Study Title:	A phase II, randomised, double blind, placebo-controlled study of the pharmacokinetics, pharmacodynamic effects, and safety, of oral FT011 in participants with diffuse systemic sclerosis
Protocol ID:	CER-FT011-SSc01
UTN:	U1111-1259-3503
IND number:	148214
EudraCT number:	2020-005116-21
Test Drug:	FT011
Indication:	Diffuse Systemic Sclerosis
Study Sponsor:	Certa Therapeutics Pty Ltd Level 9, 31 Queen Street Melbourne VIC 3000 Australia Telephone +61 (3) 9657 0704
Sponsor protocol approval	Dr Darren Kelly, CEO
Version:	2.1
Date:	01 November 2021

CONFIDENTIALITY STATEMENT

INVESTIGATOR'S STATEMENT

The undersigned Investigator agrees:

1. To conduct the study in accordance with the study protocol, International Conference on Harmonisation Good Clinical Practice and any national and local laws and regulations.
2. That alteration of the procedures described in the study protocol, other than to protect participant safety, rights, or welfare, is not allowed without prior written approval from Certa Therapeutics Pty Ltd.
3. The study-specific data of the participants will be kept in the participants' files and documented in the case report form in a complete and accurate manner. All requested study-related records will be made available for direct access to Certa Therapeutics or designee representatives for monitoring or auditing the study.
4. To allow authorised qualified delegates of Certa Therapeutics Pty Ltd or designee to perform regular visits to monitor the study data.
5. To dispose of used and unused investigational medicinal product and materials as instructed by Certa Therapeutics Pty Ltd.
6. To ensure that all persons at their site assisting with the clinical study are adequately informed and trained about the study protocol, the investigational medicinal product and their study-related duties and functions.

Investigator signature	Date
Name	Site number

1 PROTOCOL SYNOPSIS

Study Title:	A phase II, randomised, double blind, placebo-controlled study of the pharmacokinetics, pharmacodynamic effects, and safety, of oral FT011 in participants with diffuse systemic sclerosis
Study Period:	2021 - 2022
Objectives:	Primary objective: • To assess the pharmacokinetics (PK) of oral FT011 in participants with diffuse systemic sclerosis (SSc). Secondary objectives: • To assess the safety and tolerability of oral FT011 compared to placebo in participants with diffuse SSc. • To evaluate the short-term efficacy of oral FT011 compared to placebo in improving disease activity in participants with diffuse SSc. [redacted]
Number of participants:	Approximately 30 participants will be randomised and treated.
Study design	This is a multi-centre, randomised, double blind, placebo-controlled study to assess the pharmacokinetic pharmacodynamic effects and safety of FT011 in participants with diffuse systemic sclerosis. The targeted study population is patients with diffuse SSc with a disease duration of ≤10 years from onset of first non-Raynauds symptom, and a modified Rodnan Skin Score (mRSS) of 15 to 40 at the screening visit. Patients meeting all eligibility criteria will have a baseline skin biopsy (2 x 3mm punch biopsies) taken before being randomised 1:1:1 to FT011 200mg, FT011 400mg, or placebo. Participants will take their investigational medicinal product (IMP) once a day for 3 months (12 weeks), in addition to their standard-of-care scleroderma medications. They will return to the site for study visits at Weeks 4, 8, and 12. Week 12 is the end of the study Treatment Period. A final study follow-up visit will be conducted one month after they complete treatment (Week 16).

	Visit procedures will include skin thickness assessments using the mRSS at every visit, and forced vital capacity (FVC), the Scleroderma Health Assessment Questionnaire- Disability Index (SHAQ-DI), and physician and patient global assessments at all visits during the Treatment Period. A follow up skin biopsy will be taken at Week 12. On Day 1 and at Week 12 participants will have serial PK samples collected out to 8 hours post-dose, and trough samples will be collected at each interim visit. Other on-study visit assessments will include additional participant questionnaires, physical examinations, vital signs measurements, safety laboratory blood and urine tests, and electrocardiograms. Adverse events and concomitant medications will be assessed and recorded at each study visit. Additional blood samples will be collected at Day 1 and Week 12 for exploratory assessments. With the exception of methotrexate, which is excluded, participants should be maintained on their current SSc medications during the course of the Treatment Period unless they meet the following progression criteria; those who have a mRSS increase from Baseline of 5 or more may start immunosuppressive medications, or, if already taking these, have their immunosuppressive medications or doses changed. A Data Safety Monitoring Board (DSMB) will review safety and PK data at agreed recruitment and progression milestones to provide independent oversight of participant safety.
Criteria for inclusion:	Participants must meet all the following criteria: • Provide written informed consent prior to any study procedures and who agree to adhere to all protocol requirements. • Aged 18 to 75 years inclusive at the time of consent. • Have a classification of systemic sclerosis, as defined by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria with disease duration ≤10 years from first non-Raynaud phenomenon manifestation. • Have a diagnosis of diffuse cutaneous SSc defined as systemic sclerosis with skin thickening on the upper arms proximal to the elbows, on the upper legs proximal to the knees, or on the trunk. • Have skin thickening in a body area suitable for repeat biopsy. • Have a mRSS at Screening of ≥15 to ≤40. • FVC ≥50% of predicted at Screening. • If on azathioprine, mycophenolate mofetil, or hydroxychloroquine, have been on a stable dose for at least 2 months prior to baseline. • Participants must agree to use contraception according to protocol section 5.4.4.

Criteria for exclusion:	Participants must not meet any of the following criteria:
	• Pregnant or breast-feeding, or plan to become pregnant during the study.
	• Have received any IMP within 30 days or 5 half-lives prior to randomisation (4 months if the previous drug was a new chemical entity), whichever is longer.
	• Have known or suspected contraindications to the IMP.
	• Have severe or unstable SSc or end-stage organ involvement as evidenced by:
	  ○ On an organ transplantation list or has received an organ transplant including autologous stem cell transplant.
	  ○ Renal crisis within 1 year prior to Baseline.
	• Interstitial lung disease or pulmonary hypertension requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise.
	• Gastrointestinal dysmotility requiring total parenteral nutrition or requiring hospitalisation within the 6 months prior to Baseline.
	• Concomitant inflammatory myositis, rheumatoid arthritis, or systemic lupus erythematosus when definite classification criteria for those diseases are met (Bohan and Peter criteria for polymyositis and dermatomyositis)
	• SSc-like illnesses related to exposures or ingestions
	• The use of the following drugs within the specified periods:
	  ○ Methotrexate in the 2 weeks prior to Day 1
	  ○ Other anti-fibrotic agents including D-penicillamine or tyrosine kinase inhibitors (nilotinib, imatinib, dasatinib) in the month prior to Screening.
	  ○ Biologic drugs such as tumour necrosing factor (TNF) inhibitors, tocilizumab, or Janus kinase (JAK) inhibitors, in the 3 months prior to Screening.
	  ○ Rituximab in the 6 months prior to Screening.
	  ○ Cyclophosphamide oral or intravenous (IV) in the 3 months prior to Screening.
	  ○ Oral prednisolone >10 mg per day or IV steroids in the month prior to Screening.
	• Have any malignancy not considered cured (except basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix); a subject is considered cured if there has been no evidence of cancer recurrence for the 6 years prior to randomisation.

	• Have aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), or bilirubin values above the upper limit of normal (ULN) at Screening or Baseline, or evidence of hepatic disease as determined by any one of the following: history of hepatic encephalopathy, history of oesophageal varices, or history of portacaval shunt. • Estimated glomerular filtration rate (eGFR) <60mL/min, urinary albumin/creatinine ratio >30mg/g. • Haemoglobin < 80 g/L, platelets < 90 x 10^9/L, or neutrophil count < 1.4 x 10^9/L • Other than SSc, have any other medical condition or significant co-morbidities, clinically relevant social or psychiatric conditions, or any finding during Screening, which in the investigator's opinion may put the subject at risk or interfere with the study objectives.
Test product, dose, and mode of administration:	FT011 and placebo will be presented as oral capsules. FT011 capsules will contain 100mg or 200mg of FT011 and excipients. Placebo will contain microcrystalline cellulose. Participants will take two capsules once a day for the 12-week treatment period, for a total daily dose of 200mg or 400mg FT011, or matching placebo.
Duration of study per participant:	The Screening period may be up to 28 days. The on-study period consists of a 12-week treatment period and a 4 week follow up period. Total duration of the study may be up to 20 weeks.
Criteria for evaluation:	<u>Primary Outcome Measures</u> • FT011 maximum concentration (c_{max}), time to maximum concentration (t_{max}), and area under the curve (AUC) in plasma after a single dose and after 12-weeks of treatment. • Measurement of steady state FT011 levels in plasma. <u>Secondary Outcome Measures</u> Safety will be assessed by: • Treatment emergent adverse events from first dose of study drug to End of Study • Physical examination • Vital signs (blood pressure, heart rate, respiratory rate, and temperature) • 12-lead electrocardiograms (ECG) • Safety laboratory results (haematology, biochemistry, coagulation, and urinalysis) • Use of concomitant medications Efficacy will be measured by: • Change in mRSS from Baseline at each visit.

	• Change in percent predicted FVC from Baseline to Week 4, Week 8, and Week 12. • Change in SHAQ-DI Score from Baseline to Week 4, Week 8, and Week 12. • Change in Patient Global Assessment Score from Baseline to Week 4, Week 8, and Week 12. • Change in Physician Global Assessment Score from Baseline to Week 4, Week 8, and Week 12. • The proportion of patients showing an improvement (defined as ACR Composite Response Index in Diffuse Cutaneous Systemic Sclerosis (CRISS) score predicted probability of ≥0.60) at Week 12. • Change in the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) score from Baseline to Week 12. • Change in the 5-D Itch Scale from Baseline to Week 12. [redacted]
Safety Monitoring and Oversight	Participants with confirmed ALT or AST levels > 3 x ULN must have close observation that includes elicitation of a detailed history and performance of diagnostic lab studies to exclude other causes of acute liver injury. In addition, they should have their liver chemistry (ALT, AST, ALP, international normalised ratio (INR) and total bilirubin) retested at least once weekly until levels normalise or return to baseline. In the event of confirmed laboratory results meeting any of following criteria, IMP will be stopped permanently for that participant: • ALT or AST >8 x ULN • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN and either bilirubin >2 x ULN or INR >1.5 • ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) If serum creatinine is ≥ Grade 3, IMP will be stopped for that participant and they will be monitored until values return to Grade 1. IMP may then be restarted but stopped permanently if there is a recurrence of serum creatinine levels ≥ Grade 3.

	An independent DSMB will be established prior to recruitment start, with appropriate charter that defines its roles and responsibilities. The DSMB will monitor accruing trial safety results, and PK data, at intervals throughout the study. The main purpose of the DSMB will be to protect the safety interests of the participants included in the trial. If pre-defined study stopping rules are met, recruitment will be halted and the DSMB will review the data and advise whether recruitment and dosing may continue, or whether the study should be stopped. The charter will specify the intervals for formal DSMB meetings. The DSMB will convey to Certa Therapeutics Pty Ltd their recommendations as to whether the trial may continue as planned or if the trial should be modified or stopped. The final decision on whether the study should be modified or stopped will be the responsibility of Certa Therapeutics Pty Ltd; any decision to modify or stop will be communicated to investigators and regulatory authorities (RA) by Certa Therapeutics Pty Ltd or their representatives.
Statistical methods and analyses:	Sample Size Justification The sample size for this study is sized based on practical considerations and no formal sample size calculation was performed. A total of approximately 30 participants, 10 per treatment group, will be randomised and treated. Statistical Analyses A statistical analysis plan (SAP) will be written and finalised prior to database lock. The SAP will contain detailed and complete descriptions of the analyses that will be performed. *Analysis Sets* The following analysis sets will be defined: Intention-to-Treat (ITT) Set: The ITT set is defined as all participants who were randomised. Participants in this set will be analysed based on the treatment that they were randomised to. Safety Set: The safety set is defined as all participants who were randomised and received at least one dose of study medication. Participants in this set will be analysed based on the actual treatment that they received. All safety analyses will be based on the safety set. Modified Intention-to-Treat (mITT) Set: The mITT set is defined as all randomised participants who received at least one dose of study medication and who have post-baseline efficacy data for at least one of the outcome measures. All efficacy analyses will be based on the mITT set. Participants in this set will be analysed based on the treatment that they were randomised to. PK Set: The PK set is defined as all participants included in the safety set who have sufficient concentrations to allow for the calculation of at least one PK parameter. Participants who experience any adverse events or have protocol

	deviations that could affect the PK profiles may be excluded from the PK set at the pharmacokineticist's discretion. All PK analyses will be based on the PK set. Participants in this set will be analysed based on the actual treatment that they received. *General Considerations* Results will be presented by treatment group, pooled FT011 group and overall. In general, data will be summarised using descriptive statistics (number of observations, mean, median, standard deviation [SD], minimum and maximum) or frequency counts and percentages, as appropriate to the type of data. The coefficient of variation (CV), geometric mean and geometric CV will also be presented for the PK tables. Confidence intervals will be reported where appropriate. If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of 5%. Where appropriate, results will be presented graphically. All reported data will be presented in data listing. The baseline value for each endpoint is defined as the last available, non-missing value obtained prior to the first study medication administration. The handling of missing data and adjustments for multiplicity will be described in the SAP. *Pharmacokinetic Analyses* All PK analyses will be based on the PK set. Descriptive statistics by nominal collection time will be presented for the PK concentrations. Concentrations will also be presented graphically on both linear and semi-logarithmic scales. The PK parameters will be calculated using non-compartmental analysis methods. Full details will be provided in the SAP. Descriptive statistics will be presented for the PK parameters. *Safety Analyses* All safety analyses will be based on the safety set. Medical history findings and AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and medications the World Health Organisation Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classification codes. Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsen on or after the first study medication administration. The incidence of TEAEs will be summarised by MedDRA terms and treatment group. Drug-related, serious AEs (SAEs) and TEAEs leading to early study withdrawal will also be summarised. Separate summaries will be produced based on severity and relationship to study drug categories.

	Other safety endpoints including, vital signs, ECGs, safety laboratory results will be analysed descriptively. *Efficacy Analyses* All efficacy analyses will be based on the mITT set. Descriptive statistics will be presented for all efficacy endpoints and results will be presented graphically where appropriate. Whilst no formal hypothesis testing is planned, exploratory analyses may be performed to assess the treatment effect of FT011 on the efficacy outcomes. Full details of any inferential analyses will be provided in the SAP.

2 STUDY SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

	Screening	Treatment Period			End of Treatment	Follow Up[1]
Day	**Day -28 to -1**	**Day 1[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**
Window	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**+1 week**
Written informed consent	X					
Inclusion/Exclusion Criteria	X	X[3]				
Demographics	X					
Medical History	X	X				
Patient Global Assessment		X	X	X	X	
Scleroderma signs and symptoms	X	X	X	X	X	X
mRSS	X	X	X	X	X	X
SHAQ-DI		X	X	X	X	
SCTC-DI		X			X	
5-D Itch Scale		X			X	
Physical Examination	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]
Weight	X	X	X	X	X	X
Vital Signs[6]	X	X[7]	X	X	X[7]	X
Spirometry	X	X	X	X	X	
Physician Global Assessment		X	X	X	X	
12-lead ECG	X	X	X	X	X	X
Immune cell activation markers		X[8]			X[9]	
Plasma PK		X[10]	X[11]	X[11]	X[10]	
Biochemistry[12]	X	X	X	X	X	X
Haematology	X	X	X	X	X	X
Coagulation panel	X	X	X	X	X	X

[1] The follow up visit will be conducted 4 weeks after the end of treatment period, or, if the participant withdraws early, 4 weeks after their last dose of IMP

[2] For scheduling purposes, Day 1 assessments may be conducted over 2 consecutive days, as long as dosing and PK samples are collected on the second day

[3] Review and confirmation that participant continues to be eligible.

[4] Including height

[5] Symptom directed physical examination

[6] Vital signs will include supine blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature

[7] Vital signs will be measured pre-dose and immediately prior to the 8-hour post-dose PK sample

[8] To be collected pre dose and prior to other blood samples

[9] Collected pre dose and prior to other blood samples, and at 4 hours post dose

[10] Plasma collection within the 30 minutes prior to dosing, and at 1, 2, 3, 4, 5, 6, 7- and 8-hours post-dose

[11] Trough plasma collection within the 30 minutes prior to dosing

[12] Includes serum pregnancy test for women of child-bearing potential.

	Screening	Treatment Period			End of Treatment	Follow Up[1]
Day	**Day -28 to -1**	**Day 1[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**
Window	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**+1 week**
Urinalysis	X	X	X	X	X	X
Plasma/serum cytokines and chemokines (pre-dose)		X	X	X	X	
Skin punch biopsies (two pre-dose)		X[13]			X	
Prior and Concomitant Medication	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Randomisation		X				
Dispense IP		X	X	X		
IMP accountability			X	X	X	
IMP administration		← X →				

[13] Baseline (Day 1) biopsies may be collected at any time pre-dose once the participant has been confirmed as eligible, including on a different day.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	Degrees Celsius
°F	Degrees Fahrenheit
µM	Micromols
ACR	American College of Rheumatology
AE	Adverse event
ALT	alanine transaminase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BLQ	Below limit of quantification
BMI	Body mass index
CCL2	c-c motif chemokine ligand
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
Cl/F	Apparent clearance
c_{max}	Maximum concentration
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case Report Form
CRISS	Composite Response Index in Diffuse Cutaneous Systemic Sclerosis
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective tissue growth factor
CV	Coefficient of variation
CXCL4/8	CXC-type chemokines
DM	Diabetes mellitus
DN	Diabetic nephropathy
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EULAR	European League Against Rheumatism
FEV1	Forced expiratory volume in 1 second
FSGS	Focal Segmental Glomerular Sclerosis
FVC	Forced Vital Capacity
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire - Disability Index
hCav1.2	L-type calcium channel
HDPE	High density polyethylene
hERG	Human ether-a-go-go

Abbreviation	Definition
hNav1.5	sodium channel
HPMC	hydroxypropyl methylcellulose
HRCT	high resolution computed tomography
IB	Investigators Brochure
ICAM	Intercellular Adhesion Molecule 1
ICH	International Conference on Harmonisation
ID	Identification
IL	interleukin
ILD	Interstitial lung disease
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to treat
IV	intravenous
JAK	Janus kinase
kg	Kilogram
L	litres
LDH	lactate dehydrogenase
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligram
min	Minute
mITT	modified intention to treat
mL	Millilitre
mRSS	modified Rodnan skin score
NFκB	nuclear factor kappa B
ng	nanogram
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PDGF	Platelet derived growth factor
PI	Principal Investigator
PICF	Participant Information and Consent Form
PK	Pharmacokinetic(s)
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
scRNA-seq	Single cell RNA sequencing
SCTC-DI	Scleroderma Clinical Trials Consortium Damage Index
SD	Standard deviation
SD rats	Sprague Dawley rats
SHAQ-DI	Scleroderma Health Assessment Questionnaire- Disability Index
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SSc	Systemic sclerosis
STNx	subtotal nephrectomy

Abbreviation	Definition
$T_{1/2}$	Half life
TEAEs	Treatment-emergent adverse events
TGFβ	transforming growth factor beta
T_{max}	Time to maximum concentration
TNFα	tumour necrosing factor alpha
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
WHODD	World Health Organisation Drug Dictionary
WOCBP	Women of child-bearing potential

3 BACKGROUND AND RATIONALE

Investigators should be familiar with the current FT011 Investigator's Brochure (IB).

3.1 Scleroderma

Systemic sclerosis (SSc) is a rare and complex autoimmune disease, characterised by vascular damage, chronic inflammation, and fibrosis of the skin and internal organs. The current treatment recommendations include the use of immunosuppressants, such as methotrexate, mycophenolate mofetil, and cyclophosphamide, for managing the symptoms and preventing complications in SSc patients[1]. However, these treatments have poor efficacy and are associated with significant side effects, such as organ toxicities and serious infections. Nintedanib, a multiple tyrosine kinase inhibitor recently approved for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD), slowed the rate of decline in lung function in SSc-ILD[2]. Since no clinical benefit of nintedanib was observed for other manifestations of the disease, there remains an unmet need for safe and effective treatments in early diffuse SSc patients.

3.2 FT011

[redacted]

3.2.1 FT011 for treatment of Scleroderma

[redacted]

3.3 Nonclinical Studies with FT011

A comprehensive nonclinical program supporting the development of FT011 includes *in vitro* and *in vivo* primary pharmacodynamic (PD) studies, safety pharmacology studies (central nervous system [CNS], respiratory, cardiovascular), *in vitro* and *in vivo* pharmacokinetic (PK) studies and repeat-dose toxicity studies.

3.3.1 Pharmacodynamics

[redacted]

3.3.2 Toxicology

[redacted]

3.3.3 Pharmacokinetics

[redacted]

3.4 Clinical Studies with FT011

[redacted]

3.5 Study and Dose Justification

[redacted]

[redacted]

3.6 Risk: Benefit Assessment

[redacted]

4 STUDY OBJECTIVES

The objectives of this study are to assess the PK, PD, and safety of FT011 in participants with diffuse SSc.

Primary objective:

- To assess the PK of oral FT011 in participants with diffuse SSc.

Secondary objectives:

- To assess the safety and tolerability of oral FT011 compared to placebo in participants with diffuse SSc.
- To evaluate the short-term efficacy of oral FT011 compared to placebo in improving disease activity in participants with diffuse SSc.

Exploratory objectives:

- [redacted]
- [redacted]
- [redacted]

5 STUDY PLAN

5.1 Overall Trial Design

This is a multi-centre, randomised, double blind, placebo-controlled study to assess the PK and PD effects and safety of FT011 in participants with diffuse systemic sclerosis.

The targeted study population is patients with diffuse SSc with a disease duration of ≤10 years from onset of first non-Raynauds symptom, and a modified Rodnan Skin Score (mRSS) of 15 to 40 at the screening visit. Patients meeting all eligibility criteria will have a baseline skin biopsy (2 x 3mm punch biopsies) taken before being randomised 1:1:1 to FT011 200mg, FT011 400mg, or placebo.

Participants will take their investigational medicinal product (IMP) once a day for 3 months (12 weeks), in addition to their standard-of-care scleroderma medications. They will return to the site for study visits at Weeks 4, 8, and 12. Week 12 is the end of the study Treatment Period. A final study follow-up visit will be conducted one month after they complete treatment (Week 16).

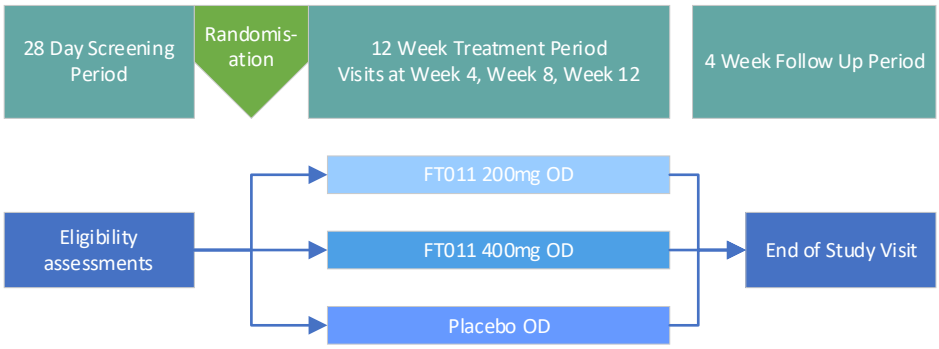
Visit procedures will include skin thickness assessments using the mRSS at every visit, and forced vital capacity (FVC), the Scleroderma Health Assessment Questionnaire- Disability Index (SHAQ-DI), and physician and patient global assessments at each visit during the Treatment Period. A follow up skin biopsy will be taken at Week 12. On Day 1 and at Week 12 participants will have serial PK samples collected out to 8 hours post-dose, and trough samples will be collected at each interim visit. Other on-study visit assessments will include additional participant questionnaires, physical examinations, vital signs measurements, safety laboratory blood and urine tests, and electrocardiograms. Adverse events and concomitant medications will be assessed and recorded at each study visit. Additional blood samples will be collected at Day 1 and Week 12 for exploratory assessments.

With the exception of methotrexate, which is excluded, participants should be maintained on their current SSc medications during the course of the Treatment Period unless they meet the following progression criteria; those who have a mRSS increase from Baseline of 5 or more may start immunosuppressive medications, or, if already taking these, have their immunosuppressive medications or doses changed.

Safety rules are in place outlining actions to be taken based on liver function laboratory values. In addition, a Data Safety Monitoring Board (DSMB) will review safety and PK data at agreed recruitment and progression milestones to provide independent oversight of participant safety.

Figure 1, below, shows the study plan.

Figure 1: Study Flow Diagram



5.2 Number of Participants

It is planned that approximately 30 adults with diffuse SSc, aged 18 – 75 years inclusive, will be randomised. Additional participants may be enrolled at the sponsor's decision as replacement for dropouts.

5.3 Study Period/Duration of Participant Participation

The duration of the study for each participant includes a Screening Period of up to 28 days, followed by a 12-week Treatment Period and a 4 week Follow Up Period. Total study duration for each participant may be up to 20 weeks.

It is anticipated that recruitment will take approximately 12 months. The study period is expected to be across 2021 and 2022.

The end of the trial is defined as the last protocol-specified data available from the last participant in the study.

5.4 Participant Selection and Withdrawal

5.4.1 Trial selection record

Investigators must keep a record of participants who were considered for the study but were not enrolled.

5.4.2 Inclusion criteria

Participants must meet all the following criteria:

1. Provide written informed consent prior to any study procedures and who agree to adhere to all protocol requirements.
2. Aged 18 to 75 years inclusive at the time of consent.
3. Have a classification of systemic sclerosis, as defined by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria with disease duration ≤10 years from first non-Raynaud phenomenon manifestation.
4. Have a diagnosis of diffuse cutaneous SSc defined as systemic sclerosis with skin thickening on the upper arms proximal to the elbows, on the upper legs proximal to the knees, or on the trunk.
5. Have skin thickening in a body area suitable for repeat biopsy.
6. Have a mRSS at Screening of ≥15 to ≤40.

7. FVC ≥50% of predicted at Screening.
8. If on azathioprine, mycophenolate mofetil, or hydroxychloroquine, have been on a stable dose for at least 2 months prior to baseline.
9. Participants must agree to use contraception according to protocol section 5.4.4.

5.4.3 Exclusion criteria

Participants must not meet any of the following criteria:

1. Pregnant or breast-feeding, or plan to become pregnant during the study.
2. Have received any IMP within 30 days or 5 half-lives prior to randomisation (4 months if the previous drug was a new chemical entity), whichever is longer.
3. Have known or suspected contraindications to the IMP.
4. Have severe or unstable SSc or end-stage organ involvement as evidenced by:
    a. On an organ transplantation list or has received an organ transplant including autologous stem cell transplant.
    b. Renal crisis within 1 year prior to Baseline.
5. Interstitial lung disease or pulmonary hypertension requiring constant oxygen therapy. This excludes oxygen used to aid sleep or exercise.
6. Gastrointestinal dysmotility requiring total parenteral nutrition or requiring hospitalisation within the 6 months prior to Baseline.
7. Concomitant inflammatory myositis, rheumatoid arthritis, or systemic lupus erythematosus when definite classification criteria for those diseases are met (Bohan and Peter criteria for polymyositis and dermatomyositis)
8. SSc-like illnesses related to exposures or ingestions
9. The use of the following drugs within the specified periods:
    a. Methotrexate in the 2 weeks prior to Day 1
    b. Other anti-fibrotic agents including D-penicillamine or tyrosine kinase inhibitors (nilotinib, imatinib, dasatinib) in the month prior to Screening.
    c. Biologic drugs such as tumour necrosing factor (TNF) inhibitors, tocilizumab, or Janus kinase (JAK) inhibitors, in the 3 months prior to Screening.
    d. Rituximab in the 6 months prior to Screening.
    e. Cyclophosphamide oral or IV in the 3 months prior to Screening.
    f. Oral prednisolone >10 mg per day or IV steroids in the month prior to Screening.
10. Have any malignancy not considered cured (except basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix); a subject is considered cured if there has been no evidence of cancer recurrence for the 6 years prior to randomisation.
11. Have aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), or bilirubin values above the upper limit of normal (ULN) at

Screening or Baseline, or evidence of hepatic disease as determined by any one of the following: history of hepatic encephalopathy, history of oesophageal varices, or history of portacaval shunt.

12. Estimated glomerular filtration rate (eGFR) <60mL/min, urinary albumin/creatinine ratio >30mg/g.
13. Haemoglobin < 80 g/L, platelets < 90 x 10^9/L, or neutrophil count < 1.4 x 10^9/L
14. Other than SSc, have any other medical condition or significant co-morbidities, clinically relevant social or psychiatric conditions, or any finding during Screening, which in the investigator's opinion may put the subject at risk or interfere with the study objectives.

5.4.4 Contraception requirements

The reproductive and development effects of FT011 have not been tested. Therefore, as a precaution, female participants should avoid becoming pregnant and male participants should avoid fathering children or donating sperm, for the duration of the study and at least three months after their last dose of IMP. If a participant becomes pregnant during the study, IMP must be stopped permanently, and the participant withdrawn from the study.

There is no requirement to use contraception if the participant or their sole partner is permanently sterile, according to one of the following criteria:

- A female who has undergone surgical sterilisation (e.g., hysterectomy, bilateral salpingectomy, or bilateral salpingo-oophorectomy).
- A female who is postmenopausal, defined as one year without menses without an alternative medical cause.
- A male who has had bilateral orchidectomy.

All other participants must be advised to use (or ensure their partner uses) at least one method of highly effective contraception (i.e., methods with a failure rate of less than 1% per year when used consistently and correctly) for the entire study period and for 3 months after their last dose of IMP. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device.
- Intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner, provided that partner is the sole sexual partner of the female trial participant and that the vasectomised partner has received medical assessment of the surgical success
- sexual abstinence defined as refraining from heterosexual intercourse, as the preferred and usual lifestyle of the subject.

As potential interactions of FT011 with hormonal contraceptives have not been examined, male partners of WOCBP participants must also use a condom.

Male participants with a partner who is a WOCBP must use a condom.

If a participant, or a male participant's partner, does become pregnant during the period specified above, the participant will be asked to inform the investigator as soon as possible and consent to follow-up of the pregnancy outcome by Certa Therapeutics or designee.

5.4.5 Concomitant Medications and Treatments

Methotrexate must not be taken within the 2 weeks prior to Day 1, or during the study.

Participants should be maintained on their current SSc medications during the Treatment Period, unless they have a mRSS increase from Baseline of 5 or more. In this case they may start immunosuppressive medications, or, if already taking those, have their immunosuppressive medications or doses changed.

The following medications are exclusionary if taken during the specified pre-study period and should not be taken during the study treatment period.

- Other anti-fibrotic agents including D-penicillamine or tyrosine kinase inhibitors (nilotinib, imatinib, dasatinib) in the month prior to Screening.
- Biologic drugs such as TNF inhibitors, tocilizumab, or JAK inhibitors, in the 3 months prior to Screening.
- Rituximab in the 6 months prior to Screening.
- Cyclophosphamide oral or IV in the 3 months prior to Screening.
- Oral prednisolone >10 mg per day or IV steroids in the month prior to Screening.

[redacted]

If these medications are required to be used during the study Treatment Period, the investigator should discuss with the Medical Monitor whether the participant may remain on study or must be withdrawn.

Any treatment or medication that is used, other than the IMP, must be noted in the source documentation and the Case Report Form (CRF). This record should include the drug name, the dose and frequency, route of administration, the start and stop date of administration, and the indication.

Medications or treatments taken in the 1 month prior to Baseline will be recorded on the prior medication CRF. Any use of medications for the treatment of AE will be recorded on the concomitant medication CRF.

5.4.6 Study Restrictions

There are no additional study restrictions.

5.4.7 Withdrawal of Participants from Study

Participants can terminate their study participation at any time. Participants who discontinue from the trial should always be asked about the reason(s) for their discontinuation and about the presence of any AEs.

The Investigator or the Medical Monitor can exclude a participant from further taking part in the trial.

Possible reasons for discontinuing a participant may include:

- Participant withdrawal of consent
- Any unacceptable AEs, in the judgement of the Investigator
- Participant's non-compliance with the protocol
- Certa Therapeutics terminates the study for financial or other reasons

If a participant withdraws or is withdrawn, they should be encouraged to attend the follow up visit.

5.4.8 Stopping Rules / Discontinuation Criteria

5.4.8.1 Individual Participant Stopping Rules

Safety laboratory testing will be performed by a study central laboratory.

If ALT or AST > 3 x ULN, the participant must have repeat testing conducted within 48 to 72 hours to confirm the values.

If the elevation is confirmed as >3 x ULN, close observation that includes elicitation of a detailed history and performance of diagnostic laboratory studies to exclude other causes of acute liver injury must be conducted. In addition, participants must have their liver chemistry (ALT, AST, ALP, international normalised ratio (INR) and total bilirubin) retested at least once weekly until levels normalise or return to baseline.

In the event of confirmed laboratory results (i.e. confirmed on retest within 48 to 72 hours) meeting any of following criteria, IMP will be stopped permanently for that participant:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and either bilirubin >2 x ULN or INR >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

If serum creatinine is ≥ Grade 3 (based on the Common Terminology Criteria for Adverse Events (CTCAE)[11]), IMP will be stopped for that participant and they will be monitored until values return to Grade 1. IMP may then be restarted but stopped permanently if there is a recurrence of serum creatinine levels ≥ Grade 3.

All participants should attend the follow up visit 4 weeks after their last dose of IMP.

5.4.8.2 Study Stopping Rules

Recruitment will be halted and there will be an immediate review by the DSMB if any of the following conditions are met:

- Three participants meet the same individual stopping rule.
- Five participants meet any individual stopping rule.
- There is any participant death assessed as related to IMP.

The DSMB will review and recommend whether to continue recruitment and dosing, or to stop the study. Participants who have not met any stopping rules may continue dosing while DSMB review is ongoing.

Additional stopping rules may be set by the DSMB.

5.4.9 Replacement of Participants

Participants who are randomised but who withdraw prior to dosing will be replaced. Additional participants may be enrolled into the study at the request of Certa Therapeutics to replace dropouts and ensure sufficient Week 12 PK samples are obtained for primary endpoint analysis. Participants who withdraw due to AE will not be replaced.

5.5 Study Treatment

5.5.1 Description of the Investigational Medicinal Product

[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]

5.5.2 Packaging and labelling

The IMP will be presented in white high-density polyethylene (HDPE) bottles, containing 70 capsules per bottle.

Labelling is in accordance with applicable requirements for each country participating in the clinical trial.

5.5.3 Investigational Medicinal Product handling and storage

IMP must be stored at 15 to 30°C (59 to 86°F) and protected from light and humidity.

Prior to dispensing, all IMP supplies must be stored in a secure area with access limited to authorised staff. The Principal Investigator (PI) or designee will ensure that the IMP at site is safely stored in compliance with the storage requirements. The PI is responsible for ensuring that the IMP is dispensed in accordance with the protocol and only to participants randomised in the study.

Authorised study personnel will dispense the IMP according to the randomisation schedule.

5.5.4 Accountability of study supplies

All material supplied is for use only in this clinical study and should not be used for any other purpose.

The PI or designee is responsible for IMP accountability, reconciliation, and record maintenance. The PI or designated site staff must maintain IMP accountability records throughout the course of the study including records of the amount of IMP received, the identification of the participant for whom the drug was dispensed, and the date(s) and quantity of the drug dispensed.

The IMP and records must be available for inspection by a study monitor during the study. Drug supplies, including unused, partially used or empty bottles, will either be returned by the Investigator or designee to Certa Therapeutics or their agent, or destroyed on site if written approval to do so is given by Certa Therapeutics and appropriate facilities and procedures are available. Records shall be maintained by the Investigator of any disposition of the IMP. These records must show the identification and quantity of IMP disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the IMP. Where IMP is destroyed on-site, a record of destruction shall be issued and submitted to Certa Therapeutics.

At the end of the trial an overall drug accountability will be performed to reconcile the number of dispensed and used/lost/returned IMP.

5.5.5 Doses and treatment regimen

Approximately 30 participants, who fulfil all the entry criteria, will be randomised in the study.

Participants will be randomly assigned to one of the following treatment arms:

- 200mg oral FT011 once per day for 3 months.
- 400mg oral FT011 once per day for 3 months.
- Oral placebo once per day for 3 months.

One dose consists of two (2) capsules.

Participants will be instructed to take two (2) capsules once per day during the treatment period. Capsules should be taken on an empty stomach with a small amount of still water, at approximately the same time each morning.

A vomited dose must not be replaced. A double dose (e.g., missed dose from previous day and dose for current day) must not be taken.

At each visit, the time of administration of the previous dose of IMP, and the time the dose is taken at the study site, must be recorded.

5.5.6 Method of assigning treatment

A unique identification (ID) code will be allocated to each participant who provides informed consent, so that participants can be identified without making assumptions about their subsequent eligibility for the trial.

If a participant fails screening and is not randomised, or discontinues from the trial, that ID will not be reused.

Participants who fail screening and are approved to be rescreened will be allocated a new ID.

As this is a double blind, placebo-controlled study, site staff, subjects, Certa Therapeutics, and delegates will be blinded as to which treatment each participant receives.

Participant eligibility will be established before randomisation. On Day 1, eligible participants will be randomised using an Interactive Response Technology (IRT) system. At each IMP dispensing visit,

participants will be allocated a bottle number by the IRT system. The participant, site, sponsor, and monitoring personnel will be blind to whether the subject is receiving FT011 or placebo.

5.5.7 Blinding and procedures for breaking the blind

The IRT system will provide the option for an investigator to break the blind. Sites will be instructed to break the blind only in situations in which the investigator determines that adequate medical care cannot be provided to a participant without knowing the treatment assignment. If a code break must occur, the investigator or designee should advise the study Medical Monitor as soon as possible. Details for contacting the Medical Monitor will be provided in the Study Reference Manual (SRM). If the code is broken for a subject, the IRT system will immediately notify Certa Therapeutics or their delegate.

If the blind has been broken, the investigator must document the date and the reason the blind was broken in the subject's notes and CRF.

5.5.8 Treatment Compliance

Participant compliance will be assessed at each study visit by capsule count. Participants will be considered compliant if they take ±10% of scheduled doses. Participants who are non-compliant should be reminded of the dosing requirements and advised that they may be withdrawn from the study if compliance does not improve.

6 STUDY PROCEDURES

6.1 Participant Information

The Investigator must provide adequate information regarding the study conduct and obtain written informed consent from the participant before any tests or investigations outlined in the study protocol are carried out.

Prior to any study procedure, the participant will be asked to provide informed consent. The participant will be given time to read and understand the Participant Information and Consent Form (PICF) and have any questions answered. They may wish to take the PICF and consider it further, or to discuss it with their family or their usual doctor before signing.

The PICF must be personally signed and dated by both the Investigator obtaining consent, and the participant.

6.2 Screening Visit (Day -28 to Day -1)

The purpose of the Screening visit is to confirm participant eligibility against inclusion and exclusion criteria.

In this study, participant eligibility must be determined within the 28 days prior to Day 1. Screening assessments may be conducted on different days during the Screening period if required due to timing, or participant availability.

Potential participants will attend the in-clinic screening. Once informed consent has been obtained, the following visit assessments and procedures will be performed:

- Review eligibility criteria.
- Record participant demographic data.

- Review and record medical history and current conditions, including SSc-specific signs and symptoms
- Investigator assessment of the mRSS (see Section 8.3)
- Physical examination, including weight and height (see Section 8.2).
- Measurement of vital signs including blood pressure, heart rate, respiratory rate, and temperature (see Section 8.2).
- Spirometry assessment of FVC and forced expiratory volume in 1 second (FEV1) (see Section 8.3)
- 12-lead ECG (see Section 8.2).
- Safety laboratory tests including haematology, biochemistry, coagulation, and urinalysis, and serum pregnancy test for WOCBP (see Section 8.2).
- Review and record current and past medications.

6.2.1 Re-Screens

One repeat test of an individual screening assessment (e.g., laboratory test) is allowed, with prior approval from Certa Therapeutics or their designee. If appropriate, and with prior approval from Certa Therapeutics or their designee, participants who fail screening may be completely re-screened once with a new ID.

Eligible participants are to be randomised within 28 days of the Screening visit (first screening assessment). Approval to randomise later than 28 days must be obtained from Certa Therapeutics or designee, and selected screening procedures may be required to be repeated first.

6.3 Treatment Period

6.3.1 Day 1 (Baseline)

Participants who meet all the inclusion and none of the exclusion criteria will be scheduled to return to the site for their Day 1 visit. This visit may be conducted over two consecutive days, as long as the dosing and PK samples are collected on the second day. The dosing day visit should be conducted in the morning, and the participant should be fasted (except for water, which is allowed) for approximately 8 hours prior to the visit.

At this visit the following will be performed:

- Confirm participant continues to meet eligibility criteria.
- Patient Global Assessment of disease severity (see Section 8.3).
- Record any new medical events since Screening, including SSc-specific signs and symptoms.
- Investigator assessment of the mRSS (see Section 8.3).
- Completion of the Scleroderma Health Assessment Questionnaire- Disability Index (SHAQ-DI) (see Section 8.3).
- Completion of the Scleroderma Clinical Trial Consortium Damage Index (SCTC-DI) (see Section 8.3).
- Completion of the 5-D Itch Scale (see Section 8.3).
- Symptom-directed physical examination (see Section 8.2).

- Weight.
- Measurement of vital signs pre-dose including blood pressure, heart rate, respiratory rate, and temperature (see Section 8.2).
- Spirometry assessment of FVC and FEV1 (see Section 8.3).
- Physician Global Assessment of disease severity (see Section 8.3).
- 12-lead ECG (see Section 8.2).
- Blood samples:
    - Pre-dose collection of blood samples for immune cell activation markers (see Section 8.4).
    - Pre-dose PK sample collected (see Section 8.1).
    - Pre-dose blood samples collected for cytokine and chemokine measurements (see Section 8.4).
    - Safety laboratory tests including haematology, biochemistry, coagulation, and urinalysis, and serum pregnancy test for WOCBP (see Section 8.2).
- Collect 2 x 3mm punch biopsy skin samples (see Section 8.4). For operational reasons, biopsies may be collected during the screening period once participants have been confirmed as eligible, as long as they are collected pre-dose.
- Review and record concomitant medications.

Eligible participants will be randomised, dispensed IMP, and will take their first dose of IMP at the study site, with the time of administration recorded.

- Participants will remain on site for PK blood samples to be collected at 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose (see Section 8.1).
- Vital signs to be recorded immediately prior to 8-hour post-dose PK sample.
- Assess and record adverse events.

At the end of the visit participants will be reminded to take 2 capsules once daily for the duration of the trial Treatment Period.

6.3.2 Week 4 and Week 8

There is a ±3-day window on each visit.

Participants should be contacted the day prior to their visit to remind them not to take their IMP on the morning of the visit until at site and instructed to do so by the study staff.

This visit should be conducted in the morning, and the participant should be fasted (except for water, which is allowed) for approximately 8 hours prior to the visit.

Participants will return to the site for the following assessments:

- Patient Global Assessment of disease severity (see Section 8.3).
- Record any SSc-specific signs and symptoms.
- Investigator assessment of the mRSS (see Section 8.3).

- Completion of the SHAQ-DI (see Section 8.3).
- Symptom-directed physical examination (see Section 8.2).
- Weight.
- Measurement of vital signs including blood pressure, heart rate, respiratory rate, and temperature (see Section 8.2).
- Spirometry assessment of FVC and FEV1 (see Section 8.3).
- Physician Global Assessment of disease severity (see Section 8.3).
- 12-lead ECG (see Section 8.2).
- Blood samples:
    - Pre-dose PK sample collected (see Section 8.1).
    - Pre-dose blood samples collected for cytokine and chemokine measurements (see Section 8.4).
    - Safety laboratory tests including haematology, biochemistry, coagulation, and urinalysis, and serum pregnancy test for WOCBP (see Section 8.2).
- Participants will take their dose of IMP at the study site, with the time of administration and that of the previous dose recorded.
- Review and record concomitant medications.
- Assess and record adverse events.
- Conduct IMP accountability and review compliance.
- Dispense new IMP bottle

6.3.3 Week 12 (End of Treatment) / Early Termination

There is a ±3-day window on this visit.

Participants should be contacted the day prior to their visit to remind them not to take their IMP on the morning of the visit until at site and instructed to do so by the study staff.

This visit should be conducted in the morning, and the participant should be fasted (except for water, which is allowed) for approximately 8 hours prior to the visit.

At this visit the following will be performed:

- Patient Global Assessment of disease severity (see Section 8.3).
- Record any SSc-specific signs and symptoms.
- Investigator assessment of the mRSS (see Section 8.3).
- Completion of the SHAQ-DI (see Section 8.3).
- Completion of the SCTC-DI (see Section 8.3).
- Completion of the 5-D Itch Scale (see Section 8.3).
- Symptom-directed physical examination (see Section 8.2).

- Weight.
- Measurement of vital signs pre-dose including blood pressure, heart rate, respiratory rate, and temperature (see Section 8.2).
- Spirometry assessment of FVC and FEV1 (see Section 8.3).
- Physician Global Assessment of disease severity (see Section 8.3).
- 12-lead ECG (see Section 8.2).
- Blood samples:
    - Pre-dose collection of blood samples for immune cell activation markers (see Section 8.4).
    - Pre-dose PK sample collected (see Section 8.1).
    - Pre-dose blood samples collected for cytokine and chemokine measurements (see Section 8.4).
    - Safety laboratory tests including haematology, biochemistry, coagulation, and urinalysis, and serum pregnancy test for WOCBP (see Section 8.2).
- Collect 2 x 3mm punch biopsy skin samples (see Section 8.4).
- Review and record concomitant medications.
- Participants will take their dose of IMP at the study site, with the time of administration and that of the previous dose recorded.
    - Participants will remain on site for PK blood samples to be collected at 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose (see Section 8.1).
    - Collection of blood samples for immune cell activation markers at 4 hours post dose (see Section 8.4).
    - Vital signs to be recorded immediately prior to 8-hour post-dose PK sample.
- Assess and record adverse events.
- Conduct IMP accountability and review compliance.

This is the end of the Treatment Period. The participant will not receive any IMP after this visit.

This visit should also be conducted as the final treatment visit in the case of early withdrawal/early termination of a participant.

6.4 Week 16 (Follow up)

There is a +1-week window on this visit. At this visit the following will be performed:

- Record any SSc-specific signs and symptoms.
- Investigator assessment of the mRSS (see Section 8.3).
- Symptom-directed physical examination (see Section 8.2).
- Weight.
- Measurement of vital signs including blood pressure, heart rate, respiratory rate, and temperature (see Section 8.2).

- 12-lead ECG (see Section 8.2).
- Safety laboratory tests including haematology, biochemistry, coagulation, and urinalysis, and serum pregnancy test for WOCBP (see Section 8.2).
- Review and record concomitant medications.
- Assess and record adverse events.

This is the final study visit.

7 TRIAL ENDPOINTS

7.1 Primary Endpoints

- FT011 c_{max}, t_{max}, and AUC in plasma after a single dose and after 12-weeks of treatment.
- Measurement of steady state FT011 levels in plasma.

Additional calculations may be performed, and metabolites may also be measured.

7.2 Secondary Endpoints

7.2.1 Safety Endpoints

Safety will be assessed by:

- Treatment emergent adverse events from first dose of study drug to End of Study.
- Physical examination.
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature).
- 12-lead ECG.
- Safety laboratory results (haematology, biochemistry, coagulation, and urinalysis).
- Use of concomitant medications.

7.2.2 Efficacy Endpoints

- Change in mRSS from Baseline at each visit.
- Change in percent predicted FVC from Baseline to Week 4, Week 8, and Week 12.
- Change in HAQ-DI Score from Baseline to Week 4, Week 8, and Week 12.
- Change in Patient Global Assessment Score from Baseline to Week 4, Week 8, and Week 12.
- Change in Physician Global Assessment Score from Baseline to Week 4, Week 8, and Week 12.
- The proportion of patients showing an improvement (defined as ACR Composite Response Index in Diffuse Cutaneous Systemic Sclerosis (CRISS) score predicted probability of ≥0.60) at Week 12.
- Change in the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) score from Baseline to Week 12.
- Change in the 5-D Itch Scale from Baseline to Week 12.

7.3 Exploratory Endpoints

[redacted]

8 TRIAL MEASUREMENTS

8.1 Pharmacokinetics

Details of the laboratory and sample collection, processing, storage, and shipment are described in the Laboratory Manual.

Blood samples for plasma PK analyses will be collected at the following time points:

- Day 1: within 30 minutes prior to IMP administration, and at 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose.
- Week 4: within 30 minutes prior to IMP administration.
- Week 8: within 30 minutes prior to IMP administration.
- Week 12: within 30 minutes prior to IMP administration, and at 1, 2, 3, 4, 5, 6, 7 and 8 hours post dose.

A window of ± 10 minutes is allowed for all time points. Collections outside of these windows will be recorded as protocol deviations. Actual collection time must be recorded.

At each visit, the time of administration of the previous dose of IMP, and the time the dose is taken at the study site, must be recorded.

The PK samples will be shipped to a central laboratory for determination of the pharmacokinetics of FT011.

Metabolites may also be measured. Remaining samples will be stored for up to 10 years and may be used for additional research into FT011 or relevant indication biomarkers.

8.2 Safety and tolerability

Safety will be assessed by recording of AEs, laboratory parameters, vital signs, physical examination, and 12-lead ECG. Where multiple procedures are scheduled for the same nominal time point, safety blood samples should be taken after all other procedures have been performed.

- The physical examination will include the following: examination of general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Height will be recorded at screening only. A symptom directed physical examination will be conducted at post-screening visits, based on signs and symptoms the patient has experienced or reported.

- Vital sign measurements should be taken after the participant has rested in a supine position for at least 5 minutes and include blood pressure (systolic and diastolic), heart rate (beats/minute), respiratory rate, and body temperature. The same arm (preferably the nondominant arm) and the appropriate size cuff should be used for each blood pressure measurement.
    - At the Day 1 and Week 12 visits, vital signs are to be recorded pre-dose and just prior to the 8-hour post dose PK sample.
- 12-lead ECGs will be performed. Participants should be in a resting supine position for 10 minutes prior to ECG collection. The Investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The heart rate from the ECG machine should not be used as part of the vital sign measurements.
- Blood and urine samples will be taken throughout the course of the study. On-study collections should be fasted. Details of the laboratory and sample collection, processing, storage, and shipment are described in the Laboratory Manual. The following specific tests will be performed at the study central laboratory:
    - Haematology: Haemoglobin, haematocrit, red blood cell count, red cell distribution width, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count with differential, and platelet count.
    - Coagulation: Activated partial thromboplastin time, prothrombin time, international normalised ratio, fibrinogen.
    - Serum Chemistry: Sodium, potassium, magnesium, bicarbonate, phosphate, calcium, urea, urate, serum albumin, total protein, gamma-glutamyl transferase, alanine transaminase, aspartate transaminase, direct bilirubin, alkaline phosphatase, glucose, cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, creatine phosphokinase, lactate dehydrogenase, and creatinine. The central laboratory will calculate and report the eGFR value.
    - Urinalysis: Mid-stream urine microscopy, culture and sensitivities, urinary albumin: creatinine ratio (ACR)
    - Serum pregnancy test: for women of childbearing potential.
- Participants will be questioned at each visit from Day 1 about any AEs they may have experienced since the previous visit. See Section 10.3 for further details on recording AEs.
- Participants will be questioned at each visit about any concomitant medications they may have taken since the previous visit. This will assist in identifying AEs.

8.3 Efficacy

- The mRSS is a validated physical evaluation of patient's skin thickness rated by clinical palpation using a 0-3 scale (0 = normal skin; 1 = mild thickness; 2 = moderate thickness; 3 = severe thickness with inability to pinch the skin into a fold for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, and, with right and left sides of the body separately evaluated, the fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. Individual values are summed and defined as the total skin score. Total score is 0 to 51 with higher scores indicating worse symptomology. Minimally clinically significant difference in MRSS is 3-5 points.[12]

- Percent predicted FVC is calculated using equations incorporating age, gender, and race. It is calculated as (FVC Observed / FVC predicted) x 100, where FVC predicted is calculated relative to a reference population. Forced expiratory manoeuvres will be performed at least in triplicate with the minimal requirement that three manoeuvres are "acceptable" and that two of these manoeuvres meet end-of-test and repeatability criteria for FVC and FEV1.
- The SHAQ-DI consists of 20 questions referring to eight component sets consisting of dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each item is scored on a 4-point scale from 0 to 3: 0 = Without any difficulty; 1 = With some difficulty; 2 = With much difficulty; 3 = Unable to do. The eight scores of the eight sections are summed and divided by 8. If one section is not completed by a subject, the summed score is divided by 7. The total score indicates the patient's self-assessed level of disability - higher scores indicate worse symptomology. This outcome measure represents the change in mean score from baseline. A negative change from baseline indicates improvement. The Scleroderma HAQ (SHAQ) includes an additional five scleroderma-specific visual analogue scales (VAS), addressing overall disease activity, Raynaud's phenomenon, finger ulcers, breathing, and intestinal problems. A composite VAS score is not created nor are the individual VAS scores incorporated into the HAQ DI score.
- The Patient's Global Assessment represents the patient's overall assessment of current SSc status on a 100-mm horizontal VAS, ranging from 0 on the extreme left end of the scale indicating "extremely poor health", and 100 on the extreme right end indicating "excellent health".
- The Physician's Global Assessment is to be completed based on examination and overall assessment of the patient. The physician's assessment of the patient's SSc status will be scored on a 100-mm horizontal VAS, ranging from 0 on the extreme left end of the scale indicating "no disease activity" (symptom free), and 100 on the extreme right end indicating "worst imaginable disease activity".
- The ACR CRISS was developed using expert consensus and data driven approaches for use in clinical trials.[13,14] The exponential algorithm determines the predicted probability of improvement from baseline, incorporating change in the mRSS, FVC percent predicted, physician and patient global assessments, and HAQ-DI. The outcome is a continuous variable between 0.0 and 1.0 (0 - 100%). A higher score indicates greater improvement.

  The application of CRISS algorithm in a randomised clinical trial is a 2-step process.

  In the first step, participants will be clinically evaluated to determine whether the participant has improved or not. A participant is considered not improved and is assigned a probability score of improving equal to 0.0, irrespective of improvement on other core items, if he/she develops:

  1. New scleroderma renal crisis.

  2. Decline in FVC % predicted ≥15% (relative), confirmed by another FVC % within a month, high resolution computed tomography (HRCT) to confirm interstitial lung disease (if previous HRCT did not show interstitial lung disease) and FVC % predicted below 80% predicted (attributable to SSc).

  3. New onset of left ventricular failure (defined as ejection fraction ≤45%) or new onset of pulmonary arterial hypertension requiring treatment (attributable to SSc).

If the participant is determined to exhibit improvement in the first step (i.e., not assigned a 0.0), the second step involves computing the predicted probability of improving (a score between 0.0 and 1.0, inclusive) using the equation:

$$\frac{exp\left[-5.54-0.81*\Delta_{MRSS}+0.21*\Delta_{FVC\%}-0.40*\Delta_{Pt-glob}-0.44*\Delta_{MD-glob}-3.41*\Delta_{HAQ-DI}\right]}{1+exp\left[-5.54-0.81*\Delta_{MRSS}+0.21*\Delta_{FVC\%}-0.40*\Delta_{Pt-glob}-0.44*\Delta_{MD-glob}-3.41*\Delta_{HAQ-DI}\right]}$$

where ΔMRSS indicates the change in mRSS from baseline to the visit, ΔFVC denotes the change in FVC % predicted from baseline to the visit, ΔPt-glob indicates the change in patient global assessment, ΔMD-glob denotes the change in physician global assessment, and ΔHAQ-DI is the change in HAQ-DI. Note that all changes are absolute changes.

Participants for which the predicted probability is greater or equal to 0.60 are considered improved, while participants for which the predicted probability is below 0.60 are considered not improved.

- The SCTC-DI is a 23-item composite damage index to quantify organ damage in systemic sclerosis.
- The 5-D itch scale is a validated brief multidimensional questionnaire designed to be useful as an outcome measure in clinical trials. The five dimensions are degree, duration, direction, disability, and distribution.

8.4 Exploratory

[redacted]

9 STUDY OVERSIGHT

9.1 Data Safety Monitoring Board

An independent DSMB will be established prior to recruitment start, with appropriate charter that defines its roles and responsibilities. The DSMB will monitor accruing trial safety results and PK data at intervals throughout the study. The main purpose of the DSMB will be to protect the interests of the participants included in the trial.

The charter will specify the intervals for formal DSMB meetings.

The DSMB will convey to Certa Therapeutics their recommendations as to whether the trial may continue as planned or if the trial should be modified or stopped. The final decision on whether the study should be modified or stopped will be the responsibility of Certa Therapeutics. Any decision to modify or stop will be communicated to investigators and regulatory authorities (RA) by Certa Therapeutics (or their representatives). The DSMB may also report PK data in a blinded fashion.

The DSMB will also review any serious adverse events (SAE) that occur during the study.

Certa Therapeutics may also decide to cease enrolment at any time if unfavourable safety data lead to the conclusion that the benefit-risk assessment for the trial is no longer positive.

10 ADVERSE EVENTS

The definitions of AEs and SAEs are given below. It is extremely important that all staff involved in the trial are familiar with the content of this section. The PI is responsible for ensuring this.

AEs and SAEs will be captured from the time of the first dose of IMP through to the final study visit.

10.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product 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), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

Laboratory reference ranges are defined by upper or lower limits of parameters of the respective laboratory. The Investigator should ensure that each parameter out of the normal range is assessed for clinical significance and potential for being an AE. It is at the discretion of the Investigator to document any change in laboratory result as an AE if he considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

The participant must be instructed to inform the Investigator about all AEs and these must be documented in the participant records and CRF together with their intensity:

- Severe are those AEs which make normal daily routine impossible.
- Moderate AEs impact the normal daily routine.
- Mild AEs do not impact normal daily routine.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilised for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 10.2.

The Investigator must assign causality to each adverse event in relation to IMP based on the following scale:

- **Not related:** AE for which there is evidence of another explanation, e.g. the adverse event is obviously explained by the participant's disease(s), is in accordance with the known effect of a concomitant medication, or has occurred prior to first administration of FT011.
- **Unlikely related:** AE with a time relationship to FT011 administration that makes a relationship improbable (but not impossible), and disease or other drugs provide plausible explanations.
- **Possibly related:** AE with a reasonable time relationship to FT011 administration, but which could also be explained by disease or other drugs. Information on FT011 withdrawal may be lacking or unclear.
- **Probably related:** AE with reasonable time relationship to FT011 administration that is unlikely to be attributed to disease or other drugs. Response to FT011 withdrawal is clinically reasonable. Rechallenge is not required.
- **Definitely related:** AE with plausible time relationship to FT011 administration which cannot be explained by disease or other drugs. Response to FT011 withdrawal is plausible (pharmacologically, pathologically), and event is definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon). Rechallenge, if performed/necessary, is satisfactory.

All AEs must be documented by the Investigator, regardless of causality.

If an AE leads to premature discontinuation of the study, the appropriate pages of the CRF must be completed.

Expected AEs are defined in the IB reference safety information. At this stage of development there are no expected AEs defined for FT011.

10.2 Serious Adverse Events

An AE shall be classified as serious if it:

- Results in death.
- Is life-threatening.

  Life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.

  Hospitalisation is defined as inpatient admission or care regardless of duration.

  Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Elective surgery, hospitalisation for social reasons (with no causing AE), or hospital admissions and/or surgical operations planned before or during this study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect.
- Is an important medical event.

  This includes events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above.

10.3 Eliciting and Recording of Adverse Events

At every study visit, participants must be asked a standard, non-directed question, such as, "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalised, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to participant safety.

AEs will be captured from the time of first IMP dose, until the final study visit. Conditions occurring prior to the first dose of IMP will be recorded as medical history. SAEs judged to be possibly related to FT011 occurring to a study participant after the SAE reporting period will be reported to the sponsor if the Investigator becomes aware of them.

It is preferable that AEs are reported as diagnoses if one can be made, rather than individual signs and symptoms. The AE description, start and stop dates, intensity, causality, and outcome must be recorded, as well as any actions taken.

Unless a diagnosis is made, or signs and symptoms are present, abnormal laboratory values, physical examination findings, abnormal vital signs, or ECG abnormalities, should only be reported as AEs if they cause the participant to discontinue from the trial, the investigator feels it is clinically significant, or they meet a criterion for a SAE.

10.4 Reporting Serious Adverse Events

10.4.1 Reporting to Sponsor

Investigators and other site personnel must report SAEs on a SAE form to Certa Therapeutics or their designee within 24 hours of becoming aware of the SAE, regardless of causality. Information regarding SAEs will be entered in to the electronic CRF, confirmed by a physician from the study site, and transmitted within 24 hours. If the electronic CRF is inaccessible, SAE reports (paper form) should be submitted by email to [redacted] within the same timelines.

Follow-up information on SAEs must also be reported by the investigational site within the same time frame. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

All SAEs will be recorded in the participant records and the CRF.

10.4.2 Reporting to Regulatory Authorities, Ethics Committees/Institutional Review Boards, and Investigators

Certa Therapeutics or their designee will report SAEs, AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]), and Safety Issues to RAs in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the EC/IRB that approved the trial. In accordance with ICH GCP guidelines, the sponsor will inform the investigator of 'findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the EC's/IRB's approval/favourable opinion to continue the trial.' In particular and in line with respective regulations, the sponsor will inform the investigator SUSARs. The investigator should retain copies of safety reports in the Investigator Site File (ISF).

When specifically required by regulations and guidelines, the sponsor will provide appropriate safety reports directly to the concerned lead EC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for notifying the relevant EC/IRB of any safety reports as required, within the period specific by the EC/IRB, and of filing copies of all related correspondence in the ISF.

10.5 Follow-up of Adverse Events and Serious Adverse Events

All AEs and all SAEs must be followed by the Investigator until resolution, until the AE stabilises or is recognised as a permanent condition by the Investigator, or until the participant is lost to follow up, whichever comes first. Follow-up investigations may be necessary according to the Investigator's medical judgement.

10.6 Pregnancy Reporting

If a participant or their partner becomes pregnant, they will be asked to consent to follow up of the pregnancy and outcome. Pregnancy will be recorded on a pregnancy notification form.

Certa Therapeutics or designee will follow-up on the outcome of the pregnancy and the health status of the neonate, including after study completion.

11 DATA MANAGEMENT

11.1 Data Management and Quality Control

A 21 CFR Part 11 compliant Electronic Data Capture (EDC) system will be used to capture data for all patients entered in the study. Data collection and entry into the CRF will be completed by authorised study site personnel designated by the Investigator. Appropriate training will be completed with the Investigator and all authorised study site personnel prior to the study being initiated and any data being entered into the CRF for any study participants.

All data must be entered in English. The CRFs should always reflect the latest observations on the participants participating in the trial; therefore, the CRFs are to be completed as soon as possible after the participant's visit. The Investigator must verify that all data entries in the CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the CRF. The PI (or designee) will be required to sign off on the CRF data.

The study monitor/Clinical Research Associate (CRA) will review the CRFs and evaluate them for completeness and consistency and compare them to the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or designee. The CRA cannot enter data into the CRFs. If corrections are needed, the CRA or Data Manager will query the site.

The CRF is essentially a data entry form and should not constitute the original, or source document, unless otherwise specified. Source documents are all documents used or obtained by the Investigator or trial site that relate to the participant's medical history, that verify the existence of the participant, the inclusion and exclusion criteria and all records covering the participant's participation in the study. They include, but are not limited to, laboratory reports, pharmacy dispensing records, hospital records, participant files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the CRA at each monitoring visit.

12 STATISTICAL ANALYSIS CONSIDERATIONS

A Statistical Analysis Plan (SAP) will be written and approved prior to database lock. The SAP (as an extension of the protocol) will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol. Methodology described in the SAP will take precedence over the protocol. Any deviations from the analyses described in the SAP will be presented in the final clinical study report.

12.1 Determination of Sample Size

The sample size for this study is sized based on practical considerations and a formal sample size calculation was not performed. A total of approximately 30 participants, 10 per treatment group, will be randomised and treated. The sample size is considered sufficient to assess the study objectives.

12.2 General Methodology

Results will be presented by treatment group, for the pooled FT011 group and overall.

In general, data will be summarised using descriptive statistics (number of observations, mean, median, standard deviation [SD], minimum and maximum) or frequency counts and percentages, as appropriate to the type of data. The coefficient of variation (CV), geometric mean and geometric CV will also be presented for the PK tables.

Confidence intervals will be reported where appropriate. If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of 5%.

Baseline will be defined as the last available, valid, non-missing assessment prior to the first study drug administration.

Only data from protocol scheduled visits/time points will be included in the summary tables. Data from unscheduled visits/time points will be included in the figures (where appropriate) and data listings.

Medical history and adverse event terms will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and prior and concomitant medications by the World Health Organisation Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classification codes. The specific dictionary versions will be documented in the SAP and in the outputs.

The software (and version) used to perform the statistical and PK analyses will be documented in the SAP.

12.3 Analysis Sets

The following analysis sets will be defined:

Intention-to-Treat (ITT) Set: The ITT set is defined as all participants who were randomised. Participants in this set will be analysed based on the treatment that they were randomised to.

Safety Set: The safety set is defined as all participants who were randomised and received at least one dose of study medication. Participants in this set will be analysed based on the actual treatment that they received. All safety analyses will be based on the safety set.

Modified Intention-to-Treat (mITT) Set: The mITT set is defined as all randomised participants who received at least one dose of study medication and who have post-baseline efficacy data for at least one of the efficacy outcome measures. All efficacy analyses will be based on the mITT set. Participants in this set will be analysed based on the treatment that they were randomised to.

PK Set: The PK set is defined as all participants included in the safety set who have sufficient concentrations to allow for the calculation of at least one PK parameter. Participants who experience any adverse events or have protocol deviations that could affect the PK profiles may be excluded from the PK set at the pharmacokineticist's discretion. All PK analyses will be based on the PK set. Participants in this set will be analysed based on the actual treatment that they received.

12.4 Analyses

12.4.1 Baseline Characteristics and Disposition

Participant enrolment and disposition will be summarised by treatment group and will include the total number of participants randomised into the study and in included into each of the defined analysis sets. The number of participants who prematurely discontinuing from the study, along with the reason for early discontinuation will also be summarised.

Demographic and other baseline characteristics data recorded at screening and prior to dosing will be summarised, by randomised treatment group.

All analyses will be based on the ITT set.

12.4.2 Safety Analysis

All safety analyses will be based on the safety set.

12.4.2.1 Adverse Events

AEs will be grouped by MedDRA system organ class and preferred term and summarised, by treatment group. The summary tables will present the number and percentage of total participants and number of events, by system organ class and by preferred term.

For the summaries of AEs, participants who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events.

All AE summaries will be restricted to treatment emergent AEs only. Treatment emergent AEs are defined as AEs which commence on or after the first study drug administration.

Drug-related SAEs and treatment emergent AE (TEAEs) leading to early study withdrawal will also be summarised.

Separate summaries will be produced based on severity and relationship to study drug categories.

All adverse events data will be listed.

12.4.2.2 Duration of Exposure and Compliance

Exposure and compliance data will be summarised and listed.

12.4.2.3 Laboratory Results

Laboratory data will be summarised and listed by treatment group and visit. Actual values and the changes from baseline will be presented. In addition, 'shift from baseline' tables will also be presented showing the changes in the reference range classifications (normal, low, high) over time.

Dipstick urinalysis results evaluation (normal or, abnormal not clinically significant or abnormal clinically significant) will be summarised by treatment group and visit using frequency tabulations.

Abnormal laboratory values (including clinical significance as assessed by the Investigator) will be flagged in the listings.

12.4.2.4 Vital Signs and Physical Examination

Vital signs will be summarised and listed by treatment group and visit. Actual values and the changes from baseline will be presented.

Physical examination findings will only be listed.

12.4.2.5 12-lead ECG Results

ECG measurement will be summarised and listed by treatment group and visit. Actual values and the changes from baseline will be presented.

In addition, a frequency tabulation of overall ECG interpretation (normal or, abnormal not clinically significant or abnormal clinically significant) will be summarised by treatment group and visit using frequency tabulations.

12.4.2.6 Prior and Concomitant Medications

Prior and concomitant medications will be grouped by the WHO-DD ATC classification Level 2 term and by preferred drug name.

Prior medications are those medications that were stopped prior to the first study drug administration. Concomitant medications are medications that are taken at least once after the first study drug administration. Medications stopping on the same day as the first study drug administration will be considered as concomitant medications.

12.4.3 Pharmacokinetic Analysis

The analysis of the plasma FT011 PK concentrations and parameters data will be based on the PK set.

Results will be presented by visit (Day 1 and Week 12) and treatment group.

12.4.3.1 Pharmacokinetic Concentrations

Plasma FT011 concentrations data will be summarised by visit and nominal collection time points using descriptive statistics including the number of concentrations below the limit of quantification (BLQ), CV, geometric mean, and geometric CV.

Results reported as BLQ will be treated as zero for the calculation of the summary statistics, and as missing for the calculation of the geometric statistics.

Spaghetti plots of the individual plasma FT011 concentrations vs. actual time profiles (relative to the dose at the visit) will be presented on linear and log-linear scales. Plots will be presented by treatment group and visit. BLQ concentrations will be set to 0 in the linear plots and will be treated as missing in the log-linear plots.

Mean concentration profiles (± SD bars) vs. nominal time curves will be presented by visit on linear and log-linear scales. All treatment groups will be presented in the same plot.

All plasma FT011 concentration data will be listed, and the listing will include the calculated elapsed time since the study drug administration at the specific visit and the time deviations between the actual and planned sample collection times.

12.4.3.2 Pharmacokinetic Parameters

Two sets of plasma FT011 PK parameters will be calculated based the concentrations collected after the single dose on Day 1 and based on the concentrations collected after the last dose at Week 12.

Plasma PK parameters will be calculated using a non-compartmental approach based on the observed concentration-time profiles. Actual sampling times relative to the dose at the visit will be used in all PK calculations. The handling of BLQ values in the parameter calculations will be described in the SAP.

The plasma PK parameters shown in Table 3 will be calculated (data permitting) from the concentration-time profiles and additional parameters may be added at the discretion of the pharmacokineticist

Table 3: Plasma PK Parameters

PK Parameter	Method
c_{max}	Maximum observed concentration.
t_{max}	Time to reach maximum concentration.
AUC_{0-8}	Area under the plasma concentration-time curve from the time of the dose administration to the time of the 8-hour post-dose concentration calculated by the linear up log down trapezoidal method.
AUC_{last}	Area under the concentration-time curve from the time of the dose administration to the time of the last measurable concentration calculated by the linear up log down trapezoidal method.

The plasma PK parameter results will be summarised by treatment group and visit using summary statistics and the geometric statistics described for the PK concentrations. Results will also be presented graphically using box-and-whiskers plots.

All plasma PK parameter results will be listed.

12.4.4 Efficacy Analysis

All efficacy analyses will be based on the mITT set.

Whilst no formal hypothesis testing is planned, exploratory analyses may be performed to assess the treatment effect of FT011 on the efficacy outcomes. Full details of any inferential analyses will be provided in the SAP.

The handling of missing data and adjustments for multiplicity will be described in the SAP.

All collected and derived results will be presented in the data listings.

12.4.4.1 Continuous Endpoints

The actual results and the change from baseline values at each post-baseline visit will be summarised by treatment group using descriptive statistics.

The mean change from baseline values (±SD) over time will also be presented graphically.

The change from baseline values will be compared between the FT011 and placebo groups using a mixed model repeated measures model with the baseline value a covariate, treatment group as fixed effect, the interaction effect between study visit and treatment group, and subject as random effect with an unstructured covariance assumption. Parameter estimates will be calculated using restricted maximum likelihood methods, and the Kenward-Rogers method will be used to calculate the degrees of freedom.

The least squares means, estimated treatment differences (compared to placebo) and the corresponding confidence intervals and p-values at each visit will be presented.

The numeric CRISS scores be analysed using a Wilcoxon test.

12.4.4.2 Binary Endpoints

Binary endpoints will be summarised using counts, percentages, and odds ratios (compared to placebo). The proportions between each FT011 group and the placebo group will be compared using a Cochran-Mantel-Haenszel test.

12.4.4.3 Categorical Endpoints

Categorical endpoints will be summarised using counts and percentages.

13 TRIAL MANAGEMENT

13.1 Contacts

Details of investigators, study sites, Medical Monitors, CRAs, Certa Therapeutics and designee contacts can be found in the SRM.

13.2 Monitoring

Study monitoring will be performed in accordance with applicable regulations, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and Certa Therapeutics and designee Standard Operating Procedures (SOPs).

Before the start of the trial, a representative of Certa Therapeutics or designee will contact the investigational site to ensure facilities are adequate and discuss responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements.

During the trial, a CRA from Certa Therapeutics or its designee will regularly visit the site to monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support as needed.

In agreement with Certa Therapeutics and the PI, monitoring activities may take place remotely. The conduct of remote monitoring visits should not replace the conduct of on-site visits entirely. If on-site monitoring visits are no longer possible, the use of central and remote monitoring programs will be used to maintain oversight of clinical sites.

The PI agrees to allow the CRA direct access to all relevant documents, including electronic medical records, and to allocate his time and the time of his staff to the CRA to discuss findings and any relevant issues.

Site staff will be provided with CRA and back up contact details in the event they have queries or require assistance.

13.3 Audits and Inspections

An audit is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, Certa Therapeutics SOPs and those of Certa Therapeutics designees, GCP, and applicable regulatory requirements.

Authorised representatives of Certa Therapeutics, its designee, a RA, or the EC may visit the centre to perform audits or inspections. The investigator should contact Certa Therapeutics or designee immediately if they are contacted by a RA about an inspection at their centre. If an audit or inspection occurs, the PI and institution agree to allow the auditor/inspector direct access to all relevant documents and allocate their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

13.4 Training of Staff

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.

Site staff may be trained for this study at meetings and initiation and study visits by Certa Therapeutics, or their designees.

The PI will maintain records of all individuals involved in the trial at their site. The PI will ensure that appropriate training relevant to the trial is given to all these staff, and that they will receive any new information relevant to the performance of this trial in a timely manner.

13.5 Changes to the Protocol

Trial procedures will not be changed without the agreement of Certa Therapeutics.

If it is necessary for the trial protocol to be amended, the amendment or a new version of the trial protocol must be notified to or approved by the relevant RA if applicable, and by the site's EC/IRB before implementation at the site, unless the safety of participants is involved. Local requirements must be followed.

If a protocol amendment requires a change to the PICF, approval of the revised PICF by Certa Therapeutics or their designee and by the EC/IRB and RA if applicable is required before the revised form can be used.

Certa Therapeutics or their designee will distribute amendments and new versions of the protocol to the PI and to the appropriate RAs as required. The PI will be responsible for submitting to their EC/IRB.

13.6 Trial Agreements

The PI and institution must comply with all the terms, conditions, and obligations of the trial agreement for this trial. In the event of any inconsistency between this protocol and the trial agreement, the trial agreement shall prevail.

13.7 Trial Timetable and Termination

The planned start date for this trial is first quarter 2021, and the proposed completion data is third quarter 2022.

Certa Therapeutics reserves the right to terminate the trial at any stage for any reason including commercial considerations.

13.8 Ethics Review

The protocol and the PICF will be submitted for approval to the appropriate EC/IRB and RA if applicable and must be approved or given a favourable opinion in writing as appropriate. In addition, the EC/IRB must approve any other written information to be provided to participants, including advertising used to recruit participants for the trial. The investigator must submit written EC/IRB approval to Certa Therapeutics or designee before they can enrol any participant into the trial.

Any amendment to the protocol will be sent to the EC/IRB and RA if applicable. No deviations from or changes to the protocol will be implemented without documented approval from the EC and RA (if required) of an amendment, except where necessary to eliminate an immediate hazard(s) to trial participant, or when the change(s) involves only logistical or administrative aspects of the trial.

The deviations from or changes to the protocol which were implemented to eliminate an immediate hazard to the trial participant and the proposed amendment, if appropriate, should be submitted to the EC/IRB and RA for review and approval as soon as possible after the event.

The PI must submit progress reports to the EC/IRB according to local regulations and guidelines. The PI must also provide the EC/IRB with any reports of SAEs from the trial site in accordance with their EC's/IRB's requirements and timelines.

13.9 Ethical Conduct of the Study

The trial will be performed in accordance with the ethical principles in the Guidelines of the World Medical Association's Declaration of Helsinki in its current revised edition, ICH GCP (E6 R2) and applicable regulatory requirements.

13.10 Insurance and Liability

Certa Therapeutics has appropriate liability insurance cover in accordance with all local legal requirements. Further details of this and financial arrangements are specified in the agreement with the trial site.

13.11 Participant Information and Informed Consent

The PI will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks, and potential benefits of the trial. Participants must also be notified that they are free to discontinue from the trial at any time. The participant should be given the opportunity to ask questions and should be allowed time to consider the information provided.

The participant's signed and dated informed consent must be obtained before conducting any procedure specifically for the trial. The site investigator must store the original, signed PICF. A copy of the signed and dated PICF must be given to the participant.

13.12 Data Protection

The PICF will explain that trial data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Participants in this database will be identified by participant ID only. The PICF will also explain that for data verification purposes, authorised representatives of Certa Therapeutics, RA, ECs/IRBs, or sites may require direct access to parts of the hospital or practice records relevant to the trial, including participant medical history.

13.13 Trial Registration

Prior to commencing recruitment, a description of this clinical trial will be available on a publicly accessible registry such as www.clinicaltrials.gov. This website will not include information that can identify individual participants.

13.14 Retention of Records

The PI is responsible for the retention or archiving of the trial records for their site. Trial records include the participant files as well as the source data, the ISF, pharmacy records, and other study documents.

The PI will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application submission or 2 years after formal discontinuation of the clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable local regulatory requirements or by an agreement with Certa Therapeutics. It is the responsibility of Certa Therapeutics to inform the PI/institution as to when these documents no longer need to be retained. Records may not be destroyed without prior written consent from Certa Therapeutics.

If the PI leaves the site or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

13.15 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international regulatory submissions, registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

An investigator shall not publish any data related to this study (poster, abstract, paper, slide presentation, etc.) without having consulted with Certa Therapeutics in advance. The objectives, the content and the results of the present clinical trial should be considered confidential. All data and results are the exclusive property of Certa Therapeutics.

Except for legal reasons, the Investigators will not reveal the result of the study to a third party without a mutual agreement about the analysis and interpretation of the data with Certa Therapeutics.

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