PLN-74809, A DUAL-SELECTIVE INHIBITOR OF INTEGRINS $\alpha_v\beta_6$ AND $\alpha_v\beta_1$, SHOWS DOSE-DEPENDENT TARGET ENGAGEMENT IN THE LUNGS OF PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF)

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Poster no. 710

BACKGROUND

Transforming growth factor-beta signaling driving fibrosis in the lungs

- Transforming growth factor-beta (TGF-β) signaling activated by α_v integrins is a key driver of fibrosis in the lungs[1]
- Overexpression of integrins $\alpha_v\beta_6$ on lung epithelial cells and $\alpha_v\beta_1$ on lung fibroblasts activates latent TGF-β,[2–5] resulting in SMAD2/3 phosphorylation, profibrotic gene expression, and resultant collagen deposition in the lungs[3]
- Elevated levels of integrins $\alpha_v\beta_3$ and $\alpha_v\beta_1$ are detectable in the lungs of patients with interstitial lung disease compared with healthy participants[3,6,7]
- High levels of integrin $\alpha_v\beta_6$ detected within lung tissue biopsies[8] and plasma[9] are predictors of worse survival rates for patients with interstitial lung disease (**Figure 1**)

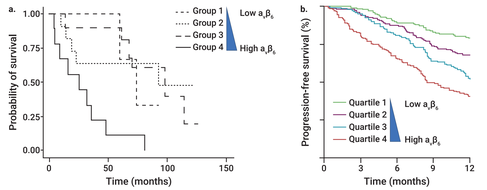
PLN-74809 for the treatment of idiopathic pulmonary fibrosis

- 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 idiopathic pulmonary fibrosis (IPF), with orphan drug designation granted by the United States Food and Drug Administration[10] (**Figure 2**)
- Dual inhibition of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ with PLN-74809 reduces fibrotic gene expression in lung tissue explanted from patients with IPF (precision-cut lung slices)[3]
  - PLN-74809 significantly reduced *COL1A1* mRNA expression when tested alone (42%; p<0.001), while nintedanib and pirfenidone alone had no effect on *COL1A1* expression when tested at their approximate clinical maximum observed drug concentration (C_{max}) levels of 75 nM and 50 µM, respectively[3]
- Localized TGF-β inhibition in the fibrotic lung, achieved by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins with PLN-74809, may provide a novel approach for treating IPF, without affecting TGF-β signaling systemically

STUDY DESIGN

- This Phase 2a, open-label, single-site study (PLN-74809-IPF-201; NCT04072315) was conducted at Stanford University, Stanford, CA, USA
- Each participant met the following criteria to be enrolled in this study:
  - ≥40 years of age
  - Confident diagnosis of IPF within 5 years prior to Screening according to Fleischner Society guidelines criteria, with high-resolution computed tomography imaging showing a typical or probable usual interstitial pneumonia pattern
  - Forced vital capacity percent of predicted ≥45%
  - Diffusing capacity for carbon monoxide percent predicted ≥30%
  - Participants receiving standard-of-care agents nintedanib or pirfenidone were allowed, provided these had been given at a stable dose for ≥3 months before the Screening Visit and were expected to remain unchanged during the study
- Safety assessments included open-ended adverse event inquiry, hematology, clinical chemistry, vital signs, 12-lead electrocardiograms, and physical examinations
- Participants underwent dynamic positron emission tomography (PET) scans at Baseline (Day -7) and on the day of PLN-74809 dosing (Day 1) (**Figure 3**) for 60 minutes after administration of [^{18}F]FP-$R_0$1-MG-F2, an anti-$\alpha_v\beta_6$ cystine knot peptide (knottin) radiotracer[3] to evaluate $\alpha_v\beta_6$ target engagement of PLN-74809
  - Post-dose imaging for the assessment of $\alpha_v\beta_6$ target engagement was performed to coincide with PLN-74809 time-to-maximum-observed drug concentration ~4 hours after its administration
  - PLN-74809 plasma pharmacokinetic samples (total and unbound concentrations) were obtained pre-dose and at 0.5, 1, 2, 3, 4, and 24 hours post-dose
- Dose levels evaluated were 60 mg, 120 mg, 240 mg, and 320 mg of PLN-74809, with participants receiving a single dose of study drug
  - These single doses were selected to approximate steady-state concentrations achieved by daily doses currently under evaluation in the ongoing, multinational Phase 2a INTEGRIS-IPF study (PLN-74809-IPF-202; NCT04396756)
  - Consenting participants could receive a second single dose at a different dose level for additional characterization of the PET ligand. If a participant received two single doses, only one Baseline pre-dose PET scan was obtained. No more than three PET scans (Baseline + 1 or 2 dosing scans) were obtained for any participant

Figure 1. TGF-β-activating integrin $\alpha_v\beta_6$ expression levels predict outcomes in patients with interstitial lung disease



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Saini G, et al. *European Respiratory Journal* Aug 2015, 46 (2) 486-494.
DOI:10.1183/09031936.00250414

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Bowman WS, et al. Proteomic biomarkers of progressive fibrosing interstitial lung disease: a multicentre cohort analysis.
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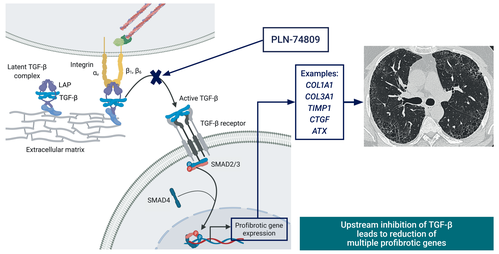
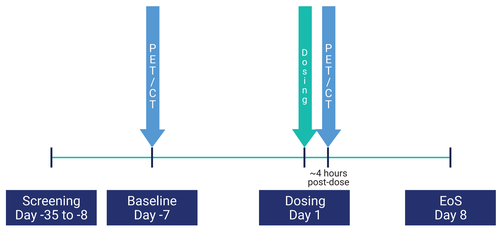
a. Kaplan–Meier survival for $\alpha_v\beta_6$ integrin expression in 43 patients with interstitial lung disease determined by IHC staining following lung biopsy. Median survival of groups 4 and 1–3 was 25 and 92 months, respectively (p=0.0039). **b.** Among 368 inflammation-associated proteins tested in plasma samples from 385 patients from the discovery cohort and 204 patients from the validation cohort, $\alpha_v\beta_6$ integrin had the strongest and most consistent association with disease progression over 12 months; OR 3.04 (95% CI 1.88, 5.15; p<0.0001).
CI, confidence interval; IHC, immunohistochemistry; OR, odds ratio; TGF-β, transforming growth factor-beta

Figure 2. Mode of action of PLN-74809



This diagram has been developed by Pliant Therapeutics, Inc.
ATX, autotaxin; COL1A1, collagen type I alpha 1 chain; COL3A1, collagen type III alpha 1 chain; CTGF, connective tissue growth factor; LAP, latency associated peptide; SMAD, family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene *Sma*; TGF-β, transforming growth factor-beta; TIMP1, tissue inhibitor matrix metalloproteinase 1

Figure 3. PLN-74809-IPF-201 study design



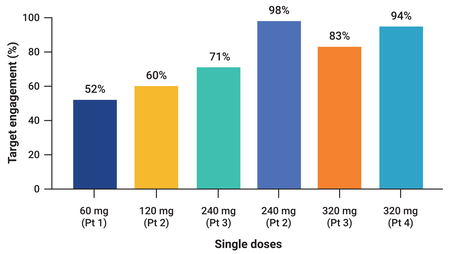
CT, computerized tomography; EoS, end of study; IPF, idiopathic pulmonary fibrosis; PET, positron emission tomography

Table 1. Baseline characteristics of 4 participants and single doses of PLN-74809 administered

Participant number	Age, years	Sex	BMI	SpO_2, %	pp FVC, %	pp DLco, %	IPF GAP index	SoC treatment	PLN-74809 dose(s)
1	77	M	23.97	97	74	—[a]	Stage II	Nintedanib	60 mg
2	69	M	26.29	97	69	48	Stage II	Nintedanib	120 mg/ 240 mg
3	84	M	22.37	99	66	61	Stage II	Nintedanib	240 mg/ 320 mg
4	83	M	27.43	99	95	93	Stage I	Nintedanib	320 mg

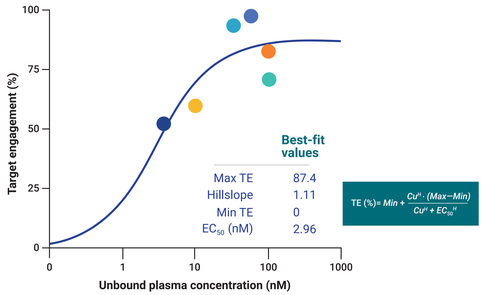
[a]DLco procedure at Screening was only included as a Protocol Amendment after the participant Screening Visit was complete; this participant only underwent spirometry at the Screening Visit
BMI, body mass index; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; GAP, gender-age-physiology; IPF, idiopathic pulmonary fibrosis; M, male; pp, percent of predicted; SoC, standard-of-care; SpO_2, peripheral capillary oxygen saturation

Figure 4. Dose-dependent target engagement of $\alpha_v\beta_6$ integrin by PLN-74809 in the lungs of participants with IPF



IPF, idiopathic pulmonary fibrosis; Pt, participant with IPF

Figure 5. Plasma concentration-dependent target engagement of $\alpha_v\beta_6$ integrin by PLN-74809 in the lungs of participants with IPF



Cu, unbound plasma concentration; EC_{50}, concentration eliciting half-maximal % target engagement; H, hillslope;
IPF, idiopathic pulmonary fibrosis; Max, maximum; Min, minimum; TE, target engagement (min - set to zero, max - maximum target engagement)

- Primary endpoint: evaluation of $\alpha_v\beta_6$ target engagement by PLN-74809 as assessed by changes in [^{18}F]FP-$R_0$1-MG-F2 radiotracer uptake in the lung following a single dose of study drug
  - Target engagement was calculated from the estimated volume of distribution, with correction for non-displaceable binding. Volume of distribution was estimated using a two-compartment model (blood and lung) with an image-derived input function
- An interim analysis was conducted when 6 out of the 12 planned pre- and post-dose PET scans were obtained

RESULTS

Interim pharmacodynamic and target engagement data from six dose administrations in 4 participants

- Four male participants aged 69–84 years received standard-of-care therapy (nintedanib) and one or two single doses of PLN-74809 (**Table 1**)
  - Two out of 4 participants received one single dose
  - Two out of 4 participants received two single doses at different dose levels with ≥14-day washout interval between doses
- A two-compartment model was determined to be optimal for describing [^{18}F]FP-$R_0$1-MG-F2 kinetics in the lungs on the pre- and post-dose dynamic PET scans
- Compared with the pre-dose (Baseline) PET/computerized tomography scan, a decrease in the knottin radiotracer volume of distribution was observed in the lungs of participants with IPF after a single-dose administration of PLN-74809
- All participants achieved >50% target engagement of $\alpha_v\beta_6$, increasing in a dose-dependent manner (**Figure 4**)
- Plasma concentrations at ~4 hours (immediately prior to PET scan) increased proportionally with the doses administered (60 mg, 120 mg, 240 mg, and 320 mg) (**Figure 5**)
- Target engagement of $\alpha_v\beta_6$ approached saturation (>90%) in 2 participants at the two highest doses administered (240 mg and 320 mg) (**Figures 4 and 5**)

Estimation of target engagement

- From the relationship between the plasma concentration of PLN-74809 and $\alpha_v\beta_6$ integrin target engagement (**Figure 5**), EC_{50} was estimated as 2.96 nM and the maximum target engagement was estimated as 87.4%
  - All participants achieved peak unbound concentrations above functional IC_{50} for $\alpha_v\beta_6$ inhibition

Safety

- No treatment-emergent adverse events related to PLN-74809 were reported for the doses administered
  - One participant was discontinued from the study due to abnormal liver function tests related to standard-of-care therapy with nintedanib (not related to PLN-74809)
- No severe or serious adverse events were reported

CONCLUSIONS

- A single dose of PLN-74809 achieved >50% target engagement of $\alpha_v\beta_6$ and penetrated highly fibrotic areas of the lung in participants with IPF
- Dose- and exposure-dependent target engagement was observed, approaching $\alpha_v\beta_6$ target saturation (>90%) in 2 participants at the two highest dose levels
- No PLN-74809-related adverse events were reported at the doses administered
- Evaluation of 12-week PLN-74809 treatment in the multinational Phase 2a INTEGRIS-IPF study (PLN 74809-IPF-202; NCT04396756) is currently underway

References: 1. Saito A, et al. *Int J Mol Sci* 2018;19(8):2460; 2. Robertson IB, et al. *Cold Spring Harb Perspect Biol* 2016;8(6):a021907; 3. Decaris ML, et al. *Respir Res* 2021;22(1):265; 4. Reed NI, et al. *Sci Transl Med* 2015;7(288):288ra279; 5. Munger JS, et al. *Cell* 1999;96(3):319–328; 6. Kimura RH, et al. *Nat Commun* 2019;10(1):4673; 7. Horan GS, et al. *Am J Respir Crit Care Med* 2008;177(1):56–65; 8. Saini G, et al. *Eur Respir J* 2015;46(2):486–494, 9. Bowman WS, et al. *Lancet Respir Med* 2022 Jan 18 [Online ahead of print]. DOI: 10.1016/S2213-2600(21)00503-8; 10. Pliant Therapeutics, Inc. [Press release]. 6 August 2018. https://ir.pliantrx.com/news-releases/news-release-details/pliant-therapeutics-receives-fda-orphan-drug-designation-lead. Accessed May 5, 2022

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