PLN-74809, a dual $\alpha_v\beta_6/\alpha_v\beta_1$, oral, selective integrin inhibitor, is well tolerated and reduces lung TGF-β activity in healthy volunteers

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Rationale

- Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ are cell-surface proteins that bind to latency-associated peptide and activate transforming growth factor-β (TGF-β), resulting in Smad2/3 phosphorylation and profibrotic gene expression.[1,2]
- In idiopathic pulmonary fibrosis (IPF), both integrins are upregulated in the lung and are thought to play a key role in the development and propagation of fibrosis;[3–5] $\alpha_v\beta_6$ is expressed on injured epithelial cells[4] and $\alpha_v\beta_1$ is expressed on fibroblasts.[6]
  - $\alpha_v\beta_6$ integrin levels are elevated in human fibrotic lung tissue as determined by immunohistochemistry (in patients with IPF or systemic sclerosis lung disease)[4] and by positron emission tomography imaging (in patients with IPF).[5]
  - $\alpha_v\beta_1$ integrin levels are elevated in human fibrotic lung tissue as determined by an electrochemiluminescence assay.[3]
- PLN-74809 is an oral, dual-selective, small-molecule inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$, which showed antifibrotic activity in precision-cut slices from bleomycin-injured murine lungs and explanted lung tissue from patients with IPF.[3]
- We have shown that inhibition of $\alpha_v\beta_6$-mediated TGF-β activation in the lung can be assessed via measurement of phosphorylated Smad2 (pSmad2) in alveolar macrophages collected by bronchoalveolar lavage (BAL).

Methods

- PLN-74809 was administered to 84 healthy volunteers in two completed Phase 1 studies to assess safety and tolerability, as well as to evaluate pharmacokinetic (PK) and pharmacodynamic (PD) profiles.

Safety

- Safety assessments in both studies included adverse events (AEs), clinical chemistry and hematology, physical examination, vital signs, and 12-lead electrocardiogram (ECG).

Study PLN-74809-P1-01

- Part A (single ascending dose): a randomized, double-blind, placebo-controlled study in four cohorts. Cohorts (eight PLN-74809- and two placebo-treated participants per cohort) received single doses of PLN-74809 (15, 30, 50, or 75 mg) or matching placebo (**Figure 1A**).
- Part B (multiple ascending dose): a randomized, double-blind, placebo-controlled study in three cohorts. Cohorts (nine PLN-74809- and two placebo-treated participants per cohort) received PLN-74809 (10, 20, or 40 mg) or matching placebo once daily (QD) for 14 days (**Figure 1B**).
- Part C (food effect): a randomized, open-label, two-period (fed–fasted), single-dose study in one cohort. Twelve participants received two single 40 mg doses of PLN-74809.
- In both Part A and Part B, PLN-74809 or matching placebo were given under fasting conditions as an oral solution.

Study PLN-74809-P1-03

- This was a randomized, double-blind, ascending-dose, placebo-controlled study with two sequential doses and four cohorts. Participants (13 PLN-74809, five placebo) received PLN-74809 (20 mg or 40 mg QD) or matching placebo under fasting conditions as an oral solution for 7 days (two cohorts per dose) (**Figure 2**).
- Samples of BAL fluid were collected via bronchoscopy prior to dosing (Day -1) and at either 3 and 12 hours or 6 and 24 hours after the last dose of PLN-74809 for determination of Smad2 phosphorylation in alveolar macrophages.
  - Cells were isolated by centrifugation and immediately frozen. Smad2 phosphorylation was measured in BAL cell lysate as the ratio of pSmad2 to total Smad2 by immunoassay. Reduction in pSmad2 was calculated as pSmad2/Smad2 following treatment relative to pSmad2/Smad2 measured at baseline.
  - BAL procedures were performed using 100 mL alternating between the right middle lobe and the lingula.
- Plasma samples for PK analysis were collected from all cohorts on Day 7 pre dose and 0.5, 1, 2, 3, 4, 6, 12, and 24 hours post dose.

Figures and tables

Figure 1. PLN-74809-P1-01 single ascending dose (A) and multiple ascending dose (B) study design

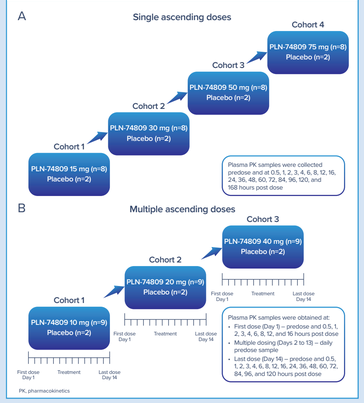
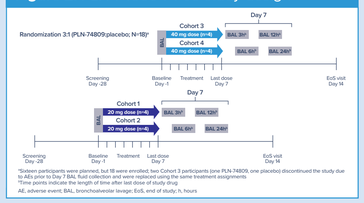
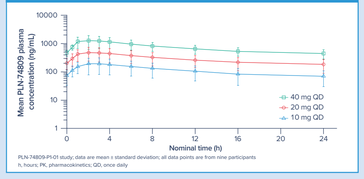


Figure 2. PLN-74809-P1-03 study design



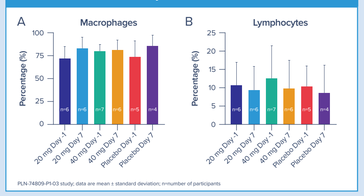
aSixteen participants were planned, but 18 were enrolled; two Cohort 3 participants (one PLN-74809, one placebo) discontinued the study due to AEs prior to Day 7 BAL fluid collection and were replaced using the same treatment assignments.
bTime points indicate the length of time after last dose of study drug.
AE, adverse event; BAL, bronchoalveolar lavage; EoS, end of study; h, hours

Figure 3. PK profiles after 14-day treatment with PLN-74809



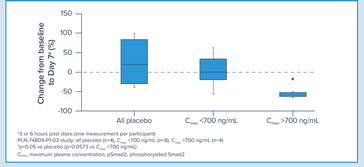
PLN-74809-P1-01 study; data are mean ± standard deviation; all data points are from nine participants
h, hours; PK, pharmacokinetics; QD, once daily

Figure 4. Macrophage (A) and lymphocyte (B) cell counts after 7-day treatment with PLN-74809



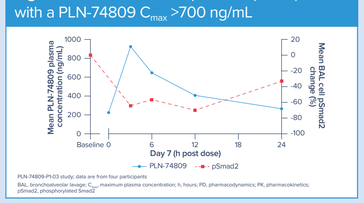
PLN-74809-P1-03 study; data are mean ± standard deviation; n=number of participants

Figure 5. Percentage change in pSmad2/Smad2 ratio at Day 7[h] vs baseline by PLN-74809 C_{max} level



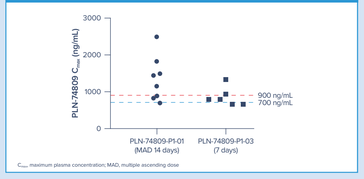
[h] or 6 hours post dose (one measurement per participant)
PLN-74809-P1-03 study; all placebo (n=4), C_{max} <700 ng/mL (n=8), C_{max} >700 ng/mL (n=4)
*p=0.05 vs placebo (p=0.0573 vs C_{max} <700 ng/mL)
C_{max}, maximum plasma concentration; pSmad2, phosphorylated Smad2

Figure 6. Mean PK/PD response in participants with a PLN-74809 C_{max} >700 ng/mL



PLN-74809-P1-03 study; data are from four participants
BAL, bronchoalveolar lavage; C_{max}, maximum plasma concentration; h, hours; PD, pharmacodynamics; PK, pharmacokinetics; pSmad2, phosphorylated Smad2

Figure 7. C_{max} values in participants receiving 40 mg/day PLN-74809



C_{max}, maximum plasma concentration; MAD, multiple ascending dose

Table 1. Participants reporting TEAEs

AE severity	Study PLN-74809-P1-01								Study PLN-74809-P1-03	
	Part A (SAD)				Part B (MAD)			Part C (FE)		
	15 mg (n=8)	30 mg (n=8)	50 mg (n=8)	75 mg (n=8)	10 mg (n=9)	20 mg (n=9)	40 mg (n=9)	40 mg (n=12)	20 mg (n=6)	40 mg (n=7)
Mild	–	1	–	1	1	4[a]	–	1	2	1
Moderate	–	1	–	–	–	–	1	1	–	–
Severe	–	–	–	–	–	–	–	–	–	–

[a]One drug-related AE (epigastric discomfort)
AE, adverse event; FE, food effect; MAD, multiple ascending dose; SAD, single ascending dose; TEAE, treatment-emergent adverse event

Results

Safety

- PLN-74809 was well tolerated in both studies, with few treatment-emergent AEs (TEAEs) reported (**Table 1**).
- Most AEs were mild, none were severe, and no dose relationship for AEs was observed.
- The most reported AE was mild constipation, reported in 5/84 treated participants.
- All AEs resolved and only one AE (mild epigastric discomfort) was considered related to the study drug.
- No deaths or serious AEs were reported.
- There were no notable changes in vital signs, ECGs, telemetry, physical examination, or clinical laboratory parameters.

PK

- Following a single-dose administration of oral PLN-74809 solution (ranging from 15 to 75 mg) to healthy participants, PLN-74809 plasma concentrations reached maximum levels after 2 to 3 hours.
- Following multiple doses of PLN-74809 solution (ranging from 10 to 40 mg QD) to healthy participants, PLN-74809 plasma concentrations reached steady state after 5 to 7 days.
- In general, exposure increased proportionally with dose on both Day 1 and Day 14 (**Figure 3**).
- Mean half-life remained relatively unchanged with increasing dose, ranging from 49.0 to 50.9 hours on Day 14.

PK/PD

- BAL fluid cell counts confirmed the expected predominance of alveolar macrophages, as well as no notable changes in the total or differential cell counts, as a result of multiple BAL procedures or PLN-74809 dosing, indicating no signs of excess inflammation (**Figure 4**).
- At 6 hours post dose, the percentage reduction from baseline of the pSmad2/Smad2 ratio in BAL fluid cell pellets (BALF-CP) in the 40 mg PLN-74809 treatment group (n=3) was significantly greater than that in the placebo group (n=2; p=0.0311) and the 20 mg PLN-74809 treatment group (n=3; p=0.0353), indicating a reduction in TGF-β activation at the 40 mg dose of PLN-74809.
- Exploratory exposure-response analysis suggested a correlation between maximum PLN-74809 plasma concentration (C_{max}) and change from baseline in the BALF-CP pSmad2/Smad2 ratio. Mean (standard deviation) percent reduction in the BALF-CP pSmad2/Smad2 ratio was 58.6% (6.9%) for participants with C_{max} >700 ng/mL compared to a 4.4% (37.6%) increase for participants with C_{max} <700 ng/mL at the earliest Day 7 time point (3 or 6 hours post dose) (**Figure 5**).
- The PK/PD relationship for those participants achieving a C_{max} >700 ng/mL (n=4) is shown in **Figure 6**.
- In total, 11/14 (79%) participants receiving 40 mg/day PLN-74809 in the two studies achieved exposure levels considered to be biologically active (**Figure 7**).

Conclusions

- PLN-74809 was well tolerated in healthy volunteers and demonstrated good oral bioavailability, achieving steady-state concentrations within 5 to 7 days and a half-life of approximately 50 hours, supporting once-daily dosing.
- BAL fluid analysis indicated that PLN-74809, when dosed at 40 mg QD for 7 days, was biologically active and reduced TGF-β activation in healthy human lungs.
  - No signs of excess inflammation from PLN-74809 dosing were observed in BAL fluid, which is consistent with 28-day and 13-week non-clinical study findings (mouse and monkey) where no pro-inflammatory signal was identified (data on file).
- Safety and PK/PD findings from these two Phase 1 studies support the evaluation of PLN-74809 at doses of 40 mg QD and greater, and provide the basis for two dose-ranging Phase 2a studies, PLN-74809-IPF-201 (NCT04072315) and PLN-74809-IPF-202 (INTEGRIS-IPF; NCT04396756), in participants with IPF.

References: 1. Chen C, et al. *J Mol Cell Cardiol* 2016;93:162–174; **2.** Walton KL, et al. *Front Pharmacol* 2017;8:461; **3.** Decaris M, et al. *Eur Respir J* 2019;54(Suppl 63):PA1286; **4.** Horan GS, et al. *Am J Respir Crit Care Med* 2008;177(1):56–65; **5.** Kimura RH, et al. *Nat Commun* 2019;10(1):4673; **6.** Reed NI, et al. *Sci Transl Med* 2015;7(288):288ra79

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Disclosures: All authors were employed by Pliant Therapeutics, Inc. at the time of their contribution to the studies reported here.

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