PLN-74809, A DUAL-SELECTIVE INHIBITOR OF $\alpha_v\beta_6$ AND $\alpha_v\beta_1$, IS WELL TOLERATED IN OVER 280 HEALTHY PARTICIPANTS

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Research supported by Pliant Therapeutics, Inc. Authors' relevant interests: FC is a consultant to Pliant Therapeutics, Inc. All other authors were employed by Pliant Therapeutics, Inc., and owned stock at the time of the study

Poster no. 419

BACKGROUND

- Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ are cell-surface proteins that regulate the activation of transforming growth factor-beta signaling in the fibrotic human lung[1,2]
- Elevated levels of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ are present in the lungs of patients with idiopathic pulmonary fibrosis and interstitial lung disease compared with healthy participants[2–5]
- 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, with orphan drug designation granted by the United States Food and Drug Administration[6]
- In non-clinical chronic safety studies, PLN-74809 showed no drug-related organ toxicity at any dose levels tested
- Overexpression of integrins $\alpha_v\beta_6$ on lung epithelial cells and $\alpha_v\beta_1$ on lung fibroblasts activates latent transforming growth factor-beta,[2,7–9] resulting in SMAD2/3 phosphorylation and profibrotic gene expression and resultant collagen deposition in the lung[2] (**Figure 1**)
- Therefore, localized inhibition of transforming growth factor-beta 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 idiopathic pulmonary fibrosis without affecting transforming growth factor-beta signaling systemically

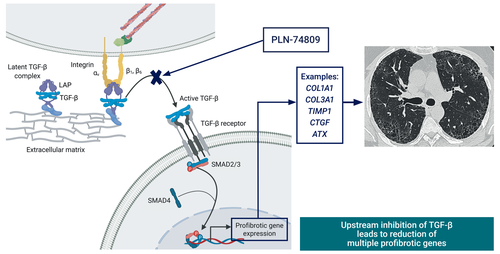
METHODS

- Across the completed Phase 1 studies with available safety data (N=7), as of October 1, 2021, 283 healthy participants received PLN-74809 and 52 received placebo
- PLN-74809 treatment duration was between 1 and 14 days, with multiple doses ranging between 10 mg and 320 mg once daily and single doses ranging between 15 mg and 640 mg
- As of November 29, 2021, a review of all available safety data from completed and ongoing Phase 1 and Phase 2 studies was conducted to issue the Development Safety Update Report, which included a total of 540 participants treated with study drug (PLN-74809 or placebo) (**Table 1**)
  - In unblinded studies, 354 participants received PLN-74809 and 53 received placebo
  - In blinded studies, 133 participants received study drug; based on the randomization ratios for these studies, approximately 99 participants received PLN-74809 and 34 received placebo
  - Therefore, approximately 453 participants were treated with PLN-74809 at the time of the analysis cut-off date
- Treatment-emergent adverse event data were pooled and assessed

RESULTS

- Overall, in the seven Phase 1 studies, 42.4% (120/283; PLN-74809) and 40.4% (21/52; placebo) of participants experienced treatment-emergent adverse events (all causality); most treatment-emergent adverse events were considered unrelated to study drug
- Drug-related treatment-emergent adverse events were reported in 12.4% (35/283; PLN-74809) and 3.8% (2/52; placebo) of participants
  - Most treatment-emergent adverse events were mild in severity, while 7.4% (21/283; PLN-74809) and 5.8% (3/52; placebo) of participants experienced treatment-emergent adverse events that were moderate in severity
  - Severe treatment-emergent adverse events were experienced by 0.4% (1/283; PLN-74809) of participants (considered unrelated to study drug)

Figure 1. 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

Table 1. Cumulative participant exposure in clinical studies

Study drug	Participants, n (N=540)
PLN-74809	354
Placebo	53
Blinded (PLN-74809 or placebo)	133[a]

[a]Based on the randomization ratios for these blinded studies, it is estimated that 99 participants have received PLN-74809 and 34 participants have received placebo

Table 2. Overview of treatment-emergent adverse events reported in healthy participants from seven Phase 1 studies[a] with available safety data

	Participants, n (%)	
	PLN-74809, all doses (n=283)	Placebo (n=52)
Any TEAE (all causality)	120 (42.4)	21 (40.4)
Drug-related TEAE	35 (12.4)	2 (3.8)
TEAE by maximum severity (all causality)		
Mild	98 (34.6)	18 (34.6)
Moderate	21 (7.4)	3 (5.8)
Severe	1 (0.4)	0 (0.0)

Table 2. (Continued)

	Participants, n (%)	
	PLN-74809, all doses (n=283)	Placebo (n=52)
Drug-related TEAE by maximum severity		
Mild	28 (9.9)	2 (3.8)
Moderate	7 (2.5)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Treatment-emergent SAE (all causality)	2 (0.7)	0 (0.0)
Drug-related SAE	0 (0.0)	0 (0.0)
TEAE leading to withdrawal from study	2 (0.7)	0 (0.0)
TEAE leading to discontinuation of study drug	3 (1.1)	1 (1.9)
TEAE leading to death	0 (0.0)	0 (0.0)

[a]Data from studies PLN-74809-P1-01, PLN-74809-P1-03, PLN-74809-104, PLN-74809-106, PLN-74809-107, PLN-74809-109 (Part 1), and PLN-74809-110
SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 3. Drug-related treatment-emergent adverse events reported in ≥2 PLN-74809-treated healthy participants from seven Phase 1 studies[a] with available safety data

	Participants, n (%)	
TEAE preferred term[b]	PLN-74809, all doses (n=283)	Placebo (n=52)
	Drug-related	Drug-related
Headache	4 (1.4)	2 (3.8)
Constipation	4 (1.4)	0 (0.0)
Nausea	3 (1.1)	0 (0.0)
Dizziness	2 (0.7)	0 (0.0)
Abdominal pain	2 (0.7)	0 (0.0)
Palpitations	2 (0.7)	0 (0.0)

[a]Data from studies PLN-74809-P1-01, PLN-74809-P1-03, PLN-74809-104, PLN-74809-106, PLN-74809-107, PLN-74809-109 (Part 1), and PLN-74809-110
[b]Preferred terms were coded using MedDRA Version 24.0
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

- Treatment-emergent adverse events led to discontinuation of the study drug in 1.1% (3/283; PLN-74809) and 1.9% (1/52; placebo) of participants, 0.7% (2/283; PLN-74809) and zero participants experienced treatment-emergent adverse events leading to withdrawal from the study, and no deaths were reported (**Table 2**)
- The two most common drug-related treatment-emergent adverse events reported in PLN-74809-treated healthy participants were headache and constipation (**Table 3**)
- No relationship between frequency or severity of treatment-emergent adverse events and PLN-74809 doses or treatment duration was observed
- Among the seven completed and ongoing Phase 1 studies, as of October 1, 2021, 4 participants experienced treatment-emergent serious adverse events that were all considered unrelated to PLN-74809
- No serious adverse events resulted in discontinuation of the study drug; all serious adverse events resolved or were resolving
- No notable changes were observed in physical examinations, laboratory parameters, vital signs, or electrocardiograms

Phase 2 data

- Preliminary safety data from four Phase 2a studies (PLN-74809-IPF-201 [NCT04072315]; INTEGRIS-IPF [blinded; NCT04396756]; INTEGRIS-PSC [blinded; NCT04480840]; and PLN-74809-ARDS-204 [NCT04565249]) in participants with idiopathic pulmonary fibrosis, primary sclerosing cholangitis, or acute respiratory distress syndrome associated with at least severe COVID-19 suggest no safety concerns
  - All treatment-emergent serious adverse events reported as of November 29, 2021, were considered unrelated to study drug by the Investigator
    - These events were expected manifestations of the underlying diseases and considered by the Investigator to be most likely due to disease progression
  - Two participants with idiopathic pulmonary fibrosis and 1 participant with primary sclerosing cholangitis who received blinded study drug experienced treatment-emergent serious adverse events that resolved
  - In the unblinded study in participants with acute respiratory distress syndrome, 4 out of the 6 enrolled participants experienced serious adverse events (3 out of 5 participants receiving PLN-74809 and 1 out of 1 participant receiving placebo)

CONCLUSIONS

- **PLN-74809 was generally well tolerated in 283 healthy participants receiving single doses up to 640 mg or multiple doses up to 320 mg once daily, administered for up to 14 days, in completed Phase 1 studies**
- **The most frequently reported drug-related adverse events were headache and constipation, and no drug-related severe adverse events were reported**
- **More recently, PLN-74809 has been administered to over 450 participants in total, including healthy participants as well as those with idiopathic pulmonary fibrosis, primary sclerosing cholangitis, or acute respiratory distress syndrome without any safety concerns**
- **These data support the continued Phase 2a evaluation of PLN-74809 in participants with idiopathic pulmonary fibrosis in the INTEGRIS-IPF study**

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Acknowledgments: Editorial assistance was provided by Alpharmaxim Healthcare Communications and funded by Pliant Therapeutics, Inc.