A Phase 1 Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of the Oral Integrin Antagonist IDL-2965 in Healthy Volunteers

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Background and Methods

Background and Study Objectives

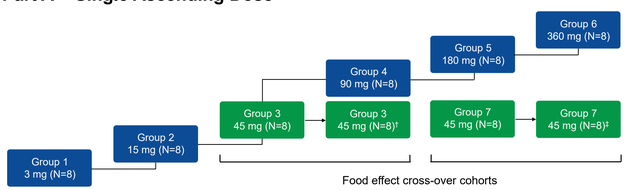
- IDL-2965 is an orally bioavailable small molecule antagonist of the integrins αvβ1, αvβ3, and αvβ6 currently under development for the treatment of serious fibrotic diseases including interstitial lung diseases and nonalcoholic steatohepatitis.
- Integrins are heterodimeric transmembrane proteins that mediate cell-cell and cell-matrix interactions. The integrins αvβ1 and αvβ6 are expressed on fibroblasts and epithelial cells, respectively, and modulate TGF-β activation; αvβ3 is expressed on fibroblasts and mediates fibroblast migration across extracellular matrix and promotes integrin-mediated myofibroblast survival.
- In animal models, low-dose IDL-2965 administered once daily exhibits potent antifibrotic effects across a range of vital organs, including the lung, liver, and kidney.
- The aim of the present study was to evaluate the safety, pharmacokinetics, and pharmacodynamics of IDL-2965 in healthy adult volunteers and patients with idiopathic pulmonary fibrosis (IPF).

Methods

- The randomized, double-blind, placebo-controlled, adaptive study is comprised of three parts: a single ascending dose study in healthy volunteers (Part A), a 14-day multiple ascending dose study in patients with IPF (Part C). Parts A and B were conducted in a clinical research unit, with subjects confined for 3 and 16 days, respectively. In each part, study subjects were randomized in a 3:1 ratio to receive oral IDL-2965 or placebo.
- In Part A, study drug was administered in the fasted state in seven sequential dose groups. The 3 mg starting dose was selected based on the minimum effective exposure according to the Ashcroft histology score in the bleomycin mouse model of lung fibrosis, equivalent to a human free-fraction normalized steady-state $AUC_{0\text{-}24}$ of 204 ng•h/mL.
  - In two dose groups, a second dose of study drug was administered ≥7 days after the first dose to evaluate the effect of food intake (high-fat meal 30 minutes pre-dose in group 3 and one hour post-dose in group 7).
- In Part B, study drug was administered in the fasted state and one hour before a light breakfast in three sequential dose groups.
- Results from Parts A and B are reported here; Part C is ongoing.

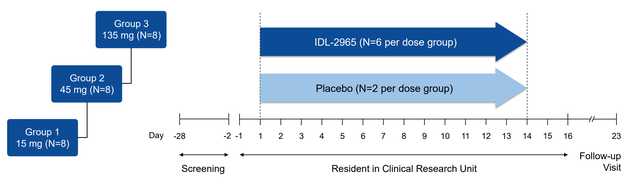
Study Design

Part A—Single Ascending Dose*



*Subjects in each group randomized in a 3:1 ratio to receive IDL-2965 or placebo. †Administered 30 minutes after a high-fat meal. ‡Administered one hour prior to a high-fat meal.

Part B—Multiple Ascending Dose*



*Study drug administered in the fasted state and one hour prior to a light breakfast.

Part A—Single Ascending Dose

Treatment-emergent Adverse Events

Subjects, n (%)	Pooled placebo (N=14)	IDL-2965 Total (N=42)	3 mg fasted (N=6)	15 mg fasted (N=6)	45 mg fasted (N=6)*	45 mg fed (N=6)*†	45 mg fasted (N=6)‡	45 mg fed (N=6)†¶	90 mg fasted (N=6)	180 mg fasted (N=6)	360 mg fasted (N=6)
Any TEAE	**8 (57.1)**	**17 (40.5)**	**2 (33.3)**	**0**	**3 (50.0)**	**2 (33.3)**	**4 (66.7)**	**1 (16.7)**	**2 (33.3)**	**3 (50.0)**	**2 (33.3)**
Mild	6 (42.9)	14 (33.3)	1 (16.7)	0	2 (33.3)	2 (33.3)	4 (66.7)	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)
Moderate	2 (14.3)	3 (7.1)	1 (16.7)	0	1 (16.7)	0	0	0	1 (16.7)	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Any serious TEAE	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
TEAE, preferred term‡											
Headache	5 (35.7)	4 (9.5)	0	0	2 (33.3)	0	1 (16.7)	0	1 (16.7)	0	0
Decreased appetite	2 (14.3)	3 (7.1)	0	0	0	1 (16.7)	0	0	0	2 (33.3)	0
Dizziness	1 (7.1)	5 (11.9)	0	0	1 (16.7)	0	2 (33.3)	0	0	1 (16.7)	1 (16.7)§
Medical device site rash	1 (7.1)	3 (7.1)	0	0	0	0	3 (50.0)	0	0	0	0
Nausea	1 (7.1)	3 (7.1)	0	0	2 (33.3)	0	0	1 (16.7)	0	0	0
Pain in extremity	0	2 (4.8)	1 (16.7)	0	0	0	0	0	0	0	1 (16.7)
Somnolence	1 (7.1)	1 (2.4)	0	0	1 (16.7)	0	0	0	0	0	0
Vomiting	0	2 (4.8)	0	0	1 (16.7)	1 (16.7)	0	0	0	0	0

*Group A3. †Subjects fed 30 minutes pre-dose. ‡Group A7. §Subjects fed one hour post-dose. ¶Occurring in >1 subject. ‡Preferred term of postural dizziness. TEAE=treatment-emergent adverse event.

- Treatment-emergent adverse events occurred in 8/14 (57.1%) subjects receiving placebo and 17/42 (40.5%) subjects who received IDL-2965. Most adverse events were mild; there were no severe or serious adverse events and no treatment discontinuations.
- No clinically significant abnormalities in vital signs, laboratory tests, or ECG findings were observed, with the exception of one subject in the 360 mg dose group that experienced transient postural dizziness accompanied by a modest reduction in orthostatic blood pressure.

Pharmacokinetic Profile—Single Dose Fasted Cohorts

Geometric mean (%CV)	3 mg	15 mg	45 mg*	45 mg†	90 mg	180 mg	360 mg
$AUC_{0\text{-}24}$, ng•h/mL	372 (36.1)	2800 (38.9)	7520 (26.8)	6970 (25.3)	12200 (26.8)	23800 (10.3)	41800 (36.2)
$AUC_{0\text{-}inf}$, ng•h/mL	1300 (68.2)	7630 (43.4)	19200 (42.4)	18200 (18.3)	26800 (47.4)	57200 (20.3)	102000 (46.8)
C_{max}, ng/mL	19.9 (36.3)	149 (40.1)	395 (26.6)	369 (27.8)	638 (31.5)	1210 (10.4)	2160 (34.5)
$T_{½}$, hr	42.2 (44.9)	21.3 (14.6)	24.4 (58.3)	23.0 (41.6)	17.9 (30.7)	17.5 (8.81)	18.8 (19.5)

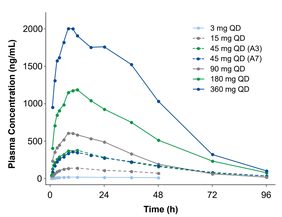
*Group A3. †Group A7. CV=Coefficient of variation.

Food Effect

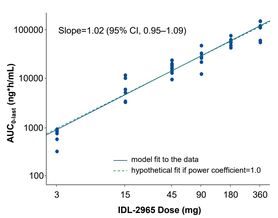
Parameter*	High-fat meal 30 minutes pre-dose (45 mg QD)†			High-fat meal 1 hour post-dose (45 mg QD)‡		
	Fed	Fasted	Ratio, fed/fasted (90%CI)	Fed	Fasted	Ratio, fed/fasted (90%CI)
$AUC_{0\text{-}inf}$, ng•h/mL	13300	19200	0.69 (0.62–0.77)	17400	18200	0.96 (0.85–1.08)
C_{max}, ng/mL	229	395	0.58 (0.52–0.65)	289	369	0.79 (0.68–0.91)
Median T_{max}, h (range)	24 (24–24)	8 (3–12)	–	12 (8–36)	10 (4–24)	–

*Data presented as the geometric mean unless otherwise specified. †Group A3 (fed dose administered ≥7 days after fasted dose). ‡Group A7 (fed dose administered ≥7 days after fasted dose).

Mean Plasma Concentration



Dose Proportionality



- Oral IDL-2965 achieved robust plasma exposures over a 120-fold range of doses.
- Pharmacokinetics were dose-proportional and the mean half-life was supportive of once-daily dosing.
- Food intake 30 minutes prior to dosing modestly reduced C_{max} and $AUC_{0\text{–}Inf}$; food intake one hour post-dose had no meaningful effect on exposure.

Part B—Multiple Ascending Dose (14-day Dosing)

Treatment-emergent Adverse Events

Subjects, n (%)	Placebo (N=6)	IDL-2965 Total (N=18)	15 mg (N=6)	45 mg (N=6)	135 mg (N=6)
Any TEAE	**2 (33.3)**	**4 (22.2)**	**1 (16.7)**	**0**	**3 (50.0)**
Mild	1 (16.7)	4 (22.2)	1 (16.7)	0	3 (50.0)
Moderate	1 (16.7)	0	0	0	0
Severe	0	0	0	0	0
Any serious TEAE	**0**	**0**	**0**	**0**	**0**
Treatment discontinuation	**0**	**0**	**0**	**0**	**0**
TEAE, preferred term					
Headache	1 (16.7%)	0	0	0	0
Medical device site rash	0	1 (5.6%)	0	0	1 (16.7%)
Pain in extremity	1 (16.7%)	0	0	0	0
Arthropod bite	0	1 (5.6%)	1 (16.7%)	0	0
Dermatitis contact	0	1 (5.6%)	0	0	1 (16.7%)
Nasopharyngitis	0	1 (5.6)	0	0	1 (16.7%)
Myalgia	1 (16.7%)	0	0	0	0
Sneezing	0	1 (5.6%)	0	0	1 (16.7%)

TEAE=treatment-emergent adverse event.

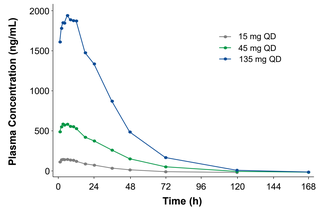
- Treatment-emergent adverse events occurred in 2/6 (33.3%) subjects in the pooled placebo group and 4/18 (22.2%) subjects in the pooled IDL-2965 group with 14 days of treatment.
- All adverse events in subjects receiving IDL-2965 were mild; there were no moderate, severe, or serious adverse events, no treatment-related adverse events, and no adverse events leading to treatment discontinuation.
- No clinically significant abnormalities in vital signs, laboratory tests, or ECG findings were observed with 14 days of dosing.

Pharmacokinetic Profile—Multiple Dose Cohort

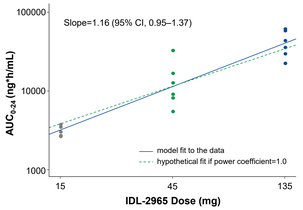
Parameter (%CV)	15 mg*		45 mg		135 mg	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
$AUC_{0\text{-}24}$, ng•h/mL	1590 (24.2)	3170 (15.4)	5370 (39.2)	12200 (69.3)	16100 (40.0)	40400 (40.8)
C_{max}, ng/mL	87.3 (26.8)	172 (20.2)	299 (37.3)	642 (62.4)	848 (40.0)	2040 (39.0)
$C_{24\ h}$, ng/mL	53.0 (21.3)	94.0 (14.6)	177 (64.3)	397 (79.4)	657 (51.9)	1360 (54.7)
$T_{½}$, h	21.3 (16.3)	15.6 (3.41)	18.7 (49.4)	21.2 (34.8)	28.2 (50.5)	19.5 (13.2)

*Excludes one subject who was not evaluable for pharmacokinetic analyses.

Mean Plasma Concentration (Day 14)



Dose Proportionality (Day 14)



- Robust steady-state plasma exposures, including mean $AUC_{0\text{-}24}$ and 24-hour trough concentrations, were achieved with QD oral administration of IDL-2965.
- Pharmacokinetics were dose proportional.
- The mean half-life ranged from 15.6 to 21.2 hours at steady state, supporting a QD dosing schedule.

Conclusions

- Once-daily oral administration of the integrin antagonist IDL-2965 to healthy adults for up to 14 days was safe and well tolerated. The proportion of subjects experiencing treatment-emergent adverse events was lower in those receiving IDL-2965 than placebo in both the single and multiple dose studies. There were no severe or serious adverse events, no treatment discontinuations, and no drug- or dose-related trends in adverse events, vital signs, laboratory tests, or ECG findings.
- Robust dose-proportional plasma concentrations were achieved following oral administration of doses ranging from 3 mg to 360 mg. Steady-state $AUC_{0\text{-}24}$ values markedly exceeded the minimum effective exposure in the bleomycin model of lung fibrosis used to set the starting dose. The observed half-life of approximately 20 hours supports a once-daily dosing schedule.
- These encouraging findings support further evaluation of IDL-2965 in multiple indications, including an ongoing biomarker-driven multiple ascending dose study in patients with IPF.