Clinical Investigation Plan

Number:	VP-dCBT-PF-101
Title:	A randomised, controlled, parallel-group clinical investigation evaluating the impact of digital cognitive behavioural therapy on psychological symptom burden in adults diagnosed with pulmonary fibrosis
Brief Title:	Controlled investigation to evaluate impact of dCBT in adult subjects with PF
Acronym:	COMPANION
Device:	digital Cognitive Behavioural Therapy in Pulmonary Fibrosis (dCBT-PF)
Version:	5.0
Sponsor:	Vicore Pharma AB Kronhusgatan 11 SE-411 05 Gothenburg, Sweden

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1. Summary

1.1. Synopsis

Title: A randomised, controlled, parallel-group clinical investigation evaluating the impact of digital cognitive behavioural therapy on psychological symptom burden in adults diagnosed with pulmonary fibrosis.

Brief Title: Controlled investigation to evaluate impact of dCBT in adult subjects with PF.

Rationale: Patients diagnosed with a fibrosing interstitial lung disease, i.e. pulmonary fibrosis (PF), may often learn that their life span will be significantly shorter and that dyspnea, cough, fatigue and physical functioning may worsen (Yohannes, 2020). It is often difficult to predict whether the course of disease will be stable, slowly declining or rapidly progressing, as is usually the case for idiopathic pulmonary fibrosis (IPF) (Wang et al., 2022). The diagnosis will often negatively impact the patient's emotional and mental wellbeing, in many cases leading to anxiety (Yohannes, 2020). The need to alter or halt daily routines due to the debilitating respiratory symptoms contributes to the negative impact on mental health (Swigris et al., 2005). dCBT-PF is a digital cognitive behavioral therapy (dCBT) developed to address the psychological impact of living with PF, specifically anxiety symptoms.

Cognitive behavioral therapy (CBT) is a recommended first-line treatment for anxiety disorders (Powers, 2015). Despite the potential benefits of treatment, patients with PF face barriers in accessing CBT, including difficulties/risks of travel to hospital, the costs of in-person therapy and stigma issues. Digital therapy offers a cost-effective alternative, available 24/7.

Objectives, Endpoints and Estimands:

Pilot investigation – Part 1:

Objectives	Endpoints
Primary	
• To evaluate the functionality of dCBT-PF in patients with IPF	• Subject feedback on functionality and experience of the dCBT-PF at Week 4
Safety	
• To evaluate the safety of dCBT-PF in patients with IPF	• Adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), serious adverse device effects (SADE) and device deficiencies which could lead to an ADE or SADE
[redacted]	
[redacted]	[redacted]

• [redacted]	[redacted]

Pivotal investigation – Part 2:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dCBT-PF versus control on patient-reported anxiety symptoms in patients with PF	• Change from baseline in anxiety symptom severity assessed by GAD-7 at Week 9
Key secondary	
• To evaluate the efficacy of dCBT-PF versus control on clinician-reported anxiety symptoms in patients with PF	• Change from baseline in anxiety symptom severity as assessed by Hamilton anxiety rating scale (HAM-A) at Week 9
• To evaluate the efficacy of dCBT-PF versus control on patient-reported health-related quality of life (HRQoL) in patients with PF	• Change from baseline in HRQoL assessed by King's Brief Interstitial Lung Disease questionniare (K-BILD) psychological domain score at Week 9 • Change from baseline in HRQoL assessed by K-BILD total score at Week 9
[redacted]	
[redacted]	[redacted]
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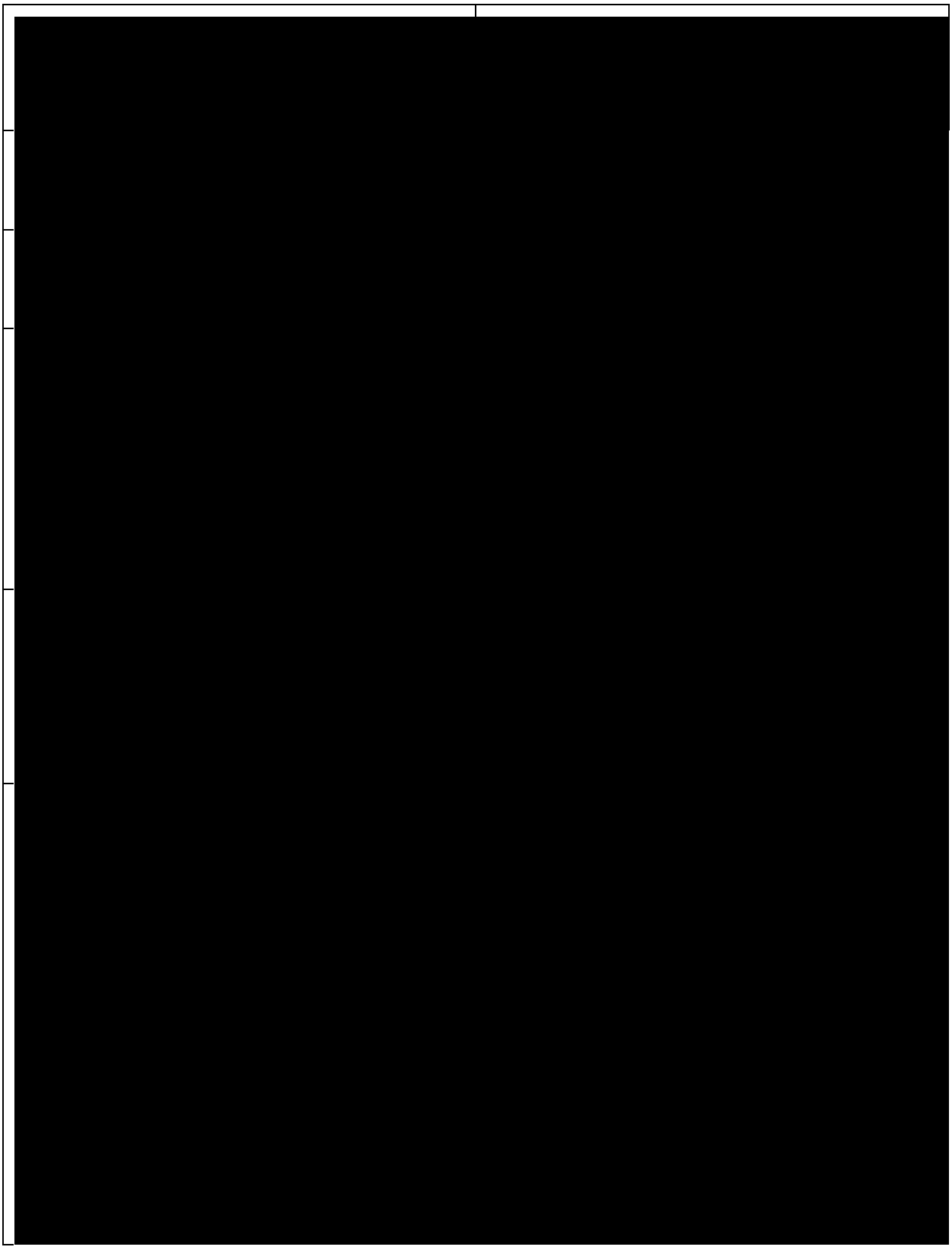
[redacted]	[redacted]



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Primary Estimand:

The change from baseline to Week 9 in GAD-7 scores, assessed for the intention-to-treat population with treatment as randomised, independent of treatment withdrawal or major deviations according to the treatment policy, with withdrawals from the clinical investigation prior to Week 9 not possible to follow-up being imputed using multiple imputation including their last known assessment. The difference between treatments with 95% confidence intervals from analysis of covariance analysis (ANCOVA) adjusting for stratification will be estimated.

Key Secondary Estimands:

The change from baseline to Week 9 in each of HAM-A, K-BILD psychological and K-BILD total scores, assessed for the intention-to-treat population with treatment as randomised, independent of treatment withdrawal or major deviations according to the treatment policy, with withdrawals from the clinical investigation prior to Week 9 not possible to follow-up being imputed using multiple imputation including their last known assessment. The difference between treatments with 95% confidence intervals from ANCOVA adjusting for stratification will be estimated.

Overall Design:

This investigation consists of two parts;

- Part 1 is the pilot phase of the clinical investigation with the key purpose of testing the functionality of dCBT-PF.
- Part 2 is the pivotal phase of the clinical investigation with the key purpose of evaluating the efficacy of dCBT-PF versus a control on patient-reported psychological symptom burden in patients with PF.

Part 1 – pilot investigation:

Part 1 is a single-arm, 4-week, open clinical investigation. Part 1 will enroll 10-20 subjects with IPF. All subjects will receive dCBT-PF. [redacted]

Prior to initiation of part 2, an update to the dCBT-PF will be performed, based on the provided feedback during part 1 of the investigation.

Part 2 – pivotal investigation:

Part 2 part is a 9-week, randomised, assessor-blind, controlled, parallel-group clinical investigation with a 3-week follow-up period evaluating the impact of dCBT-PF on psychological symptom burden in adults with PF. Recruitment for Part 2 will continue until end July 2023, or when a maximum of 250 subjects with PF have been enrolled, whatever comes first. Subjects will be 1:1 to dCBT-PF or an open-label waitlist control group. Subjects in the

control group will receive access to dCBT-PF treatment after the follow-up visit at Week 12 (see Section 6.5).

Randomization will be stratified by anxiety severity based on the GAD-7 score at baseline:

- Mild: 5-9 points
- Moderate: 10-14 points
- Severe: >15 points

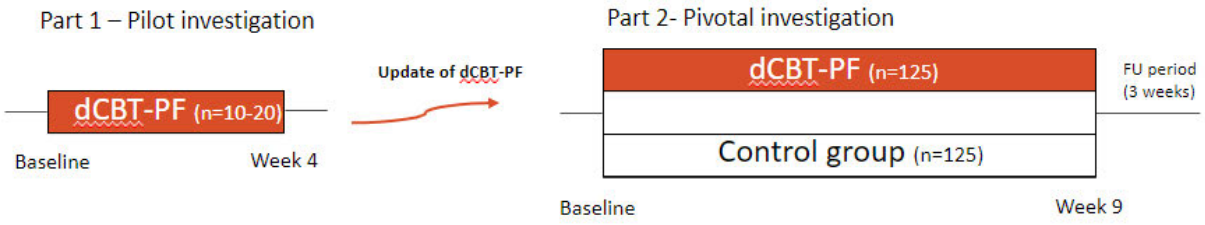
Approximately 400 subjects with PF are expected to be screened to achieve 250 enrolled and randomly assigned subjects.

Eligibility will be determined at pre-screening (V0) and baseline (V1), and eligible subjects will be randomised to either dCBT-PF or a waitlist control group. GAD-7 and K-BILD questionnaires will be completed at baseline, every 3rd week during the treatment period and at the end of the 3-week follow-up period. [redacted]

All assessments will be conducted remotely via telehealth or phone calls i.e., no in-person visits. Individual subject participation in the clinical investigation from time of randomisation is expected to be approximately 12 weeks.

The primary endpoint is the change from baseline in anxiety symptom severity assessed by GAD-7 at Week 9. The key secondary endpoints are change from baseline in HAM-A, K-BILD psychological domain score and K-BILD total score at Week 9. Type 1 errors will be controlled using a fixed sequential testing hierarchy.

1.2. Schema



1.3. Schedule of Activities (SoA)

Table 1: Flow chart for investigational procedures – Pilot phase

	Pre-screening[1]	**Eligibility**		**End-of-Investigation**
Visit/assessment	**V0**	**V1**	**V2**	**V3**
Visit window	**Baseline** (- 14 days)		**Week 2**[2] (±3 days)	**Week 4**[2] (±3 days)
Eligibility/General				
Informed consent	(x)[1]	x		
Eligibility criteria	x	x		
Demographics		x		
Medical history		x		
Disease characteristics		x		
Prior and concomitant medication		x	x	x
Adverse events / Adverse device effects			x	x
Intervention				
Video call to receive intervention instructions[3]		x		
dCBT-PF		x ----------x		
Adherence to dCBT-PF			x	x
Assessments and Procedures				
GAD-7	x	x	x	x
[redacted]				
Video interview to evaluate dCBT-PF			x	x

[1] The pre-screening and baseline visit can be combined per subject preference, and provided that the informed consent form is signed prior to any performed assessments with data collection. If the informed consent form is signed at the pre-screening visit, and prior to completing the GAD-7 [redacted] this assessment would not be required at Baseline if visit window is within 14 days.

[2] Visit windows for visit 2 and 3 are relative to the date of initiating the intervention (dCBT-PF).

[3] The call to provide intervention instructions can be performed with a window of +3 days following confirmed eligibility.

Table 2: Flow chart for Investigation procedures – Pivotal phase

	Pre-screening	**Eligibility**			**End-of-Treatment**	**Follow-up**
Visit/assessment	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**
Visit window	(-60 days)	**Screening/ Baseline** (-7 days. Day 1 = Treatment start)	**Week 3**[1] Day 22 (±3 days)	**Week 6**[2] Day 43 (±3 days)	**Week 9**[2] Day 64 (±7 days)	**Week 12** Day 85 (±3 days)
	Eligibility/General					
Consent for site to support with collecting CT report	x					
Informed consent		x				
Informed consent (applicable for control group subjects only)[2]						x
Eligibility criteria	x	x				
Demographics		x				
Medical history		x				
Disease characteristics		x				
Prior and concomitant medication		x	x	x	x	
Adverse events/ Adverse device effects			x	x	x	x
Question on negative wellbeing and distress[3]			x	x	x	x
	Treatment					
Randomization		x				
Video call to receive treatment instructions		x				(x[4])
dCBT-PF / control		x ---------- x				
Adherence to dCBT-PF			x	x	x	

[1] Visit windows for visit 2, 3 and 4 are relative to the date of initiating the intervention (dCBT-PF) (Day 1).
[2] Consent to be obtained for subjects in the control group, who want to gain access to the dCBT-PF after completing the investigation (cf. Section 6.5).
[3] Cf. Section 2.3.1 and 7.2.
[4] Applicable for subjects in the control group, who consent to getting access to the dCBT-PF after completing the investigation (cf. Section 6.5).

	Assessments and Procedures					
GAD-7	x	x	x	x	x	x
K-BILD		x	x	x	x	x
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[5] HAM-A, used to assess clinician-rated signs and symptoms of anxiety, should be completed no more than 2 days after completion of the patient reported outcome questionnaires.

2. Introduction

dCBT-PF is a digital cognitive behavioral therapy (dCBT) that has been developed to help address the psychological impact of living with PF, specifically symptoms of anxiety.

2.1. Rationale for Clinical Investigation

PF is comprised of a wide range of serious and debilitating fibrosing ILDs. Up to 60% of patients suffering from PF have been shown to experience anxiety, which may significantly impact their quality of life (Coelho et al., 2010). Although cognitive behavioral therapy (CBT) is recommended as a first-line treatment for anxiety disorder (Powers, 2015), patients with PF may face barriers in accessing CBT, including difficulties/risks of travel to hospital, the costs of in-person therapy and stigma issue.

dCBT-PF is a dCBT developed to address the psychological impact of living with PF, specifically anxiety symptoms. dCBT-PF is available as an app-based treatment and does not require visits to a psychologist.

The main purpose of this investigation is to evaluate the effectiveness of dCBT-PF on patient-reported psychological symptom burden in adult patients diagnosed with PF.

2.2. Background

PF and anxiety

The term interstitial lung disease (ILD) refers to a large and heterogeneous group of parenchymal lung disorders (Cottin et al., 2019) characterized by damage to the lung tissue caused by various degrees of fibrosis and/or inflammation. The primary site of injury is the interstitium, i.e. the space between the alveolar epithelium and the capillary endothelium (American Thoracic & European Respiratory, 2002), (European Respiratory, n.d.). There are more than 300 ILDs with similar symptoms of breathlessness, usually caused by inhibition of oxygen exchange in the alveoli. Approximately 65% of patients are affected by an ILD of unknown cause, which include idiopathic pulmonary fibrosis (IPF) and other idiopathic interstitial pneumonias (IIP), ILDs associated with connective tissue disorders such as rheumatoid arthritis (RA), systemic sclerosis (SSc) (Kaul et al., 2021; Nili et al., 2022) and sarcoidosis. Known casuses for ILD include pneumoconiosis (asbestosis, silicosis), hypersensitivity pneumonitis and post-infectious ILD (European Respiratory, n.d.). The distribution of ILDs shows large variation geographically, but studies in North America has generally shown IPF and ILD related to connective tissue disorder to be the most common ILD subtypes (Kaul et al., 2021). IPF is associated with progressive pulmonary fibrosis, but patients diagnosed with other ILDs are also at risk of developing progressive pulmonary fibrosis, often with a phenotype not dissimilar to IPF (Cottin et al., 2019). Although the underlying disease may in some cases be managed by medication, the development of progressive pulmonary fibrosis implies a non-remitting course of disease, associated with an increasing risk of morbidity and mortality.

The prognosis of IPF is poor, with an estimated life expectancy of 3-5 years after diagnosis which is shorter than many malignancies (Vancheri et al., 2010). The prognosis for the other diseases leading to PF varies, and it is often difficult to predict whether the course of disease will

be either stable, slowly declining or rapidly progressing with a poor prognosis (Wang et al., 2022).

The age- and sex-adjusted prevalence of fibrosing ILD per 100,000 in the US population has been estimated at approximately 117.82, of which 70.30 were assessed to have chronic fibrosing ILD with a progressive phenotype (Olson et al., 2021).

Specifically looking at IPF, there are approximately 3 million people worldwide living with the disease. Debilitating symptoms typically appear between the ages of 50 and 70 years and, while the disease is most common in men, the number of cases in women is increasing (Olson et al., 2018). With PF related to connective tissue disorder or sarcoidosis, disease onset is usually earlier in life (30-50), and affects women as often as men.

The knowledge of being diagnosed with a fibrosing ILD, i.e. PF, comes as a shock to many patients as there is often no identified cause and patients may feel they lose control of living the way they want. They may fear they will no longer be able to fulfill their role in life, whether that be as a parent, spouse, or grandparent. In the case of IPF, this is often at a time in life when patients are slowing down to enjoy retirement. People with PF learn that daily activities may have to change - normal routines like taking walks or travel must be adjusted around the debilitating respiratory symptoms of the disease, as well as the use of oxygen tanks and tubes, safety measures for protection against COVID-19, and perhaps a persistent and embarrassing cough. This has a negative impact on mental health, particularly in patients experiencing a noticeable deterioration in physical symptoms. Several studies have reported that symptoms of depression and anxiety are common in patients with PF. In various ILD populations, the prevalence of anxiety has been reported as 21-60% and no significant association between the type of underlying ILD and anxiety was shown (Coelho et al., 2010; Glaspole et al., 2017; Holland et al., 2014; Lee et al., 2017). The prevalence of anxiety has been shown to be associated with a decreased health-related quality of life (Lee et al., 2017).

As part of market research, Vicore Pharma has performed a large number of interviews with IPF and other PF patients in the US. Interviews have revealed that these patients tend to isolate when they have fear of infection or doubts about the safety of an activity. An episode of shortness of breath can be experienced as suffocation, leading to a less self-assured state and increased isolation, and resulting in a vicious cycle.

Another piece of the Vicore Pharma market research analysis showed that 102 of 161 patients with IPF (63% (Vicore, 2021) and 35 of 56 patients with PF (63%) experienced anxiety as defined as a score of 5 or more on the Generalized Anxiety Disorder 7 item scale (GAD-7) (Vicore, 2021).

Despite these profound impacts of the diagnosis on mental health, the usual standard of care for IPF in the US does not include referral to a psychologist (Raghu et al., 2015). There is a high unmet medical need to appropriately adress these mental aspects, including anxiety, that are experienced by patients with PF.

Rationale for the use of a digital therapeutic in PF

The dCBT-PF product is a digital cognitive behavioral therapy (dCBT) developed to reduce symptoms of anxiety in patients suffering from PF and, thus, address the unmet medical need in this specific patient population.

The practice of CBT was first developed in the 1960s. CBT is a psychosocial intervention focusing on the reworking of a patient's behaviors and thinking patterns (Driessen & Hollon, 2010). CBT is a recommended first-line treatment for anxiety disorders according to international guidelines (Powers, 2015).

The dCBT-PF is also incorporating acceptance and commitment therapy (ACT), an empirically based psychological intervention based on CBT. ACT focuses to a greater degree on acceptance and mindfulness strategies for behavior change (Gloster, 2020).

ACT is a form of clinical behavioural analysis developed in the 1980'ties (Hayes et al., 2013). A meta-analysis showed that ACT is efficacious for all conditions that were examined, including anxiety, depression, substance use, pain, and transdiagnostic groups. Results also showed that ACT was generally superior to inactive controls (e.g. waitlist, placebo), treatment as usual, and most active intervention conditions (Gloster, 2020).

Digital therapeutics (DTx) are software-as-a-medical-device products. Several DTx products are on the market in the US, for patients with depression, anxiety, type 1 and type 2 diabetes, substance abuse disorders, chronic pain, irritable bowel syndrome, attention deficit hyperactivity disorder, insomnia, and post-traumatic stress disorder.

Treatment of anxiety is the intended use of several of these software-as-medical-device products. Daylight, a CBT DTx product has demonstrated reduced symptoms of anxiety compared with a waitlist control (Carl et al., 2020). Ensemble is another example of a CBT-based digital therapy for anxiety or depression. Deprexis, a digital CBT for treating mild to severe depression, was also recently launched on the market in the US (Zwerenz et al., 2017).

The potential benefits of using CBT in the management of anxiety in patients with PF has recently been highlighted (Wijsenbeek et al., 2019).

Patients with PF are often susceptible to lung infections and may experience poor clinical outcomes after respiratory infections compared to the general population, as has been shown for IPF (Naqvi et al., 2021). In other ILDs, e.g. connective tissue associated ILD, treatment with immunosuppressive medications may contribute to the risk of infection and negative outcomes (Molina-Molina et al., 2022), (Naqvi et al., 2021). Patients with severe PF are often not highly mobile and may carry oxygen tanks and are hesitant to have frequent visits to a hospital. This combined with an overall lack of access to psychologists, coupled with a pandemic associated fear of in-person clinic visits, enhances a need for digital alternatives to traditional CBT in patients with PF.

The dCBT-PF product is developed to reduce symptoms of anxiety in patients diagnosed with PF and address the unmet medical need in this specific patient popoulation.

Initially, the dCBT-PF product was intended for patients with IPF to support the population targeted in Vicore Pharma's ongoing drug development program, but in the months leading up to the final product, through patient interviews and discussions with expert pulmonologists, in addition to a suggestion by FDA at a pre-submission meeting on March 21, 2022, Vicore Pharma and Alex Therapeutics decided to expand the availability of the product to all patients with PF, including IPF.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential Residual Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy (Control Measure)
dCBT-PF		
Negative wellbeing / distress (ADE or ASADE)	Negative wellbeing /distress have been observed in patients after initiation of CBT	Eligibility criteria to safeguard that population will exclude patients at high risk for negative impact on wellbeing/distress (i.e., patients with a history of hospital admissions due to suicidal behavior or attempts (self-reported) or patients with a diagnosis of major depressive disorder (self-reported) Questions will be asked to enquire about any potential adverse events, and depending on the response, the appropriate action will be taken to ensure that the well-being of the subject is safeguarded (including reporting and follow-up of any AEs and ADEs) The dCBT-PF will include disclaimers to encourage subjects to contact their PCP or National suicide hotline, if there is a need for professional support

No other residual risks are anticipated to cause ADEs.

2.3.2. Benefit Assessment

Studies have reported that symptoms of anxiety are common in patients with PF. Studies have indicated the proportion of patients with anxiety in broad ILD populations may be as high as 60% (Coelho et al., 2010; Glaspole et al., 2017; Holland et al., 2014; Lee et al., 2017)

CBT is a recommended first-line treatment for anxiety disorders (Powers, 2015). Despite the potential benefits of treatment, patients with PF face barriers in accessing CBT, including difficulties/risks of travel to hospital. Studies have shown that patients with chronic lung diseases including IPF have poor clinical outcomes with COVID-19 disease (Gerayeli et al., 2021; Naqvi et al., 2021). As a result of the COVID-19 pandemic, pulmonologists have reported that patients

with PF have been less willing to visit hospital clinics or have face to face consultations with a psychologist or therapist. A digital solution for treatment of anxiety will make it possible for PF patients to receive CBT without any travelling or visits to a hospital clinic or a psychologist.

Subject's randomised to active therapy (dCBT-PF) may see an improvement in anxiety and quality of life. The CBT based digital therapeutics have long lasting benefits after end of therapy (Carl et al., 2020).

All subjects will receive online consultations with the site staff and will contribute to the development of a new therapy specifically developed for PF patients with anxiety.

2.3.3. Overall Benefit Risk Conclusion

The overall benefit risk balance is considered positive. This is based on the consideration that none, or a limited number of, ADEs are expected using dCBT, the virtual nature of the clinical investigation and potential benefits in treating anxiety with dCBT.

3. Objectives, Endpoints, and Estimands

Pilot investigation – Part 1:

Objectives	Endpoints
Primary	
• To evaluate the functionality of dCBT-PF in patients with IPF	• Subjects feedback on functionality and experience of the dCBT-PF at Week 4
Safety	
• To evaluate the safety of dCBT-PF in patients with IPF	• AEs, ADEs, SAEs, SADE and device deficiencies which could lead to an ADE or SADE
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Pivotal investigation – Part 2:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dCBT-PF versus control on patient-reported anxiety symptoms in patients with PF	• Change from baseline in anxiety symptom severity assessed by GAD-7 at Week 9
Key secondary	
• To evaluate the efficacy of dCBT-PF versus control on clinician-reported anxiety symptoms in patients with PF	• Change from baseline in anxiety symptom severity as assessed by Hamilton anxiety rating scale (HAM-A) at Week 9
• To evaluate the efficacy of dCBT-PF versus control on patient-reported health-related quality of life (HRQoL) in patients with PF	• Change from baseline in HRQoL assessed by K-BILD psychological domain score at Week 9 • Change from baseline in HRQoL assessed by K-BILD total score at Week 9

Safety	
• To evaluate the safety of dCBT-PF versus control in patients with PF	• AEs, ADEs, SAEs, SADEs and device deficiencies which could lead to an ADE or SADE
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted] • Change from baseline in QoL assessed by Brunnsviken Brief Quality of life scale (BBQ) at Week 9

Primary Estimand:

The change from baseline to Week 9 in GAD-7 scores, assessed for the intention-to-treat population with treatment as randomised, independent of treatment withdrawal or major deviations according to the treatment policy, with withdrawals from the clinical investigation prior to Week 9 not possible to follow-up being imputed using multiple imputation including their last known assessment. The difference between treatments with 95% confidence intervals from ANCOVA adjusting for stratification will be estimated.

Key Secondary Estimands:

The change from baseline to Week 9 in each of the HAM-A, K-BILD psychological and K-BILD total scores, assessed for the intention-to-treat population with treatment as randomised, independent of treatment withdrawal or major deviations according to the treatment policy, with withdrawals from the clinical investigation prior to Week 9 not possible to follow-up being imputed using multiple imputation including their last known assessment. The difference between treatments with 95% confidence intervals from ANCOVA adjusting for stratification will be estimated.

4. Investigation Design

4.1. Overall Design

This investigation consists of two parts;

Part 1:

- A pilot investigation with the purpose of testing the functionality of the developed dCBT-PF.
- This is a single-arm, 4-week, open investigation that will enroll 10-20 subjects with IPF. All subjects will receive dCBT-PF.

Prior to initiation of part 2, an update to the dCBT-PF will be performed, based on the provided feedback during part 1.

Part 2:

- A pivotal investigation with the purpose of evaluating the efficacy of dCBT-PF versus a control group on patient-reported psychological symptom burden in subjects with PF.
- A 9-week, randomised, assessor-blind, controlled, parallel-group clinical investigation evaluating the impact of dCBT-PF on psychological symptom burden in adults with PF. Recruitment for Part 2 will continue until end July 2023, or when a maximum of 250 subjects with PF have been enrolled, whatever comes first. Subjects will be randomised 1:1 to dCBT-PF or an open-label control group.
- Randomization will be stratified by anxiety severity (GAD-7 score 5-9, 10-14 or >15 points) at baseline.

4.2. Scientific Rationale for Design of Clinical Investigation

The proposed clinical investigation design is based on the guidance provided by FDA, EMA and the international organization for standardization (ISO) (EU, 2017; FDA, 1996; ISO, 2020) and recently conducted DTx clinical investigations utilizing dCBT as a treatment of anxiety or depression (Carl et al., 2020; Gu et al., 2020).

Parts 1 and 2 of the investigation will enroll IPF and PF subjects, respectively, with a GAD-7 score of ≥ 5, defined as mild to severe anxiety. PF patients, including IPF, are considered to have a level of anxiety appropriate for dCBT-PF treatment as it maps to psychological norms of a treatable level (Spitzer et al., 2006). Studies suggest that anxiety and depression significantly influence quality of life in patients with PF (Lee et al., 2017).

Part 1 will recruit patients with self-reported IPF.

Part 2 will recruit patients with self-reported PF, who have radiological findings of PF (interstitial changes) on a CT scan report, as confirmed by the PI. Historical CT scans, not older than 5 years, are used for this assessment. As most cases of PF are irreversible (Yu & Tang, 2022), this time span is considered acceptable.

dCBT-PF is not recommended for patients with active drug or alcohol addiction, history of suicidal behaviour, major depressive disorder, manic or psychotic disorders, and these patients will thus be excluded from the clinical investigation.

The overall aim of part 1 is to collect user feed-back on the functionality of the dCBT-PF from IPF patients with anxiety.

Part 2 will use the GAD-7 questionnaire to assess the primary endpoint. The GAD-7 questionnaire is considered responsive to evaluate the level of generalized anxiety disorder. The GAD-7 questionnaire has been used to assess effect on anxiety symptom severity in recently conducted CBT DTx investigations (Carl et al., 2020).

The planned dCBT-PF treatment duration is 9 weeks with an intended daily use of 10 minutes. Traditional CBT conducted via sessions with a psychologist, or a psychotherapist can vary considerably in length and duration, with sessions lasting between 30 to 60 minutes and treatment containing 5 to 20 sessions (NHS, 2019). The dCBT-PF consist of 7 interventional CBT modules (Therapy modules) and 3 non-interventional modules (PF Essentials). A target treatment duration of 9 weeks in the pivotal part of the clinical investigation is considered justifiable based on both traditional and digital CBT experience.

To minimize bias, the clinical investigation will have a randomised, assessor-blind, controlled design. Subjects will be randomised 1:1 to dCBT-PF or an open-label waitlist control group and the randomization will be stratified by self-reported anxiety severity based on GAD-7 score to ensure an equal distribution in both groups (active and control).

Implementation of a placebo-app (sham) would not provide sufficient blinding and was considered to create substantial bias in the design of the clinical investigation. A clinician-reported outcome, HAM-A, assessed by a blinded clinician, is implemented to support the primary endpoint.

The proportion of PF patients with mild to moderate anxiety (scoring 5-14 on a 0-21 scale) may be as high as 60% in patients with PF (Coelho et al., 2010; Glaspole et al., 2017; Holland et al., 2014; Lee et al., 2017). Although live sessions with a psychotherapist providing traditional CBT could be effective for PF patients, psychological therapy or other mental health interventions are not part of standard of care in patients with PF (Raghu et al., 2015).

4.3. End of Clinical Investigation Definition

End of clinical investigation is defined as the date of the last visit of the last subject. A subject is considered to have completed the clinical investigation if he/she has completed the Week 12 visit (follow-up).

5. Investigation Population

Part 1 of this clinical investigation will enroll adult subjects with IPF and mild to severe anxiety (i.e., a GAD-7 score ≥5).

Part 2 will enroll adult subjects with PF and mild to severe anxiety (i.e., GAD-7 score ≥5).

Prospective approval of deviations to recruitment and enrollment criteria, also known as waivers or exemptions, is not permitted.

5.1. Eligibility criteria for the Part 1, pilot phase

Subjects are eligible to be included in the investigation only if the following criteria are fulfilled:

5.1.1. Inclusion criteria (Part 1, pilot)

1. Age ≥22 years at the time of signing the informed consent
2. Self-reported IPF diagnosis
3. A GAD-7 composite score of ≥5 at baseline (Visit 1)
4. If currently on prescribed medication for depression/anxiety, a stable dose for at least 4 weeks prior to baseline (Visit 1)
5. Capable of using a mobile device (compatible with dCBT-IPF) and common applications, in the judgement of the investigator or designee, and has an appropriate mobile or tablet device
6. Written informed consent, consistent with Good Clinical Practice and local laws, obtained before the initiation of any procedures related to the clinical investigation
7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this clinical investigation plan (CIP)

5.1.2. Exclusion criteria (Part 1, pilot)

1. Manic disorders, psychotic disorders, suicidal ideation, schizophrenia, self-harm, or alcohol/drug abuse during the past 6 months prior to baseline (Visit 1) as judged by the investigator or designee
2. Cognitive impairment e.g., dementia preventing engagement with dCBT-IPF as judged by the investigator or designee
3. Verbal and/or written communication problems limiting ability to engage with dCBT-IPF as judged by the investigator or designee
4. Inability to comply with investigation procedures, due to severe medical conditions or otherwise as judged by the investigator or designee
5. Life expectancy of less than 6 months as determined by the need for palliative care as judged by the investigator or designee
6. Currently receiving CBT

5.2. Eligibility criteria for the Part 2, pivotal phase

Subjects are eligible to be included in the investigation only if the following criteria are fulfilled:

5.2.1. Inclusion criteria (Part 2, pivotal)

1. Age ≥22 years at the time of signing the informed consent
2. Self-reported PF diagnosis
3. A GAD-7 composite score of ≥5 at pre-screening and baseline (Visit 1)
4. If currently on prescribed medication for depression/anxiety, a stable dose for at least 4 weeks prior to baseline (Visit 1)
5. CT (Computed Tomography) within 5 years prior to baseline (Visit 1) with signs of pulmonary fibrosis (interstitial changes), as judged by the investigator or designee
6. Capable of using a mobile device (compatible with dCBT-PF) and common applications, in the judgement of the investigator or designee, and has an appropriate mobile or tablet device
7. Written informed consent, consistent with Good Clinical Practice and local laws, obtained before the initiation of any procedures related to the clinical investigation
8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this clinical investigation plan (CIP)

5.2.2. Exclusion criteria (Part 2, pivotal)

1. Self-reported manic disorders, psychotic disorders, schizophrenia, or alcohol/drug abuse during the past 6 months prior to baseline (Visit 1), as judged by the investigator or designee
2. Self-reported history of hospital admissions due to suicidal behavior or attempts, as judged by the investigator or designee
3. Self-reported previous or current diagnosis of major depressive disorder, as judged by the investigator or designee
4. Verbal and/or written communication problems limiting ability to engage with dCBT-PF as judged by the investigator or designee
5. Inability to comply with investigation procedures, due to e.g. cognitive impairment or severe medical conditions as judged by the investigator or designee
6. Currently receiving CBT
7. Participation in the pilot phase of the clinical investigation

5.3. Lifestyle Considerations

There are no lifestyle considerations in the investigation.

5.4. Screen Failures

A screen failure occurs when a subject who consents to participating in the clinical investigation is not subsequently randomly assigned to dCBT-PF or the control group.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Re-prescreening/re-screening is allowed for the following screen failure reasons -

- Inclusion criterion 4: If stable dose is confirmed
- Inclusion criterion 5: If a CT scan report becomes available
- Inclusion criterion 6: If the subject obtains an appropriate mobile or tablet device
- Exclusion criterion 2: Subjects who pre-screen failed due to PHQ-9 question 9 under CIP V4.0, and were otherwise eligible, can be re-prescreened.
- Exclusion criterion 3: Subjects who pre-screen failed due to PHQ-9 composite score under CIP V4.0, and were otherwise eligible, can be re-prescreened.
- Exclusion criterion 6: If no longer receiving CBT

For subjects that will be re-(pre)screened all assessments will be redone. The subject ID under which the subject was previously re-(pre)screened will be recorded as part of the clinical database.

5.5. Subject reimbursement

For the pilot and pivotal phases, subjects will receive $100.00 and $250.00, respectively, as compensation at the completion of their participation in the investigation.

6. Investigational Medical Device

The investigational device is the dCBT-PF. dCBT-PF will be used by the subject according to the CIP.

Note - For the pilot phase, the investigational device was referred to as dCBT-IPF, as it was initially intended to IPF patients only. In the months leading up to the final product, through patient interviews and discussions with expert pulmonologists, in addition to a suggestion by FDA at a pre-submission meeting on March 21, 2022, Vicore Pharma and Alex Therapeutics decided to expand the availability of the product to patients with PF. This change was implemented prior to initiating the pivotal phase and is reflected in the CIP version 4.0. Consequently, throughout the CIP the investigational device name is changed to dCBT-PF.

6.1. Description of Medical Device

In part 1 (pilot investigation) each subject will receive dCBT-PF.

In part 2 (pivotal investigation) each subject will be randomised to receive treatment with dCBT-PF or be allocated to the control group.

The dCBT-PF device is a stand-alone digital CBT intervention, used without clinician supervision, delivered as a mobile phone or tablet (Android or iOS) application.

Subjects will, prior to use, receive instructions on how to download and use the dCBT-PF.

The dCBT consists of 7 interventional CBT modules (therapy modules) and 3 non-interventional modules (IPF essentials). The therapy modules are CBT or ACT-based digital therapy. The IPF essentials are educational material related to IPF. The therapy modules take 9 weeks to complete if used as intended. An overview of the modules is presented in Table 3. During the intervention period, the subjects will be instructed to use the dCBT-PF for approximately 10 minutes per day for an estimated time of 4 weeks in the pilot investigation and 9 weeks in the pivotal investigation.

Subjects assigned to dCBT-PF therapy in part 1 (pilot investigation) will use 4 of the modules.

In part 2 (pivotal investigation) the subjects will complete all modules. This intervention corresponds to approximately 14 face-to-face sessions with traditional CBT. The therapy modules of the dCBT-PF focus on psychoeducation and introduces concepts and ideas from CBT and ACT through text, video, and audio. [redacted] The IPF essential modules focus on educational aspects for IPF patients.

Table 3 Therapy modules

Module	Content
1 Intro and motivations	[redacted] (Barlow, 2014; Harris, 2019; Miller, 2013).
2. Why am I feeling like this?	Psychoeducation [redacted] (Barlow, 2011; Barlow, 2002, 2014; Harris,

	2019; Howard & Dupont, 2014; Livermore et al., 2015; Miller, 2013; Ramnerö, 2008).
3. Why am I acting like I do?	[redacted] (Barlow, 2011; Barlow, 2014; Harris, 2019; Ramnerö, 2008)
4. What's important in my life?	[redacted] (Barlow, 2011; Barlow, 2014; Harris, 2019; Hayes, 2012; Ramnerö, 2008).
5. Living my life fully	[redacted] (Barlow, 2011; Barlow, 2002, 2014; Harris, 2019; Hayes, 2012).(Barlow, 2011; Barlow, 2002, 2014; Harris, 2019; Hayes, 2012)
6. Handling difficult thoughts and feelings	[redacted] (Harris, 2019; Hayes, 2012).
7. Sustainable change	[redacted] (Barlow, 2011; Barlow, 2002, 2014).

Table 4 IPF essentials modules

1. Living with IPF	[redacted]
2. Caring for myself	[redacted].
3. Physical activity	[redacted].

6.2. Preparation, Handling, Storage, and Accountability

Subjects randomised to the dCBT-PF will receive a unique product code. This product code gives access to the dCBT-PF. Subjects will download an app and use the dCBT-PF on their own mobile or tablet device.

Subjects will receive instructions on how to download the dCBT-PF app from written instructions and/or via a virtual onboarding session with the site staff.

Access to the dCBT-PF will be revoked after the subject has completed the clinical investigation.

The number of days the dCBT-PF has been accessed, the time spent, and the number of modules completed will be logged in the dCBT-PF system and will be transferred to the database for the clinical investigation.

6.3. Measures to Minimize Bias: Randomization

This is a randomised, assessor-blind, controlled, parallel-group, clinical investigation. Subjects, care providers, investigators, sponsor, and CRO/vendor staff know if the subject is randomised to dCBT-PF or the control group. The control group is implemented to serve as a baseline for determining the effectiveness of the intervention. The control group will not receive any treatment but will follow the same assessment as the group randomised to dCBT-PF. Subjects in the control group will receive access to dCBT-PF treatment after the follow-up visit at Week 12 (see Section 6.5).

The clinician assessing rating anxiety based on the HAM-A questionnaire will be blinded to treatment to reduce reporter bias.

Randomization will be stratified by: Anxiety severity (GAD-7 score 5-9, 10-14 or >15 points) at baseline to prevent imbalance in anxiety level between the dCBT-PF and control group.

6.4. Investigational Device Compliance

Subjects randomised to the dCBT-PF will receive access to the dCBT-PF app. Adherence to the dCBT-PF will be measured in terms of the number of days the dCBT-PF app is accessed, time spent, and the number of modules completed during the treatment period.

Adherence to the dCBT-PF will be assessed by a weekly compliance report prepared by Alex Therapeutics. The reports will indicate the compliance adherence by color coding. If compliance is less than expected, the site staff should discuss the reason and educate the subject to comply with the investigation. Intervention start and stop dates will also be recorded in the dCBT-PF database and will be transferred to the database for the clinical investigation.

6.5. Continued Access to the Investigational Device after End of the Clinical Investigation

Subjects allocated to the control group will receive access to the dCBT-PF when their participation in the investigation is completed, i.e., after the end of the 3-week follow-up period.

Access for the control group will be provided under an Exclusive Release of the product, following the FDA medical device enforcement discretion guidelines i.e., outside of the scope of this CIP. Obtaining subject consent, as well providing instructions for getting access to the dCBT-PF treatment, will be performed under this CIP, to allow for the GAD-7 data, collected through the dCBT-PF by Alex Therapeutics, the Legal Manufacturer of the product, to be used for quality control purposes and for the patient's own insight. The data collected will be anonymized.

6.6. Prior and Concomitant Therapy

Concomitant therapy is defined as any therapy (including over-the-counter, prescription medicines, oxygen supplementation, recreational drugs, vitamins, treatment from a psychologist or psychiatrist and/or herbal supplements) or other specific categories of interest that the subject is receiving or continues at the time of enrollment or receives after start of treatment with the dCBT-PF.

All concomitant therapy taken according to the subject at baseline (Visit 1) should be recorded. In addition, relevant prior therapy taken up to 4 weeks prior to baseline (Visit 1) should be recorded. Relevant prior therapy is defined as antifibrotic treatment, psychological therapy including counseling, antidepressants, or anti-anxiety treatments. Other relevant prior therapy can be reported at investigator's discretion.

Concomitant therapy and prior therapy must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

7. Discontinuation of Investigational Medical Device and Subject Discontinuation/Withdrawal

Discontinuation of the clinical investigation is detailed in Appendix 1 (see Section 10.1).

7.1. Discontinuation of Investigational Medical Device treatment

A subject should be discontinued from the dCBT-PF if, in the opinion of the investigator it is medically necessary or if it is the wish of the subject.

If treatment with dCBT-PF is discontinued, the investigator or designee should make all efforts to ensure that the subject will remain in the clinical investigation and ensure that the subject attends the remaining visits.

7.1.1. Temporary Discontinuation

There are no specific criteria for temporary discontinuation of dCBT-PF treatment. If a temporary discontinuation is required according to the investigator's judgement, the stop and start date and reason for a temporary discontinuation should be reported in the case report form (CRF). If the subject is still within the treatment period of the clinical investigation when a temporary discontinuation is no longer required, treatment with the dCBT-PF can be restarted.

7.2. Subject Discontinuation/Withdrawal from the Clinical Investigation

- A subject may withdraw from the clinical investigation at any time at his/her own request i.e., withdrawal of consent.
- Subjects expressing significant new or worsened negative wellbeing or distress during the study will be withdrawn from the clinical investigation (cf. separately IRB approved 'Suicide Ideation Process').
- The subject will be permanently discontinued from using the dCBT-PF at the time of withdrawal from the clinical investigation.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

A subject will be considered lost to follow-up if he/she repeatedly fails to call in for required visits and is unable to be contacted by the clinical investigational site.

The following actions must be taken if a subject fails to call in for a required clinical investigation visit or complete the questionnaire:

- The site must attempt to contact the subject and reschedule the missed assessments as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the clinical investigation.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, at least 3 telephone calls

plus additional methods such as SMS/email). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the clinical investigation.

8. Clinical Investigation Assessments and Procedures

- Clinical investigation procedures and their timing are summarized in the SoA. Procedures will be performed via telehealth or phone calls.
- Waivers or exemptions are not allowed.
- Adherence to the clinical investigation design requirements, including those specified in the SoA, is essential and required for conduct of the clinical investigation.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

8.1. Pre-screening and Screening/Baseline Assessments

Planned timepoints for all pre-screening and screening/baseline assessments are provided in the SoA.

8.1.1. Pre-screening assessment

Eligibility at pre-screening will be assessed by GAD-7 and patient reported medical information. Upon registering at the investigation landing page, subjects will be prompted to complete the prescreen GAD-7 questionnaires. Subjects are required to have a GAD-7 composite score of ≥5 at both pre-screening and baseline to be eligible. If the GAD-7 composite score at pre-screening is <5, no further assessments will be performed.

Subjects will be asked for additional self-reported information relevant to assess eligibility.

If the subject is confirmed eligible per pre-screening assessments, the consent form for support with medical records (CT scan, cf. Section 8.1.3) can be obtained.

The information collected at the pre-screening assessment is done prior to obtaining informed consent, and the data obtained will consequently not be included in the clinical database. It will only be used for the purpose of assessing eligibility criteria.

8.1.2. Screening/Baseline assessments

Subjects confirmed eligible based on the pre-screening assessments will be requested to provide a CT scan report confirming their PF diagnosis or provide their physician information in order for Curebase to request the report on their behalf. Once received, a video call with the site staff/Clinical Research Coordinator (CRC) will take place to obtain consent and conduct the baseline visit procedures. The Principal Investigator (PI) will then evaluate eligibility after informed consent has been obtained and baseline visit has been completed.

8.1.2.1. Demographics

Demographic and baseline characteristics will be obtained. The following information will be collected:

- Age
- Race and ethnicity
- Sex

8.1.2.2. Medical History

All current medical conditions and relevant previous medical conditions should be recorded.

For the pilot phase, subjects can be included based on self-reported IPF diagnosis. If available, medical history information may also be recorded for the pilot phase.

For the pivotal phase, the following information is required:

- PF diagnosis confirmation (self-reported)
- Date of PF diagnosis (self-reported, approximate/incomplete date is accepted if not known)
- CT report (no more than 5 years old). A non-high-resolution CT may be sufficient to confirm the diagnosis. Inclusion criteria 5 will always be assessed based on investigator judgement and should the CT scan report not be sufficient to confirm the diagnosis, an HRCT scan report can be requested to confirm eligibility.
- Other relevant diseases reported by the subject.

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1. General Anxiety Disorder-7

Anxiety severity will be assessed by GAD-7 by the subject using an electronic diary on their own smartphone, tablet device or computer.

The GAD-7 questionnaire includes the following questions (paper version displayed):

GAD-7 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Source: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright® 1999 Pfizer Inc. All rights reserved. Reproduced with permission

The response scores of the first 7 questions are added to create a composite score (range 0-21), with higher scores indicating a higher level of anxiety.

Composite scores of ≤4, 5-9, 10-14, and ≥15 represent minimal, mild, moderate, and severe anxiety, respectively.

8.2.2. Kings brief interstitial lung disease questionnaire

PF HRQoL will be assessed by K-BILD by the subject using an electronic diary on their own smartphone, tablet device or computer.

The K-BILD questionnaire includes the following questions (paper version displayed):

1. In the last 2 weeks, I have been short of breath climbing stairs or walking up an incline or hill.

1. Every time
2. Most times
3. Several Times
4. Sometimes
5. Occasionally
6. Rarely
7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung symptoms?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks have you avoided doing things that make you short of breath?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A lot of the time
6. Most of the time
7. All of the time

6. In the last 2 weeks, have your lung symptoms made you feel annoyed or down?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, I have felt the urge to to inhale deeply and frequently known as "air hunger."

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, how often have you experienced "wheezing" or whistling sounds from your chest?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last two weeks how much of the time have you felt your lung disease is getting worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

12. In the last 2 weeks have you expected your lung symptoms to get worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

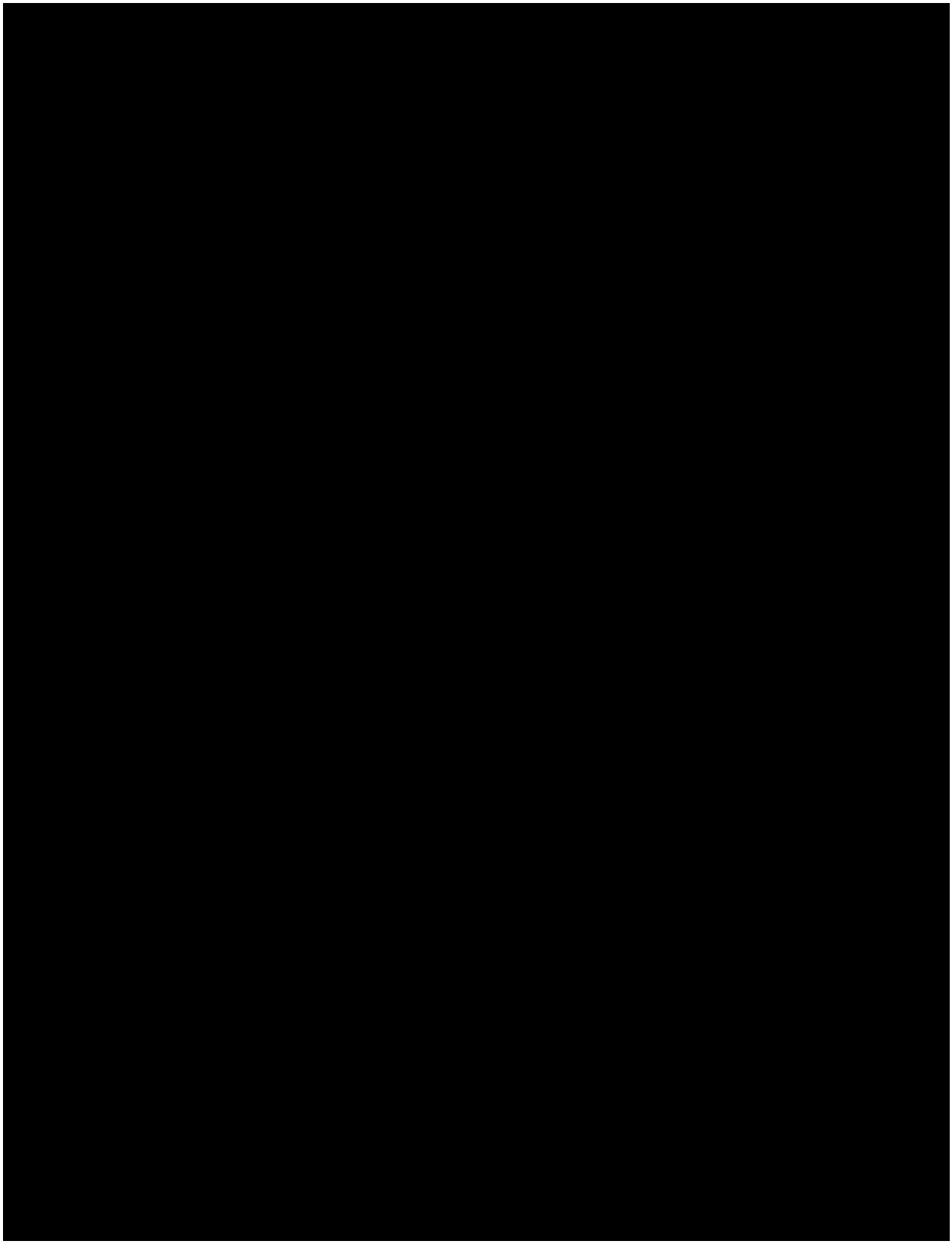
1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount
2. A large amount
3. A considerable amount
4. A reasonable amount
5. A small amount
6. Hardly at all
7. Not at all

Thank you for completing this questionnaire.

Scores will be calculated for each domain (breathlessness and activities, chest symptoms and psychological) and for the total questionnaire. The K-BILD domain and total scores ranges are 0-100; 100 represents the best health status.



[redacted]

[redacted]DAY.

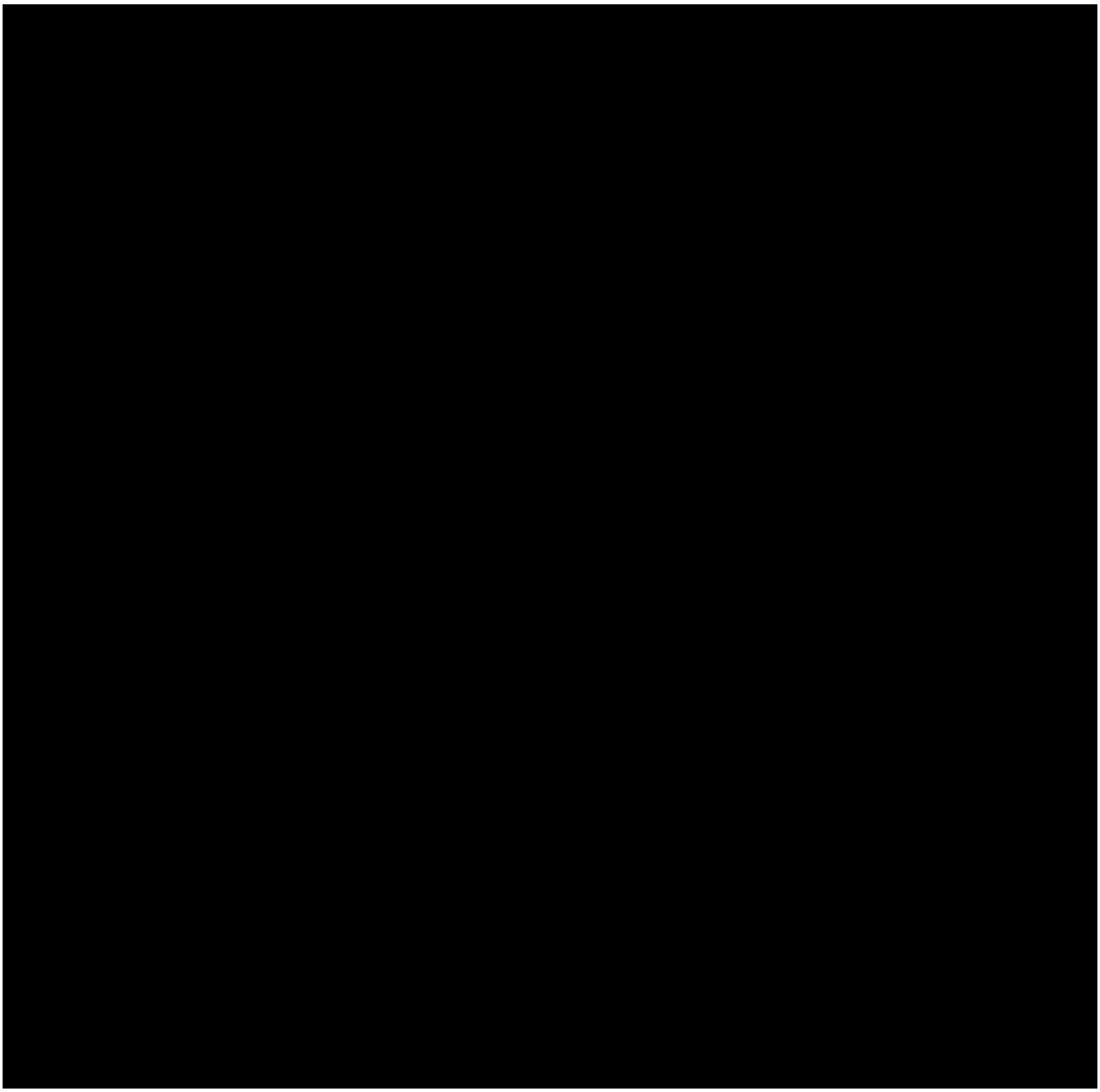
[redacted]

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑



8.2.5. Hamilton anxiety rating scale

The HAM-A scale will be used to assess clinician-rated signs and symptoms of anxiety. Ratings will be performed by clinician-based interviews with the subject. The clinician will be independent to the site staff conducting the investigation and blinded to the subject's treatment assignment. The subject will be instructed not to mention their investigational treatment during the interviews. A structured interview guide for the HAM-A scale (SIGH-A; past week recall) will be used to complete the assessments.

HAM-A will be completed no more than 2 days after the subject has completed the patient-reported questionnaires. The HAM-A will be completed electronically; the paper version is displayed below.

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 **Anxious mood** [0] [1] [2] [3] [4]

Worries, anticipation of the worst, fearful anticipation, irritability.

2 **Tension** [0] [1] [2] [3] [4]

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 **Fears** [0] [1] [2] [3] [4]

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 **Insomnia** [0] [1] [2] [3] [4]

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 **Intellectual** [0] [1] [2] [3] [4]

Difficulty in concentration, poor memory.

6 **Depressed mood** [0] [1] [2] [3] [4]

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 **Somatic (muscular)** [0] [1] [2] [3] [4]

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 **Somatic (sensory)** [0] [1] [2] [3] [4]

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 **Cardiovascular symptoms** [0] [1] [2] [3] [4]

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 **Respiratory symptoms** [0] [1] [2] [3] [4]

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 **Gastrointestinal symptoms** [0] [1] [2] [3] [4]

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 **Genitourinary symptoms** [0] [1] [2] [3] [4]

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

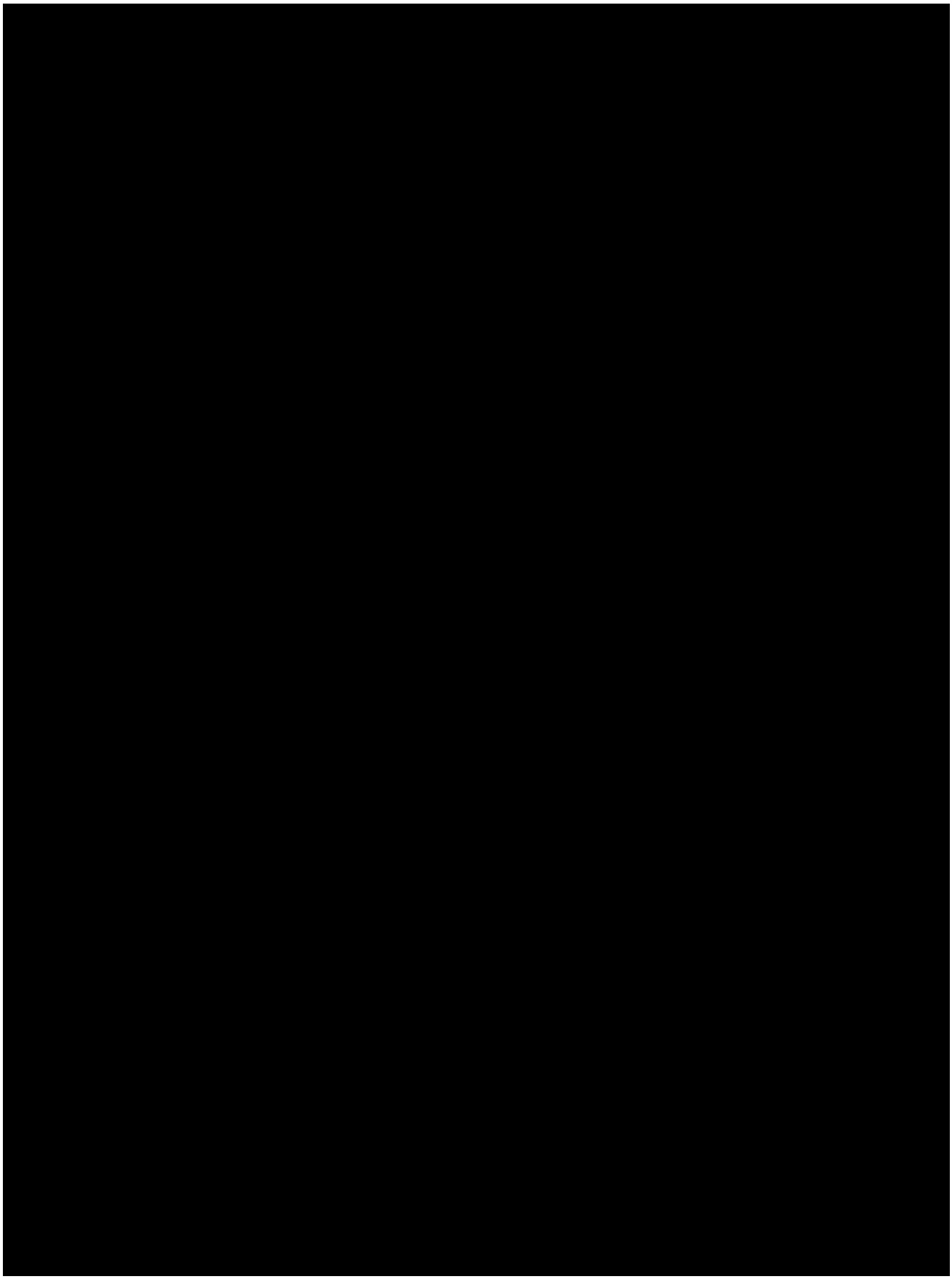
13 **Autonomic symptoms** [0] [1] [2] [3] [4]

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 **Behavior at interview** [0] [1] [2] [3] [4]

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

HAM-A is a 14-item questionnaire rating the intensity of psychic and somatic anxiety on a 5-point severity scale. Each item ranging from 0 (not present) to 4 (very severe) will be summed up to give a total possible score of 0 to 56, where lower scores indicate less anxiety.



[redacted]

8.2.7. Video interview to evaluate functionality (applicable for pilot phase only)

In the pilot phase, subjects will be interviewed by delegated Alex Therapeutics staff following a separate semi-structured interview guide. Topics can include:

1. **Is the product helpful?**
    a. What new learnings have the product provided?
    b. Has the product led to any real change in everyday life?
    c. Has it affected your overall anxiety and mood?
2. **Is the product intuitive?**
    a. Was the product able to instinctively understand your mood?
3. **Is the product engaging?**
    a. Do people stay for the whole program?
    b. Where do people drop-off?
    c. Where is motivation lacking?
    d. Is there any particular content that is hard to understand and/or bothersome
4. **Is it specific enough to IPF patients?**
    a. Do IPF patients recognize themselves in content and examples?
    b. Is there something that is not addressed?

Video interviews will be transcribed, and outcomes will be summarized in a separate report.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions and reporting requirements for AEs, ADEs, SAEs, and SADEs can be found in Appendix 2 (see Section 10.2).

AEs will be reported by the subject and will be classified as AEs, ADEs, SAEs, and SADEs according to the definitions provided in Section 10.2. ADEs and SADEs can only occur in the dCBT-PF group as there are no intervention in the control group. All ADEs, SAEs and SADEs should be reported in the CRF. Aes, not fulfilling the definition of an ADE, SAE, and SADE, should only be reported if they are related to a psychological disorder or a procedure of the clinical investigation.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, ADE, SAE, or SADE. They further remain responsible for following up on AEs, ADEs, SAEs, or SADEs.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

AEs, ADEs, SAEs and SADEs will be collected from signing of the ICF at baseline (V1) and until Week 4 (pilot phase) or Week 12 (pivotal phase), respectively, at the timepoints specified in the SoA (see Section 1.3). Aes, ADEs, SAEs and SADEs are followed until they have reached a final outcome or the subject's participation in the clinical investigation ends, whichever comes first.

All SAEs and SADEs will be recorded and reported to the sponsor immediately and under no circumstance should this exceed 24 hours after SAE / SADE awareness. The investigator or designee will submit any updated SAE/SADE data to the sponsor within 48 hours of it being available. For all reportable events, the sponsor will adhere to local reporting timelines.

Information on relevant AEs, ADEs, SAEs, and SADEs must be entered in the CRF.

Investigators are not obligated to actively seek information on AEs, ADEs, SAEs, or SADEs after conclusion of the clinical investigation participation. However, if the investigator learns of any SAE or SADE, including a death, at any time after a subject has been discharged from the clinical investigation, and he/she considers the event to be reasonably related to the intervention or participation in the clinical investigation, the investigator must promptly notify the sponsor regardless of the time that has elapsed (post-clinical investigation events).

8.4.2. Method of Detecting AEs, ADEs SAEs, and SADEs

Care will be taken not to introduce bias when detecting AEs, ADEs, SAEs, and/or SADEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs, ADEs SAEs, and SADEs

After the initial AE/ADE/SAE/SADE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and SADEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (see Section 7.3).

8.4.4. Regulatory Reporting Requirements for reportable events

- Prompt notification – within 24 hours of SAE/SADE awareness – by the investigator to the sponsor of a SAE/SADE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of the IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify relevant regulatory authorities about the safety of the intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)s, and investigators.
- An investigator who receives an investigator safety report describing a SAE/SADE or other specific safety information (e.g., summary or listing of SAEs/SADEs) from the sponsor will review and then file it in the investigator site file and will notify the IRB, if appropriate according to local requirements.

8.5. Reporting of Device deficiencies

The definition for device deficiencies can be found in Section 10.2.6. Device deficiencies will be collected from start of dCBT-PF use and until Week 4 (pilot phase) or Week 9 (pivotal phase). Device deficiencies will be reported by the subject or the site.

Device deficiencies can only occur in the dCBT-PF group.

Device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate must be reported to the sponsor within 24 hours of device deficiency awareness. The sponsor will report this type of device deficiencies to the regulatory authority, if required, institutional review board (IRB)s, and investigators. This will be according to national legislation.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to enrolling the first subject in the pivotal phase of the clinical investigation, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The aim of this clinical investigation is to show superiority of dCBT-PF over a control group regarding selected efficacy measures. The null hypothesis to be tested for each endpoint will be that there is no difference between dCBT-PF and control, against the alternative hypothesis that dCBT-PF is better than control. All tests will be done using 2-sided alternatives.

[redacted]

9.2. Analysis Sets

For the purposes of analysis, the following analysis set has been defined:

Subject Analysis Set	Description
Intention to treat (ITT) analysis set	All randomised subjects. Subjects will be included in the analyses according to the intervention they were randomised to.
Safety set	All enrolled subjects. Subjects will be analyzed according to the actual intervention received, dCBT-PF or control.

9.3. Statistical Analyses

9.3.1. General Considerations

All tests will be 2-sided at a 5% significance level.

Baseline will be defined as the last non-missing assessment obtained prior to randomization.

Stratification will be done based on baseline disease severity defined as the total score on the GAD-7 questionnaire (GAD-7 score 5-9, 10-14 or ≥15 points) at baseline (Visit 1).

The actual stratification will be used as factors in the statistical analysis, subjects included in wrong stratum at randomization will be moved to their correct strata belonging in the analyses.

Continuous variables will be summarized using (arithmetic) means, standard deviation (SD), median, minimum, and maximum value, categorical variables will be summarized using numbers and percentages.

The ITT analysis set is used for the main analysis of all endpoints related to the efficacy objectives. Sensitivity analyses related to efficacy objectives will be described in the SAP. The safety analysis set is used to analyze the endpoints and assessments related to safety.

All data regarding subject characteristics, efficacy and safety will be listed.

9.3.2. Primary Endpoint/Estimand Analysis

The primary endpoint, change from baseline in patient-reported anxiety symptom severity assessed by GAD-7 at Week 9, will be compared between treatment groups using an ANCOVA model with treatment and strata (baseline anxiety severity) as factors, the baseline GAD-7 score as covariate and the baseline by strata interaction.

The adjusted mean difference between groups will be given together with 95% confidence intervals and associated 2-sided p-value.

Withdrawals prior to Week 9 not possible to follow-up will be imputed using multiple imputation taking subjects baseline characteristics, treatment, and post-treatment GAD-7 scores into account.

The ITT analysis set will be used for the main analysis of the primary endpoint. Sensitivity analyses will be performed with alternative methods for imputation (for instance using the average of the opposite treatment group as base) and a tipping point analysis will also be performed investigating the impact on the treatment effect by successive shifts introduced in the imputation for the active group. Sensitivity analysis will be described in the SAP. In all analyses subjects will be included as randomised. All collected data post-intervention will be used to assess the endpoint.

9.3.3. Secondary Endpoints Analysis

The ITT analysis set will be used for the main analysis of key secondary and exploratory endpoints. Subjects will be included in analyses as randomised. All collected data post-intervention will be used to assess the endpoints. The key secondary endpoints are:

- Change from baseline in clinician-reported anxiety symptom severity as assessed by Hamilton anxiety rating scale (HAM-A) at Week 9
- Change from baseline in HRQoL assessed by K-BILD psychological domain score at Week 9
- Change from baseline in HRQoL assessed by K-BILD total score at Week 9

The key secondary endpoints will be tested in a pre-specified hierarchical order following the test of the primary endpoint. Other exploratory endpoints will be tested independently without adjustment for multiple tests.

The key secondary endpoints, change from baseline in HAM-A, K-BILD psychological domain and total scores at Week 9, will be compared between treatment groups using an ANCOVA model with treatment and strata (baseline anxiety severity) as factors and the baseline score as covariate.

Withdrawals from the clinical investigation prior to Week 9 not possible to follow-up will be imputed using multiple imputation taking subjects baseline characteristics, treatment, and post-treatment scores into account.

Other continuous endpoints assessed at baseline and post-intervention will be compared using similar ANCOVA models as for the primary (with interaction; GAD-7 based endpoints) or key secondary endpoints (without interaction) with treatment effect expressed as difference in mean scores. PGIC scores will be compared using a similar ANOVA model omitting the covariate. Endpoints assessing proportion of subjects (binary outcome) will be compared using logistic regression models adjusting for treatment and strata (baseline anxiety severity) as factors. Categorical endpoints will be summarized by category and compared using the chi2-test.

9.3.4. Safety Analyses

Safety analysis will be based on the safety set.

AEs will be analyzed using quantitative and qualitative measures. AEs will be summarized by treatment group for all AEs, ADEs, SAEs, SADEs (unanticipated SADE (USADE), or anticipated SADE (ASADE)), deaths, AEs leading to discontinuation of dCBT-PF or to withdrawal from investigation, and device deficiencies. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term for each treatment group. ADEs and SADEs only applies to the dCBT-PF therapy group.

9.3.5. Other Analyses

The subject flow including total number of screened subjects, number of randomised subjects, completers, withdrawn subjects (including reason for withdrawal) and subjects included in each of the analysis sets will be summarized by group and for the total.

Health care utilisation will be summarized by type of health care utilisation and by treatment group.

The number of subjects with major deviations will be summarized by category of violation and by treatment group.

Adherence to the device will be summarized using descriptive statistics for the subjects randomised to dCBT-PF.

Demographic and baseline characteristics will be summarized using descriptive statistics for each treatment group and for the total number of randomised subjects. Medical history will be coded using MedDRA and summarized by system organ class and preferred term for each treatment group. Prior medications will denote medications used prior to first dose of

investigational medical device independent and stopped at latest at randomization. Concomitant therapy will denote medications started prior to but continuing after randomization or medications with a start date at or after the randomization date. Prior and concomitant therapy will be summarized separately by Anatomical Therapeutic Chemical levels 2 and 4.

Subgroup analyses of the primary and key secondary endpoints will be made to assess consistency of the intervention effect across at least the following subgroups:

- Age group: <65 vs ≥65 years
- Sex: female vs male
- Baseline disease severity (GAD-7 score at baseline: 5-9, 10-14, ≥15)

If the number of subjects is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to data analysis. Further details on the statistical analysis will be provided in a statistical analysis plan.

Answers to functionality interview of the DTx will be evaluated using qualitative methods and will be reported separately.

9.4. Sample Size Re-estimation

No sample size re-estimation will be made as a result of the data collected in the pilot part of the investigation.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Clinical investigation Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This clinical investigation will be conducted in accordance with the CIP and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
- Applicable FDA, ISO and GCP guidelines.
- Applicable laws and regulations.

The CIP, substantial amendments, ICF and other relevant documents (e.g., subject facing material and advertisements) will be submitted to an IRB and reviewed and approved by the IRB before the clinical investigation is initiated.

Any amendments to the CIP will require IRB approval before implementation of changes except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the clinical investigation to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the clinical investigation at the site and adherence to requirements of 21 CFR (part 812), ISO 14155, medical device regulation (MDR), the IRB and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the clinical investigation and for 1 year after completion of the clinical investigation.

10.1.3. Informed Consent Process

The investigator or his/her representative will via the telehealth system explain the nature of the clinical investigation, including the risks and benefits, to the subject and answer all questions regarding the clinical investigation.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 812, local regulations, ISO

14155, MDR, data privacy, and data protection requirements, where applicable, and the IRB or site.

Subjects must be reconsented, as applicable, to the most current version of the ICF(s) during their participation in the clinical investigation.

A copy of the signed ICF(s) must be provided to the subject.

10.1.4. Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal clinical investigation-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be directly examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

An independent data monitoring committee (DMC) will be established to provide oversight of the pivotal phase of the investigation.

The functions and responsibilities of the DMC will be described in a DMC charter.

Throughout the duration of the investigation, the DMC will evaluate all SADEs on an ongoing basis. In addition, the DMC will meet at least once during the investigation (timepoint(s) to be defined in the charter) to review safety and efficacy data to oversee the safety of the investigation, subjects, and the scientific validity and integrity of data collected as part of the investigation.

The DMC will provide appropriate written recommendations to the Sponsor regarding investigation continuation and/or investigational plan modifications.

Any safety related DMC recommendations that may result in investigational plan changes or to the management of subjects in the investigation will be reported to the IRB.

10.1.6. Dissemination of Clinical Investigation Data

Information about the clinical investigation will be posted on the US National Institutes of Health’s website www.clinicaltrials.gov prior to the first subject entering the pivotal phase of the clinical investigation.

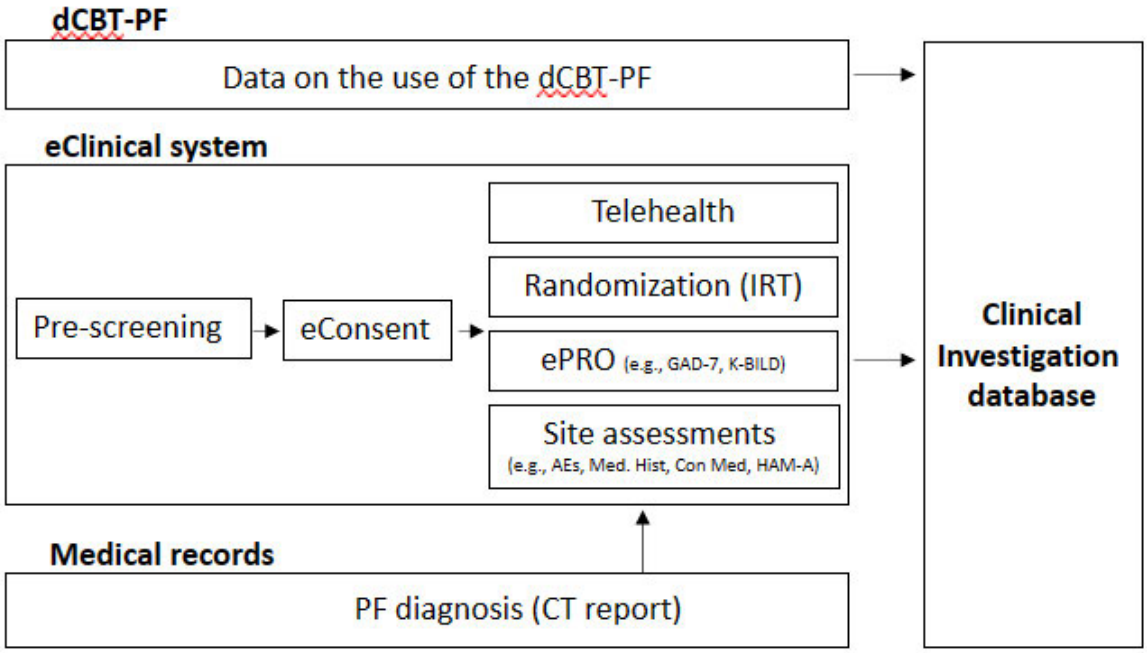
10.1.7. Data Quality Assurance

All subject data relating to the clinical investigation will be collected at the virtual site in one central clinical system. Data will be entered by the subjects in an electronic patient reported

outcome (ePRO) system or by the site staff. An overview of the data flow is provided in Figure 1.

- The clinical system will have the following functionalities:
    - Pre-screening system
    - Telehealth system
    - eConsent
    - ePRO system
    - Randomisation (IRT)
    - Site assessments EDC system
    - Source documentation
- Information on use of the dCBT-PF will be collected in the dCBT-PF database and will be transferred to the clinical investigation database
- Medical records (CT report) confirming the PF diagnosis will uploaded in the source documentation system (not applicable for the pilot part of the investigation).

Figure 1: Data flow



- The investigator must permit clinical investigation-related monitoring, audits, IRB review, and regulatory agency inspections.
- Monitoring details describing strategy, including definition of critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management

and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- The sponsor or designee is responsible for the data management of this clinical investigation, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this clinical investigation must be retained by the investigator for 10 years after completion of the clinical investigation or after the last device is sold, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents is in this clinical investigation considered prior medical records, including the documentation for the diagnosis of PF (CT report), used to enter relevant medical history details (not applicable for the pilot part of the investigation).
- Majority of the clinical data in this clinical investigation will be entered directly into the CRF and no source data verification will be performed.
- Data reported entered in the site assessment CRF system that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
- Definition of what constitutes source data, and its origin can be found in the monitoring plan.

10.1.9. Clinical Investigation and Site Start and Closure

First Act of Recruitment

The clinical investigation start date is the date on which the clinical investigation will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the clinical investigation start date.

Clinical investigation/Site Termination

The sponsor or designee reserves the right to close the clinical investigation site or terminate the clinical investigation at any time for any reason at the sole discretion of the sponsor. Clinical investigation sites will be closed upon clinical investigation completion. A clinical investigation site is considered closed when all required documents and have been collected and a clinical investigation-site closure visit has been performed.

The investigator may initiate clinical investigation-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a clinical investigation site by the sponsor or investigator may include but are not limited to:

For clinical investigation termination:

- Discontinuation of further device development.

For site termination:

- Failure of the investigator to comply with the CIP, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected.

If the clinical investigation is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the clinical investigation of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

- The primary publication should be published by the sponsor prior to any other investigator-initiated publications, manuscripts, abstracts, or presentations.
- The results of this clinical investigation may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of clinical investigation results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: AEs, ADEs, SAEs and SADEs: Definitions

10.2.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including laboratory finding) in subjects (i.e., participants in the clinical investigation), users or other persons, whether or not related to the investigational medical device and whether or not anticipated or unanticipated. Notes: • Includes events related to the investigational medical device or the comparator, and the procedures involved *Comparator* is used in the control group and can be: • Medical device • Therapy (e.g., active treatment, normal clinical practice) • Placebo • No treatment Lack of efficacy per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. AEs, not fulfilling the definition of an ADE, SAE, and SADE, should only be reported if they are related to a psychological disorder or a procedure of the clinical investigation.

10.2.2. Definition of ADE (Adverse Device Effect)

ADE Definition
An ADE is an AE related to the use of the investigational medical device. Includes: • Events resulting from insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction (0) of the investigational medical device • Events resulting from use error or intentional misuse • Events related to comparator if comparator is medical device

10.2.3. Definition of SAE (Serious Adverse Event)

An SAE is defined as any untoward medical occurrence that meets one or more of the criteria listed:
a. Results in death
b. Serious deterioration in the health of the subject, user or other persons as defined by one or more of the following: A life-threatening illness or injury A permanent impairment of a body structure or a body function including chronic disease Inpatient hospitalization* or prolonged hospitalization Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or body function Note*: Planned hospitalization for a pre-existing condition, or a procedure required by CIP without serious deterioration in health, is not considered a SAE
c. **Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment**.

10.2.4. Definition and categorization of SADEs (Serious Adverse Device Effects)

SADE definition
A SADE is an adverse event effect (ADE, 10.2.2) that has resulted in any of the consequences characteristic of an SAE) SADE is categorized as: • ASADE – anticipated SADE, or • USADE – unanticipated SADE USADE definition from 21 CFR part 812: Any SADE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2.5. Recording and follow-up on of AE, ADEs, SAEs or SADEs

AE, ADE, SAE, SADE and device deficiency recording

- AEs/ADEs/SAEs/SADEs will be collected from signing the ICF. Device deficiencies will be collected from start of dCBT-PF use.
- A pre-existing medical condition should be reported if the condition increases in severity (e.g. from non-severe to severe).
- At each visit the subject should be asked about AEs in an objective manner, *e.g.*: "Have you experienced any problems since the last visit?".
- All AEs/ADEs/SAEs/SADEs should be followed until they have reached a final outcome (Resolved, resolved with sequelae, death) or the subject's participation in the trial ends, whichever comes first.
- The outcome "Ongoing" can be used as the final outcome for events that are not expected to resolve over time.
- ADEs, SADEs should be followed on a regular basis according to the investigator's clinical judgment until a final outcome has been established.

Causality of AEs (relationship to device or procedure)

- Not related
- Possible
- Probable
- Causal

The AEs fulfilling causality criteria possible, probable and casual are all classified as ADEs

Event status

The Investigator is obliged to record the most appropriate outcome using the following categories:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

10.2.6. Device deficiencies

Device deficiency definition
Device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include: • Malfunctions (failure to perform in accordance with its intended purpose when used according to instructions) • Use errors (inability of user to use the device properly, which user might be aware or unaware about) • Inadequacy in the information supplied by manufacturer including labelling related to investigational medical device or the comparator

10.3. Appendix 3: Organisation

Clinical Research Organization

Curebase Inc.
340 S. Lemon Ave 3356
Walnut, CA 91789
USA

Roles and responsibilities:

- Project management
- eClinical software including EDC, eSource, eConsent, ePRO, telehealth and randomization systems
- Digital clinical investigation services including IRB submissions, remote monitoring, data management, vendor management, safety event management, data standardization, statistical analyses, and eTMF management
- Clinical site services

Device manufacturer

Alex Therapeutics
Upplandsgatan 7
111 23 Stockholm
Sweden

Roles and responsibilities:

- Legal dCBT-PF device manufacturer
- Administration and hosting of dCBT-PF database

10.4. Appendix 4: Abbreviations

ACT	Acceptance & Commitment Therapy
AE	Adverse event
ADE	Adverse device effect
ALAT	Latin American Thoracic Association
ANCOVA	Analysis of covariance analysis
ASADE	Anticipated serious adverse device effect
ATS	American thoracic society
[redacted]	[redacted]
CBT	Cognitive behavioral therapy
CIP	Clinical investigation plan
CRC	Clinical Research Coordinator
CRF	Case report form
CT	Computed Tomography
dCBT	Digital cognitive behavioral therapy
dCBT-IPF	Digital cognitive behavioural therapy in idiopathic pulmonary fibrosis (DTx name applicable for the pilot phase)
dCBT-PF	Digital cognitive behavioural therapy in pulmonary fibrosis
Dtx	Digital therapeutics
ePRO	Electronic patient reported outcomes
[redacted]	[redacted]
ERS	European respiratory society
FVC	Forced vital capacity
GAD-7	7-item generalized anxiety disorder questionnaire
GCP	Good clinical practice

HAM-A	Hamilton anxiety rating scale
HRCT	High-Resolution Computed Tomography
[redacted]	[redacted]
ICF	Informed consent form
IRB	institutional review board
IPF	Idiopathic pulmonary fibrosis
ISO	International organization for standardization
ITT	Intention to treat
JRS	Japanese respiratory society
K-BILD	King's brief interstitial lung disease questionniare
MDR	Medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
PCP	Primary Care Provider
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal Investigator
SAE	Serious adverse event
SADE	Serious adverse device effect
SoA	Schedule of activities
SD	Standard deviation
USADE	Unanticipated serious adverse device effect

11. Amendment History

Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Description of Change**	**Rationale for changes**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Document	Description of Change	Rationale for changes	Applicable for sections
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	Adjustment for the assessment for the pivotal phase.	To reflect the above listed changes and ensure a better operational flow.	1.2, 8.1, 8.1.1., 8.1.2.2, 8.2.2

[redacted]			
		Text for sample size determination updated after FDA advise.	
	Section [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Document	Description of Change	Rationale for changes	Applicable for sections
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

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13. Sponsor and Coordinating Investigator Signatures

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