BEACON-IPF: A GLOBAL PHASE 2B/3 STUDY OF BEXOTEGRAST FOR TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

Wim A. Wuyts, MD, PhD,[1] Lisa Lancaster, MD,[2] Toby M. Maher, MD, PhD,[3] Christopher J. Ryerson, MD,[4] Michael Kreuter, MD,[5] Tamera J. Corte, MD,[6] Claudia Valenzuela, MD,[7] Chris N. Barnes, PhD,[8] Éric A. Lefebvre, MD,[8] Gregory P. Cosgrove, MD,[8] Kevin Flaherty, MD,[9] Luca Richeldi, MD, PhD,[10] Vincent Cottin, MD, PhD[11,12]

[1]University Hospitals Leuven, Department of Pneumology, Unit for Interstitial Lung Diseases, Leuven, Belgium; [2]Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine, Nashville, TN, USA; [3]University of Southern California, Keck School of Medicine, Los Angeles, CA, USA; [4]Department of Medicine & Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada; [5]Mainz Lung Center, Pneumology Departments, University Medical Center and Marienhaus Clinic Mainz, Mainz, Germany; [6]Central Clinical School, Sydney Medical School, University of Sydney, Sydney, NSW, Australia; [7]Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain; [8]Pliant Therapeutics Inc., South San Franscisco, CA, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]Unità Operativa Complessa di Pneumologia, Fondazione Policlinco Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [11]National Reference Centre for Rare Pulmonary Diseases (Orphalung), Louis Pradel Hospital, ERN-LUNG, Lyon, France; [12]Claude Bernard University Lyon 1, UMR754, INRAE, Lyon, France

Abstract number: 0139

BACKGROUND

Unmet Needs in IPF

- Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, interstitial lung disease and is associated with a poor prognosis[1]
- 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[2,3]
- There is an unmet need for novel, effective therapies for IPF that are efficacious, are well tolerated and target the mechanistic action of fibrosis, such as transforming growth factor β (TGF-β) activation

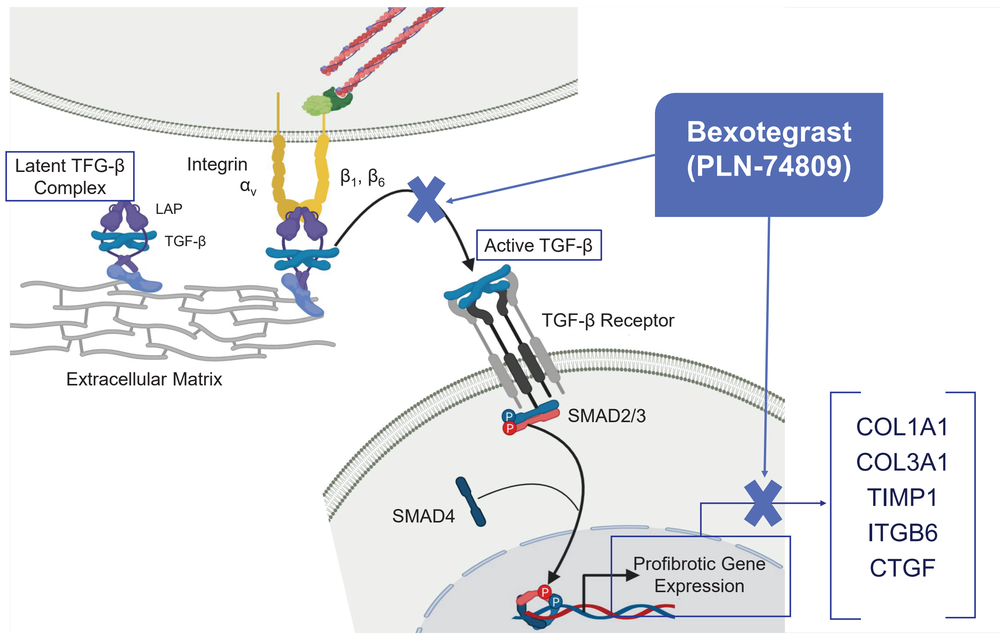
Rationale for Integrin Therapies in IPF

- Elevated TGF-β signaling is a hallmark of fibrogenesis in IPF (**Figure 1**)[4,5]
  - $\alpha_v\beta_6$ integrin, expressed by lung epithelial cells, and $\alpha_v\beta_1$ integrin, expressed by lung fibroblasts, are overexpressed in the lungs of patients with IPF and can activate TGF-β[6-8]
  - TGF-β mediates fibrosis through fibroblast activation and proliferation, which drives collagen synthesis and results in tissue stiffness[9-11]
- Selective $\alpha_v\beta_6$ integrin, $\alpha_v\beta_1$ integrin, and dual $\alpha_v\beta_6/\alpha_v\beta_1$ integrin inhibition reduced type 1 collagen gene expression in explanted lung tissue slices from patients with IPF and fibrotic mouse lung tissue[8]
- As systemic inhibition of TGF-β carries safety risks,[12,13] specific targeting of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins may provide a localized, safer approach to TGF-β inhibition in the fibrotic lung

Rationale for Bexotegrast

- Bexotegrast (PLN-74809) is an oral, once-daily, dual-selective $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin inhibitor that acts preferentially at sites of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin–driven fibrosis (**Figure 1**)
- Treatment with bexotegrast has the potential to provide disease-modifying benefit to patients with IPF by inhibiting collagen deposition, thus slowing the progressive decline of lung function and improving symptoms and quality of life
  - In a multicenter, randomized, double-blind, dose-ranging, placebo-controlled Phase 2 study of participants with IPF (INTEGRIS-IPF; NCT04396756), a reduction in the progressive decline of forced vital capacity and evidence of antifibrotic activity were observed with bexotegrast (n=89) compared with placebo (n=31)
    - Bexotegrast demonstrated a favorable safety profile for ≤40 weeks of treatment regardless of background therapy use[14]
  - In a recent single-center, randomized, double-blind, placebo-controlled, 12-week Phase 2 study in participants with IPF (PLN-74809-IPF-205; NCT05621252), changes in positron emission tomography imaging of the lungs using a probe for type 1 collagen, as well as dynamic contrast-enhanced magnetic resonance imaging in participants treated with bexotegrast 160 mg (n=7), showed a reduction in collagen supporting the inhibition of fibrogenesis and suggesting potential favorable remodeling of the lung[15]

Figure 1. $\alpha_v\beta_6$ and $\alpha_v\beta_1$ Integrins Promote Fibrosis Through Activation of TGF-β[8,16,a]

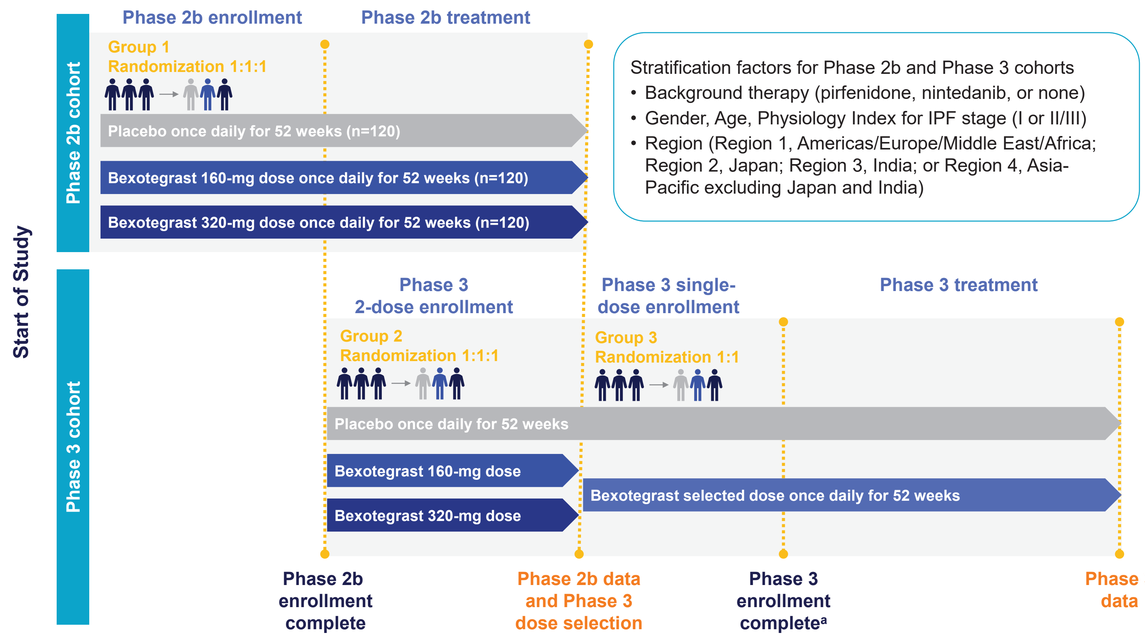


COL1A1, collagen type I alpha 1; COL3A1, collagen type III alpha 1; CTGF, connective tissue growth factor; HSC, hepatic stellate cell; IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; LAP, latency-associated peptide; PSC, primary sclerosing cholangitis; SMAD, family of proteins similar to the gene products of the Drosophila gene "mothers against decapentaplegic homolog 1" (MAD) and the C elegans gene SMA; TGF-β, transforming growth factor β; TIMP1, tissue inhibitor matrix metalloproteinase 1.
[a] This image is based on preclinical models.

CLINICAL TRIAL DESIGN

- BEACON-IPF (NCT06097260) is a randomized, double-blind, dose-finding, placebo-controlled, operationally seamless, adaptive Phase 2b/3 study evaluating the efficacy and safety of bexotegrast compared with placebo in participants with IPF (**Figure 2** and **Table 1**)
  - 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 favorable doses
  - 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
    - The Phase 2b cohort will inform dose selection and final sample size of the Phase 3 cohort
  - This design includes 2 independent populations in which to evaluate bexotegrast's effects, providing an opportunity to replicate results within a single trial

Figure 2. BEACON-IPF Study Design



[a] The Phase 3 final sample size will be informed by Phase 2b blinded sample size re-estimation procedure.

Table 1. Study Endpoints

Primary Endpoint
Change from baseline in FVC at Week 52
Secondary endpoints
Time to disease progression[a]
Change from baseline in FVC for participants receiving background therapy at baseline
Change from baseline in the following Symptom domains: • Living with Pulmonary Fibrosis Dyspnea Domain • Living with Pulmonary Fibrosis Cough Domain • King's Brief Interstitial Lung Disease total scores
Change from baseline in quantitative lung fibrosis scores by HRCT
Proportion of participants with treatment-emergent AEs and serious AEs

AE, adverse event; FVC, forced vital capacity; FVCpp, percent predicted forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis.
[a] Disease progression is defined as 1 of the following events: an adjudicated respiratory-related hospitalization, an adjudicated acute IPF exacerbation event or all-cause mortality. In addition, a second disease progression definition will include a ≥10% absolute decline in FVCpp.

- Key inclusion and exclusion criteria are shown in **Table 2**

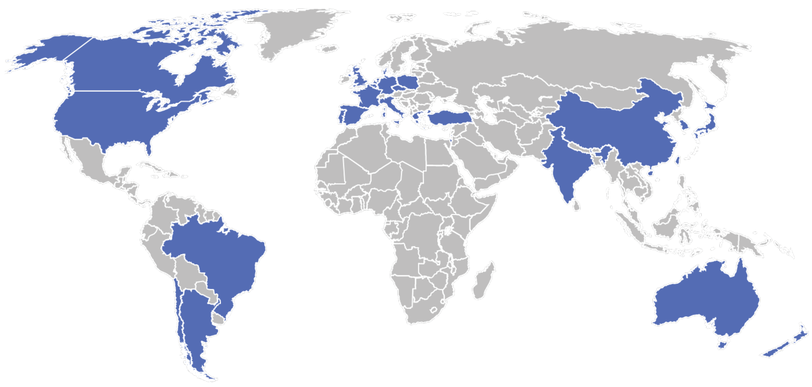
Table 2. Key Eligibility Criteria

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 upon 2018 guidelines[a] 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 randomization or any other condition that prevents the correct assessment of spirometry performance (eg, broken rib)
FVCpp ≥45%	(FEV_1)/FVC ratio <0.7 at screening
DL_{CO}pp (hemoglobin adjusted) ≥30% and <90%	Known or suspected acute IPF exacerbation 6 months prior to screening
Current treatment for IPF with background therapy is allowed if at a stable dose for ≥12 weeks prior to screening[b]	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
eGFR ≥30 mL/min/1.73 m^2 according to the Cockcroft-Gault equation for creatinine clearance	Self-reported smoking of any kind (not limited to tobacco) ≤12 weeks prior to screening or unwillingness to avoid smoking throughout the study
Female participants of nonchildbearing potential must be surgically sterile or postmenopausal	History of malignancy within the past 5 years or ongoing malignancy
	History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening
	Pregnant or lactating female participants
	Combined treatment with both nintedanib and pirfenidone

DL_{CO}pp, percent predicted diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FVCpp, percent predicted forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; MI, myocardial infarction.
[a] Based on American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2018 guidelines.[17]
[b] 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.

Enrollment

- BEACON-IPF is a multinational study to be conducted in 26 countries (**Figure 3**)



- Argentina
- Australia
- Belgium
- Brazil
- Canada
- Chile
- China
- Czech Republic
- Denmark
- France
- Germany
- Greece
- India
- Israel
- Italy
- Japan
- Netherlands
- New Zealand
- Poland
- Portugal
- South Korea
- Spain
- Taiwan
- Turkey
- United Kingdom
- United States

References: 1. Lederer DJ, Martinez FJ. *N Engl J Med*. 2018;1811-23; 2. King Jr TE, et al. *N Engl J Med*. 2014;2083-92; 3. Richeldi L, et al. *N Engl J Med*. 2014;2071-82; 4. Shi N, et al. *Immunol Res*. 2022;:276-88; 5. Aschner Y, Downey GP. *Am J Respir Cell Mol Biol*. 2016;647-55; 6. Saini G, et al. *Eur Respir J*. 2015;486-94; 7. Horan GS, et al. *Am J Respir Crit Care Med*. 2008;56-65; 8. Decaris ML, et al. *Respir Res*. 2021;265; 9. Frangogiannis NG. *J Exp Med*. 2020;e20190103; 10. Saito A, et al. *Int J Mol Sci*. 2018;2460; 11. Epstein Shochet G, et al. *Respir Res*. 2020;1-10; 12. Budi EH, et al. *J Pathol*. 2021;358-73; 13. Mitra MS et al. *Toxicol Sci*. 2020;24-34; 14. Lancaster L, et al. *Am J Respir Crit Care Med*. 2024;424-34; 15. Montesi SB, et al. European Respiratory Society (ERS) Congress 2024. Oral OA1058; 16. Saito A, et al. *Int J Mol Sci*. 2018;19:2460; 17. Raghu G, et al. *Am J Respir Crit Care Med*. 2018;e44-e68.

Presented at the International Colloquium on Lung and Airway Fibrosis (ICLAF) 2024; October 12-16, 2024; Athens, Greece

Disclosures: W. Wuyts received grants/fees paid to their institution from Pliant Therapeutics Inc, Roche, Boehringer Ingelheim, Sanofi and Alentis. **L. Lancaster** received grants from Roche, Pliant Therapeutics Inc, FibroGen, Boehringer Ingelheim, Novartis, Celgene, Galecto, Bristol Myers Squibb, Bridge Biotherapeutics, Horizon, CSL Behring and NeRRe; consulting fees from DevPro Biopharma, Pieries, AstraZeneca, Oxygenium, Roche, Bellerophon, Senhwa, Daewoong, Daiichi-Sankyo, Nashville Biosciences, Veracyte, United Therapeutics, Structure Therapeutics, Fortress Biotech, Tvardi, ureTech and SynDevRx; honoraria from Boehringer Ingelheim, Genentech, Veracyte and United Therapeutics; has a patent pending for Aut02; and participated on a data safety monitoring board or advisory board for DevPro Biopharma, Pieris, Oxygenium, Bellerophon, Veracyte, United Therapeutics and Aerami. **T. M. Maher** received consulting fees from Boehringer Ingelheim, Hoffman-La Roche, AstraZeneca, Bayer, Blade, Bristol Myers Squibb, CSL Behring, Galapagos, Galecto, GSK, IQVIA, Pfizer, Pliant Therapeutics Inc, Respivant, Sanofi, Theravance, Trevi Therapeutics, Veracyte and Vicore; and participated on a data safety monitoring or advisory board for FibroGen, Blade and NeRRe Therapeutics; **C. J. Ryerson** received institutional grants from Boehringer Ingelheim; consulting fees from Boehringer Ingelheim, Pliant Therapeutics Inc, AstraZeneca, Trevi Therapeutics and Veracyte; honoraria from Boehringer Ingelheim, Cipla and F Hoffmann La Roche; expert testimony fees from Boehringer Ingelheim; and meeting support from Boehringer Ingelheim and Cipla. **M. Kreuter** received grants paid their previous institution from Boehringer Ingelheim and Roche. **T. J. Corte** received personal fees for speaking commitments, travel and advisory board membership from Boehringer Ingelheim, Endeavour BioMedicines, Pliant Therapeutics Inc, Roche, Bristol Myers Squibb, Vicore, Bridge Therapeutics and DevPro; and received institutional fees for unrestricted grants from Boehringer Ingelheim, Roche, Galapagos, Biogen, Bristol Myers Squibb and Actelion. **C. Valenzuela** received honoraria/consulting fees from BMS, Boehringer Ingelheim and Roche. **C. N. Barnes, É. A. Lefebvre** and **G. P. Cosgrove** are employees and shareholders of Pliant Therapeutics Inc. **K. Flaherty** received institutional grants from Boehringer Ingelheim; consulting fees from Arrowhead, AstraZeneca, Bellerophon, CSL Behring, Daewoong, DevPro, DisperSol, FibroGen, F Hoffman La Roche/Genentech, Horizon, ImmuNet, Insilco, Lupin, NeRRe Therapeutics, Pliant Therapeutics Inc, Polarean, Pure Health, Pure Tech, Respivant, Shionogi, Sun Pharmaceuticals, Trevi, United Therapeutics and Vicore; and is the Steering Committee Chair for the Pulmonary Fibrosis Foundation. **L. Richeldi** received grants/research support from Roche and Boehringer Ingelheim; and received honoraria or consultation fees from Boehringer Ingelheim, Promedior, Biogen, FibroGen, Sanofi-Aventis, Promedior, RespiVant, Roche, Celgene, Nitto and Veracyte. **V. Cottin** received consulting fees from Pliant Therapeutics Inc.

Acknowledgments: This study was sponsored by Pliant Therapeutics, Inc. Support for third-party writing assistance for this presentation, furnished by Denise Kenski, PhD, of Nucleus Global, was provided by Pliant Therapeutics, Inc. This poster was developed in accordance with Good Publication Practice (GPP 2022) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication. Bexotegrast is an investigational drug in which safety and efficacy are still being evaluated and is not approved by any health authority.

Contact information: gcosgrove@pliantrx.com