Responsiveness and meaningful change thresholds of the Living with Pulmonary Fibrosis (L-PF) questionnaire Dyspnoea and Cough scores in patients with progressive fibrosing interstitial lung diseases

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ABSTRACT

Background The Living with Pulmonary Fibrosis (L-PF) questionnaire assesses symptoms and quality of life in patients with fibrosing interstitial lung diseases (ILDs). Its Dyspnoea and Cough domains, whose items’ responses are based on a 24-hour recall, have scores ranging from 0 to 100, with higher scores indicating greater symptom severity. We evaluated the ability of these domain scores to detect change and estimated their meaningful change thresholds in patients with progressive fibrosing ILDs.

Methods The INBUILD trial enrolled subjects with progressive fibrosing ILDs other than idiopathic pulmonary fibrosis. The L-PF questionnaire was completed at baseline and week 52. The responsiveness of the Dyspnoea and Cough scores was evaluated by comparing changes in these scores with 52-week changes in three anchors: forced vital capacity % predicted and two self-reported items, one for global physical health and one for global quality of life. We used a triangulation approach including anchor-based and distribution-based methods to estimate meaningful change thresholds.

Results The analyses included 542 subjects with an L-PF Dyspnoea score at baseline and week 52, and 538 subjects with an L-PF Cough score at baseline and week 52. The L-PF Dyspnoea and Cough scores were responsive to change over 52 weeks. Triangulation of anchor-based and distribution-based estimates resulted in meaningful change thresholds of 6 to 7 points for the L-PF Dyspnoea score and 4 to 5 points for the L-PF Cough score to differentiate subjects who were stable or improved from those who deteriorated.

Conclusion These analyses support the responsiveness, one aspect of validity, of the L-PF Dyspnoea and Cough domains scores as measures of symptom severity in patients with progressive fibrosing ILDs. Estimates for meaningful change thresholds in these domain scores may be of value in interpreting the effects of interventions in these patients.

Trial registration number NCT02999178.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an inexorably progressive fibrosing interstitial lung disease (ILD).1 A number of other ILDs may also be associated with a progressive fibrosing phenotype, characterised by an increasing extent of fibrosis, decline in lung function, worsening symptoms and quality of life and early mortality.2–4 In patients with fibrosing ILDs, dyspnoea, cough and fatigue can affect patients’ physical and emotional well-being and health-related quality of life (HRQL),5 which tends to decline as patients’ lung function worsens.6,7 Patient-centred outcomes are important tools for assessing the effects of disease and interventions on aspects of patients’ lives, including symptoms and HRQL.8 The Living with Idiopathic Pulmonary Fibrosis (L-IPF) questionnaire, which includes two modules that assess symptoms or their impacts, was...
The Living with Pulmonary Fibrosis (L-PF) questionnaire is a slightly modified version of the L-PF questionnaire and was developed to assess health status and quality of life in patients with IPF. The L-PF questionnaire demonstrated sound psychometric properties in these patients, including discriminant properties between those with different disease severities. The L-PF questionnaire is accessible via: https://eprovide.mapi-trust.org/instruments/

**Table 1** Changes in L-PF Dyspnoea and Cough scores across strata of 52-week change in FVC % predicted strata

| Change in FVC % predicted† | Large deterioration | Moderate deterioration | Minimal deterioration | Stable | Minimal improvement | Moderate improvement | Large improvement |
|----------------------------|---------------------|-----------------------|----------------------|--------|---------------------|---------------------|-------------------|
|                            | Mean (SD) change from baseline | N                  | Mean (SD) change from baseline | Mean (SD) change from baseline | Mean (SD) change from baseline | Mean (SD) change from baseline | Mean (SD) change from baseline |
| L-PF Dyspnoea score        | 170                 | 13.4 (17.2)           | 103                  | 4.8    | (15.5)              | 67                   | 1.1               | (12.9)            |
| L-PF Cough score           | 168                 | 8.8                   | (23.3)               | 102    | 0.2                 | 67                   | −3.2              | (20.1)            |

FVC, forced vital capacity; L-PF, Living with Pulmonary Fibrosis.

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Table 2  Changes in L-PF Dyspnoea and Cough scores across strata of 52-week change in global physical health score

| Change in L-PF global physical health score† | Large deterioration | Minimal/Moderate deterioration | Stable | Minimal/Moderate Improvement | Large improvement |
|---------------------------------------------|---------------------|--------------------------------|--------|-----------------------------|------------------|
| N Mean (SD) change from baseline | N Mean (SD) change from baseline | N Mean (SD) change from baseline | N Mean (SD) change from baseline | N Mean (SD) change from baseline | F-statistic‡ | Pairwise comparisons§ |
| L-PF Dyspnoea score 6 17.6 (28.8) 159 | 8.7 (16.8) 244 | 5.7 (14.5) 120 | 0.6 (15.6) 6 | 5.7*** | 6** |
| L-PF Cough score 5 5.8 (27.7) 157 | 4.8 (24.8) 242 | 1.5 (23.3) 121 | −5.9 (23.8) 8 | 0.0 (22.6) 3.6** | 6** |

L-PF Symptoms scores range from 0 to 100, with higher scores indicating greater impairment.

*p<0.05, **p<0.01, ***p<0.001.

†Question 20: on average, over the last 7 days, how have you felt in terms of physical health? Scale: 0 (extremely poor) to 4 (excellent). Large deterioration: change of −3 or −4; minimal/moderate deterioration: change of −2 or −1; stable change of 0; minimal/moderate improvement: change of +1 or +2; large improvement: change of +3 or +4.

‡One-way analyses of variance (generalised linear model) overall F-statistic.

§Pairwise comparisons using Scheffe’s method: 1=large deterioration versus minimal/moderate deterioration, 2=large deterioration versus stable, 3=large deterioration versus minimal/moderate improvement, 4=large deterioration versus large improvement, 5=minimal/moderate deterioration versus stable, 6=minimal/moderate deterioration versus minimal/moderate improvement, 7=minimal/moderate deterioration versus large improvement, 8=stable versus minimal/moderate improvement, 9=stable versus large improvement, 10=minimal/moderate improvement versus large improvement.

L-PF, Living with Pulmonary Fibrosis.
stable/improved (improvement or decline in FVC ≤2% predicted or change in global rating anchors of 0 to +4).

Distribution-based analyses were performed to provide supplementary results. We evaluated the SEM, estimated as the baseline SD of the measure multiplied by the square root of 1 minus its reliability coefficient, and 0.2×SD and 0.5×SD of the scores at baseline. One SEM may be considered a meaningful change threshold and changes of 0.5×SD and 0.2×SD may be considered upper and lower boundaries for a meaningful change.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS
A total of 663 subjects were enrolled in the INBUILD trial at 153 sites in 15 countries. Their baseline characteristics have been described. Briefly, mean (SD) age was 65.8 (9.8) years and FVC was 69.0 (15.6) % predicted; 53.7% of subjects were male and 62.1% had a usual interstitial pneumonia-like fibrotic pattern on HRCT. The most common diagnoses were hypersensitivity pneumonitis (26.1%), autoimmune disease-related ILDs (25.6%), idiopathic non-specific interstitial pneumonia (18.9%) and unclassifiable ILD (17.2%). A total of 542 subjects with an L-PF Dyspnoea score at baseline and week 52, and 538 subjects with an L-PF Cough score at baseline and week 52, were included in these analyses.

Responsiveness of L-PF Dyspnoea and Cough scores
There were large and statistically significant differences in changes in Dyspnoea and Cough scores between subjects with stable versus large deterioration in FVC % predicted and between subjects with minimal versus large deterioration in FVC % predicted (table 1). There was a statistically significant difference in change in Dyspnoea score between subjects with moderate versus large deterioration in FVC % predicted. There were no statistically significant differences in changes in Dyspnoea or Cough scores between subjects with stable versus minimal deterioration in FVC % predicted. Changes in Dyspnoea and Cough scores were significantly different between subjects with minimal/moderate deterioration versus minimal/moderate improvement in either global rating anchor (tables 2 and 3).

Meaningful change thresholds in L-PF Dyspnoea score
For the Dyspnoea domain, the half-way points between changes in scores for subjects who were stable and those with minimal deterioration in FVC % predicted, global physical health score and global quality of life score were 1.1, 7.1 and 7.6, respectively. Similar half-way points were observed for the global rating anchors when minimal/
Moderate deterioration was considered instead of minimal deterioration (Table 4).

For the Dyspnoea score, ROC analyses revealed meaningful change thresholds between deterioration and stability/improvement of 5.6 for FVC % predicted, 6.3 for global physical health and 1.7 for global quality of life (Table 5).

In distribution-based estimates of thresholds of meaningful change in the Dyspnoea score, the SEM was 4.4, 0.2×SD was 4.3 and 0.5×SD was 10.8.

Triangulation of the anchor-based and distribution-based estimates for the Dyspnoea domain score resulted in a meaningful change threshold of 6 to 7 points to differentiate subjects who were stable from those who deteriorated.

**Meaningful change thresholds in L-PF Cough score**

For the Cough domain, the half-way points between changes in scores for subjects who were stable and those with minimal deterioration in FVC % predicted, global physical health score and global quality of life score were −2.8, 2.8 and 3.5, respectively (Table 4). Similar half-way points were observed for the global ratings anchors when minimal/moderate deterioration was considered instead of minimal deterioration (Table 4).

| Table 4 | Meaningful change thresholds for L-PF Dyspnoea and Cough domain scores |
|---------|-------------------------------------------------|
| **L-PF Dyspnoea score** | **Change in FVC % predicted** | **Change in L-PF global physical health score** | **Change in L-PF global quality of life score** |
| **L-PF Cough score** | **Change in FVC % predicted** | **Change in L-PF global physical health score** | **Change in L-PF global quality of life score** |
| **Patients with minimal deterioration versus patients who were stable** | | | |
| Minimal deterioration | 1.1 (12.9) | 8.5 (17.2) | 9.8 (15.7) | −3.2 (20.1) | 4.1 (22.9) | 7.5 (23.0) |
| Stable | 1.0 (13.7) | 5.7 (14.5) | 5.4 (14.4) | −2.3 (24.7) | 1.5 (23.3) | −0.5 (21.2) |
| Half-way point | 1.1 | 7.1 | 7.6 | −2.8 | 2.8 | 3.5 |
| **Patients with minimal/moderate deterioration versus patients who were stable** | | | |
| Minimal/Moderate deterioration | n/a | 8.7 (16.8) | 9.4 (16.1) | n/a | 4.8 (24.8) | 6.9 (24.4) |
| Stable | n/a | 5.7 (14.5) | 5.4 (14.4) | n/a | 1.5 (23.3) | −0.5 (21.2) |
| Half-way point | 7.2 | 7.4 | 3.2 | 3.2 |

Mean (SD) changes from baseline.
FVC, forced vital capacity; L-PF, Living with Pulmonary Fibrosis; n/a, not analysed.

| Table 5 | Results from receiver operating characteristic (ROC) curve analysis: sensitivity and specificity of L-PF questionnaire Dyspnoea and Cough scores to distinguish deterioration (vs stability/improvement) based on FVC % predicted, L-PF global physical health and quality of life scores |
|---------|-------------------------------------------------|
| **Deterioration in FVC % predicted** | **Youden's index** | **Cut-point** | **Sensitivity** | **Specificity** |
| L-PF Dyspnoea score | 0.26 | 5.6 | 0.49 | 0.77 |
| L-PF Cough score | 0.18 | 4.2 | 0.50 | 0.67 |
| **Deterioration in L-PF questionnaire global physical health score** | | | |
| L-PF Dyspnoea score | 0.19 | 6.3 | 0.52 | 0.67 |
| L-PF Cough score | 0.12 | 16.7 | 0.35 | 0.78 |
| **Deterioration in L-PF questionnaire global quality of life score** | | | |
| L-PF Dyspnoea score | 0.18 | 1.7 | 0.67 | 0.51 |
| L-PF Cough score | 0.16 | 4.2 | 0.55 | 0.61 |

*Index defining the cut-point that maximises sensitivity and specificity.
FVC, forced vital capacity; L-PF, Living with Pulmonary Fibrosis.
For the Cough score, ROC analyses revealed meaningful change thresholds between deterioration and stability/improvement of 4.2 for FVC % predicted, 16.7 for global physical health and 4.2 for global quality (table 5).

In distribution-based estimates of thresholds of meaningful change in the Cough score, SEM was 8.6, 0.2×SD was 5.3 and 0.5×SD was 13.3.

Triangulation of the anchor-based and distribution-based estimates for the Cough domain score resulted in a meaningful change threshold of 4 to 5 points to differentiate subjects who were stable from those who deteriorated.

**DISCUSSION**

Our analyses suggest that in patients with progressive fibrosing ILDs other than IPF, the Dyspnoea and Cough domain scores from the L-PF questionnaire Symptoms module are responsive to changes in disease severity and in patients’ perceptions of their physical health and quality of life. We observed significant differences in changes in L-PF Dyspnoea and Cough scores between subjects who had a large deterioration in FVC % predicted versus those with stable FVC % predicted, and between subjects who experienced deterioration versus improvement in global assessment anchors.

There is no consensus on the best approach to estimating meaningful change thresholds for patient-reported outcomes. Food and Drug Administration guidance recommends that anchor-based approaches incorporate ‘patient ratings’ of change, however, such transition items, which require patients to assess their current state, recall their prior state and mentally subtract the difference (eg, “Is your shortness of breath a lot better/the same/a lot worse?”), are fraught with problems. Ideally, the correlation between the transition item and baseline score is equal and opposite to the correlation between the transition item and the score at follow-up, but with recall periods of longer than 4 weeks, transition ratings tend to be (inappropriately) highly correlated with the patient’s current state. The two patient response anchors we used alleviated this potential for bias by asking patients to rate their state at baseline and at week 52; we then performed the subtraction to yield the transition item.

For many transition items, stability and degree of change are arbitrarily defined by the investigator. Some investigators may consider ‘somewhat worse/better’ to represent a minimal change, while others may consider ‘a bit worse/better’ or ‘minimally worse/better’ to be a minimal change. How patients interpret such descriptors, and how investigators categorise anchors, can affect estimates of meaningful change thresholds. For example, when using a 15-point quality of life transition item with ratings ranging from −7 to +7, ratings of −1 to +1 have been considered to represent no change and ratings of −3 to −2, +2 and +3 to represent minimally important changes, but meaningful change estimates may have been different if stability had been defined as a rating of 0 and minimally important changes as ratings of −2 to −1, +1 and +2. For our global rating anchors, we considered a change of 0 to represent stability and changes of −1 to −2, +1 and +2 to represent minimal/moderate change. Some patients with transition scores of 0 may have changed minimally and some with transition scores of 1 or 2 may have been stable. We attempted to account for this inherent uncertainty by using a half-way point approach rather than simply subtracting mean scores between groups of interest.

As patients with progressive ILDs are unlikely to experience improvement in disease status, in the ROC analyses, we identified a change threshold between worsening and stability/improvement. This approach aligns with the clinical behaviour of progressive ILDs and with current therapeutic approaches, which slow rather than reverse disease progression.

Change in FVC is used as a primary end point in clinical trials to assess the efficacy of treatments for ILDs. A decline in FVC is associated with mortality. While there is no established definition of ILD progression, absolute declines of >5% or >10% in FVC % predicted are widely regarded as indicating progression, although smaller declines may also be relevant. Scores from patient-reported outcomes that assess symptoms or HRQL typically correlate weakly with FVC in patients with ILDs, suggesting that these measures yield information unique from physiological measures of ILD severity. This suggests that although commonly used as an anchor in validation studies, FVC may not be a suitable anchor in all circumstances.

Strengths of our analyses include the use of a large and heterogeneous population of subjects with progressive fibrosing ILDs. The use of triangulation that incorporated both anchor-based and distribution-based approaches aligns with accepted methodology, including from regulatory bodies, but we acknowledge that distribution-based methods may overestimate meaningful change thresholds. Limitations include that the trial was not designed to evaluate the measurement properties of patient-reported outcomes, so additional metrics that could have been used as anchors were not included. For example, another cough-specific patient-reported outcome would have been a more appropriate anchor for the Cough domain. The content validity of the L-PF questionnaire has not been demonstrated for all the languages and cultures that participated in the trial. Whether our findings are applicable to patients with fibrosing ILDs beyond those who met the inclusion criteria for the INBUILD trial is unknown.

In conclusion, our analyses support the responsiveness of the Dyspnoea and Cough domains of the L-PF questionnaire Symptoms module as measures of symptom severity in patients with progressive fibrosing ILDs. Estimates of meaningful change thresholds in these scores may be of value in interpreting the effects of interventions in these
patients. Additional analyses are encouraged to confirm or refine these findings.

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Contributors JJS, DMB, KR and HM contributed to the planning of the analyses. DMB and HM contributed to the conduct of the analyses. JJS, DMB, KR, HM, MB and YI contributed to the interpretation of the data and the writing of the manuscript. HM is responsible for the overall content of the manuscript as guarantor.

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Competing interests Yes.

Patient consent for publication Not applicable.

Ethics approval The trial was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation. The protocol was approved by an independent ethics committee or institutional review board at each participating centre (additional details can be found in online supplemental appendix 1). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. On approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended on request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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REFERENCES
1 Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44–68.
2 Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrotic interstitial lung diseases. Eur Respir J 2020;55:2000085.
3 Favero P, Piluso M, De Giacomoni F, et al. Progressive fibrosing interstitial lung diseases: prevalence and characterization in two Italian referral centers. Respir Res 2020;9:1–8.
4 Nasser M, Larrieu S, SI-Mohamed S, et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the progress study). Eur Respir J 2021;57:2002718.
5 Swigris JJ, Brown KK, Abdulqawi R, et al. Patients’ perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2019;28:180075.
6 Kreuter M, Wuys WTS, Wijsenbeek M, et al. Health-related quality of life and symptoms in patients with IPF treated with nintedanib: analyses of patient-reported outcomes from the INPULSIS® trials. Respir Res 2020;21:36.
7 Marquzu PN, Szentes BL, Kreuter M, et al. Determinants of health-related quality of life decline in interstitial lung disease. Health Qual Life Outcomes 2020;18:334.
8 Aronson KI, Danoff SK, Russell A-M, et al. Patient-centered outcomes research in interstitial lung disease: an American Thoracic Society research statement. Am J Respir Crit Care Med 2021;204:e3–23.
9 Swigris JJ, Andrae DA, Churney T, et al. Development and initial validation analyses of the living with idiopathic pulmonary fibrosis questionnaire. Am J Respir Crit Care Med 2020;202:1689–97.
10 Swigris J, Cutts K, Maie N, et al. The living with pulmonary fibrosis questionnaire in progressive fibrosing interstitial lung disease. ERJ Open Res 2021;7:00145-2020.
11 Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56:395–407.
12 Food and Drug Administration. Guidance for industry. patient-reported outcome measures: use in medical product development to support labeling claims, 2009. Available: https://www.fda.gov/media/77832/download
13 Kalluri M, Luppi F, Vancheri A, et al. Patient-reported outcomes and patient-reported outcome measures in interstitial lung disease: where to go from here? Eur Respir Rev 2021;30:210026.
14 Flihaerty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27.
15 Fluss R, Faraggi D, Reiser B. Estimation of the Y, significance test, and power. Biom J 2005;47:458–72.
16 Wyrych KW, Nienaber NA, Tierney WM, et al. Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. Med Care 1999;37:469–78.
17 Wyrych KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol 1999;52:861–73.
18 Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008;61:102–9.
19 Gayatt GH, Norman GR, Juniper EF, et al. A critical look at transition ratings. J Clin Epidemiol 2002;55:960–8.
20 Juniper EF, Gayatt GH, Griffith LE, et al. Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 1996;98:843–5.
21 Juniper EF, Gayatt GH, Willan A, et al. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;47:81–7.
22 Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–82.
23 King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.
24 Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518–28.

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25 Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2020; 8:147–57.

26 Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47:588–96.

27 Goh NS, Hoyles RK, Denton CP, et al. Short-Term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69:1670–8.

28 Gimenez A, Storrer K, Kuranishi L, et al. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. Thorax 2018;73:391–2.

29 Khanna D, Mittoo S, Aggarwal R, et al. Connective tissue disease-associated Interstitial Lung Diseases (CTD-ILD) - report from OMERACT CTD-ILD Working Group. J Rheumatol 2015;42:2168–71.

30 Paterniti MO, Bi Y, Rekii D, et al. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. Ann Am Thorac Soc 2017;14:1395–402.

31 Swigris JJ, Wilson H, Esser D, et al. Psychometric properties of the St George’s respiratory questionnaire in patients with idiopathic pulmonary fibrosis: insights from the INPULSIS trials. BMJ Open Respir Res 2018;5:e000278.

32 Prior TS, Hoyer N, Hilberg O, et al. Responsiveness and minimal clinically important difference of SGRQ-I and K-BILD in idiopathic pulmonary fibrosis. Respir Res 2020;21:91.

33 Kim JW, Clark A, Birring SS, et al. Psychometric properties of patient reported outcome measures in idiopathic pulmonary fibrosis. Chron Respir Dis 2021;18:14799731211033925.

34 Stratford PW, Riddle DL. When minimal detectable change exceeds a diagnostic test-based threshold change value for an outcome measure: resolving the conflict. Phys Ther 2012;92:1338–47.
### Supplemental Appendix 1: List of independent ethics committees and institutional review boards

The protocol was approved by an independent ethics committee or institutional review board at each participating centre. The names of the independent ethics committees and institutional review boards that approved the protocol are listed here.

#### Argentina

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD-MM-YYYY) |
|---------------------------|------------------------------------|------------------------------------|
| Comité de Ética e Investigación Fundación Sanatorio Giannes / Francisco Acuña de Figueroa 1225, Ciudad Autónoma de Buenos Aires, C1180AAK, Argentina | CTP Version 1.0<br>CTP Version 2.0 | 14/FEB/2017<br>26/JUL/2017 |
| Comité de Ética en Investigación – CINME / Viamonte 2278 C.A.B.A, Ciudad Autónoma de Buenos Aires, 1056, Argentina | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 13/DEC/2016<br>03/MAY/2017<br>19/SEP/2018 |
| CEI CEMER - Comité de Ética en Investigación de CEMER / Esmeralda 1550 (B1002DQD), Florida, Vicente López, Provincia de Buenos Aires, Argentina | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 03/JAN/2017<br>24/APR/2017<br>22/OCT/2018 |
| Comité de Ética en Investigación Clínica (CEIC) – Barclay / Laurea 1381 Piso 3 A, (C1117ABK), CABA, Argentina | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 15/DEC/2016<br>05/APR/2017<br>21/SEP/2018 |
| Comité de Ética Independiente Consultorios Integrados / Italia 424-428, Rosario, Santa Fe, S1002DEJ, Argentina | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 21/FEB/2017<br>04/MAY/2017<br>01/NOV/2018 |
| Comité Independiente de Ética de Investigación en Salud Prof. Dr. Marcelino Ruscalleda / Av. Colón 2057, Córdoba, Córdoba, X5002DCE, Argentina | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 23/MAR/2017<br>15/JUN/2017<br>27/SEP/2018 |

#### Belgium

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD-MM-MM/YYYY) |
|---------------------------|------------------------------------|------------------------------------|
| Ethische commissie onderzoek UZ/KU Leuven | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 03/JAN/2017<br>04/APR/2017<br>11/SEP/2018 |
| UZ Leuven - Campus Gosseliesberg | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 03/JAN/2017<br>04/APR/2017<br>11/SEP/2018 |
| Commissier Medische Ethiek Herestraat 49, Leuven 3000, Belgium | CTP Version 1.0<br>CTP Version 2.0<br>CTP Version 3.0 | 03/JAN/2017<br>04/APR/2017<br>11/SEP/2018 |
| Country      | IEC or IRB (name/address)                                    | Protocol and/or Amendment number(s)                      | Date of Final Approval (DD/MMM/YYYY) |
|-------------|-------------------------------------------------------------|----------------------------------------------------------|--------------------------------------|
| **Canada**  |                                                            |                                                          |                                      |
|             | Concordia Hospital Ethics Committee 1095 Concordia Avenue   | CTP Version 1.0                                          | 21/NOV/2016                          |
|             | Winnipeg, Manitoba, R2K 3S8                                 | CTP Version 2.0                                          | 08/MAR/2017                          |
|             |                                                             | CTP Version 3.0                                          | 12/SEP/2018                          |
|             | University Health Network Research Ethics Board             | CTP Version 1.0                                          | 01/MAY/2017                          |
|             | 10th Floor, Suite 1056 700 University Ave. Toronto, Ontario | CTP Version 2.0                                          | 11/SEP/2017                          |
|             | M5O 1Z5                                                     | CTP Version 3.0                                          | 28/SEP/2018                          |
|             | Le comité d’ethique de la recherché du CIUSSS de l’Estrie – | CTP Version 1.0                                          | 10/FEB/2017                          |
|             | CHUS 3001 12th Avenue Nord, Sherbrooke, Quebec, J1H 5N4     | CTP Version 2.0                                          | 08/MAY/2017                          |
|             |                                                             | CTP Version 3.0                                          | 13/OCT/2018                          |
|             | Hamilton Integrated Research Ethics Board Suite 102 283     | CTP Version 1.0                                          | 25/JAN/2017                          |
|             | Wellington Street North Hamilton, Ontario L8L 8E7          | CTP Version 2.0                                          | 16/MAY/2017                          |
|             |                                                             | CTP Version 3.0                                          | 16/OCT/2018                          |
| **Chile**   |                                                            |                                                          |                                      |
|             | Comité Ético Científico-Servicio Salud Concepción / San    | CTP Version 1.0                                          | 24/NOV/2016                          |
|             | Martín 1436, Concepción, Bio-Bio, 4070038, Chile           | CTP Version 2.0                                          | 23/JUN/2017                          |
|             |                                                             | CTP Version 3.0                                          | 23/OCT/2017                          |
|             | Comité de Ética Científico del Servicio de Salud           | CTP Version 1.0                                          | 11/NOV/2018                          |
|             | Metropolitano Oriente / Avda. Salvador 364, Providencia     | CTP Version 2.0                                          | 20/JUN/2017                          |
|             | Metropolitan, Chile                                        | CTP Version 3.0                                          | 09/OCT/2018                          |
|             | Comité de Ética Científico del Servicio de Salud           | CTP Version 1.0                                          | 30/MAY/2017                          |
|             | Metropolitano Oriente / Avda. Salvador 364, Providencia     | CTP Version 2.0                                          | 20/JUN/2017                          |
|             | Metropolitan, Chile                                        | CTP Version 3.0                                          | 09/OCT/2018                          |
| **China**   |                                                            |                                                          |                                      |
|             | Ethic Committee of Peking Union Medical College Hospital   | CTP Version 2.0                                          | 12/SEP/2017                          |
|             |                                                             | CTP Local Amendment 1.0 China                            | 30/DEC/2017                          |
|             |                                                             | CTP Version 3.0                                          | 23/OCT/2018                          |
|             | Ethic Committee of The First Hospital of China Medical     | CTP Version 2.0                                          | 20/AUG/2017                          |
|             | University                                                | CTP Local Amendment 1.0 China                            | 30/JAN/2018                          |
|             |                                                             | CTP Version 3.0                                          | 27/NOV/2018                          |
|             | Medical Ethic Committee of Nanjing Drun Tower Hospital     | CTP Version 2.0                                          | 22/AUG/2017                          |
|             | The Affiliated Hospital of Nanjing University Medical      | CTP Local Amendment 1.0 China                            | 07/FEB/2018                          |
|             | School                                                    | CTP Version 3.0                                          | 25/SEP/2018                          |
|             | Ethic Committee of First Affiliated Hospital of Guangzhou  | CTP Version 2.0                                          | 12/SEP/2017                          |
|             | Medical University                                        | CTP Local Amendment 1.0 China                            | 25/JAN/2018                          |
|             |                                                             | CTP Version 3.0                                          |                                      |
| **France**  |                                                            |                                                          |                                      |
|             | CPP SUD MEDITERRANEE V                                     | CTP Version 1.0                                          | 28/FEB/2017                          |
|             | CHU de NICE - Hôpital de CMIIEZ De Philippe BABE            | CTP Local Amendment 1.0 France                           | 28/FEB/2017                          |
|             | Bitsimont Grand Hôtel - 5ème étage 4 avenue Reine Victoria | CTP Version 2.0                                          | 04/APR/2017                          |
|             | CS. 91179                                                 | CTP Version 3.0                                          | 02/OCT/2018                          |
|             | 66003 NICE CEDEX 1                                         |                                                          |                                      |
### Germany

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
|---------------------------|-------------------------------------|------------------------------------|
| 40002 DEU7, 49003-DEU3, 49005-DEU10, 49007-DEU1, 49008-DEU11, 49059-DEU2, 49011-DEU3, 49111-DEU4, 49012-DEU5 Leading EC: Ethikkommission Medizinische Fakultät Heidelberg, Alte Glockengießerei 11/1 D-69115 Heidelberg | CTP Version 2.0  CTP Local Amendment 1.0 Germany  CTP Version 3.0 | 23/FEB/2017 07/FEB/2018 13/SEP/2018 |

### Italy

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
|---------------------------|-------------------------------------|------------------------------------|
| Comitato Etico Regione Toscana Area Vasta Sud-Est (CEAVSE) - Azienda Ospedaliero Universitaria Senese e USL 7 di Siena - presso Farmacia Ospedaliera Viale Bracci, 16 53100 SIENA | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 21/NOV/2016 20/FEB/2017 22/JAN/2019 |
| Comitato Etico Provinciale di Modena Azienda Ospedaliero-Universitaria Policlinico di Modena Ingresso n. 3, Piano Terra presso Direzione Assistenza Farmaceutica Via del Pozzo, 71 41124 MODENA | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 24/JAN/2017 14/MAR/2017 Not available yet |
| Comitato Etico Area Vasta Romagna IRST Via P. Maroncelli, 40 47014 - Meldola (FC) | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 24/NOV/2016 23/MAR/2017 07/FEB/2019 |
| Comitato Etico Provincia Monza e Brianza ASST di Monza e o Ufficio Sperimentazioni Cliniche A.O. San Gerardo Via Pergelesi, 33 20900 - MONZA | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 14/DEC/2016 22/MAR/2017 13/FEB/2019 |
| Comitato Etico Catania 1 Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele di Catania Via S. Sofia, 78 95123 CATANIA | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 21/DEC/2016 13/MAR/2017 18/FEB/2019 |
| Comitato Etico Policlinico Gemelli Università Cattolica del Sacro Cuore Largo F. Vito, 1 00168 ROMA | CTP Version 1.0  CTP Version 2.0  CTP Version 3.0 | 15/DEC/2016 16/MAR/2017 19/FEB/2019 |
| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MM/YYYY) |
|--------------------------|-----------------------------------|-----------------------------------|
| The IRB of J.R. Tokyo General Hospital 2-1-3, Yoyogi, Tokyo, Shibuya-ku, 151-0053, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 15 MAR 2017 15 MAR 2017 19 SEP 2018 |
| The IRB of Kobe City Medical Center General Hospital 2-1-1 Minatojima-mirai-machii, Chuo-ku, Hyogo, Kobe, 650-2047, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 12 SEP 2017 12 SEP 2017 20 SEP 2018 |
| The IRB of Sapporo Medical University Hospital 16 Chuo-ku, Miminami 1-jo Nishi, Hokkaido, Sapporo, 060-8542, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 10 FEB 2017 10 FEB 2017 11 OCT 2018 |
| The IRB of Center Hospital of the National Center for Global Health and Medicine 1-21-1 Toyama, Tokyo, Shinjuku, 162-8655, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 22 FEB 2017 22 FEB 2017 21 SEP 2018 |
| The IRB of National Hospital Organization Hiogo Medical Center 55, Totsuno-shi, Hyogo, Hiogo, 670-8520, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 08 MAR 2017 08 MAR 2017 07 SEP 2018 |
| The IRB of Tokushima University Hospital 2-5-1 Kummunen-cho, Tokushima, Tokushima, 770-8503, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 16 FEB 2017 16 FEB 2017 20 SEP 2018 |
| The IRB of Medical Hospital, Tokyo and Dental University 1-5-45 Yushima, Tokyo, Bunkyo-ku, 113-8519, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 28 FEB 2017 28 FEB 2017 26 SEP 2018 |
| The IRB of Nagasaki University Hospital 1-7-1 Sakamoto, Nagasaki, Nagasaki, 852-8501, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 24 MAR 2017 24 MAR 2017 21 SEP 2018 |
| The IRB of Niigata Medical School Hospital 1-1-9, Sendai, Tokyo, Bunkyo-ku, 113-0022, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 06 MAR 2017 06 MAR 2017 26 SEP 2018 |
| The IRB of National Hospital Organization Borakasugusaki National Hospital 825 Tsurumizu, Tokiizumi-cho, Ibaraki, Niigata-ken, 950-8553, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 24 FEB 2017 24 FEB 2017 28 SEP 2018 |
| The IRB of Hamamatsu University Hospital 1-2-1 Handayama, Higashi-ku, Shizuoka, Hamamatsu, 431-3192, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 02 MAR 2017 02 MAR 2017 06 SEP 2018 |
| The IRB of Kanagawa Cardiovascular and Thoracic Center 6-16-1 Tomikidaiigakubo, Kanagawa-ku, Kanagawa, Yokohama, 226-0051, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 14 FEB 2017 14 FEB 2017 12 SEP 2018 |
| The IRB of Matsushita clinic 6-15-12, Nishi cho, Tokyo, Shinagawa-ku, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 16 FEB 2017 16 FEB 2017 19 SEP 2018 |
| The IRB of Toset General Hospital 160 Nishiwake-cho, Achi, Seta, 480-8642, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 02 FEB 2017 02 FEB 2017 28 SEP 2018 |
| The IRB of Osaka Medical College Hospital 2-7 Daigaokyo-cho, Osaka, Takatsuki, 566- 8666, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 24 FEB 2017 24 FEB 2017 11 SEP 2018 |
| The IRB of National Hospital Organization Kikukicho Chest Medical Center 1180 Nagatsuka-cho, Kita-ku, Osaka, Sari, 591- 555, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 13 FEB 2017 13 FEB 2017 14 SEP 2018 |
| The IRB of National University Corporation Tokushima University Tokushima University Hospital 1-5, Horiyama-cho, Aoki, Miyagi-ku, Sendai, 104-0874, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 29 MAR 2017 29 MAR 2017 28 SEP 2018 |
| The IRB of Tomonosu Hospital and Tomonosu Hospital 2-2, Tomonosu, Tokyo, Minato-ku, 105-3001, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 08 JUN 2017 08 JUN 2017 27 SEP 2018 |
| The IRB of Jichi Medical University Hospital 311-1 Yukiwakai, Tezukaguchi, Shimotsuke, 322-0848, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 27 SEP 2017 27 SEP 2017 30 OCT 2018 |
| The IRB of Social Welfare Organization Imperial Gift Foundation, Inc. Saiseikai Kimamoto Hospital 5-2-1 Chinami, Minami-ku, Kimamoto, Kimamoto, 861-0193, Japan | CTP Version 2.0 CTP Local Amendment 1.0 Japan CTP Version 3.0 | 28 SEP 2017 28 SEP 2017 27 SEP 2018 |
### Korea

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
|--------------------------|-------------------------------------|-------------------------------------|
| Institutional Review Board (IRB) of Asan Medical Center (AMC), 2nd floor of Asan In-University Life Science, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Korea | CTP Version 1.0 | 19/JAN/2017 |
|                          | CTP Version 2.0                     | 30/MAR/2017 |
|                          | CTP Version 3.0 / Koren Version 1.0 | 06/SEP/2018 |
|                          | CTP Version 3.0 / Koren Version 2.0 | 25/OCT/2018 |
| Institutional Review Board (IRB), 3rd floor of Health care innovation park Seoul National University Bundang Hospital, 82, Gumiro 175 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea (13620) | CTP Version 1.0 | 07/MAR/2017 |
|                          | CTP Version 2.0                     | 27/MAR/2017 |
|                          | CTP Version 3.0 / Koren Version 1.0 | 06/SEP/2018 |
|                          | CTP Version 3.0 / Koren Version 2.0 | 29/OCT/2018 |
| Institutional Review Board (IRB), 4th floor of St. Gojunggyuran, Bucheon St. Mary's Hospital, 327, Sosa-eo, Wonnuri-gu, Bucheon-si, Gyeonggi-do, Republic of Korea (14647) | CTP Version 1.0 | 17/FEB/2017 |
|                          | CTP Version 2.0                     | 18/APR/2017 |
|                          | CTP Version 3.0 / Koren Version 1.0 | 09/NOV/2018 |
|                          | CTP Version 3.0 / Koren Version 2.0 | 14/DEC/2018 |

### Poland

| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
|--------------------------|-------------------------------------|-------------------------------------|
| [Central IEC, sites POL1 to POL5] | CTP Version 2.0 | 14/MAR/2017 |
|                          | Local Protocol Amendment Version 1.0 | 13/JUN/2017 |
|                          | CTP Version 3.0 | 16/OCT/2018 |
| Bioethics Committee by Medical University of Lodz Pt. Hallera 1B 90-647 Lodz POLAND | CTP Version 2.0 | 14/MAR/2017 |
|                          | Local Protocol Amendment Version 1.0 | 13/JUN/2017 |
|                          | CTP Version 3.0 | 16/OCT/2018 |
| Russian Federation |   |   |   |
|-------------------|---|---|---|
| [Central IEC, site RUS1 to RUS6] Ethics Council of Ministry of Healthcare of Russian Federation Chairman: Chumakova Alexander Grigorievich Rakhimovskiy lane 3 127994 Moscow RUSSIAN FEDERATION | CTP Version 1.0 | 22/NOV/2016 |   |
|   | CTP Version 2.0 | 20/FEB/2017 |   |
|   | CTP Version 3.0 | 04/SEP/2018 |   |
| [Local IEC, site RUS1] The Federal Agency of Scientific Organization, Federal State Budgetary Scientific Institution Research Institute for Complex Issues of Cardiovascular Diseases. Local Ethics Committee D. Kosovoy boul. 15/5002 Krasnoye RUSSIAN FEDERATION | CTP Version 2.0 | 14/MAR/2017 |   |
|   | CTP Version 3.0 | 09/OCT/2018 |   |
| [Local IEC, site RUS2] Local Ethics Committee, First Moscow State Medical University n.a. I.M.Sechenov of Higher Professional Education, State budgetary educational institution 8, build. 2, Trubetskaya str. 119991 Moscow RUSSIAN FEDERATION | CTP Version 2.0 | 20/APR/2017 |   |
|   | CTP Version 3.0 | 10/OCT/2018 |   |
| [Local IEC, site RUS3] Local Ethics Committee of Federal State Budgetary Educational Institution "Scientific Research Institute of Pulmonology" of Federal Medico-Biological Agency | CTP Version 2.0 | 16/MAR/2017 |   |
|   | CTP Version 3.0 | 06/FEB/2019 |   |
| [Local IEC, site RUS5] Local Ethics Committee of Federal State Budgetary Educational Institution of Higher Education “Academician I.P.Pavlov First St. Petersburg State Medical University” 10, Rentgen str. 197101 Saint-Petersburg RUSSIAN FEDERATION | CTP Version 2.0 | 27/MAR/2017 |   |
|   | CTP Version 3.0 | 20/OCT/2018 |   |
| [Local IEC, site RUS6] Local Ethics Committee of State Autonoumous Healthcare Institution of Yaroslavl Region Clinical Hospital for Emergency Medical Care n.a. N.V.Solovyev 11, Zagorodny Sad 155003 Yaroslavl RUSSIAN FEDERATION | CTP Version 2.0 | 23/MAR/2017 |   |
|   | CTP Version 3.0 | 11/OCT/2018 |   |

| Spain |   |   |   |
|-------|---|---|---|
| CElm Hospital Universitario La Paz Pasco de la Castellana, 261 28046 Madrid Spain | CTP Version 1.0 | 22/DEC/2016 |   |
| Sites ESP1, ESP2, ESP3, ESP4, ESP5, ESP6, ESP7, ESP8, ESP9, ESP10, ESP11, ESP12 | CTP Version 2.0 | 09/MAR/2017 |   |
|   | CTP Version 3.0 | 06/Sep/2018 |   |
| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
|---------------------------|-------------------------------------|-------------------------------------|
| East Midlands – Leicester Central Research Ethics Committee The Old Chapel Royal Standard Place Nottingham NG1 6FS UK | CTP Version 2.0 CTP Version 3.0 | 03/MAR/2017 07/SEP/2018 |
| United States |
|----------------|
| Site 10001 | Chesapeake IRB  
            Suite 110  
            6940 Columbia Gateway Drive  
            Columbia MD 21046  
            Advansa Institutional Review Board  
            Suite 110  
            6940 Columbia Gateway Drive  
            Columbia MD 21046 | Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  
                        Initial Approval - CTP Version 2.0  
                        CTP Version 3.0  | 05/DEC/2010  
                     20/JAN/2017  
                     20/AUG/2018  
                     03/APR/2017  
                     20/AUG/2018  
                     06/JUL/2017  
                     02/AUG/2018  
                     24/MAY/2017  
                     10/OCT/2018  
                     16/AUG/2017  
                     12/SEP/2018  
                     20/MAR/2017  
                     20/AUG/2018  
                     12/JUN/2017  
                     06/SEP/2018  
                     16/MAR/2017  
                     07/SEP/2018  
                     10/MAY/2017  
                     17/OCT/2018  
                     06/APR/2017  
                     20/DEC/2018 |
| United States | IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MM/YYYY) |
|--------------|---------------------------|-----------------------------------|-----------------------------------|
| Site 10013   | University of South Carolina Division of Pulmonary, Critical Care and Sleep Medicine 1 Richland Medical Park Drive, Suite 300 Columbia, South Carolina 29203 | Initial Approval – CTP version 2.0 | 21/APR/2017 |
| Site 10014   | Western Institutional Review Board Suite 120 1019 39th Avenue SE Puyallup WA 98374 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 05/JUN/2017 07/NOV/2018 |
| Site 10015   | Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 15/FEB/2017 20/AUG/2018 |
| Site 10016   | Western Institutional Review Board Suite 120 1019 39th Avenue Puyallup WA 98374 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 19/AUG/2017 23/AUG/2018 |
| Site 10118   | Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 1.0 CTP Version 2.0 CTP Version 3.0 | 30/NOV/2016 20/AUG/2018 |
| Site 10119   | Advansa Institutional Review Board Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 31/MAY/2017 19/DEC/2018 |
| Site 10120   | The University of Chicago Institutional Review Board MC 7132, I-625 5841 South Maryland Avenue Chicago IL 60637 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 01/MAY/2017 29/OCT/2018 |
| Site 1021    | Johns Hopkins University IRB 1620 McEldery Street Baltimore MD 21287 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 20/JAN/2017 20/AUG/2018 |
| Site 1021    | Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 1.0 CTP Version 2.0 CTP Version 3.0 | 20/JAN/2017 20/AUG/2018 |
| United States | IEC or IRB (name/address)                                                                 | Protocol and/or Amendment number(s)         | Date of Final Approval (DD/MMM/YYYY) |
|---------------|------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------|
|               | Site 10022, Chesapeake IRB, Suite 110, 6940 Columbia Gateway Drive, Columbia MD 21046       | Initial Approval - CTP Version 2.0, CTP Version 3.0 | 22/FEB/2017, 20/AUG/2018             |
|               | Advansa Institutional Review Board, Suite 110, 6940 Columbia Gateway Drive, Columbia MD 21046 |                                            |                                      |
|               | Site 10023, Columbia University Human Research Protection Office Institutional Review Boards, 1st Floor, 154 Haven Avenue, New York NY 10032 | Initial Approval - CTP Version 2.0, CTP Version 3.0 | 30/MAR/2017, 26/SEP/2018            |
|               | Site 10027, UCLA Office of the Human Research Protection Program, Suite 830, 10889 Wilshire Boulevard, Los Angeles CA 90025-1406 | Initial Approval - CTP Version 2.0         | 17/MAY/2017                         |
|               | Site 10028, University of Utah IRB Research Administration, Building 512, 75 South 2000 East, Salt Lake City UT 84112 | Initial Approval - CTP Version 2.0, CTP Version 3.0 | 05/APR/2017, 19/SEP/2018            |
|               | Site USA28, Weill Cornell Medical College IRB, Box 89, 1300 York Avenue, New York NY 10065 | Initial Approval - CTP Version 2.0, CTP Version 3.0 | 11/JUL/2017, 23/OCT/2018            |
|               | Site USA29, Chesapeake IRB, Suite 110, 6940 Columbia Gateway Drive, Columbia MD 21046       | Initial Approval – CTP Version 1.0, CTP Version 2.0, CTP Version 3.0 | 29/NOV/2016, 20/JAN/2017, 20/AUG/2018 |
|               | Advansa Institutional Review Board, Suite 110, 6940 Columbia Gateway Drive, Columbia MD 21046 |                                            |                                      |
|               | Site USA30, The Methodist Hospital Research Institute d/b/a Houston Methodist Research Institute (HMRI), 6565 Fannin Street, Houston TX 77030 | Initial Approval - CTP Version 2.0, CTP Version 3.0 | 30/JUN/2017, 20/NOV/2018            |
|               | Site USA31, Cleveland Clinic Foundation, Desk OS-1 9500 Euclid Avenue, Cleveland OH 44195   | Initial Approval – CTP Version 2.0, CTP Version 3.0 | 18/JUL/2017, 29/OCT/2018            |
| Site | IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MM/YY/YY) |
|------|---------------------------|-------------------------------------|-------------------------------------|
| USA32| Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 1046 | Initial Approval – CTP Version 1.0 CTP Version 2.0 CTP Version 3.0 | 08/DEC/2016 20/JAN/2017 20/AUG/2018 |
| USA33| BRANY IRB Suite 210 1981 Marcus Avenue Lake Success NY 11042 | Initial Approval – CTP Version 1.0 CTP Version 2.0 | 15/MAY/2017 31/MAY/2017 |
| USA35| Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 1046 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 02/FEB/2017 20/AUG/2018 |
| USA37| Beth Israel Deaconess Medical Center Committee on Clinical Investigations IRB 1st Floor 109 Brookline Avenue Boston MA 02215 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 01/AUG/2017 07/DEC/2018 |
| USA39| Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 1046 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 14/SEP/2017 20/AUG/2018 |
| USA40| Chesapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 1046 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 31/JAN/2017 20/AUG/2018 |
| United States |
|----------------|-----------------|-----------------|
| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MMM/YYYY) |
| Site USA41 University of Maryland Human Research Protections Office 2nd Floor 620 West Lexington Street Baltimore MD 21201 | Initial Approval - CTP Version 2.0 Initial Approval - CTP Version 2.0 CTP Version 3.0 | 12/APR/2017 04/APR/2017 18/SEP/2018 |
| Site USA42 Creighton University Institutional Review Board Criss I 2500 California Plaza Omaha NE 68178 | Initial Approval - CTP Version 2.0 | 24/FEB/2017 30/AUG/2018 |
| Site USA43 Baylor Scott and White Research Institute IRB Suite 501 3310 Live Oak Street Dallas TX 75204 | Initial Approval - CTP Version 2.0 | 29/AUG/2017 25/OCT/2018 |
| Site USA46 University of Kentucky Office of Research Integrity 315 Kinkaid Hall Lexington KY 40506 | Initial Approval - CTP Version 2.0 | 10/MAR/2017 20/AUG/2018 |
| Site USA47 Chestapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 2.0 | 30/MAY/2017 16/OCT/2018 |
| Site USA48 Loyola University Medical Center 2160 South First Avenue Maywood IL 60153 | Initial Approval - CTP Version 2.0 | 06/JUL/2017 20/AUG/2018 |
| Site USA51 Chestapeake IRB Suite 110 6940 Columbia Gateway Drive Columbia MD 21046 | Initial Approval - CTP Version 2.0 | 05/MAY/2017 26/JUL/2018 |
| Site USA52 Henry Ford Health System IRB 2-F One Ford Place Detroit MI 48202 | Initial Approval - CTP Version 2.0 | 30/JUN/2017 29/AUG/2018 |
| Site USA54 University of Texas Health Science Center IRB Mail Code: 7830 5703 Floyd Curl Drive San Antonio TX 78229 | Initial Approval - CTP Version 2.0 |  |
| United States |
|----------------|----------------|----------------|
| IEC or IRB (name/address) | Protocol and/or Amendment number(s) | Date of Final Approval (DD/MM/YYYY) |
| Site USA55 | Initial Approval – CTP Version 2.0 | 07/JUL/2017 |
| University of Minnesota Medical Center Division of Pulmonary, Allergy and Critical Care 420 Delaware Street SE Mayo Mail Code (MMC) 276 Minneapolis, MN 55455 | | |
| Site USA56 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 04/OCT/2017 12/OCT/2018 |
| Partners Healthcare Human Research Committee IRB Suite 710 399 Revolution Drive Somerville MA 02145 | | |
| Site USA57 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 10/JUN/2017 10/DEC/2018 |
| Penn State Milton S. Hershey Medical Center Penn State College of Medicine Human Subjects Protection Office/Institutional Review Board PO Box 855, Mailcode A115, ASB Room 1140 90 Hope Drive Hershey PA 17033 | | |
| Site USA58 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 20/SEP/2017 04/JAN/2019 |
| UC Davis Institutional Review Board Suite 1400, Room 1429 2912 Stockton Boulevard Sacramento CA 95817 | | |
| Site USA59 | Initial Approval - CTP Version 2.0 CTP Version 3.0 | 06/JUN/2017 04/SEP/2018 |
| Spectrum Health Systems IRB 100 Michigan Avenue NE, MC-38 Grand Rapids MI 49503 | | |
| Site USA60 | Initial Approval – CTP Version 2.0 CTP Version 3.0 | 07/JUL/2017 02/NOV/2018 |
| Northwestern University Institutional Review Board 7th Floor 750 North Lake Shore Drive Chicago IL 60611 | | |
| Site USA62 | Initial Approval – CTP Version 2.0 CTP Version 3.0 | 12/OCT/2017 25/OCT/2018 |
| Cedars-Sinai Medical Center Bums & Allen Research Institute Research Compliance & Quality Suite 742 8383 Wilshire Boulevard Beverly Hills CA 90211 | | |
| Site USA64 | Initial Approval – CTP Version 2.0 CTP Version 3.0 | 17/AUG/2017 08/OC/2018 |
| UT Southwestern Institutional Review Board Room BL.0.100 5323 Harry Hines Boulevard Dallas Texas 75390-8443 | | |
| Site USA67 | Initial Approval – CTP Version 2.0 CTP Version 3.0 | 10/AUG/2017 20/AUG/2018 |
| Western Institutional Review Board (WIRB) Suite 120 1019 39th Avenue SE Poulsbo WA 98370-2115 | | |