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Bexotegrast for treatment of idiopathic pulmonary fibrosis (BEACON-IPF): study protocol for a multinational, phase 2b/3, double-blind, randomised, multicentre, controlled trial

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ABSTRACT

Introduction Bexotegrast is an oral, once-daily, dual-selective inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ in development for idiopathic pulmonary fibrosis (IPF). In the phase 2a study INTEGRIS-IPF study (NCT04396756), bexotegrast was well tolerated and showed antifibrotic activity.

Methods and analysis BEACON-IPF (NCT06097260) is a randomised, double-blind, placebo-controlled, dose-finding, operationally seamless, adaptive phase 2b/3 study evaluating the efficacy and safety of bexotegrast over 52 weeks in participants with IPF. The phase 2b dose selection cohort will enrol 360 participants randomised 1:1:1 to once-daily bexotegrast 160 mg, 320 mg or placebo. After enrolling the last participant in the phase 2b cohort and while conduct is ongoing, the phase 3 cohort will immediately begin enrolment with a 'seamless group' using the same 1:1:1 randomisation. Once the phase 2b cohort has completed and a dose has been selected, the remainder of the phase 3 cohort will be enrolled. Participants in the phase 2b cohort receiving the non-selected dose will be eligible for an open-label study at the selected phase 3 dose. Background therapy with pirfenidone or nintedanib is permitted in ≤70% of the study population. Participants must be adults (≥40 years), have an IPF diagnosis ≤7 years per 2018 international guidelines, per cent predicted forced vital capacity (FVCpp) ≥45% and diffusing capacity for carbon monoxide (haemoglobin adjusted) ≥30%. The primary endpoint is change from baseline in absolute FVC at week 52. Additional endpoints include safety and tolerability, time to disease progression, participant-reported symptom assessments and quantitative lung fibrosis extent.

Ethics and dissemination This study was approved by Advarra institutional review board (IRB; OHRP and Food and Drug Administration registration 00000971) and at each participating site by IRBs and local ethics review committees. Participants will provide written informed consent before taking part. Study results will be disseminated in peer-reviewed journals and international conferences targeted to medical, academic and patient communities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic, interstitial lung disease that is ultimately fatal; current approved treatments neither halt the progression of IPF nor consistently improve a patient's quality of life.

⇒ Bexotegrast, an oral, once-daily dual-selective inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, is in development for IPF and has demonstrated favourable safety and efficacy results in early-stage clinical trials.

WHAT THIS STUDY ADDS

⇒ This study will evaluate the efficacy and safety of bexotegrast in patients with IPF, including its impact on disease progression and quality of life.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results from this study have potential implications for disease management for patients with IPF.

Trial registration number NCT06097260.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, interstitial lung disease.[1 2] As the disease advances, patients with IPF experience increased lung architectural distortion, resulting in cough, dyspnoea and respiratory failure.[1 2] IPF is associated with a poor prognosis; the median survival of untreated patients with IPF is between 3 and 5 years after diagnosis.[3 4] Current approved therapies for IPF include pirfenidone and nintedanib, which slow disease progression but do not improve symptom burden, lung function or patient quality of life.[5–7]

While the exact aetiology of IPF is unknown, elevated transforming growth factor-beta (TGF-β) signalling is a hallmark of the disease.[8 9] Overexpression of $\alpha_v\beta_6$ integrins on lung epithelial cells and $\alpha_v\beta_1$ integrins on lung fibroblasts activates latent TGF-β, resulting in fibroblast activation and proliferation, increased collagen synthesis and tissue stiffness.[9–13] Systemic inhibition of TGF-β carries safety risks such as cardiotoxicity and autoimmunity[9 14]; thus, selective targeting of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins within the fibrotic lung may provide a localised approach to TGF-β inhibition.

Bexotegrast (PLN-74809) is an oral, once-daily, dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins in development for the treatment of IPF and primary sclerosing cholangitis. In vitro studies and animal models suggest that bexotegrast is a potent, selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins that has antifibrotic efficacy.[12] Treatment with bexotegrast has the potential to provide disease-modifying benefit to patients with IPF by inhibiting continued collagen deposition, thus slowing the progressive decline of lung function and improving symptoms and quality of life with or without the use of background therapy with pirfenidone or nintedanib. The available data from over 740 participants, including 106 with IPF, who received bexotegrast in phase 1 and phase 2 studies demonstrated a favourable safety and tolerability profile of ≤320 mg bexotegrast once daily over 40 weeks.[15 16] In a single-centre, randomised, double-blind, 12-week phase 2 study in participants with IPF (NCT05621252), changes in positron emission tomography imaging using a probe for type 1 collagen, as well as dynamic contrast-enhanced MRI for participants treated with bexotegrast 160 mg, suggested potential favourable remodelling of the lung driven by a reduction of new collagen deposition as a result of the inhibition of fibrogenesis and restoration of homeostatic processes.[17] In a multicentre, multinational phase 2a study of participants with IPF (INTEGRIS-IPF; NCT04396756), suggested antifibrotic effects were seen with bexotegrast compared with placebo and bexotegrast demonstrated a favourable safety profile for ≤40 weeks of treatment.[15] The findings from the INTEGRIS-IPF study provided support for continued evaluation and late-stage development.

IPF is a disease encompassing multiple pathways that are not all understood, leading to therapeutic challenges in its treatment. Many drugs targeting multiple mechanisms of action have been developed and were successful in phase 2 studies, only to not succeed in longer phase 3 studies.[18–21] In order to most effectively and quickly understand the potential benefit of bexotegrast in late-stage clinical trials, an operationally seamless, adaptive phase 2b/3 study design was used. The adaptive study design allows for flexibility and modifications to the trial while the study is ongoing, such as changes to sample size and allocation of participants to the most favourable doses.[22] The operationally seamless component allows for a continuous transition from one phase to another, with data from one phase informing the next, which can improve trial conduct efficiency and expedite development. In addition, this design provides two independent populations in which to evaluate bexotegrast's effects, providing an opportunity to replicate results within a single trial.

The study design is consistent with several recently successful studies within various therapy areas such as endocrinology[23] and oncology,[24] in which the treatments under investigation either received approval from the US Food and Drug Administration or are fast-tracked for approval. This study is split into a phase 2b cohort that will inform dose selection and final sample size of the phase 3 cohort. BEACON-IPF is a randomised, double-blind, dose-finding, placebo-controlled, operationally seamless, adaptive phase 2b/3 study that investigates the efficacy and safety of bexotegrast compared with placebo over 52 weeks in participants with IPF.

METHODS AND ANALYSIS

Study design

BEACON-IPF is a multinational study to be conducted at up to 268 centres in 25 countries, including Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Czechia, Denmark, France, Germany, Greece, India, Israel, Italy, Japan, the Netherlands, New Zealand, Poland, Portugal, South Korea, Spain, Taiwan, the UK and the USA. The study is being conducted in 2 cohorts with 3 enrolment groups: phase 2b (group 1) and phase 3 (group 2 and group 3). Participation in the three groups is country specific; most countries are expected to participate in all three enrolment groups. Following a screening period, the phase 2b dose-selection cohort will enrol 360 participants randomised 1:1:1 to once-daily bexotegrast 160 mg, 320 mg or placebo for 52 weeks (figure 1). Randomisation will be performed in a blinded manner using interactive response technology, based on a previously generated randomised code, immediately prior to dosing on the morning of the first dose (day 1). At study entry, eligible participants in the phase 2b cohort will be stratified by type of background therapy (pirfenidone, nintedanib or none), gender-age-physiology index for IPF stage (I or II/III), and by region (region 1: Americas/Europe/Middle East/Africa; region 2: Japan; region 3: India or region 4: Asia-Pacific excluding Japan and India). On completion of the last participant in the phase 2b (group 1) cohort and while conduct is still ongoing in the cohort, the phase 3 cohort will immediately begin enrolment with group 2, the 'seamless group', using 1:1:1 randomisation. At entry, eligible participants in the phase 3 cohort will be stratified the same as in the phase 2b segment. Phase 3 final dose selection will occur once the last phase 2b participant has completed 52 weeks of treatment. After phase 3 dose selection, the phase 3 cohort (group 3) will complete enrolment using a 1:1 randomisation with the selected dose for further development. All participants will undergo study visits at baseline, weeks 4, 12, 24, 36

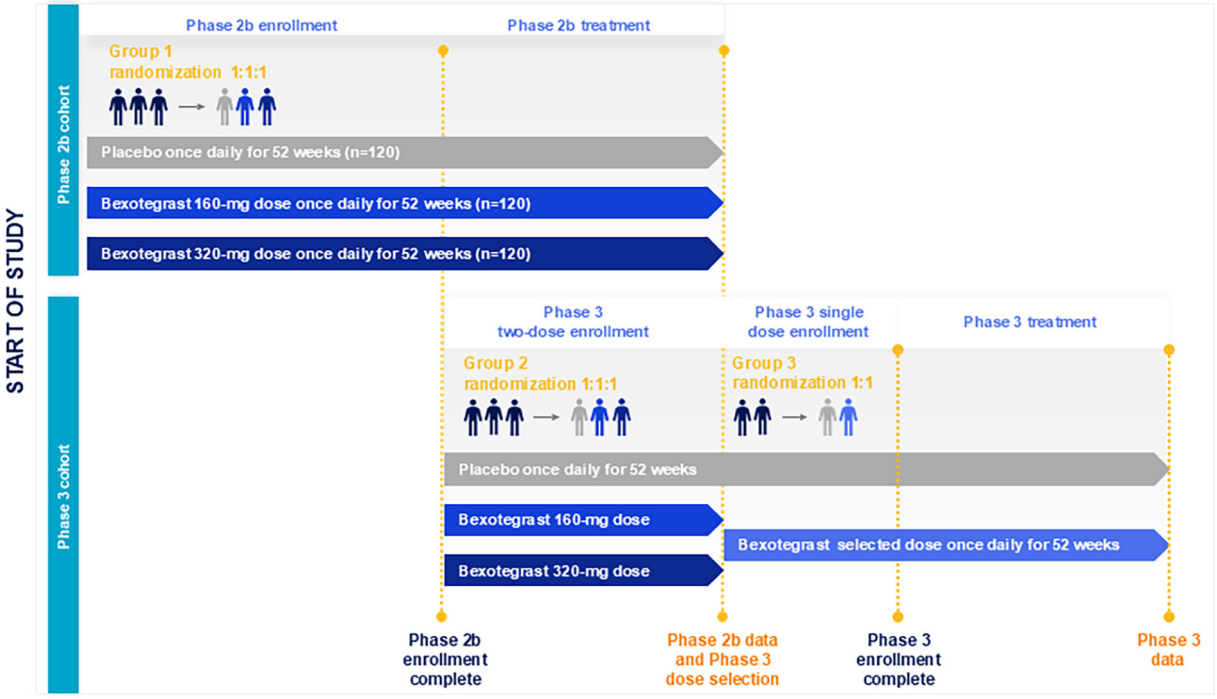

Figure 1 BEACON-IPF study design. IPF, idiopathic pulmonary fibrosis.

and 52 and after a 14-day safety follow-up period. All participants who complete 52 weeks of treatment in any enrolment group will be eligible to enrol in an open-label extension study. In addition, participants receiving the non-selected dose in group 2 will also be eligible to enrol in the same open-label study at the selected phase 3 dose. The study commenced in April 2023 and was anticipated to end in March 2027. It was terminated early during the phase 2b cohort after the last participant's last visit in April 2025, after an independent data and safety monitoring board and expert panel determined that bexotegrast doses ≥160 mg had an unacceptable risk to benefit profile.

During the implementation of the phase 2b cohort, a blinded sample-size estimation procedure[25 26] using phase 2b participants who completed 52 weeks of treatment will be conducted to inform whether the SD used to estimate the sample size for the phase 3 cohort is adequate to maintain the statistical power for phase 3. If the previous estimate for the SD is deemed inadequate, resulting in a potentially underpowered phase 3 trial, the sample size for the phase 3 cohort will be adjusted. The exact sample size of the phase 3 cohort will be informed by phase 2b results and the maximum planned sample size for both cohorts is 1113 participants.

Population

To be eligible to participate in BEACON-IPF Phase 2b cohort, participants need to be ≥40 years of age; have an IPF diagnosis for ≤7 years per 2018 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Association guidelines; have a per cent predicted forced vital capacity (FVCpp) ≥45%; and have a diffusing capacity for carbon monoxide (DL_{CO}) (haemoglobin adjusted) ≥30% and <90%. Female participants of non-childbearing potential must be surgically sterile or post-menopausal. Female participants of childbearing potential must use a highly effective contraceptive method with a failure rate of <1% per year during the screening and treatment period and for 4 weeks after the last dose of study drug.

Participants receiving pharmacologic therapy for pulmonary hypertension, who have clinical evidence of active infection or who have any other condition that prevents the correct assessment of spirometry performance, may not enrol in the study. Other exclusion criteria include a forced expiratory volume in the 1 s/FVC ratio <0.7, acute IPF exacerbation[27] ≤6 months prior to screening and renal impairment (defined as eGFR <30 mL/min/1.73 m^2). Participants with a history of smoking of any kind ≤12 months prior to screening, hepatic impairment characterised as liver dysfunction or a history of unstable or deteriorating cardiac or pulmonary disease other than IPF may not enrol. A full list of key inclusion and exclusion criteria for the phase 2b/3 cohorts can be found in table 1.

Background therapy for IPF with pirfenidone or nintedanib is permitted, provided participants are at a stable dose for ≥12 weeks prior to screening. No more than 70% of participants will be enrolled on background therapy. Participants who are not taking background therapy at study entry will be allowed to initiate either nintedanib or pirfenidone at any time during the study.

Table 1 BEACON-IPF key eligibility criteria

Inclusion criteria	Exclusion criteria
≥40 years of age prior to screening	Receiving pharmacologic therapy for pulmonary hypertension
IPF diagnosis ≤7 years prior to screening based on 2018 guidelines* and confirmed with central review. An HRCT scan performed ≤2 years prior to screening may be used for eligibility	Clinical evidence of active infection, including, but not limited to bronchitis, pneumonia or sinusitis that can affect FVC measurement during screening or at randomisation or any other condition that prevents the correct assessment of spirometry performance (eg, broken rib)
FVCpp ≥45%	(FEV1)/FVC ratio <0.7 at screening
DL_{CO}pp (haemoglobin adjusted) ≥30% and <90%	Active viral infection with HIV or hepatitis A, B or C
Current treatment for IPF with background therapy is allowed, if at a stable dose for ≥12 weeks prior to screening†	Known or suspected acute IPF exacerbation 6 months prior to screening
eGFR ≥30 mL/min/1.73 m^2 according to the Cockcroft-Gault equation for creatinine clearance	Extent of emphysema that is greater than the extent of fibrotic changes on the most recent HRCT scan (as determined by central reader); an HRCT scan performed ≤2 years prior to the screening date may be used
Female participants of non-childbearing potential must be surgically sterile or postmenopausal. Female participants of childbearing potential must use a highly effective contraceptive method with a failure rate of <1% per year during the screening and treatment period and for 4 weeks after the last dose of study drug.	Self-reported smoking of any kind (not limited to tobacco) ≤12 weeks prior to screening or unwillingness to avoid smoking throughout the study
	Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the Screening Period
	History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected non-invasive cutaneous squamous cell carcinoma or treated cervical carcinoma in situ
	Documented hepatic impairment (characterised as liver dysfunction with a Child-Pugh classification of A, B or C or end-stage liver disease) or renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage kidney disease
	History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including, but not limited to unstable angina pectoris or MI, congestive heart failure or uncontrolled clinically significant arrhythmias
	Pregnant or lactating female participants
	Medical or surgical conditions known to affect drug absorption (eg, major gastric surgery) or surgical procedures planned during study period
	Combined treatment with both nintedanib and pirfenidone

*Based on American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2018 guidelines.
†If not currently receiving treatment for IPF (either treatment naïve or discontinued prior treatment), participant must not have taken background therapy within 8 weeks prior to screening.
DL_{CO}pp, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in the 1 s; FVC, forced vital capacity; FVCpp, percent predicted FVC; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; MI, myocardial infarction; ULN, upper limit of normal.

Outcomes

The primary objective is to characterise the effect of bexotegrast versus placebo on the change in FVC over 52 weeks of treatment as assessed by the primary endpoint of change from baseline in absolute FVC at week 52. All spirometry and DL_{CO} testing will be conducted in a consistent time frame across study visits, as well as centrally overread for quality and repeatability per ATS 2019 and 2017 guidelines.[28 29]

Secondary objectives include evaluating the safety and tolerability of bexotegrast, as measured by the proportion of participants with treatment-emergent adverse events (AEs) and serious AEs; the effect of treatment with bexotegrast based on background therapy use, specifically those without background therapy use at baseline; and evaluation of the treatment effect of bexotegrast on disease progression. For this study, disease progression is defined as one of the following events: an adjudicated

respiratory-related hospitalisation,[30] an adjudicated acute IPF exacerbation event or all-cause mortality. In addition, the disease progression definition will include a ≥10% absolute decline in FVCpp. Additional secondary objectives will evaluate the effect of bexotegrast on overall symptom and functional improvement using the Living with Pulmonary Fibrosis (L-PF) Dyspnoea Domain, L-PF Cough Domain and King's Brief Interstitial Lung Disease total scores as well as the change in quantitative lung fibrosis scores, using high-resolution CT. Population analysis sets are illustrated in figure 2.

Statistical analysis

Both cohorts of the study will be statistically powered to detect differences in FVC between bexotegrast and placebo. For the phase 2b cohort, a sample size of 120 participants in each treatment group will provide ≥80% power to detect a 120 mL difference in FVC between at least one dose of bexotegrast and placebo using a type I error rate of 0.05.

A blinded sample size re-estimation procedure[25 26] will be applied when approximately two-thirds of the Phase 2b participants have had the opportunity to complete week 52 (ie, no ongoing participants will be included in this sample size re-estimation procedure). The blinded, pooled SD for change from baseline in FVC will be used for this calculation. This type of blinded interim analysis would not inflate the type I error rate for the final statistical test.[31] Dependent on the blinded group 1 sample size re-estimation procedure, a sample size of 168 to 251 participants in each treatment group in the phase 3 cohort will provide ≥90% power to detect a 120 mL difference in FVC between the selected dose of bexotegrast and placebo, assuming a type I error rate of 0.01.

For the primary endpoint, statistical significance will be declared if the analyses in either dose group are statistically significant ($p<0.05$). In both cohorts, the high dose will be evaluated using the majority of the type I error rate using a graphical multiplicity adjustment procedure. Because this study is operationally seamless, no participant will be included in both the phase 2b and phase 3 cohorts, resulting in the potential to replicate the phase 2b results with the phase 3 cohort within a single study design.

For the primary analysis, intercurrent events (except for death and lung transplant) will be handled via a treatment policy strategy, similar to an intention-to-treat approach, including all patients whether or not they remain on treatment. Missing data are assumed to be missing at random and will not be imputed, with the exception of death, which will use a multiple imputation procedure. Sensitivity analyses to the primary endpoint will be provided using multiple imputation strategies based on the primary reason for the data missingness for each participant.[32]

The primary endpoint, change from baseline in absolute FVC, will be estimated using a mixed-effects for repeated measures analysis. The model will include a continuous effect for baseline FVC, discrete effects for treatment, background therapy treatment, gender-age-physiology (GAP) stage at screening, enrolment region and study visit with a treatment-by-visit interaction. Secondary continuous endpoints will use a similar analysis strategy as the primary endpoint. Time-to-event endpoints will be analysed using a Cox proportional hazards model. The model will include study-drug treatment, background therapy, age and FVCpp at baseline. Proportion-based endpoints will be analysed using a logistic regression model using a similar covariate structure as the primary endpoint. Participant identification numbers will be used to ensure data confidentiality using appropriate sample and data management systems.

Trial oversight

An independent data safety and monitoring board composed of pulmonologists, a hepatologist and a

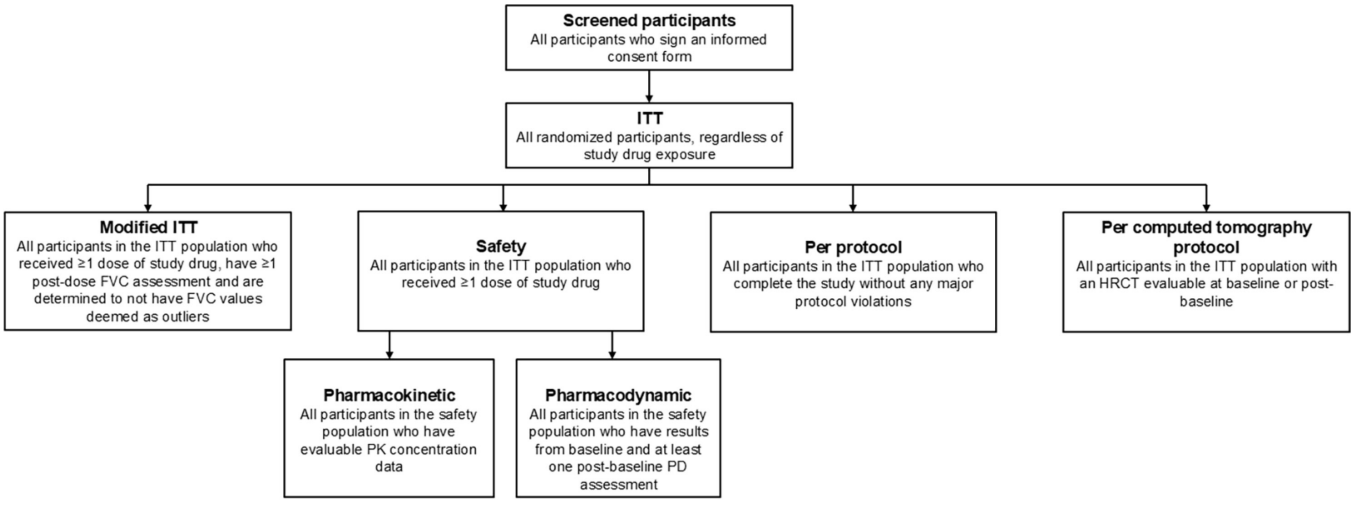

Figure 2 BEACON-IPF analysis sets. FVC, forced vital capacity; HCRT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; ITT, intention-to-treat; PD, pharmacodynamic; PK, pharmacokinetic.

statistician who are unblinded to the treatment allocation will meet on a regular basis to evaluate safety data. In addition, a separate independent pulmonary event adjudication committee composed of pulmonologists will evaluate all events of IPF progression, acute exacerbations[27] and increased IPF symptom events.

Patient and public involvement

Patients with IPF (n=9) and caregivers (n=1) were invited to participate in an advisory board to provide their feedback on the BEACON-IPF study design in July 2022. The discussion covered the seamless phase 2b/3 study design, eligibility criteria, efficacy and safety endpoints, and supporting resources for the study. An important consideration was to determine whether the phase 2b study participants would remain on blinded study drug for a 52-week or a longer duration (eg, until the completion of the phase 3 study) in order to accrue longer-term efficacy and safety data on bexotegrast. It was determined that a 52-week duration followed by the availability of an open-label safety study was highly preferable, which was consistent with the input from IPF thought leaders. Feedback was also sought about exploratory endpoints such as quantitative lung fibrosis and its meaning and implications to patients. Additional guidance on the bexotegrast programme from patient representatives was sought at the Pulmonary Fibrosis Foundation Summit in September 2023. The burden of intervention and time required was assessed to support a rigorous and robust trial supporting potential global regulatory submission. Patients will not be directly involved in the dissemination of study results, but a plain language summary will accompany the main trial manuscript. Study results will be disclosed to patients in accordance with regional regulatory guidance.

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Contributors CNB, ÉAL and GPC designed the study and wrote the protocol. WW, LL, TM, CJR, MK, TJC, CV, CNB, ÉAL, GPC, KRF, LR and VC reviewed and provided critical input to the study design and protocol. CNB, ÉAL and GPC wrote the first draft of the manuscript, and WW, LL, TM, CJR, MK, TJC, CV, CNB, ÉAL, GPC, KRF, LR and VC provided additional input. The authors worked collaboratively and made the decision to submit the final manuscript for publication. ÉAL is the guarantor.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by Advarra institutional review board (OHRP and FDA registration 00000971). The protocol was approved by the institutional review board at each participating centre. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines but terminated in April 2025. All participants provided written informed consent. An example of the participant consent form is available in the Supplemental Files. Study results will still be disseminated in peer-reviewed journals and international conferences targeted towards medical, academic and patient communities. To support the comprehension of our results at all levels, we will provide plain-language summaries of our data so that patients, caretakers and providers can make informed decisions during their IPF journey. A plain-language infographic is provided in the Online Data Supplement.

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REFERENCES

1 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;378:1811–23.
2 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.
3 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431–40.
4 Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. *Respir Med* 2015;109:661–70.
5 King TE Jr, 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.
6 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.
7 Rozenberg D, Sitzer N, Porter S, *et al*. Idiopathic pulmonary fibrosis: a review of disease, pharmacological, and nonpharmacological strategies with a focus on symptoms, function, and health-related quality of life. *J Pain Symptom Manage* 2020;59:1362–78.
8 Shi N, Wang Z, Zhu H, *et al*. Research progress on drugs targeting the TGF-β signaling pathway in fibrotic diseases. *Immunol Res* 2022;70:276–88.
9 Aschner Y, Downey GP. Transforming growth factor-β: master regulator of the respiratory system in health and disease. *Am J Respir Cell Mol Biol* 2016;54:647–55.
10 Horan GS, Wood S, Ona V, *et al*. Partial inhibition of integrin alpha(v)beta6 prevents pulmonary fibrosis without exacerbating inflammation. *Am J Respir Crit Care Med* 2008;177:56–65.
11 Saini G, Porte J, Weinreb PH, *et al*. αvβ6 integrin may be a potential prognostic biomarker in interstitial lung disease. *Eur Respir J* 2015;46:486–94.
12 Decaris ML, Schaub JR, Chen C, *et al*. Dual inhibition of αvβ6 and αvβ1 reduces fibrogenesis in lung tissue explants from patients with IPF. *Respir Res* 2021;22:265.
13 Frangogiannis N. Transforming growth factor-β in tissue fibrosis. *J Exp Med* 2020;217:e20190103.
14 Diebold RJ, Eis MJ, Yin M, *et al*. Early-onset multifocal inflammation in the transforming growth factor beta 1-null mouse is lymphocyte mediated. *Proc Natl Acad Sci U S A* 1995;92:12215–9.
15 Lancaster L, Cottin V, Ramaswamy M, *et al*. Bexotegrast in patients with idiopathic pulmonary fibrosis: the INTEGRIS-IPF clinical trial. *Am J Respir Crit Care Med* 2024;210:424–34.
16 Cosgrove GP, Pencek R, Clark A, *et al*. Update on the safety and tolerability of bexotegrast, a dual-selective inhibitor of integrins αvβ6 and αvβ1, in development for idiopathic pulmonary fibrosis and primary sclerosing cholangitis. *Am J Respir Crit Care* 2024;209:A6619.
17 Montesi SB, Cosgrove GP, Turner S, *et al*. Late breaking abstract - bexotegrast reduces type 1 collagen deposition in participants with idiopathic pulmonary fibrosis (ipf) after 12 weeks of therapy. *Eur Respir J* 2024;64:OA1058.
18 Noth I, Anstrom KJ, Calvert SB, *et al*. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;186:88–95.
19 King TE, Brown KK, Raghu G, *et al*. BUILD-3: A randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184:92–9.
20 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, *et al*. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010;363:620–8.
21 Raghu G, Richeldi L, Fernandez Perez ER, *et al*. Pamrevlumab for idiopathic pulmonary fibrosis: the ZEPHYRUS-1 randomized clinical trial. *JAMA* 2024;332:380–9.
22 Pallmann P, Bedding AW, Choodari-Oskooei B, *et al*. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018;16:29.
23 Geiger MJ, Skrivanek Z, Gaydos B, *et al*. An adaptive, dose-finding, seamless phase 2/3 study of a long-acting glucagon-like peptide-1 analog (dulaglutide): trial design and baseline characteristics. *J Diabetes Sci Technol* 2012;6:1319–27.
24 Martin M, Chan A, Dirix L, *et al*. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2- advanced breast cancer (BELLE-4). *Ann Oncol* 2017;28:313–20.
25 Friede T, Kieser M. Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. *Pharm Stat* 2011;10:8–13.
26 Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Stat Med* 2003;22:3571–81.
27 Collard HR, Ryerson CJ, Corte TJ, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis. an International Working Group report. *Am J Respir Crit Care Med* 2016;194:265–75.
28 Graham BL, Steenbruggen I, Miller MR, *et al*. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019;200:e70–88.
29 Graham BL, Brusasco V, Burgos F, *et al*. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017;49:1600016.
30 Durheim MT, Collard HR, Roberts RS, *et al*. Association of hospital admission and forced vital capacity endpoints with survival in patients with idiopathic pulmonary fibrosis: analysis of a pooled cohort from three clinical trials. *Lancet Respir Med* 2015;3:388–96.
31 Lawrence Gould A, Shih WJ. Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. *Commun Stat Theory Methods* 1992;21:2833–53.
32 Austin PC, White IR, Lee DS, *et al*. Missing data in clinical research: a tutorial on multiple imputation. *Can J Cardiol* 2021;37:1322–31.