PLN-1474, AN ORAL, SELECTIVE $\alpha_v\beta_1$ INTEGRIN INHIBITOR, IS WELL TOLERATED IN HEALTHY VOLUNTEERS

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All authors are employed by Pliant Therapeutics, Inc., and owned stock at the time of the study

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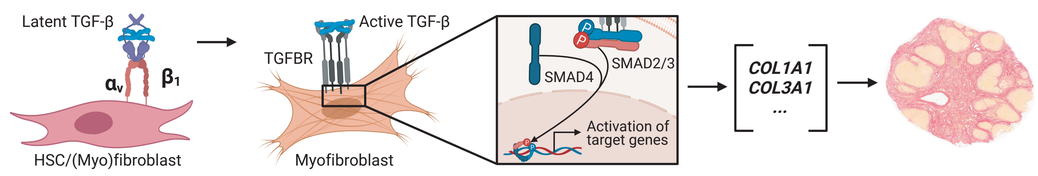
RATIONALE

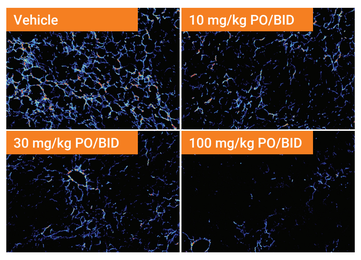
- Integrin $\alpha_v\beta_1$ is expressed on activated hepatic stellate cells and activates transforming growth factor-beta (TGF-β), a key driver of liver fibrosis (**Figure 1**). Integrin $\alpha_v\beta_1$ is upregulated (and downstream TGF-β signaling is increased) in liver samples from human metabolic dysfunction-associated steatohepatitis (MASH) and mouse models of MASH[1]
- PLN-1474 is an oral, selective inhibitor of integrin $\alpha_v\beta_1$ that has demonstrated antifibrotic activity in a mouse model of MASH, as well as in cirrhotic precision-cut liver slices generated from livers of patients with MASH
  - In the choline-deficient, amino-acid defined, high-fat diet murine model of MASH, 6-week therapeutic treatment with PLN-1474 resulted in reduced hepatic fibrosis as measured by second harmonic generation imaging (**Figure 2**)
  - PLN-1474 significantly reduced collagen gene expression (*COL1A1*) in precision-cut liver slices from human MASH liver explants (**Figure 3**)

Figure 1. Role of $\alpha_v\beta_1$ in liver fibrosis



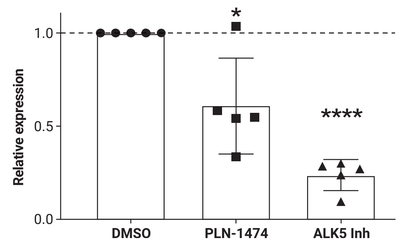
COL1A1, collagen type I alpha 1 chain; *COL3A1*, collagen type III alpha 1 chain; HSC, hepatic stellate cells; SMAD, family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene *Sma*; TGF-β, transforming growth factor-beta; TGFBR, transforming growth factor-beta receptor

Figure 2. Second harmonic generation imaging of hepatic collagen



BID, twice daily; PO, oral

Figure 3. Collagen gene expression (*COL1A1*) in human precision-cut liver slices



*p<0.05; ****p<0.0001
ALK5 Inh, activin receptor-like kinase 5 inhibitor; *COL1A1*, collagen type I alpha 1; DMSO, dimethylsulfoxide

- The aim of this study was to assess the safety, tolerability, and pharmacokinetics (PKs) of PLN-1474 in healthy participants, as well as the effect of food on the PKs of PLN-1474

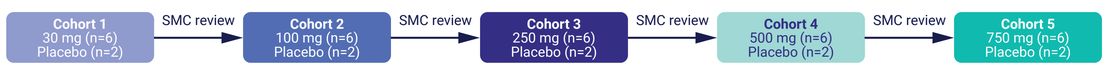
METHODS

Study design

- PLN-1474-101 was a Phase 1, first-in-human, three-part study of PLN-1474 in healthy participants (18–55 years of age)
  - Parts A and B: randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety, tolerability, and PKs of single ascending doses (SADs; **Figure 4a**) and multiple ascending doses (MADs; **Figure 4b**) of PLN-1474 under fasting conditions
  - Part C: randomized, open-label, single-dose (100 mg), two-period (fed-fasted or fasted-fed), crossover study evaluating the effects of food on the PKs of PLN-1474 (schematic not presented)

Figure 4. Dose-escalation schematic

a) Part A, SAD



b) Part B, MAD

BID, twice daily; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose; SMC, safety monitoring committee

Study endpoints

- The safety and tolerability of PLN-1474 were evaluated by adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and dipstick urinalysis), vital sign measurements, electrocardiograms (ECGs), and physical examinations
- Plasma and urine PK parameters of PLN-1474 were calculated by non-compartmental methods

Data sets

- Safety population: all randomized participants who received ≥1 dose of PLN-1474 or placebo
- PK concentration population: all randomized participants who received ≥1 dose of PLN-1474 or placebo and completed ≥1 PK blood draw resulting in ≥1 quantifiable plasma concentration
- PK analysis population: all randomized participants who received a dose of PLN-1474 or placebo on Day 1 and had sufficient PK data for analysis (Parts A and B) or all participants who provided data for both the fasted and fed conditions (Part C)
- Concentration-QT interval analysis population: all participants who received ≥1 dose of PLN-1474 or placebo, had a valid pre-dose and ≥1 post-dose QT/heart rate-corrected QT interval (QTc) measurement, and had a time-matched PK concentration (if receiving PLN-1474)

RESULTS

Participants

- In total, 84 participants were randomized and all received PLN-1474 or placebo
  - Part A, 40 participants; Part B, 32 participants; Part C, 12 participants
- The Baseline characteristics of all participants are shown in **Table 1**; characteristics were well balanced across the different dose levels

Table 1. Baseline demographics

	Part A		Part B		Part C
Characteristic	All PLN-1474 (n=30)	All placebo (n=10)	All PLN-1474 (n=24)	All placebo (n=8)	All PLN-1474 (n=12)
Female, n (%)	10 (33)	5 (50)	8 (33)	1 (13)	3 (25)
Age, mean years (SD)[a]	40.7 (10.42)	42.5 (7.46)	39.0 (10.87)	34.5 (8.49)	40.6 (8.63)
Race, n (%)					
Asian	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Black or African American	3 (10)	1 (10)	3 (13)	0 (0)	0 (0)
Black or African American, American Indian/Alaska Native	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
White	25 (83)	8 (80)	21 (88)	8 (100)	12 (100)
White, Black, or African American	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity, n (%)					
Hispanic or Latino	20 (67)	7 (70)	14 (58)	8 (100)	9 (75)
Not Hispanic or Latino	10 (33)	3 (30)	10 (42)	0 (0)	3 (25)
Weight, mean kg (SD)	76.52 (12.862)	79.32 (9.718)	76.62 (10.603)	78.83 (9.420)	79.80 (12.976)
Height, mean cm (SD)	170.1 (9.39)	170.3 (10.04)	169.7 (10.24)	170.3 (9.78)	171.9 (11.15)
Body mass index, mean kg/m^2 (SD)	26.271 (2.3024)	27.310 (1.9921)	26.567 (2.3331)	27.111 (1.5872)	26.948 (2.7617)

[a]Age is derived from birth date to date of informed consent
SD, standard deviation

Safety and tolerability

- Most treatment-emergent AEs (TEAEs) were mild (Grade 1); none were severe (Grade ≥3)
- There were no discontinuations due to AEs, no deaths, and no serious TEAEs
- Across Parts A, B, and C combined, the most common TEAEs for participants randomized to PLN-1474 were headache (n=5), rash papular (n=3), pruritus (n=2), constipation (n=2), and arthralgia (n=2) (data not presented)
- TEAEs experienced by >1 participant receiving either PLN-1474 or placebo (in each part of the trial) are listed in **Table 2**
  - In Part C, no individual TEAEs were experienced by >1 participant
- There was no dose relationship for TEAEs and no treatment-related trends in clinical laboratory values, vital signs, ECGs, or physical examinations

Table 2. TEAEs experienced by >1 participant – proportion of participants reporting the event

Part A, SAD							
AE, n (%)	30 mg (n=6)	100 mg (n=6)	250 mg (n=6)	500 mg (n=6)	750 mg (n=6)	All PLN-1474 (n=30)	Placebo (n=10)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)
Headache	0 (0)	1 (17)	0 (0)	1 (17)	0 (0)	2 (7)	0 (0)

Part B, MAD						
AE, n (%)	60 mg BID (n=6)	150 mg BID (n=6)	375 mg BID (n=6)	750 mg QD (n=6)	All PLN-1474 (n=24)	Placebo (n=8)
Constipation	0 (0)	1 (17)	1 (17)	0 (0)	2 (8)	0 (0)
Headache	0 (0)	0 (0)	2 (33)	0 (0)	2 (8)	0 (0)
Rash papular	0 (0)	0 (0)	2 (33)	0 (0)	2 (8)	0 (0)

AE, adverse event; BID, twice daily; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose; TEAE, treatment-emergent adverse event

Pharmacokinetics

- PLN-1474 was rapidly absorbed and achieved maximum concentrations within approximately 1 hour of dosing; its mean half-life ranged from approximately 5 to 17 hours (**Table 3** and **Figure 5**)
- Increases in exposure (area under the curve [AUC] and C_{max}) were slightly less than dose proportional
- The geometric mean AUC_{tau} following 375 mg PLN-1474 twice daily (BID; i.e., AUC_{0-12}) was approximately half of the AUC_{tau} following 750 mg PLN-1474 once daily (QD; i.e., AUC_{0-24}), suggesting comparable overall exposure would be expected across a 24-hour period at steady state, regardless of whether a single (750 mg QD) or divided (375 mg BID) dose was administered
- No meaningful effect of food on drug exposure was observed
- Urinary excretion of the drug over a 36-hour sampling period is presented for both single and multiple doses in **Tables 3a** and **3b**, respectively

Table 3. Summary of PLN-1474 PK parameters (PK analysis population) under fasting conditions

a) Following single oral dose (Part A, SAD)[a]

Parameter	30 mg PLN-1474 (n=6)	100 mg PLN-1474 (n=6)	250 mg PLN-1474 (n=6)	500 mg PLN-1474 (n=6)	750 mg PLN-1474 (n=6)
AUC_{last}, h•ng/mL[b]	6722 (26.4)	20420 (24.7)	37210 (20.4)	72810 (15.3)	98270 (26.9)
AUC_{inf}, h•ng/mL[b]	6982 (25.9)	20750 (24.2)	37680 (20.3)	73350 (15.5)	98810 (26.9)
C_{max}, ng/mL[b]	2412 (28.8)	6023 (28.7)	13490 (38.1)	26130 (18.3)	34970 (42.8)
T_{max}, h[c]	0.751 (0.50, 4.00)	0.510 (0.50, 1.00)	0.516 (0.50, 1.01)	0.754 (0.50, 2.00)	1.003 (0.51, 2.00)
$t_{½}$, h[d]	4.967 ± 1.5232 (30.7)	5.533 ± 1.1050 (20.0)	6.346 ± 1.7751 (28.0)	12.172 ± 4.0971 (33.7)	11.928 ± 3.8105 (31.9)
Total f_e, %[d]	33.225 ± 9.5347 (28.7)	31.971 ± 8.1855 (25.6)[e]	33.522 ± 12.5098 (37.3)	39.657 ± 8.9032 (22.5)	36.964 ± 5.2455 (14.2)

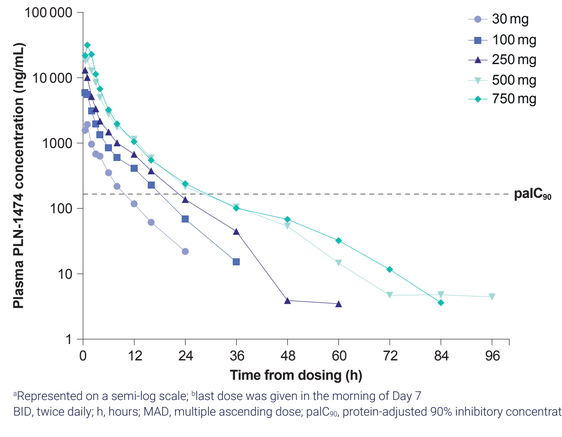
b) Following multiple oral doses (Part B, MAD – Day 7)

Parameter	60 mg PLN-1474 BID[f] (n=6)	150 mg PLN-1474 BID[f] (n=5)[g]	375 mg PLN-1474 BID[f] (n=6)	750 mg PLN-1474 QD (n=6)
AUC_{tau}, h•ng/mL[b]	10560 (20.8)	18890 (34.4)	49560 (18.4)	NC
AUC_{0-24}, h•ng/mL[b]	21120 (20.8)[h]	37780 (34.4)[h]	111540 (18.4)[h]	99310 (32.7)[i]
AUC_{last}, h•ng/mL[b]	11700 (21.9)	22170 (34.1)	61280 (30.1)	103900 (32.4)
$C_{max,ss}$, ng/mL[b]	3915 (12.8)	6383 (31.2)	17210 (53.6)	41860 (38.0)
$T_{max,ss}$, h[c]	1.002 (0.50, 1.01)	0.998 (0.50, 1.00)	0.999 (0.50, 3.00)	0.794 (0.50, 1.00)
$t_{½}$, h[d]	9.400 ± 4.3382 (46.2)	15.523 ± 9.4132 (60.6)	13.712 ± 6.8141 (49.7)	17.384 ± 5.8402 (33.6)
Total f_e, %[d]	28.174 ± 16.3431 (58.0)	37.899 ± 2.6121 (6.9)	42.613 ± 11.8406 (27.8)	17.320 ± 10.9663 (63.3)

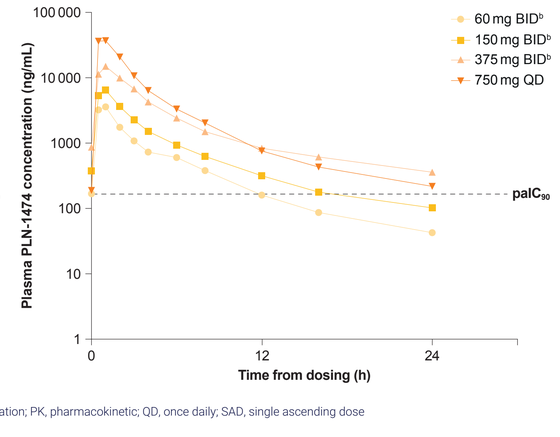
[a]Sampling for PK analysis occurred up to Day 8 following dosing; [b]presented as geometric mean (geometric CV%); [c]presented as median (minimum, maximum); [d]presented as arithmetic mean ± SD (CV%); [e]n=5, as one participant had no quantifiable PLN-1474 concentrations in urine; [f]last dose was given in the morning of Day 7; [g]PK parameters for one participant were excluded due to missing blood collections on Day 1; [h]AUC_{0-24} for BID regimens is estimated as 2 × AUC_{tau}; [i]AUC_{tau} is presented for 750 mg QD
AUC, area under the curve; AUC_{inf}, AUC from 0 hours to infinity; AUC_{last}, AUC from 0 hours to the time of the last measured concentration; AUC_{tau}, AUC from 0 hours to the end of the dosing interval; BID, twice daily; C_{max}, maximum concentration; CV%, coefficient of variation; f_e, fraction of the drug excreted unchanged in urine; h, hours; MAD, multiple ascending dose; NC, not calculated; PK, pharmacokinetic; QD, once daily; SAD, single ascending dose; SD, standard deviation; ss, steady state; $t_{½}$, half-life; T_{max}, time to maximum concentration

Figure 5. Arithmetic mean plasma PLN-1474 concentration vs. time profiles (PK concentration population)

a) Following single oral doses (Part A, SAD)[a]



b) Following multiple oral doses for 7 days (Part B, MAD – Day 7)[a]



[a]Represented on a semi-log scale; [b]last dose was given in the morning of Day 7
BID, twice daily; h, hours; MAD, multiple ascending dose; $palC_{90}$, protein-adjusted 90% inhibitory concentration; PK, pharmacokinetic; QD, once daily; SAD, single ascending dose

Concentration-QTc

- Concentration-QTc analysis demonstrated no effect of PLN-1474 on QTc using Fridericia's method (QTcF)

CONCLUSIONS

- PLN-1474 is a novel selective $\alpha_v\beta_1$ integrin inhibitor that was readily absorbed and well tolerated in healthy participants following single and multiple oral doses up to 750 mg per day
- Findings from this first-in-human study warrant the evaluation of PLN-1474 in patients with MASH and advanced liver fibrosis

Reference: 1. Schaub J, et al. *J Hepatol* 2016;70(Suppl 1S):e45–e80. Abstract PS-091

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