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for GCP and applicable regulatory requirements.

Furthermore, I confirm that I have read and understood the present clinical trial protocol and agree to conduct the trial in compliance with this. I fully understand that any changes from the clinical trial protocol constitute a deviation which will be notified to Sponsor.

Coordinating Investigator:

[redacted]

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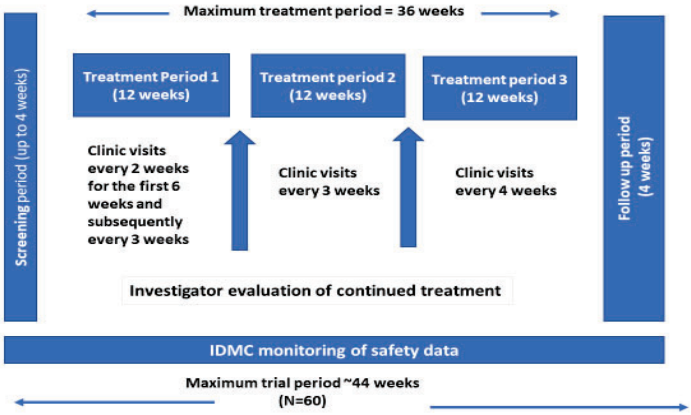
1 PROTOCOL SUMMARY

Trial Title	A Phase 2, Multi-Centre, Open-Label, Single-Arm Trial Investigating the Safety, Efficacy and Pharmacokinetics of C21 in Subjects with Idiopathic Pulmonary Fibrosis
Trial ID	VP-C21-005
Trial Phase	Phase 2
Objectives	**Primary Objective** To investigate the safety of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF. **Secondary Objectives** To evaluate: • The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 12 weeks • The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 24 weeks • The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 36 weeks • The pharmacokinetic (PK) profile of C21 200 mg daily dose (100 mg *b.i.d.*) after multiple dosing **Exploratory Objectives** To investigate a range of laboratory parameters as potential biomarkers of inflammation, proliferation and fibrosis following oral administration of C21 200 mg daily dose (100 mg *b.i.d.*).
Endpoints	**Primary Endpoints** Nature and frequency of adverse events occurring over the trial period. **Secondary Endpoints** • Change from baseline in forced vital capacity (FVC) value over 12, 24, and 36 weeks • Plasma concentration of C21 and derived PK parameters evaluated in a sub-set of subjects **Exploratory Endpoints** Blood samples will be saved for potential future analyses of biomarkers reflecting fibrosis and inflammation.
Trial Design	This is an multi-centre, open-label, single-arm trial investigating the safety and efficacy of C21 in which subjects with IPF will be treated for a maximum of 36 weeks. The aim is to enroll a total of 60 subjects with a completed 12-week visit.. To ensure careful and ongoing evaluation of the individual risk/benefit profiles, each subject will undergo a medical evaluation by the investigator at the end of every 12-week treatment period, where the investigator will evaluate if continuation into the next 12-week treatment period is considered safe for the individual subject.

	
Inclusion Criteria	1) Written informed consent, consistent with ICH-GCP R2 and local laws, obtained before the initiation of any trial related procedure 2) A diagnosis of IPF within 5 years prior to Visit 1, as per either ATS/ERS/JRS/ALAT/Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018) 3) Age ≥40 years 4) FVC ≥60% predicted at Visit 1 and 2 (*Specific for UK:* FVC ≥80% predicted at Visit 1 and 2 or FVC ≥60% predicted at Visit 1 and 2 for subjects previously treated with antifibrotic treatment e.g., nintedanib and/or pirfenidone, or refused such treatments) 5) FEV1/FVC ratio ≥0.7 prebronchodilator at Visit 1 and 2 6) Oxygen saturation (SpO2) >85% by pulse oximetry while breathing ambient air at rest at Visit 1 7) High-resolution computed tomography (HRCT) within 36 months prior to Visit 1 with central reading demonstrating either a or b, and c: a. A pattern consistent with usual interstitial pneumonitis (UIP) according to either ATS/ERS/JRS/ALAT or Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018): i.UIP ii.Probable UIP b. A pattern indeterminate for UIP according to either ATS/ERS/JRS/ALAT or Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018) and a historical biopsy consistent with IPF c. Extent of fibrosis > extent of emphysema 8) Fully vaccinated against COVID-19 prior to screening (Visit 1). Subjects are considered fully vaccinated for COVID-19 ≥14 days after they have received vaccination dose(s) according to local label
Exclusion Criteria	1) Previous use of antifibrotic treatment for an interstitial lung disease (e.g. nintedanib or pirfenidone) for > 6 months 2) Smoking (including e-cigarettes) within 6 months prior to Visit 1 3) Body mass index (BMI) >35 or <18 4) IPF exacerbation within 3 months prior to Visit 1, as defined by Collard et al. (2016): • 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 (if no previous computed tomography is available, the qualifier "new" can be dropped) • Deterioration not fully explained by cardiac failure or fluid overload 5) Concurrent serious medical condition with special attention to cardiac or ophthalmic conditions (e.g. contraindications to cataract surgery), or moderate to severe hepatic impairment, which in the opinion of the investigator makes the subject inappropriate for this trial 6) Malignancy within the past 5 years with the exception of *in situ* removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I 7) Treatment with any of the medications listed below within 4 weeks prior to Visit 1: • Strong Cytochrome p450 (CYP) 3A4 inducers (e.g. rifampicin, phenytoin, St. John's Wort) • Strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • Medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range • Experimental drugs • Antifibrotic treatment • Any systemic immunosuppressive therapies other than: o Inhaled corticosteroids which can be used throughout the trial period provided the dose is kept stable o Corticosteroids for the treatment of acute exacerbations o The continuation of stable doses of ≤15 mg daily doses of prednisolone or equivalent 8) Treatment with any of the medications listed below within 2 weeks prior to Visit 1: o Proton pump inhibitors (PPIs) more than once daily o Histamine H2 receptor antagonists (H2RAs) o Sulphasalazine and rosuvastatin o High dose breast cancer resistance protein sensitive substrates (other than sulphasalazine or rosuvastatin) 9) Any of the following findings at Visit 1: o Prolonged QTcF (QT interval with Fridericia's correction) (>450 ms), clinically significant cardiac arrhythmias or any other clinically significant abnormalities in the resting ECG, as judged by the investigator o Increased AST or ALT >3 times upper limit of normal (ULN), or bilirubin >1.5 times ULN o Positive results for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb) or human immunodeficiency virus 1+2 antigen/antibody (HIV 1+2 Ag/Ab) o Positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) 10) Inability to generate lung function data at Visit 1 meeting the minimum standards of the ATS/ERS 2005 guideline (Miller et al. 2005), as determined by central review 11) Clinically significant abnormal laboratory value at Visit 1 indicating a potential risk for the subject if enrolled in the trial as evaluated by the investigator 12) Pregnant or breast-feeding female subjects 13) Female subjects of childbearing potential not willing to use contraceptive methods asdescribed in Section 5.3.1 14) Male subjects not willing to use contraceptive methods as described in Section 5.3.1 15) Subjects not willing to adhere to dietary restrictions during the trial period as described in Section 5.4 16) Participation in any other interventional trial during the trial period

	17) Subjects known or suspected of not being able to comply with this trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder) 18) Discontinuation or change of previous antifibrotic treatment (e.g. nintedanib or pirfenidone) due to disease progression
IMP and dietary restrictions	IMP will be administered twice daily by the subject at home as follows: • Morning dose: Two 50 mg capsules (100 mg C21) to be taken after minimum 2 hours fasting with a glass of water • Afternoon/evening dose: Two 50 mg capsules (100 mg C21) to be taken after minimum 2 hours fasting with a glass of water In relation to IMP administrations, subjects should adhere to restrictions regarding food intake: • No food intake for 2 hours prior to taking the C21 capsules • No food intake for 1 hour after taking the C21 capsules Once daily PPIs must be taken 1 hour after the morning dose of C21
Allowed medication	If considered unlikely to interfere with IMP or the outcome of the trial results, concomitant medication may be given according to local standard of care. In addition, the following medications are allowed: o Inhaled corticosteroids provided the dose is kept stable throughout the trial period o Stable daily dose of <15 mg prednisolone, or equivalent o Corticosteroids for the treatment of acute exacerbations o PPIs if once daily and taken 1 hour after the morning dose of C21
Disallowed medication	**4 weeks before Visit 1 and during the trial period**: • Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort) • Strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • Medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range • Experimental drugs • Any systemic immunosuppressive therapy other than: o Inhaled corticosteroids which can be used throughout the trial period o The continuation of a stable daily dose of <15 mg prednisolone, or equivalent • Antifibrotic treatment (e.g. nintedanib, pirfenidone) **2 weeks before Visit 1 and during the trial period:** • PPIs more than once daily • H2RAs • Sulphasalazine, rosuvastatin • High dose breast cancer resistance protein sensitive substrates (other than sulphasalazine or rosuvastatin) **12 hours before spirometry/FVC assessments:** • Long acting bronchodilators **4 hours before spirometry/FVC assessments** • Short acting bronchodilators **Throughout the duration of the trial:** • Antifibrotics • Systematic and continuous use of PPIs more than once daily and H2RA medications

2 SCHEDULE OF PROCEDURES

Table 1 Flow Chart for Trial Procedures

Visit	Screening	Treatment Period 1						Treatment Period 2				Treatment Period 3			End-of-Trial [1]
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Week Number		0	2	4	6	9	12	15	18	21	24	28	32	36	40
Visit Window (days allowed from previous visit)		3-30	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	2-4 weeks after last dose
Eligibility / General															
Informed consent	x														
Check eligibility criteria	x	x[2]													
Demographics	x														
Height	x														
SpO_2	x														
HRCT [3]	x														
Medical/disease history	x	x													
Previous/concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Safety		x													
Physical examination	x[4]	x[4]	x	x	x	x	x	x	x	x	x	x	x	x	x[4]
Body weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Holter ECG[5]		x													

Visit	Screening	Treatment Period 1						Treatment Period 2				Treatment Period 3			End-of-Trial [1]
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**
Week Number	**-1**	**0**	**2**	**4**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**28**	**32**	**36**	**40**
Slit lamp examination[6]	x														x
Treatment evaluation[7]							x				x				
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Efficacy															
Spirometry[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IMP															
IMP Administration		x	IMP home treatment 100 mg *b.i.d.*												
(Re)Instruct subject[9]		x	x	x	x	x	x	x	x	x	x	x	x		
Hand-out to subject		x	x	x	x	x	x	x	x	x	x	x	x		
Return from subject			x	x	x	x	x	x	x	x	x	x	x	x	
Compliance check			x	x	x	x	x	x	x	x	x	x	x	x	
Drug accountability			x	x	x	x	x	x	x	x	x	x	x	x	

1) An end-of-trial visit for all subjects who received IMP must be performed minimum 2 weeks and maximum 4 weeks after the last dose of IMP. The end-of-trial visit must also be performed if a subject is withdrawn from the trial for any reason.
2) Re-evaluation of in-/exclusion criteria including review of results from Visit 1 laboratory tests and slit lamp examination.
3) Historical high-resolution computed tomography (HRCT) no older than 36 months from date of Visit 1 will be collected for central review prior to enrolment
4) A complete physical examination will be performed at Visit 1, 2 and 15. At Visits 3-14 only a short physical examination will be performed (see Section 8.2.4)
5) All ECGs will be centrally reviewed
6) Slit lamp examination is to be performed by an ophthalmologist prior to Visit 2 and at Visit 15, where the results will be reviewed by the investigator
7) Medical evaluation by investigator for continued treatment with C21 for an additional 12 weeks
8) For spirometry measurements, gender, height and age values obtained at Visit 1 are used. FEV_1 and FVC values are obtained as described in Section 8.1.1
9) Re-instruct subjects on dietary requirements (see Section 5.4) and prohibited medication (see Section 5.2)

Visit	Screening	Treatment Period 1						Treatment Period 2				Treatment Period 3			End-of-Trial [1)]
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Week Number	-1	0	2	4	6	9	12	15	18	21	24	28	32	36	40
Laboratory Sampling															
HCV Ab	x														
HBsAg	x														
HIV 1+2 Ag/Ab	x														
Biochemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Haematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [10)]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Expl. biomarkers		x					x				x			x	x
Pregnancy testing[11)]	x[12)]	x[12)]	x	x	x	x	x	x	x	x	x	x	x	x	x[12)]
Pharmacokinetics[13)]		x					x				x			x	

10) Urinanalysis: Dipstick for bilirubin, glucose, ketones, protein, specific gravity, urobilinogen and pH
11) Only applicable for female subjects of childbearing potential, as defined in Section 5.3.1.
12) At Visit 1, 2 and 15 blood tests (beta-HCG) are performed for pregnancy. At Visits 3-14 urine dipsticks are performed
13) Collection prior to morning dose and at 30 min, 1 hour, 2 hours, 3 hours and 4 hours post-dose in a selected group of 20 subjects.

3 BACKGROUND AND RATIONALE

3.1 Indication Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible and devastating interstitial lung disease with no existing cure (King et al., 2011). IPF is characterised by a progressive deposition of extracellular matrix (ECM) proteins and fibrous tissue in the lungs, resulting in destruction of lung architecture and reduced lung capacity (Sakai and Tager, 2013). The aetiology of IPF is unknown. However, several risk factors are reported to be associated with development of IPF including cigarette smoking, environmental exposures, microbial pathogens, and genetic factors (Raghu et al., 2011). Symptoms of IPF include shortness of breath, fatigue, and a dry intractable cough. IPF is usually lethal and death is most commonly caused by acute or subacute respiratory failure due to progression of lung fibrosis (Ley et al., 2011). Increasing pulmonary vascular pressure often leads to pulmonary hypertension (PH) and subsequently to heart failure. The prevalence of PH in patients with IPF is between 32 and 85% (Farkas et al., 2011). The prognosis of IPF is poor, with an estimated life expectancy of 3-5 years after diagnosis which is shorter than many malignancies (Vanchari et al., 2010). The mortality is also on the rise in the UK and globally (Navaratnam et al., 2019).

Worldwide, approximately 3 million people are living with IPF and it is classified as an orphan disease in the EU and the USA. The incidence of IPF is estimated to be 2.8 to 19 per 100,000 people per year and increases with age. Debilitating symptoms typically appear between the ages of 50 and 70 years and, while the disease is most common in men, the number of cases in women is increasing (Olson et al., 2018). Lung transplantation is rare; just 214 lung transplants were carried out for pulmonary fibrosis in England in 2017-18 (British Lung Foundation), although it is recommended in a small group of patients with moderate to severe IPF and improves survival rates. Median post-transplantation survival in IPF is estimated to 4.5 years (Kistler et al., 2014). However, patients are often referred late in the course of the disease and may die while waiting for a transplant (King et al., 2011).

IPF is often associated with comorbidities including lung cancer, pulmonary hypertension, chronic obstructive pulmonary disease, and ischaemic heart disease (Raghu et al., 2015). The impact of comorbidities on the prognosis of IPF is not well established; however, mortality has been reported to be higher in patients with the comorbidities mentioned above, and treatment of comorbidities may therefore contribute to improved survival and quality of life (Raghu et al., 2015).

3.2 Current Treatment for Idiopathic Pulmonary Fibrosis

Currently, there is no cure for IPF and treatment options are limited. Two antifibrotic drugs, nintedanib and pirfenidone, are approved and conditionally recommended for the treatment of patients with mild to moderate IPF (Raghu et al., 2015). Both nintedanib and pirfenidone slow disease progression without causing a long-term cure, while having significant, primarily gastrointestinal, side effects (Raghu et al., 2015).

Two drugs (pirfenidone and nintedanib) have shown to slow down the decline of forced vital capacity (FVC) in IPF patients by up to 50%, and have been approved in multiple countries. However, these medicines are not curative and there is a lack of consensus on the effectiveness of

them in different disease stages such as "preserved lung capacity". Not all patients can gain access, and the ones that do, can suffer quite profound gastrointestinal side effects.

Thus, a major medical unmet need still exists for finding more efficacious treatment for IPF, targeting not only disease progression of IPF but also comorbidities including pulmonary hypertension and with acceptable safety and tolerability profiles.

3.3 Investigational Medicinal Product

The investigational medicinal product (IMP) C21, is a selective angiotensin II (AngII) type 2 receptor (AT_2R) agonist presented as capsules for oral administration.

Several studies demonstrate that AngII and angiotensin type 1 receptors (AT_1R) are involved in the pathogenesis of lung fibrosis, including IPF (Uhal et al., 2011; Marshall et al., 2004; Schüttert et al., 2003). The role of the AT_2R in IPF is not fully established, but it is suggested that the AT_2R mediates counteractive effects to the AT_1R by mediating antifibrotic effects such as reducing fibroblast proliferation, cell growth, and ECM synthesis in addition to antiapoptotic and vasodilatory effects (Königshoff et al., 2007; Uhal et al., 2011).

An upregulation of AT_2Rs was demonstrated in septal and vascular areas (Parra et al., 2014) and in fibrotic fibroblasts from human IPF lungs (Königshoff et al., 2007) as well as in animal models of lung fibrosis and hyperoxia-induced lung injury (Königshoff et al., 2007; Wagenaar et al., 2013; Rey-Parra et al., 2012). Königshoff et al. (2007) demonstrated a differential expression of AT_1Rs and AT_2Rs in primary mouse fibrotic fibroblasts after bleomycin-induced lung injury when compared to healthy mice. In these experiments, the surface expression of AT_2Rs on interstitial fibroblasts was increased after lung injury when compared to healthy animals whereas the surface expression of AT_1Rs was similar in fibrotic and normal fibroblasts. Interestingly, AngII-induced proliferation of fibroblasts was mediated primarily via the AT_1R in healthy fibroblasts whereas AngII induced antiproliferation via an AT_2R-dependent mechanism in fibrotic fibroblasts, demonstrating a shift in the response to AngII in fibrotic lungs, probably due to an upregulation of AT_2Rs (Königshoff et al., 2007).

It has been demonstrated in 2 different animal models that C21 reduces pulmonary fibrosis. In the first study, pulmonary hypertension and fibrosis were induced in rats by a monocrotaline injection, and treatment with C21 for 2 weeks not only prevented, but also reversed pulmonary interstitial and perivascular fibrosis (Bruce et al., 2015). This effect was associated with significant improvements in right heart function and decreased pulmonary vessel wall thickness.

In a second study, pulmonary fibrosis and associated pulmonary hypertension were induced in rats by bleomycin treatment (Rathinasabapathy et al., 2018). Treatment with C21 for 2 weeks almost completely prevented the progression of lung fibrosis and in addition, reduced pulmonary hypertension and muscularisation of the pulmonary vessels, and normalised cardiac function. In both models, C21 treatment also decreased gene expression of markers of fibrosis and inflammation (including transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, collagen I and III, and tissue inhibitor of metalloproteinases [TIMP]).

Thus, C21 represents a potential novel treatment of fibrotic lung diseases such as IPF capable of reducing inflammation, proliferation, fibrosis, and vasculopathy.

3.4 Preclinical Safety

C21 has undergone an extensive nonclinical safety and toxicology evaluation including safety pharmacology, single and repeated dose toxicity up to 13 weeks in rat, dog, and cynomolgus monkey, genotoxicity, and phototoxicity studies. The key findings from the safety pharmacology studies and toxicology studies are presented in Table 2.

Table 2 Summary of Key Safety and Toxicology Findings

[redacted]

For further details, please refer to the current Investigator's Brochure.

3.5 Clinical Safety

Safety and tolerability of C21 have been evaluated in three Phase 1 trials of which 2 trials are completed (C21-001-16, C21-002-16) and 1 trial is in the reporting phase (C21-003 [preliminary data]). During these trials, C21 was evaluated in single ascending dose (SAD) and multiple ascending dose (MAD) trials at doses up to 200 mg twice daily for up to 8 days in healthy subjects and at doses up to 100 mg daily for up to 8 days in obese subjects. These trials included 83 subjects receiving at least 1 dose of C21.

[redacted]

No serious adverse events (SAEs) or deaths were observed during the 3 Phase 1 trials.

In addition, a Phase 2a trial in subjects with Raynaud's phenomenon secondary to SSc (SSc-RP) to show proof of mechanism of C21 on vasodilation is currently ongoing.

For further details, please refer to the current Investigator's Brochure.

3.6 Rationale for Trial

Current therapies for IPF have limited efficacy (see Section 3.2), with severe side effects leading to discontinuation of treatment in 29-51% of patients demonstrated as in a real-life cohort on anti-fibrotics in North East England (Murphy et al., 2019). Hence there is a substantial medical need for new therapeutic alternatives. The current clinical trial is the first investigation of the efficacy of C21 in IPF patients. Data from the trial will guide and support the design of further clinical investigations of C21 in this indication.

3.7 Rationale for Trial Design

Given the urgent need for effective medicines in IPF, proof of concept for C21 is sought within this open-label, single-arm, multi-centre trial evaluating the safety, efficacy, and pharmacokinetics of subjects with IPF.

Since this is the first trial where patients are administered repeated doses of C21, the primary objective of the trial will be to evaluate the safety (including tolerability) of C21 in an IPF population.

The expected average FVC reduction in untreated IPF patients is 120 mL/24 weeks (Richeldi et al., 2014), with the same rate of decline independent of disease severity (Kolb et al., 2017) (see also Section 13.3). The consistent information on the natural course of the disease supports an open-label single-arm design. Since the individual rate of decline in lung function (FVC) is not constant, a minimum duration of IMP exposure of 24 weeks is considered necessary to investigate the efficacy of C21, with respect to demonstrating a significantly lower rate of decline in FVC than expected for this population, and durability of this response. Thus, extended treatment up to a maximum of 36 weeks may be offered as long as it is considered safe by the investigator to continue treatment, on an individual patient level.

A sample size of 60 subjects is considered sufficient for an initial investigation of safety and efficacy, whilst preventing unnecessary exposure of subjects to trial drug (see rationale for sample size regarding efficacy in Section 13.1).

3.8 Rationale for Dose and Dosing Regimen

C21 is being developed for oral treatment of IPF, a progressive, irreversible and life-threatening disease that presents a huge challenge to the patients, their families, and the health care system. The results of the Phase 1 healthy volunteer trials for C21 (C21-003; preliminary data) indicate an acceptable safety and tolerability profile for the 100 mg *b.i.d.* (bis in die; twice daily) dose. [redacted] Moreover, regular review by an Independent Data Monitoring Committee will be implemented to monitor safety during the conduct of the trial. This finding is therefore not considered to present any significant safety risk to subjects in the trial.

[redacted]

Overall, the safety profile of C21 as available from preclinical data and from the Phase 1 trials is interpreted as favourable for further study of the intended indication 'Treatment of Idiopathic Pulmonary Fibrosis'.

3.9 Risk-Benefit Assessment

The risks to subjects in the present trial will be reduced by using C21 doses which have been evaluated in a recently completed Phase 1 trial (C21-003) (preliminary data) and found to have an acceptable safety profile; moreover centrally read telemetry data did not identify any clinically significant findings.

[redacted]

In addition, the risks will be minimised by strict compliance with the eligibility criteria and by close clinical monitoring. An independent data monitoring committee (IDMC) will also meet regularly to review the safety data and provide appropriate recommendations to the Sponsor on the overall safety of trial participants (see Section 14).

All subjects participating in the trial will be followed closely by medically qualified staff throughout the trial period (see Section 2 and Section 6.1). Adverse events will be carefully documented, and the subjects will receive relevant treatment should they occur.

IPF is a progressive, irreversible and fatal disease. Patients with IPF may receive benefit from stabilisation of their disease with C21.

Repetitive lung function measurement manoeuvres during the trial can lead to cough, shortness of breath, dizziness, or exhaustion, but since the subjects only carry out forced manoeuvres during clinic visits (not at home), these are always performed under medical supervision to ensure availability of medical aid if required. The assessments are part of the regular and well-established assessments for this patient population.

Furthermore, the protocol defines withdrawal criteria to secure the safety of subjects with severe progression of disease.

If the physician judges it necessary for the subject to receive a different treatment during the trial period, the subject will be withdrawn from the trial and receive relevant treatment.

Based on the above, it is considered ethically justifiable to include patients in the present trial, as the potential benefits of C21 are judged to balance possible disadvantages connected with participation in the trial.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

To investigate the safety of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF.

4.2 Secondary Objectives

To evaluate:

- The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 12 weeks
- The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 24 weeks
- The efficacy of C21 200 mg daily dose (100 mg *b.i.d.*) administered orally to subjects with IPF for 36 weeks
- The pharmacokinetic (PK) profile of C21 200 mg daily dose (100 mg *b.i.d.*) after multiple dosing

4.3 Exploratory Objectives

To investigate a range of laboratory parameters as potential biomarkers of inflammation, proliferation and fibrosis following oral administration of C21 200 mg daily dose (100 mg *b.i.d.*).

4.4 Primary Endpoint

Nature and frequency of adverse events occurring over the trial period.

4.5 Secondary Endpoints

- Change from baseline in forced vital capacity (FVC) value over 12, 24, and 36 weeks
- Plasma concentration of C21 and derived PK parameters evaluated in a sub-set of subjects

4.6 Exploratory Endpoints

Blood samples will be saved for potential future analyses of biomarkers reflecting fibrosis and inflammation.

5 TRIAL POPULATION

5.1 Inclusion Criteria

1) Written informed consent, consistent with ICH-GCP R2 and local laws, obtained before the initiation of any trial related procedure
2) A diagnosis of IPF within 5 years prior to Visit 1, as per either ATS/ERS/JRS/ATLAT/Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018)
3) Age ≥40 years
4) FVC ≥60% predicted at Visit 1 and 2 (*Specific for UK:* FVC ≥80% predicted at Visit 1 and 2 or FVC >60 % predicted at Visit 1 and 2 for subjects previously treated with antifibrotic treatment e.g., nintedanib and/or pirfenidone, or refused such treatments)
5) FEV1/FVC ratio ≥0.7 prebronchodilator at Visit 1 and 2
6) Oxygen saturation (SpO2) >85% by pulse oximetry while breathing ambient air at rest at Visit 1
7) High-resolution computed tomography (HRCT) within 36 months prior to Visit 1 with central reading demonstrating either a or b, and c:
    a. A pattern consistent with usual interstitial pneumonitis (UIP) according to ATS/ERS/JRS/ALAT or Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018)
        i. UIP
        ii. Probable UIP or
    b. A pattern indeterminate for UIP according to either ATS/ERS/JRS/ALAT or Fleischner guidelines (Raghu et al., 2018; Lynch et al., 2018) and a historical biopsy consistent with IPF
    c. Extent of fibrosis > extent of emphysema
8) Fully vaccinated against COVID-19 prior to screening (Visit 1). Subjects are considered fully vaccinated for COVID-19 ≥14 days after they have received vaccination dose(s) according to local label

5.2 Exclusion Criteria

1) Previous use of antifibrotic treatment for an interstitial lung disease (e.g. nintedanib or pirfenidone) for >6 months
2) Smoking (including e-cigarettes) within 6 months prior to Visit 1
3) Body mass index (BMI) >35 or <18
4) IPF exacerbation within 3 months prior to Visit 1, as defined by Collard et al. (2016):
   - 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 (if no previous computed tomography is available, the qualifier "new" can be dropped)
   - Deterioration not fully explained by cardiac failure or fluid overload
5) Concurrent serious medical condition with special attention to cardiac or ophthalmic conditions (e.g. contraindications to cataract surgery), or moderate to severe hepatic impairment, which in the opinion of the investigator makes the subject inappropriate for this trial
6) Malignancy within the past 5 years with the exception of *in situ* removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I
7) Treatment with any of the medications listed below within 4 weeks prior to Visit 1:
   - Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, St. John's Wort)
   - Strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir)
   - Medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range
   - Experimental drugs
   - Antifibrotic treatment
   - Any systemic immunosuppressive therapies other than:
     - Inhaled corticosteroids which can be used throughout the trial period provided the dose is kept stable
     - Corticosteroids for the treatment of acute exacerbations
     - The continuation of a stable daily dose of ≤15 mg prednisolone, or equivalent
8) Treatment with any of the medications listed below within 2 weeks prior to Visit 1:
   - Proton pump inhibitors (PPIs) more than once daily
   - Histamine H2 receptor antagonists (H2RAs)
   - Sulphasalazine and rosuvastatin

- High dose breast cancer resistance protein sensitive substrates (other than sulphasalazine or rosuvastatin)

9) Any of the following findings at Visit 1:
   - Prolonged QTcF (QT interval with Fridericia's correction) (>450 ms), clinically significant cardiac arrhythmias or any other clinically significant abnormalities in the resting ECG, as judged by the investigator
   - Increased AST or ALT >3 times Upper Limit of Normal (ULN), or bilirubin >1.5 times ULN
   - Positive results for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb) or human immunodeficiency virus 1+2 antigen/antibody (HIV 1+2 Ag/Ab)
   - Positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG])
10) Inability to generate lung function data at Visit 1 meeting the minimum standards of the ATS/ERS 2005 guideline (Miller et al. 2005), as determined by central review
11) Clinically significant abnormal laboratory value at Visit 1 indicating a potential risk for the subject if enrolled in the trial as evaluated by the investigator
12) Pregnant or breast-feeding female subjects
13) Female subjects of childbearing potential not willing to use contraceptive methods as described in Section 5.3.1
14) Male subjects not willing to use contraceptive methods as described in Section 5.3.1
15) Subjects not willing to adhere to dietary restrictions during the trial period as described in Section 5.4
16) Participation in any other interventional trial during the trial period
17) Subjects known or suspected of not being able to comply with this trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder)
18) Discontinuation or change of previous antifibrotic treatment (e.g. nintedanib or pirfenidone) due to disease progression

5.3 Restrictions During the Trial

5.3.1 Contraception Requirements

Women of child bearing potential must practice abstinence (if that is their preferred lifestyle) from Visit 1 to Visit 15, or must agree to use a highly effective method of contraception with a failure rate of <1% to prevent pregnancy (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], intrauterine device or intrauterine hormone-releasing system) from at least 4 weeks prior to first IMP administration to 4 weeks after last IMP administration. Their male partner must agree to use a condom during the same time frame, unless he has had a demonstrated successful vasectomy more than 6 months prior to first IMP administration.

Males should use condom and their female partner of child-bearing potential must use a contraceptive method with a failure rate of <1% to prevent pregnancy (see above) and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after the last IMP administration.

5.4 Dietary Restrictions

In relation to IMP administrations, subjects should adhere to restrictions regarding food intake:

- No food intake for 2 hours prior to taking the C21 capsules
- No food intake for 1 hour after taking the C21 capsules

Once daily PPIs must be taken 1 hour after the morning dose of C21

5.5 Screening failure

A screen failure occurs when a subject who consents to participate in the clinical trial is not subsequently assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) can only be rescreened after discussion with the Medical Monitor.

5.6 Withdrawal Criteria

5.6.1 Evaluation for Withdrawal after each 12 Week Treatment Period

After completion of each 12-week treatment period, the investigator will make a medical evaluation and decide if the subject may continue into the next 12-week treatment period. The decision will be based on:

- No immediate need for other antifibrotics
- A positive risk/benefit balance

Failure to pass the medical evaluation will result in the subject being withdrawn from the trial (see Section 5.4.2).

5.7 Withdrawal from Trial

A subject will be withdrawn from trial if any of the following occurs:

- A decline from baseline in FVC value of > 10% predicted on 2 consecutive occasions and an FVC <60% predicted (*Specific for UK:* FVC <80 % predicted ; or FVC <60% predicted for subjects previously treated with nintedanib and/or pirfenidone, or refused such treatments)
- A decline from baseline in FVC value of 5-10% predicted on 2 consecutive occasions and worsening of respiratory symptoms and FVC <60% predicted (*Specific for UK:* FVC <80 % predicted; or FVC <60% predicted for subjects previously treated with nintedanib and/or pirfenidone, or refused such treatments)
- Consistent failure to comply with dietary requirements in Section 5.4, according to the investigators
- The investigator judges it necessary due to medical reasons
- Failure to pass the medical evaluation after each 12-week treatment period (see Section 5.6.1)
- It is the wish of the subject to withdraw for any reason
- Pregnancy

An end-of-trial visit (Visit 15) must be completed for all subjects withdrawn from the trial.

Subjects withdrawn due to pregnancy will be followed – as consented to – until termination or delivery and the infant must be followed at least until the age of one month.

Subject who withdraws prior to week 12 will be replaced until 60 subjects have completed the 12-week visit.

6 TRIAL DESIGN

6.1 Overall Trial Design

This is a multi-centre, open-label, single-arm trial investigating the safety and efficacy of C21 in which subjects with IPF will be treated for a maximum of 36 weeks. In total, approximately 60 subjects will be recruited.

To ensure careful and ongoing evaluation of the individual risk/benefit profiles, each subject will undergo a medical evaluation by the investigator at the end of every 12-week treatment period, where the investigator will evaluate if continuation into the next 12-week treatment period is considered safe for the individual subject.

In addition, throughout the duration of the trial, an independent data monitoring committee (IDMC) will evaluate all serious adverse events (SAEs) on an ongoing basis in accordance with the IDMC charter. The IDMC will monitor all available safety data during regular meetings as

defined in the IDMC charter and provide appropriate recommendations to the Sponsor on the overall safety of trial participants (see Section 14).

The subjects will attend up to 15 visits to the clinic:

- Visit 1: Screening
- Visits 2 – 7: Treatment period 1
- Visits 8 – 11: Treatment period 2
- Visits 12 – 14: Treatment period 3
- Visit 15: End-of-trial

IMP will be administered as home treatment twice daily (*b.i.d.*) during all treatment periods 1-3.

Final safety follow-up assessments at Visit 15 (end of trial visit), must be performed for all subjects who have received trial treatment. Visit 15 must be scheduled 2-4 weeks after the last IMP administration (see Section 7.3).

The maximum duration of the trial for any subject will be approximately 44 weeks, including a screening period of up 4 weeks, a treatment period up to 36 weeks and a visit for safety follow up to be conducted maximum 4 weeks after the last dose of IMP (please see clinical trial design in Figure 1).

6.2 Number of Subjects

The trial will enroll a sufficient number of subjects to ensure at least 60 subjects with a completed 12-week visit.

6.3 Trial Diagram

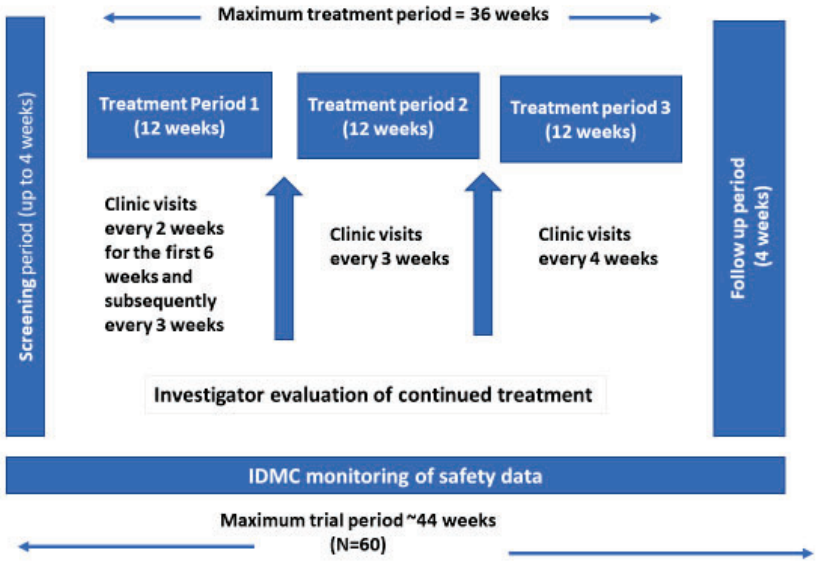


Figure 1. VP-C21-005 Clinical Trial Design

6.4 Trial Duration and Participating Centers

Planned first subject screened: Q3 2020

Planned last subject enrolled: Q1 2022

Planned last subject last visit: Q1 2023

The end of trial date is defined as the date the last subject attends the last visit.

The trial will be conducted at trial sites globally.

6.5 Schedule of Events

6.5.1 Screening (Visit 1)

Prior to and no later than at start of screening (Visit 1) i.e. before any trial related activity takes place, the investigator or a qualified designee will explain the nature of the trial, it's purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. All explanations shall be in layman's language. The subject will be provided with a copy of the information sheet. The subject must be given sufficient time to consider the trial before deciding whether to participate.

After signed informed consent is obtained from the subject, the screening procedures can be initiated.

All subjects giving informed consent to participate in the trial will receive a screening number. During the screening visit, the subject is evaluated for eligibility (please refer to Section 5.1 and 5.2).

The following procedures are performed:

- Written Informed Consent to be obtained
- Assignment of screening number
- Pregnancy testing (beta-HCG)
- Check of in- & exclusion criteria
- Assessment of eligibility which includes review of demographics, medical history, concomitant illnesses and medication, COVID-19 vaccination status, physical examination, height, weight, BMI and measurement of blood pressure, pulse and body temperature
- Medical history and concomitant medication
- 12-lead ECG
- Spirometry
- SpO_2
- HRCT to be collected and sent for central review
- Slit lamp examination to be performed prior to Visit 2
- Blood sampling for HBsAG, HCVab, HIV 1+2 Ag/Ab and safety (See Table 1 and Section 8)
- Urinanalyses (dipstick) for bilirubin, glucose, ketones, protein, specific gravity, urobilinogen, pH
- Information on restrictions prior to IMP administration (see Section 5.3)
- Reporting of adverse events (AEs)

6.5.2 Treatment Periods (Visits 2-14)

The total treatment period may last for maximum 36 weeks, comprising three 12 week treatment periods. At the end of treatment period 1 (Visit 7) and treatment period 2 (Visit 11), a medical evaluation is performed by the investigator to assess if treatment can be continued for an additional 12 weeks (see Section 5.4.1)

- Treatment period 1 (Visit 2-7)
  - Subjects will attend the clinic every 2 weeks for the first 6 weeks (Visit 2-5) and subsequently every 3 weeks for the last 6 weeks (Visit 6-7)
- Treatment period 2 (Visit 8-11)
  - Subjects will attend the clinic every 3 weeks for 12 weeks (visit 8-11)
- Treatment period 3 (Visit 12-14)
  - Subjects will attend the clinic every 4 weeks for 12 weeks (Visit 12-14)

The procedures to be performed at each visit are specified below.

Visit 2

Visit 2 can be scheduled as soon as the relevant screening assessments are available. Visit 2 must occur 3-30 days from Visit 1 (screening) to ensure that no eligibility assessments are older than 30 days when treatment is initiated.

The following procedures are performed:

- Re-evaluation of in- & exclusion criteria (including physical examination, assessment of vital signs, ECG, spirometry, slit lamp and laboratory results from Visit 1)
- Concomitant medication
- Pregnancy testing (beta-HCG)
- Assignment of enrollment number
- 12-lead ECG
- Holter ECG
- Blood sampling for safety and biomarker assessments (See Table 1 and Section 8)
- Urinanalysis (dipstick for bilirubin, glucose, ketones, protein, specific gravity, urobilinogen and pH)
- Spirometry
- IMP administration
- PK sampling
- Hand-out of medication
- Re-instructions regarding dietary restrictions prior to IMP administration (see Section 5.4)
- Reporting of AEs

Visits 3-14

- Concomitant medication
- Pregnancy testing (urine dipstick)
- Physical examination, (including body weight and vital signs)
- Blood sampling for safety
- 12-lead ECG
- Urinanalysis (dipstick for bilirubin, glucose, ketones, protein, specific gravity, urobilinogen and pH)
- Spirometry
- Return of medication
- IMP compliance check
- Drug accountability
- Hand-out of medication (not applicable for visit 14)
- Re-instructions regarding dietary restrictions prior to IMP administration (see Section 5.4. Not applicable for visit 14)
- Reporting of AEs

Additionally for Visit 7, 11 and 14 (end of each 12 week treatment period)

- Medical evaluation by investigator for continued treatment with C21 for an additional 12 weeks (Visits 7 and 11 only)

- Blood sampling for PK analyses prior to the morning dose and at 30 min, 1 hour, 2 hours, 3 hours and 4 hours post-dose in a selected group of 20 subjects
- Blood sampling for exploratory biomarker analyses

6.5.3 End-of-Trial (Visit 15)

Visit 15 is performed minimum 2 weeks and maximum 4 weeks after the last IMP administration.

The following procedures are performed:

- Recording of concomitant medication
- 12-lead ECG
- Blood sampling for safety and biomarker assessments (See Table 1 and Section 8)
- Urinanalysis
- Pregnancy test (beta-HCG)
- Physical examination including body weight (See Table 1 and Section 8.2.4)
- Vital signs
- Spirometry
- Slit lamp examination
- Concomitant medication
- Reporting of AEs

If a subject is withdrawn from treatment (see Section 5.7), a Visit 15 (end-of-trial visit) must be performed.

7 TRIAL TREATMENT

7.1 Investigational Medicinal Product

C21 is presented as a capsule for oral administration. The drug substance is [redacted] 50-mg C21 oral capsule.

Table 3 Qualitative and Quantitative Composition of the IMP

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.2 Packaging, Labelling and Storage

IMP will be delivered as 50 mg capsules packed in plastic container units with 56 capsules in each.

Each unit will be labelled in local language.

At the trial site, IMP must be stored separately from normal clinic stocks in a securely locked area only accessible to authorised trial personnel. Storage temperature must be monitored and kept at room temperature (15-25° C).

Labeling of the IMP will be done in compliance with Good Manufacturing Practice (GMP) Annex 13 (GMP 2003) and local regulatory requirements.

IMP will be dispensed to subjects at Visits 2-13. The subjects will be instructed to store the IMP at room temperature (15-25° C) in their own homes.

7.3 IMP Administration

IMP will be administered twice daily by the subject at home as follows:

- Morning dose: Two 50 mg capsules (100 mg C21) to be taken with a glass of water after minimum 2 hours fasting
- Afternoon/evening dose: Two 50 mg capsules (100 mg C21) to be taken with a glass of water after minimum 2 hours fasting

Subjects will be required not to eat anything for 1 hour after taking the C21 capsules.

7.4 Compliance Check and Drug Accountability

Compliance with C21 administration will be assessed by capsule count performed by the trial staff at visits 3-14. Details of the capsule count and compliance check will be recorded in the patient medical record.

After IMP accountability has been completed, all unused and partly used IMP will be returned to the Sponsor or Sponsor's designee for destruction. All returned IMP will be reconciled.

7.5 Blinding of the Trial

Not applicable.

7.6 Procedures for Unblinding

Not applicable.

7.7 Prior and Concomitant Medications

Concomitant medications are all medications being continued by the subject at trial entry, and all medications 4 weeks prior to screening and received in addition to IMP during the trial period.

At each visit, the investigator or qualified designee will ask the subject about concomitant medication. All concomitant medications will be documented in the subject's medical records and in the electronic case report form (eCRF). Any changes in concomitant medications (e.g. new treatment, discontinuation of treatment or change in dosage) during the trial period must be documented in the subject's medical records and in the eCRF.

The following information will be recorded in the eCRF:

- Generic name (preferred) or trade name
- Reason for prescription
- Dose unit and frequency
- Route of administration
- Start date (if started > 3 months prior to Visit 1, then this can be stated instead of recording a date)
- Stop date (unless ongoing at trial termination)

7.7.1 Allowed Concomitant Medication

If considered unlikely to interfere with IMP or the outcome of the trial results, concomitant medication may be given according to local standard of care.

In addition, the following medications are allowed:

- Inhaled corticosteroids provided the dose is kept stable throughout the trial period
- Stable daily dose of ≤15 mg prednisolone, or equivalent.
- Corticosteroids for the treatment of acute exacerbations
- PPIs if once daily and taken 1 hour after the morning dose of C21

7.7.2 Disallowed Concomitant Medication

The following treatments are not allowed:

4 weeks before Visit 1 and during the trial period	• Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort) • Strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • Medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range[1)] • Experimental drugs • Any systemic immunosuppressive therapy other than: o Inhaled corticosteroids which can be used throughout the trial period o The continuation of a stable daily dose of <15 mg prednisolone, or equivalent • Antifibrotics (e.g. nintedanib, pirfenidone)
2 weeks before Visit 1 and during the trial period	• PPIs more than once daily • H2RAs • Sulphasalazine, rosuvastatin • High dose breast cancer resistance protein sensitive substrates (other than sulphasalazine or rosuvastatin)
12 hours before spirometry/FVC assessments	Long acting bronchodilators
4 hours before spirometry/FVC assessments	Short acting bronchodilators
Throughout the duration of the trial	• Systematic and continuous use of PPIs more than once daily and H2RA medications

[1]) e.g. alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, phenytoin, pimozide, quinidine, sirolimus, tacrolimus, theophylline, pirfenidone, celecoxib and warfarin. Investigators will need to consult the product information of a concomitant drug as these lists may not be exhaustive.

8 ASSESSMENTS

8.1 Efficacy Assessments

8.1.1 Spirometry

Throughout the trial, spirometry will be performed using equipment provided to all sites by the Sponsor, who will ensure that the equipment meets the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline (Miller et al. 2005).

All spirometry reports will be stored as source data (see Section 11.2).

Spirometry procedures will be performed according to a manual. To reduce variability every effort should be made to assure consistent testing conditions throughout the trial:

- The same spirometry equipment should be used for all assessments performed by a subject within the trial
- All staff conducting the spirometry tests must have received appropriate training which must be documented

- Whenever possible the same technician should perform all manoeuvres for an individual subject.
- Whenever possible, spirometry should be conducted at the same time of day (+/-1 hour) as the baseline measurement

The subject's gender, age and height as reported at Visit 1 are entered into the spirometer and will be used throughout the trial.

Spirometry is an effort-dependent test which requires careful instruction and cooperation of the subject. The subject is recommended to be positioned in a seated position with nose clip to reduce risks related to dizziness or syncope. The technician should ensure that the subject maintains a good seal around the mouthpiece and confirm that the subject's posture is correct. The subject should be instructed to perform tidal breathing followed by a maximal inspiration until no further air can be inhaled, followed rapidly by maximum forced expiration until no more air can be exhaled or the volume time cure displays a plateau marked by flow rates of <25ml/sec for at least one second. This should be followed by a maximal inspiration. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria 2005 (Miller et al. 2005) for acceptability and repeatability.

The highest FVC and FEV_1 from any of the acceptable curves are recorded. The highest FVC and FEV_1 may not necessarily result from the same acceptable curve.

Spirometry data will be assessed by a central reader for quality control and be classified for acceptability. In addition an assessment for plausibility will be performed.

8.1.2 Biomarkers

Blood samples for potential analysis of biomarkers related to inflammation and fibrosis will be obtained at Visit 2 and the end of each treatment period (Visits 7, 11, 14 and 15).

Details of sampling and storage will be specified in the laboratory manual.

8.1.3 Pharmacokinetics

Blood samples for pharmacokinetic will be analysed in a subset (20) of subjects. The samples will be collected at Visit 2, and at the end of each treatment period at Visit 7, Visit 11 and Visit 14 prior to the morning dose and at 30 min, 1 hour, 2 hours, 3 hours, and 4 hours post-dose.

8.2 Safety Assessments

8.2.1 Adverse Events

Adverse events (AEs) will be reported from signing of informed consent until end-of-trial participation (Visit 15).

8.2.2 Medical History and Concomitant Illnesses

The medical history including date of first diagnosis of disease under study and concomitant illnesses will be obtained by interviewing the subject or by checking his/her medical records.

8.2.3 Pregnancy Test

Women of childbearing potential will undergo pregnancy tests at all visits [1)].

- Visit 1, 2 and Visit 15: Blood sample
- Visit 3 -Visit 14: Urine dip-stick

1) Women of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of Follicle-stimulating Hormone 25-140 IE/L and oestradiol <183 pmol/l is confirmatory).

8.2.4 Physical Examination

A complete physical examination including assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities will be performed at Visit 1, 2, and Visit 15.

A short version of the physical examination including assessments of selected body systems at the judgement of the investigator will be performed at all other visits (3-14) and must include a cardiovascular examination.

Each body system will be reported as “normal”, “abnormal – non clinically significant” or “abnormal –clinically significant”. Any clinically significant abnormalities prior to initiation of IMP should be specified and recorded as medical history. New clinically significant abnormalities occurring after initiation of IMP should be reported as AEs.

8.2.5 Vital Signs

Systolic and diastolic blood pressure, pulse, and body temperature will be measured in supine position after 10 minutes of rest.

8.2.6 Electrocardiogram

12-lead electrocardiography (ECG) will be recorded at all visits to the clinic (Visit 1-15).

Holter ECG will be recorded at Visit 2 from at least 30 mins prior to IMP administration until at least 180 mins after.

ECG evaluations will be performed by a central reader.

Any clinically significant ECG abnormalities prior to initiation of IMP should be specified and recorded as medical history. New clinically significant abnormalities occurring after initiation of IMP should be reported as AEs.

8.2.7 Safety Laboratory Parameters

Safety laboratory parameters which are to be taken at every visit to the clinic:

- Haematology: Haemoglobin (Hb), haematocrit (erythrocyte volume fraction), platelet count (thrombocyte particle concentration [TPC]), leucocyte count, mean corpuscular volume (MCV)
- Biochemistry: Albumin, alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, blood urea nitrogen (BUN), calcium, creatinine, c-

reactive protein (CRP), gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase (LD), potassium, sodium
- Urinanalysis: Dipstick for bilirubin, glucose, ketones, protein, specific gravity, urobilinogen, and pH

Any laboratory abnormality, judged by the investigator to be a clinically relevant worsening since Visit 1, should be reported as an AE if the laboratory abnormality requires clinical intervention or further investigation, unless the laboratory abnormality is associated with an already reported event.

8.3 Other Assessments

8.3.1 Demographics and other Baseline Characteristics

Demographic and baseline characteristics include but are not limited to age at screening, sex, height, and weight.

8.3.2 Slit Lamp Examination

A slit lamp examination will be performed by an ophthalmologist prior to Visit 2 and at Visit 15, where the results in the form of a written report including acuity, lens state, and any contraindications to cataract surgery will be reviewed by the investigator. The conduct of the slit lamp examination could be delegated to a registered optometrist, provided that the report is reviewed and approved by an ophthalmologist.

Each slit lamp examination will be reported as “normal”, “abnormal – non clinically significant” or “abnormal –clinically significant”. Any clinically significant abnormalities prior to initiation of IMP should be specified and recorded as medical history. New clinically significant abnormalities occurring after initiation of IMP should be reported as AEs.

9 ADVERSE EVENTS

9.1 Adverse Event Definitions

An adverse event (AE), an adverse drug reaction (ADR) and a serious adverse event (SAE) are defined according to ICH Guideline E2A (ICH 1994).

An AE is any untoward medical occurrence in a subject administered the IMP and which may or may not have a causal relationship with this IMP. An AE can therefore be any unfavorable and unintended sign (e.g. a significant abnormal laboratory finding, symptom, or disease temporally associated with the use of the IMP, whether or not considered related to the IMP.

An ADR is any noxious and unintended response to an IMP related to any dose of the IMP.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed)

A non-SAE is any AE that does not meet the definition of an SAE.

The following will not be considered an AE:

- Pre-planned procedure (documented at Visit 1) unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent form
- Concomitant illness identified as a result of screening procedures. However, if symptoms are worsened and/or become serious as defined in Section 9.1, this must be reported as a SAE.

9.2 Adverse Event Assessment Definitions

9.2.1 Severity

The investigator should assess the severity of all AEs according to the following definitions:

- Mild: awareness of sign or symptom, but easily tolerated (acceptable).
- Moderate: discomfort to interfere with usual activities (disturbing).
- Severe: incapacity to work or to perform usual activities (unacceptable).

Note the distinction between seriousness and severity: The term severe is used to describe the intensity of the event and a severe event is not necessarily serious. The seriousness criteria serve as a guide for defining regulatory reporting obligations.

9.2.2 Relationship to IMP

Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The investigator will be asked to assess causal relationship to the trial treatment according to the following classifications:

Related:

- Time relationship exists; and previous knowledge of the trial product supports a causal relationship although another cause cannot be ruled out; and/or improvement on dechallenge or dose reduction has occurred (if performed); and/or recurrence of symptoms on rechallenge has occurred (if performed); and/or a specific laboratory test supports a causal relationship

Not related:

- No time relationship between administration of the trial product and occurrence or worsening of the AE exists; and/or another cause is confirmed and no indication for involvement of the trial product in the occurrence/worsening of the AE exists. The alternative, most likely other cause(s) should be indicated

9.2.3 Outcome

The investigator will be asked to record the most appropriate outcome of the following:

- Recovered
- Ongoing
- Not recovered
- Recovered with sequelae
- Death
- Unknown

9.3 Reporting of Adverse Events

All events meeting the definition of an AE must be reported in the period from the subject has signed the informed consent form until the end of trial participation (Visit 15).

At each visit the subject will be asked about AEs in an objective manner, *e.g.*: “Have you experienced any problems since the last visit?”

Only medically qualified personnel (investigators) must assess AEs.

AEs must be reported on the AE form. In the eCRF the diagnosis should be recorded, if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

AEs concerning cardiac or ophthalmic conditions are of special interest and must be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

SAEs, in addition, must be reported within 24 hours of obtaining knowledge of the event. The information to be reported will include assessment of severity, causal relationship to IMP or trial procedures, action taken, outcome, and a narrative description of the course of the event. Additional information may be subsequently provided.

The SAE form and all other relevant documents supporting the reported SAE (*e.g.* diagnostic procedures, hospital records, autopsy reports) must be faxed or scanned/emailed to the Sponsor or Sponsor's designee.

The independent ethics committees (IEC) and regulatory authorities will be notified of SAEs according to current regulation and local requirements.

All suspected unexpected serious adverse reactions (SUSARs) are subject to expedited reporting to regulatory authorities.

The expectedness of a SUSAR will be assessed against the reference safety information. Any SUSARs will be reported by the clinical research organisation (CRO) to the relevant competent authority. SUSARS will also be reported to the IEC by the site/CRO. Fatal and life threatening SUSARs will be reported as soon as possible and no later than seven calendar days from the date of first knowledge of the event. Relevant follow-up information will subsequently be expedited within an additional eight days. All other SUSARs will be expedited no later than 15 calendar days of first knowledge of the event.

For AEs concerning hair symptoms, additional information may be collected, such as location and extent of hair loss, outcomes of dermatologist consultations, results from special investigations, and any photographs taken.

9.4 Follow-up on Adverse Events

All AEs should be followed until they are resolved or the subject's participation in the trial ends, whichever comes first.

SAEs and non-serious AEs considered related to trial drug should be followed on a regular basis according to the investigator's clinical judgment until a final outcome has been established.

9.5 Pregnancies

Any pregnancy that occurs during trial participation must be reported and administration of trial drug must be terminated immediately. A pregnancy must be reported to Sponsor or designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and infant. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs, as applicable. Spontaneous abortion must be reported as an SAE.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male trial participants who become pregnant while the participant is enrolled in the trial. Pregnancy information must be reported to Sponsor as described above.

10 CHANGES TO TRIAL CONDUCT

10.1 Protocol Amendments

Before implementation of substantial changes (as defined in EU guidance documents [European Commission 2006, 2010]) unless considered an Urgent Safety Measure, approval/favourable opinion must be obtained from the appropriate regulatory authority(ies) and IEC(s).

10.2 Premature Termination of the Trial

In case of premature termination of the trial, health authorities, and IECs will be notified in writing, including the reason for premature termination.

Conditions that may warrant premature termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the subjects enrolled in the trial
- A decision of the Sponsor to discontinue development of the drug

10.3 Premature Termination of a Trial Site

The Sponsor can decide to prematurely terminate a site. Conditions that may warrant termination include, but are not limited to:

- Insufficient adherence to protocol requirements
- Failure to enrol subjects at an acceptable rate

11 DATA HANDLING AND RECORD KEEPING

11.1 Data from Clinical Trial Sites

Data from clinical trial sites will be entered in an eCRF.

The investigator will sign relevant eCRF sections by use of an electronic signature. Only the investigator (i.e. medically qualified personnel) can sign data on medical assessments. Any corrections made by the investigator or authorised staff to the eCRF after original entry will be documented in an audit trail. The person making the change and the date, time and reason for the change will be identified in the audit trail. Changes to the data already approved/signed by an investigator will require re-signature by the investigator. The investigator (principal investigator or sub-investigator) will sign all patient data in the eCRF by an electronic signature.

Subject data will be recorded anonymously and the subjects will be identified only by a screening number.

The monitor will check the eCRF for accuracy and completion and perform source data verification. Data entered in the eCRF will be verified against source data. The level of source data verification is described in Section 11.2.

11.2 Source Data

All data entered in the eCRF should be verifiable by source data in the subject's medical record or other records at the trial site, as applicable:

- Details of the trial (trial ID and subject screening and enrollment number)
- Date(s) of informed consent of the subject
- Data of each trial visit including signature and /or initials of person(s) conducting the visit
- Data and information of any relevant telephone contact with the subject and signature and/or initials of person(s) conducting or receiving the call
- Subject's date of birth
- Diagnosis of IPF including start date, HRCT date and report/image
- Medical history and concomitant illness including start and stop dates
- Concomitant medication including start and stop dates
- Overall conclusion of the subject's eligibility
- Conclusion and results for each in-/exclusion criterion with respect to fulfillment of trial eligibility or not
- Physical examination
- Slit lamp data
- Height and body weight
- Blood pressure, pulse, body temperature and ECG

- All laboratory samplings and data, including date and time of blood sampling (including subjects in PK subset)
- Investigator's evaluation of haematology and biochemistry results being out of range
- Date and times of blood sampling
- Spirometry data
- All AEs, SAEs and pregnancies described in details
- IMP dispensed and date of dispensing, IMP retrieval and date of retrieval
- Premature withdrawal of subject from the trial including reason and withdrawal criteria fullfilled
- Investigator treatment evaluations

11.3 Coding of Data

Medical history and AEs will be coded using the lastest version of Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medication will be coded using the latest version of World Health Organisation (WHO) Drug Reference List.

11.4 Subject Confidentiality

The confidentiality of the subject data and subject records shall be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

12 RETENTION OF DOCUMENTS

The monitor will instruct the investigator to maintain source documents and the signed informed consent form for each subject.

Furthermore, the monitor will instruct the investigator to archive essential documents for the duration defined in the ICH Guideline E6 (Note for Guidance on Good Clinical Practice [ICH 1997]) or for 15 years, whichever comes first.

The duration of archiving defined in the ICH Guideline E6 is as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will notify the investigator when retention of the trial-related records is no longer required.

13 STATISTICAL METHODS

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate statistical analysis plan, which will be signed and approved prior to the database lock.

13.1 Sample Size and Power Considerations

Sample size is based on assumptions of a 40 mL decline in FVC/24 weeks and a standard deviation of 200 mL With 55 evaluable subjects there is a 90% power that the 90% confidence interval for the decline in FVC at 24 weeks exclude the value 120 mL, a value considered to represent the natural course decline in 24 weeks for an untreated subject. The total of 60 subjects will be included to compensate non-evaluable subjects for reasons such as early drop out.

Analysis Data Sets

The full analysis set (FAS) will consist of all subjects who have received at least one dose of IMP and who has at least one post-baseline assessment of efficacy.

The per protocol analysis set (PPAS) will be a subset of FAS and consist of all subjects without any major protocol deviations that are judged to compromise the analysis of the data and with data collection up to at least week 24. All protocol deviations will be judged as major or minor prior to database lock.

The safety analysis set (SAS) will consist of all subjects who have received at least one dose of IMP.

The pharmacokinetic (PK) dataset will consist of all subjects selected for PK assessments and with at least one post-dose plasma sample analysed.

13.2 Subject Disposition

13.2.1 Baseline Characteristics

Demographics, medical history, baseline characteristics, and prior medications will be listed and summarised in terms of descriptive statistics: mean, standard deviation, median, and range for continuous outcomes and frequencies and percentages for categorical outcomes.

13.3 Efficacy Analysis

13.3.1 Efficacy Endpoint Analysis

The change in FVC from baseline to week 12, 24, and 36 will be calculated for each subject and summarised using the population mean and corresponding 90% two-sided confidence intervals. For early withdrawn subjects, the value representing week 24 will be calculated assuming a decline rate of 60 mL/12 weeks for the period between last visit and week 24.

As a secondary approach, a mixed model will be fitted to the FVC data collected from each time point within a subject up to week 36 or last visit if withdrawn earlier. A linear or piece-wise linear relation for the FVC decline using one or several slopes will be used to model the data depending on the actual curve shape. Model parameters will be summarised. Model will be used to assess the

average decline in FVC after 12, 24, and 36 weeks of treatment together with 90% two-sided confidence intervals.

The number of rapid decliners in FVC, fulfilling the withdrawal criteria during the trial, will be summarised.

FVC and FEV1 will further be summarised by visit using descriptive statistics and visualised using mean value plots (with imputation). For FVC, further a plot of the model fit, that is observed means verssus the model predicted curve, will be constructed.

13.3.2 Pharmacokinetic Data

Plasma concentrations of C21 and derived pharmacokinetic parameters will be summarised by time point using descriptive statistics.

13.3.3 Biomarker Data

Biomarker data will be exploratory and the analyses data-driven. Collected data will be visualised graphically and summarised descriptively.

13.3.4 Statistical/Analytical Issues

13.3.4.1 Missing Data

To summarise the change in FVC from baseline to week 24, missing data at week 24 will be imputed assuming a decline rate of 60 mL/12 weeks for the period between last visit and week 24. No imputation will be done for the mixed model or for the safety summaries.

13.3.4.2 Examination of Subgroups

Important demographic and baseline value-defined subgroups may be investigated.

Subgroups or alternate imputations to investigate the impact of the COVID-19 pandemic on the analyses due to an expected increased number of subjects with missing data will also be investigated.

A detailed description will be provided in the Statistical Analysis Plan.

13.4 Safety Analysis

13.4.1 Adverse Events

An overview of all treatment-emerging AEs including severity, relationship to IMP, serious AEs (SAEs) and AEs leading to withdrawals of treatment and withdrawal from trial or death will be presented by treatment group.

AEs will be summarised by treatment group, system organ class (according to MedDRA), and preferred term (according to MedDRA) displaying number of subjects in treatment group, number and percentage of subjects having the AE as well as number of AEs. Furthermore, AEs will be summarised according to severity, relationship, outcome, and seriousness.

SAEs and AEs leading to withdrawal from treatment will be listed and tabulated, if appropriate.

13.4.2 Electrocardiogram

12-lead ECG data will be summarised by visit including the change from baseline. The number of abnormal assessments will be summarised by visit and for changes from baseline to end-of-trial.

13.4.3 Vital Signs

Vital signs data (blood pressure and pulse) will be summarised by visit including the change from baseline.

13.4.4 Laboratory Safety Assessments

Continuous laboratory data will be summarised by visit including the change from baseline. Categorical data will be summarised by visit using frequency and percentages. Laboratory parameters will be categorised as 'low', 'normal' or 'high' (*i.e.* below, within, or above the reference ranges, respectively) and summarised by visit and for changes from baseline to end-of-trial in a shift table.

13.4.5 Physical examination

Abnormal findings on the physical examination will be summarised by visit.

14 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (IDMC) has been established and will have their first meeting before the trial starts.

The functions and responsibilities of the IDMC is described in an IDMC charter.

Throughout the duration of the trial, the IDMC will evaluate all SAEs on an ongoing basis.

Further, the IDMC will monitor the overall safety of the trial during regular meetings and provide appropriate written recommendations to the Sponsor regarding trial continuation, protocol modifications or trial suspension.

Any safety related IDMC recommendations that may result in protocol changes or to the management of subjects in the trial will be reported to the Competent Authorities (CAs) and IECs. A letter of trial continuation after each IDMC meeting will be supplied to the CAs and IECs if required.

15 GOOD CLINICAL PRACTICE

This trial will be carried out in compliance with the protocol, ICH-GCP R2, Standard Operating Procedures of the CROs and applicable regulatory requirements.

The investigator agrees, when signing this protocol, to adhere to the instructions and procedures described in it, to the principles of the Declaration of Helsinki, ICH-GCP R2 and applicable regulatory requirements.

16 ETHICS

16.1 Independent Ethics Committees / Health Authorities

Before implementing this trial, the protocol, the proposed subject information and subject consent form, and other documents as required, will be reviewed by properly constituted independent ethics committees (IECs) and by the national regulatory authorities.

A signed and dated statement that the protocol and subject information and subject consent form have been approved by the IECs and regulatory authorities will be obtained before trial initiation.

For each individual IEC, the name and occupation of the chairman and the members of the IEC will be collected as well as a statement that the IEC works in accordance with ICH GCP.

IECs will receive updates on trial progress according to local regulations.

16.2 Informed Consent

The subject's signed and dated informed consent to participate in the trial will be obtained prior to any trial related procedure being carried out.

Before any trial related procedure the investigator will explain to the potential subject the aims, methods, reasonably expected benefits. and potential hazards of the trial and any discomfort participation in the trial may entail. Subjects will be informed that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. Subjects will be informed that if they choose not to participate, this will not affect the care the subject will receive for the treatment of his or her disease. Finally, subjects will be informed that their records may be accessed by health authorities and authorised Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable laws or regulations.

All subjects will be given opportunity to ask questions and will be given sufficient time to consider before consenting. The subjects may choose to be accompanied, *e.g.* by a family member, during the information process. After having consented, a copy of the informed consent form will be given to the subject.

17 AUDITS AND INSPECTIONS

A representative of the Sponsor may visit the trial site(s) at any time during the trial or after completion of the trial to conduct an audit of the trial. These audits will require access to all trial records, including source documents, for inspection and comparison with the CRFs. Subject privacy will, however, be respected. The investigator and other trial personnel will be responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor's representative.

Similar auditing procedures (inspections) may also be conducted by agents of regulatory health authorities, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should notify the Sponsor's representative or Sponsor immediately, if he/she has been contacted by a regulatory agency concerning an upcoming inspection.

18 MONITORING

Before trial initiation a monitor from the Sponsor's representative will review the protocol and the CRF with the investigators and their trial personnel. During the trial the monitor will visit the trial site regularly to check the completeness of subject records, the accuracy of entries in CRFs, the adherence to the protocol and to GCP, the progress of enrolment and the handling and accounting of IMP. Key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor direct access to source data/documents (*e.g.* relevant hospital or medical records) to confirm their consistency with the entries in CRFs. No information in these records about the identity of the subjects must leave the trial site.

19 REPORTING OF RESULTS

19.1 Integrated Clinical Trial Report

Data will be reported in an integrated clinical trial report in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Study Report (ICH 1995). The signatory investigator will review and sign the integrated clinical trial report.

The results and interpretation of the exploratory biomarker analyses may not be included in the clinical trial report but may be reported and/or published separately at a later stage.

19.2 Use of Information

All unpublished information relating to this trial and/or to the trial drug is considered confidential by the Sponsor and shall remain the sole property of the Sponsor.

The investigator must accept that the Sponsor may use the information from this clinical trial in connection with the development of the IMP, and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other governments, stock exchange market, and commercial partners.

19.3 Publication of Results

Basic information of this trial will be posted by the Sponsor on the website: www.clinicaltrials.gov before the first subject enters the trial.

The Sponsor is committed to publishing the trial results, whether positive or negative, in a peer-reviewed journal (Wager, 2003; Graf 2009).

The criteria for authorship as set out by the Committee of Medical Journal Editors (www.icmje.org) will be applied.

The contributorship model will be applied and contributors who do not meet the criteria for authorship will be listed in an acknowledgments section with descriptions of the role of each contributor in order to ensure indexation in the National Library of Medicine.

Publications are subject to the following conditions:

- Data are the property of the Sponsor and cannot be published without prior authorisation from the Sponsor
- Publications should be drafted with protection of individual privacy, intellectual property, and contract rights in mind, and also conform to legislation and current national practices in patent and other laws
- The primary publication (*i.e.* the results from all centers) should be published before, or in parallel with, any secondary publications
- Publications shall not disclose any Sponsor confidential information or property

20 INSURANCE AND LIABILITY

The Sponsor has subscribed to an insurance policy covering, in its terms and provision, its legal liability for injuries caused to participating subjects and arising out of trial procedures performed in accordance this protocol, in accordance with applicable law and with the ICH Guideline E6 (Note for Guidance on Good Clinical Practice) (ICH 1997).

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22 ABBREVIATIONS

Ab	Antibody
ADR	Adverse drug reaction
AE	Adverse event
Ag	Antigen
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AngII	Angiotensin II
AST	Aspartate aminotransferase
AT_1R	Angiotension type 1 receptor
AT_2R	Angiotension type 2 receptor
AUC	Area under the curve
b.i.d.	bis in die (i.e. twice a day)
BMI	Body mass index
BUN	Blood urea nitrogen
CA	Competent authorities
C_{max}	Maximum plasma concentration
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CYP	Cytochrome p450
eCRF	Electronic case report form
ECG	Electrocardiography
ECM	Extracellular matrix
FAS	Full analysis set
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCVAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
H2RA	Histamine H2 receptor antagonist
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IPF	Idiopathic pulmonary fibrosis
LD	Lactate dehydrogenase
MAD	Multiple ascending dose
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observed adverse effect level
PH	Pulmonary hypertension
PK	Pharmacokinetic
PPAS	Per protocol analysis set
PPI	Proton pump inhibitor
RP	Raynaud's phenomenon
SAD	Single ascending dose

SAE	Serious adverse event
SAS	Safety analysis set
SpO_2	Oxygen saturation
SSc	Systemic sclerosis
SSc-RP	Raynaud's phenomenon secondary to SSc
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
t_{max}	Maximal plasma concentration
TPC	Thrombocyte particle concentration
UIP	Usual interstitial pneumonitis
WHO	World Health Organisation

23 PROTOCOL AMENDMENT HISTORY

Protocol amendment summary of changes table

Document	Description of change	Rationale for change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]