PLN-74809 SHOWS FAVORABLE SAFETY AND TOLERABILITY AND INDICATES ANTIFIBROTIC ACTIVITY IN A PHASE 2A STUDY FOR THE TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

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RATIONALE

Transforming growth factor-beta signaling drives fibrosis in the lungs

- Transforming growth factor-beta (TGF-ß) activation by α_v integrins is a key driver of fibrosis in the lung[1,2]
  - Systemic TGF-ß blockade carries toxicity risks[2]
- Overexpression of $\alpha_v\beta_6$ (lung epithelial cells) and $\alpha_v\beta_1$ (lung fibroblasts)[2-6] activates latent TGF-ß, promoting profibrotic gene expression and resulting in collagen deposition in the lungs[2-5,7]
- Elevated levels of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ are detectable in the lungs of patients with idiopathic pulmonary fibrosis (IPF)[2,6]
  - Elevated levels of $\alpha_v\beta_6$ integrins detected in lung tissue biopsies[6] and plasma[8] have been associated with decreased survival in patients with IPF and interstitial lung disease, respectively

Bexotegrast for the treatment of idiopathic pulmonary fibrosis

- 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, with orphan drug[9,10] and fast-track[11] designation granted by the European Medicines Agency and United States Food and Drug Administration
  - Dual inhibition of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ with bexotegrast reduced fibrotic gene expression in lung tissue explanted from patients with IPF (precision-cut lung slices)[2]
  - Localized TGF-ß inhibition in the fibrotic lung, achieved by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins with bexotegrast, may provide a novel approach for treating IPF, without affecting TGF-ß signaling systemically

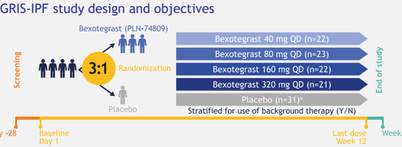
Aim

- This poster summarizes the interim 12-week results of INTEGRIS-IPF (NCT04396756), a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study evaluating the safety, tolerability, pharmacokinetics (PKs), and efficacy of once-daily treatment with bexotegrast in participants with IPF with or without a background therapy of pirfenidone or nintedanib

METHODS

- To be enrolled in this study, each participant met the following criteria:
  - Diagnosis of IPF for ≤5 years prior to Screening based on American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Respiratory Society (ALAT) 2018 guidelines[12]
  - ≥40 years of age
  - Diffusing capacity of the lungs for carbon monoxide ≥30%
  - Forced vital capacity (FVC) percent predicted (FVCpp) ≥45%
  - Participants receiving a background therapy of pirfenidone or nintedanib were permitted, provided these had been given at a stable dose for ≥3 months before Screening and were expected to remain unchanged during the study
  - No known or suspected acute IPF exacerbation within 6 months of Screening
- Participants were randomized in an approximately 3:1 ratio to receive bexotegrast (40 mg, 80 mg, 160 mg, or 320 mg) or placebo (**Figure 1**)

Figure 1. INTEGRIS-IPF study design and objectives



[a]One participant, randomized to placebo, received both placebo and bexotegrast 320 mg for approximately 1 week due to incorrect study-drug dispensation, which was identified after the Week 12 interim analysis. No AEs were reported for this participant and they are only included in the denominator of the placebo group for these analyses
AE, adverse event; QD, once daily; Y/N, yes/no

- The primary endpoint of this study was the safety and tolerability of bexotegrast, which included the nature and proportion of adverse events (AEs), safety laboratory values, vital signs, physical examinations, and 12-lead electrocardiograms (ECGs)
- The secondary endpoint was the PKs of bexotegrast
  - Total and unbound bexotegrast maximum concentration (C_{max}) and area under the concentration time curve from 0 to 24 hours post-dose ($AUC_{0\text{-}24}$) were calculated using a population PK model for 40 mg, 80 mg, 160 mg, and 320 mg doses on Days 1, 28, and 84
- The exploratory endpoints included change in FVC, quantitative lung fibrosis (QLF) score, and serum biomarkers (type III collagen synthesis neoepitope [PRO-C3], type VI collagen synthesis neoepitope [PRO-C6], and integrin beta-6 [ITGB6])
  - Absolute change from Baseline to Week 12 in FVC (mL) and >10% absolute decline in FVCpp were assessed using standardized clinical site spirometry and central quality control and validation
  - QLF score was assessed by high-resolution computed tomography (CT) on Day 1 and at Week 12 in participants with paired examinations that met technical specifications for quantitative assessment
  - Prespecified analyses of serum or plasma sample changes from Baseline to Week 12 in fibrosis-related biomarkers were conducted

RESULTS

- 119 participants met the eligibility criteria and were randomized and treated (bexotegrast, n=88; placebo, n=31) (**Figure 1**). Baseline demographics and disease characteristics are listed in **Table 1**

Table 1. Baseline demographics and disease characteristics

Demographics	Bexotegrast 40 mg (n=22)	Bexotegrast 80 mg (n=23)	Bexotegrast 160 mg (n=22)	Bexotegrast 320 mg (n=21)	Bexotegrast pooled (n=88)	Placebo (n=31)
Male sex, n (%)	18 (81.8)	19 (82.6)	16 (72.7)	20 (95.2)	73 (83.0)	27 (87.1)
Mean age, years (SD)	69.2 (7.11)	74.2 (4.70)	71.5 (6.63)	70.6 (7.31)	71.4 (6.64)	72.1 (6.20)
Mean time since IPF diagnosis, months (SD)	22.2 (12.44)	28.6 (17.08)	27.8 (12.43)	35.6 (29.06)	28.5 (19.11)	34.0 (21.62)
Background therapy use, n (%)	17 (77.3)	19 (82.6)	19 (86.4)	17 (81.0)	72 (81.8)	24 (77.4)
None	5 (22.7)	4 (17.4)	3 (13.6)	4 (19.0)	16 (18.2)	7 (22.6)
Pirfenidone	5 (22.7)	10 (43.5)	12 (54.5)	8 (38.1)	35 (39.8)	11 (35.5)
Nintedanib	12 (54.5)	9 (39.1)	7 (31.8)	9 (42.9)	37 (42.0)	13 (41.9)
Mean duration of background therapy use at randomization, months (SD)	19.5 (11.53)	20.2 (11.52)	20.1 (11.63)	24.4 (21.88)	21.0 (14.48)	22.6 (17.85)
Mean FVC, mL (SD)	2976.5 (861.01)	3128.7 (814.20)	2863.0 (725.39)	3193.7 (674.01)	3039.7 (771.20)	3073.9 (773.54)
FVCpp, mean (SD)	74.8 (14.70)	82.7 (13.47)	78.8 (16.36)	77.7 (15.41)	78.5 (15.01)	77.7 (16.44)
DLco percent predicted, corrected for hemoglobin level, mean (SD)	57.2 (14.74)	51.8 (14.67)	48.6 (15.11)	47.9 (13.18)[a]	51.5 (14.69)[b]	50.1 (15.23)

[a]Data available for 20 participants; [b]data available for 87 participants
DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; pp, percent predicted; SD, standard deviation

- During post hoc review of the complete 12-week data, 1 outlier in the FVC dataset was identified using statistical (Grubbs' test) and clinical criteria (clinical plausibility and comparison to pre- and post-values for the participant). Efficacy analyses were performed on the modified intent-to-treat population (mITT: excluding outlier), bexotegrast (pooled) n=88, and placebo n=30

Safety

- Overall, bexotegrast demonstrated a favorable safety profile (**Table 2**)
  - The majority of treatment-emergent AEs (TEAEs) were mild to moderate in severity. One death occurred in the bexotegrast 320 mg group due to acute respiratory failure in a participant with pre-existing atrial fibrillation 8 days following elective atrioventricular node ablation. Of TEAEs, 90.4% were Grade 1 or 2 in severity; no serious AEs (SAEs) were deemed related to study drug, and there were 6 withdrawals (320 mg, 3 [14.3%]; placebo, 3 [9.7%]) and 5 early terminations (320 mg, 3 [14.3%]; placebo, 2 [6.5%])

Table 2. Nature and frequency of TEAEs

	Participants, n (%)					
Participants with any:	Bexotegrast 40 mg (n=22)	Bexotegrast 80 mg (n=23)	Bexotegrast 160 mg (n=22)	Bexotegrast 320 mg (n=21)	Bexotegrast pooled (n=88)	Placebo (n=31)
TEAE	16 (72.7)	15 (65.2)	14 (63.6)	17 (81.0)	62 (70.5)	21 (67.7)
TEAE related to study drug	4 (18.2)	7 (30.4)	4 (18.2)	4 (19.0)	19 (21.6)	10 (32.3)
Grade ≥3 TEAE	2 (9.1)	0 (0.0)	2 (9.1)	2 (9.5)	6 (6.8)	2 (6.5)
Grade ≥3 TEAE related to study drug	0 (0.0)	0 (0.0)	1 (4.5)[a]	0 (0.0)	1 (1.1)	0 (0.0)
SAE	1 (4.5)	0 (0.0)	2 (9.1)	1 (4.8)	4 (4.5)	3 (9.7)
SAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to interruption of study drug	0 (0.0)	0 (0.0)	1 (4.5)[b]	1 (4.8)[c]	2 (2.3)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)[c,d,e]	3 (3.4)	3 (9.7)
TEAE leading to early termination from the study	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)[c,d,e]	3 (3.4)	2 (6.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)[d]	1 (1.1)	0 (0.0)

[a]Grade 3 event of diarrhea in a participant taking pirfenidone; [b]participant had a TEAE of COVID-19 that led to interruption of study drug; [c]abdominal pain/diarrhea in participant with pre-existing ulcerative colitis; [d]acute respiratory failure in a GAP Stage III participant with pre-existing atrial fibrillation 8 days following elective atrioventricular node ablation; [e]diarrhea in participant with concomitant use of nintedanib
COVID-19, coronavirus disease 2019; GAP, gender-age-physiology; SAE, serious adverse event; TEAE, treatment-emergent adverse event

- There were no notable changes in laboratory parameters, vital signs, physical examination findings, or ECG findings associated with study drug
- The most common TEAE was diarrhea, experienced by 15 participants (17.0%) in the bexotegrast (pooled) group and 3 participants (9.7%) in the placebo group
  - 14 of the 15 participants experiencing diarrhea in the bexotegrast (pooled) group were taking a background therapy for IPF; 1 participant not receiving a background therapy had pre-existing ulcerative colitis
  - Events of diarrhea were mostly mild to moderate in severity with only one Grade 3 event of diarrhea occurring in a participant taking bexotegrast and pirfenidone; 2 participants discontinued bexotegrast due to mild diarrhea

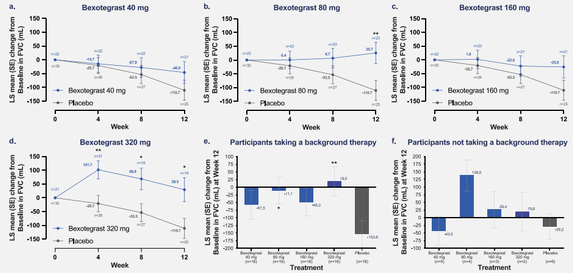
Pharmacokinetics

- Following application of the PK model, predicted total and unbound bexotegrast C_{max} and $AUC_{0\text{-}24}$ increased over the 40-320 mg dose range
  - At Day 84, geometric mean total C_{max} and $AUC_{0\text{-}24}$ in the bexotegrast 40 mg group were 881 ng/mL and 13,000 ng×hr/mL, respectively, and in the bexotegrast 320 mg group 4230 ng/mL and 66,800 ng×hr/mL, respectively
  - At Day 84, geometric mean unbound C_{max} and $AUC_{0\text{-}24}$ in the bexotegrast 40 mg group were 2.69 ng/mL and 38 ng×hr/mL, respectively, and in the bexotegrast 320 mg group 42.2 ng/mL and 445 ng×hr/mL, respectively
  - Concentrations of bexotegrast in participants with IPF increased approximately proportionally with increasing dose

Efficacy

- Participants in the bexotegrast (pooled) group experienced a significant reduction in FVC decline vs. placebo at Week 12 (-3.6 mL vs. -110.7 mL; p=0.0093) (mITT population): bexotegrast 40 mg (-46.0 mL, standard error [SE]=39.64), 80 mg (+25.7 mL, SE=38.57), 160 mg (-25.6 mL, SE=40.49), and 320 mg (+29.5 mL, SE=43.35) groups and placebo (-110.7 mL, SE=36.38) (**Figures 2a**, **2b**, **2c**, and **2d**, respectively). Statistically significant differences vs. placebo were identified in the 80 mg (p=0.0093) and 320 mg groups (p=0.0122) at Week 12 (**Figures 2b** and **2d**, respectively)
  - The treatment effect of bexotegrast was also observed in the subgroup analysis of participants taking and not receiving a background therapy for IPF (**Figures 2e** and **2f**, respectively). In participants taking a background therapy, those randomized to bexotegrast had a significant reduction in FVC decline vs. those randomized to placebo at Week 12 (-24.7 mL vs. -152.6 mL; p=0.0102) (**Figure 2e**)

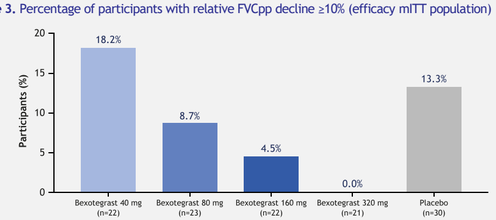
Figure 2. Change in FVC from Baseline to Week 12 (efficacy mITT population)



Change in FVC from Baseline through Week 12 in all participants receiving **a.** 40 mg, **b.** 80 mg, **c.** 160 mg, and **d.** 320 mg bexotegrast compared with placebo and change in FVC from Baseline at Week 12 in **e.** those taking a background therapy at the time of Screening, and **f.** those not taking a background therapy at the time of Screening. Change from Baseline analyzed using an MMRM
*p<0.05 vs. placebo; **p<0.01 vs. placebo
FVC, forced vital capacity; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; SE, standard error

- A dose-dependent downward trend in percentage of participants with relative FVCpp decline ≥10% was observed over the 12-week treatment period
  - Proportion of bexotegrast-treated participants with relative FVCpp decline ≥10%: bexotegrast 40 mg (18.2%), 80 mg (8.7%), 160 mg (4.5%), and 320 mg (0.0%) groups vs. placebo (13.3%) (**Figure 3**)
  - FVCpp decline ≥10% is associated with increased mortality risk and disease progression[13,14]

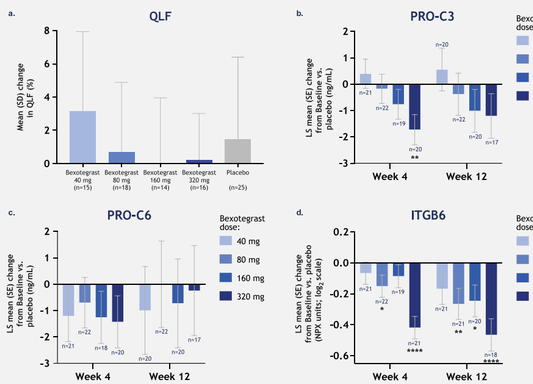
Figure 3. Percentage of participants with relative FVCpp decline ≥10% (efficacy mITT population)



FVCpp, forced vital capacity percent predicted; mITT, modified intent-to-treat

- Quantitative assessment of lung imaging demonstrated that mean percent change in QLF score decreased dose-dependently from Baseline to Week 12 with no or limited progression at 160 mg and 320 mg (**Figure 4a**)
- There was a dose-dependent decrease in PRO-C3 and ITGB6 observed with bexotegrast (**Figures 4b** and **4d**, respectively), with a reduction in PRO-C6 across all bexotegrast dose groups relative to placebo (**Figure 4c**)

Figure 4. Change in exploratory endpoints: QLF score and serum biomarkers



Change in exploratory endpoints from Baseline to Week 12 for **a.** QLF, and to Weeks 4 and 12 for serum biomarkers **b.** PRO-C3, **c.** PRO-C6, and **d.** ITGB6. The data in panel **a** are from the per CT protocol population (a subset of the ITT population with available HRCT imaging data and HRCT images) who completed the study without any major protocol violations within the prespecified time interval between Screening and Randomization. The data in panels **b**, **c**, and **d** are from the pharmacodynamic analysis population. Change from Baseline in biomarker concentration was analyzed using an MMRM
*p<0.05 vs. placebo; **p<0.01 vs. placebo; ***p<0.0001 vs. placebo
CT, computed tomography; HRCT, high-resolution computed tomography; ITGB6, integrin beta-6; ITT, intention-to-treat; LS, least squares; MMRM, mixed model for repeated measures; NPX, Normalized Protein eXpression; PRO-C3, type III collagen synthesis neoepitope; PRO-C6, type VI collagen synthesis neoepitope; QLF, quantitative lung fibrosis; SD, standard deviation; SE, standard error

CONCLUSIONS

- Bexotegrast was well tolerated across all dose groups over 12 weeks of treatment; most TEAEs were mild or moderate in severity, with no drug-related SAEs.
- Bexotegrast concentration increased approximately proportionally with increasing dose
- Bexotegrast-treated participants experienced a reduction in FVC decline over 12 weeks vs. placebo, with the treatment effect observed with and without the use of a background therapy
  - There was a dose-dependent downwards trend in the proportion of participants with FVCpp decline ≥10%, a well-established predictor of death and disease progression in IPF[13,14]
- There was a dose-dependent antifibrotic effect observed with QLF imaging, with no or limited progression at 160 mg and 320 mg
- A decrease in serum biomarkers of collagen synthesis (PRO-C3 and PRO-C6) and ITGB6 was observed relative to placebo

Future research

- Long-term safety and efficacy data released in Q2 of 2023 provided evidence of a favorable long-term safety profile and durable improvement in FVC[15]
- Initiation of BEACON-IPF, a Phase 2b, randomized, double-blind, dose-ranging, placebo-controlled study, is planned for mid-2023 to evaluate the efficacy and safety of 2 doses of bexotegrast (160 mg and 320 mg) administered for 52 weeks by participants with IPF taking and not taking a background therapy (pirfenidone or nintedanib)

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