PK/PD assessment of an oral, selective $\alpha_V\beta_6/\alpha_V\beta_1$ integrin dual antagonist, PLN-74809, for the treatment of idiopathic pulmonary fibrosis

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Rationale

Integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$ are cell surface proteins that bind to and activate latent TGF-β, resulting in Smad phosphorylation and pro-fibrotic gene expression. In IPF, both integrins are upregulated in the lung and are thought to play a role in the development and propagation of fibrosis. We have identified an orally available small molecule inhibitor with equal potency towards $\alpha_V\beta_6$ and $\alpha_V\beta_1$ that prevents integrin-mediated activation of TGF-β.

PLN-74809 has a ligand binding IC_{50} <10 nM for both murine and human $\alpha_V\beta_6$ and $\alpha_V\beta_1$, and an IC_{50} against TGF-β activation of <200 nM, with high selectivity relative to other integrins. Phase 1 studies of PLN-74809 in healthy volunteers have demonstrated good oral bioavailability and tolerability with a $t_{1/2}$ supportive of once daily dosing. When adjusted for plasma protein binding in humans the predicted IC_{50} in plasma is approximately 700 ng/ml.

Inhibition of $\alpha_V\beta_6$-mediated TGF-β activation in the lung can be detected through measurement of Smad phosphorylation in alveolar macrophages. In healthy and fibrotic animals, oral dosing with PLN-74809 resulted in a time- and dose-dependent inhibition of Smad phosphorylation in alveolar macrophages and lung tissue reflecting a reduction in TGF-β signaling. Moreover in bleomycin treated mice inhibition of Smad phosphorylation correlated with reduction in fibrosis.

SEE POSTER #PA1286 FOR DETAILED DESCRIPTION OF THE PRECLNICAL PHARMACOLOGY

Methods

Multiple ascending dose study was a randomized, double-blind, ascending dose, placebo-controlled, multiple dose study (14 days) in 3 cohorts. Cohorts (9 PLN-74809- and 2 placebo-treated participants per cohort) received multiple oral doses of study drug (PLN-74809 or matching placebo) under fasting conditions as an oral solution. Participants received 10 mg, 20 mg and 40 mg PLN-74809 once daily (QD) for 14 days.

Pharmacodynamic study was a randomized, double-blind, placebo-controlled, multiple dose study (7 days) in 4 cohorts. Cohorts (3 PLN-74809- and 1 placebo-treated participants per cohort) received multiple oral doses of study drug (PLN-74809 or matching placebo) under fasting conditions as an oral solution. Participants received 20 mg and 40 mg PLN-74809 once daily (QD) for 7 days. A sample of bronchiolar lavage (BAL) fluid was collected prior to dosing and then at 3 and 12 or 6 and 24 hours following the last dose of PLN-74809. Cells were isolated by centrifugation and immediately frozen. Smad phosphorylation was measured in BAL cell lysate as the ratio of phosphorylated Smad2 (pSmad) to total Smad2 by immunoassay. Reduction in pSmad was calculated as pSmad2/Smad2 following treatment relative to pSmad2/Smad2 measured at baseline.

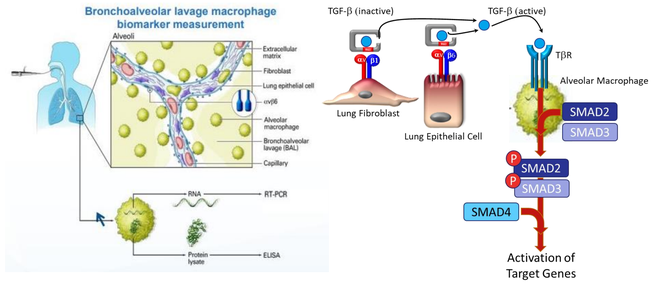
Results

1) Integrin $\alpha_V\beta_6$ and $\alpha_V\beta_1$ were present at elevated levels in fibrotic human and mouse lung tissue.
2) pSMAD levels are highly correlated with collagen levels in normal and fibrotic lungs and modulated by PLN-74809 in animal models.
3) Phase 1 studies of PLN-74809 in healthy volunteers demonstrated good oral bioavailability, tolerability and pharmacokinetics.
4) PLN-74809 inhibited Smad phosphorylation in an exposure and time dependent manner.

Conclusion

PLN-74809 was well-tolerated in healthy participants and inhibited TGF-β activation in alveolar macrophages.

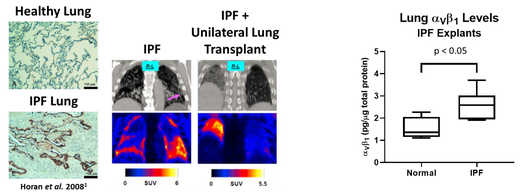
$\alpha_V\beta_6$ Activates Latent TGF-β in Alveolar Epithelial Cells Resulting in Smad Phosphorylation in the Resident Macrophages



1 TGF-β Activating Integrins $\alpha_V\beta_6$ and $\alpha_V\beta_1$ are Present at Elevated Levels in Fibrotic Lung Tissue

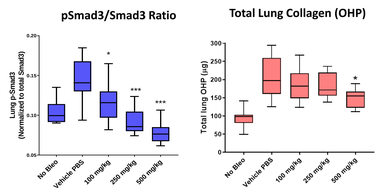
IHC staining and PET imaging show elevated $\alpha_V\beta_6$ levels in IPF lung tissue

ELISA-based assay shows elevated $\alpha_V\beta_1$ levels in IPF lung tissue



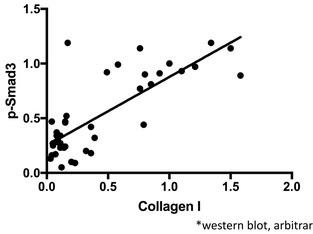
2 Smad Phosphorylation Correlates with Collagen in Fibrotic Lungs

Dual $\alpha_V\beta_6/\alpha_V\beta_1$ inhibition with PLN-74809 significantly and dose-dependently reduced pSmad3/Smad3 ratio and OHP deposition in bleo-injured mouse lungs



Correlation between pSmad/Smad levels[a] and soluble collagen in lung biopsies take from patients with suspected IPF and rejected transplant tissue

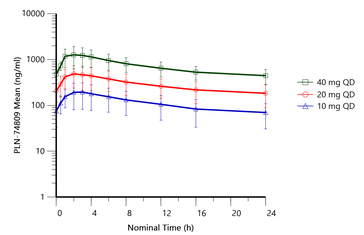
[a]Data courtesy of Hal Chapman lab UCSF



*western blot, arbitrary units

3 Safety Pharmacokinetic Properties of PLN-74809 in Single and Multiple Ascending Dose Studies

Summary PK Curves by Cohort after 14 days Dosing

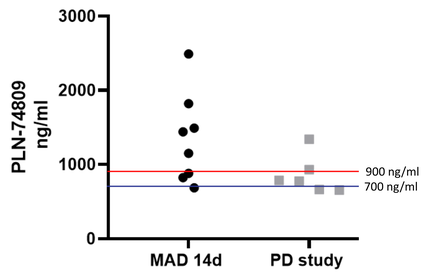


Safety Summary

AE Severity	SAD				MAD			PD (BAL)	
	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)	20 mg (N=6)	40 mg (N=7)
Mild		1	--	1	1	4*	--	2	1
Moderate		1	--	--	--	--	1	--	--
Severe	--	--	--	--	--	--	--	--	--

*1 drug-related AE (epigastric discomfort)

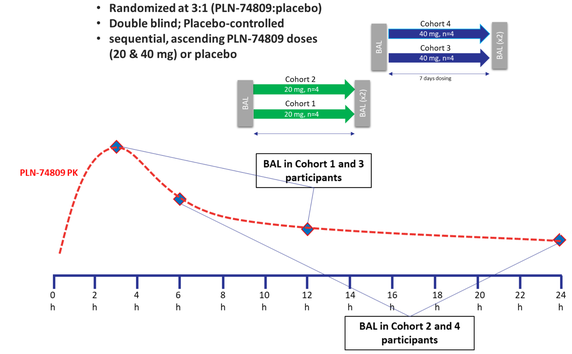
Distribution of Cmax Values 40mg/day



Cmax distribution in subjects receiving PLN-74809 for 7 or 14 days 11/14 subjects achieved clinically effective exposures

4 Pharmacodynamic assessment of PLN-74809 in Healthy Volunteers

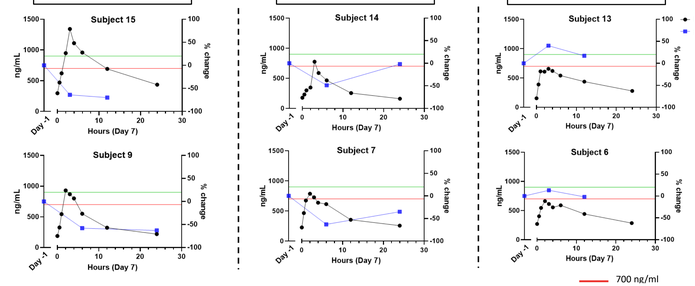
- Randomized at 3:1 (PLN-74809:placebo)
- Double blind; Placebo-controlled
- sequential, ascending PLN-74809 doses (20 & 40 mg) or placebo

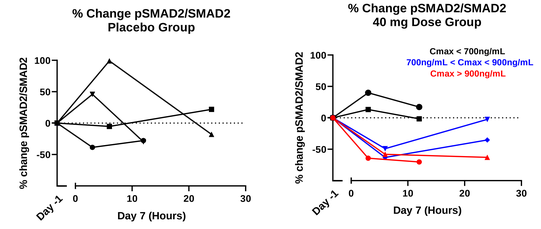


Cmax > 900 ng/mL Sustained PD Effect

Cmax = 700-900 ng/mL Transitory PD Effect

Cmax < 700 ng/mL No PD Effect





Conclusions

- Levels of $\alpha_V\beta_6$ and $\alpha_V\beta_1$, two integrins that activate latent TGF-β through binding to LAP, are increased in fibrotic lung tissue
- PLN-74809 pharmacokinetics are suitable for once daily oral dosing
- PLN-74809 modulates lung epithelial cell $\alpha_V\beta_6$ activity, inhibiting TGF-β signaling in alveolar macrophages in healthy participants
- 79% of subjects receiving repeat 40 mg/day PLN-74809 achieved biologically active exposure levels in Ph1 studies
- Phase 2 studies in IPF participants are ongoing

Key Abbreviations: BALF – Bronchoalveolar Lavage Fluid; OHP,- Hydroxyproline; SAD – Single ascending dose MAD – Multiple ascending dose; PD – Pharmacodynamic; LAP - latency-associated peptide

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