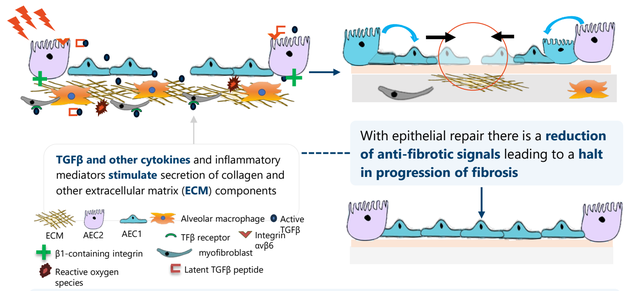
Results from Phase 1, Randomized, Double-blind, Single and Multiple Ascending Dose Studies Characterizing the PK, Safety and Tolerability of ORJ-001, a Selective β1 Integrin Agonist Peptide in Healthy Volunteers.

Poster Board Number: 405

Introduction

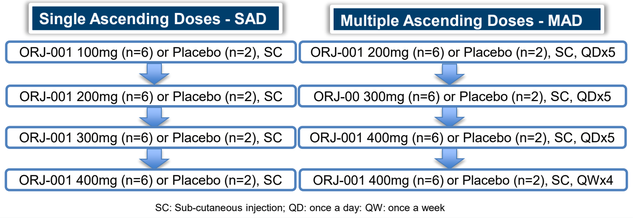
Repeated injury to alveolar epithelial cells (AECs) and abnormal repair responses may be key triggers of idiopathic pulmonary fibrosis. Demonstration that β1 integrin-deficient AECs induce inflammation and lung tissue destruction, suggests a critical role for β1 integrin in alveolar homeostasis in the lung. In the therapeutic bleomycin model of pulmonary fibrosis, ORJ-001, a β1 integrin agonist peptide for subcutaneous injection, showed reduction in established lung fibrosis and regeneration of alveolar epithelium, providing scientific basis to initiate development of ORJ-001 as a treatment for IPF. In 4-week toxicology studies, the No Observed Adverse Effect Level (NOAEL) was 500mg/kg/day and 200mg/kg/day in mice and monkeys, respectively.

Proposed mechanism of action of ORJ-001 in IPF



Integrin **agonism increases FAK signaling to restores the function of AEC2 to differentiate into AEC1** and to **promote repair of alveoli**, demonstrated by tight junction protein expression and proliferation of AEC1. By repairing the damage to the epithelium, pro-inflammatory and pro-fibrotic signals decrease.

Study Schematics



SC: Sub-cutaneous injection; QD: once a day. QW: once a week

Study Design

Doses were chosen based on Human Equivalent Dose (HED) of the Pharmacologically Active Dose (PAD) range in the bleomycin model of pulmonary fibrosis.
The first block in each dose group consisted of 2 sentinel participants; 1 received ORJ-001 and the other received placebo. The second block, scheduled 24h (SAD) or 5 days (MAD) after the sentinel dosing, consisted of the remaining 6 participants: ORJ-001 (n = 5) or placebo (n = 1).
Dose escalation was determined by the Safety Review Committee following review of at least 2 weeks (SAD) or 6 days (MAD) of safety data at least 48 hours of PK data from the preceding dose group.
Safety assessments included analyses of adverse events, laboratory tests, vital signs, electrocardiograms and presence of anti-drug antibodies (ADA). The pharmacokinetic profile of ORJ-001 was assessed at multiple timepoints up to 12 hours post-dose.
The studies were conducted in a single center in Australia, by Novotech CRO.

Results

Table 1. Baseline characteristics- SAD

	ORJ-001					Placebo	Overall
	100mg n=6	200mg n=6	300mg n=6	400mg n=6	Pooled n=24	n=8	N=32
Mean Age (years)±SD	33.5±14.8	30.7±14.8	26.5±9.8	33.8±8.9	31.1±11.9	29.8±9.7	30.8±11.3
Sex n(%):							
Female	4 (66.7)	1 (16.7)	1 (16.7)	2 (33.3)	8 (33.3)	3 (37.5)	11 (34.4)
Male	2 (33.3)	5 (83.3)	5 (83.3)	4 (66.7)	16 (66.7)	5 (62.5)	21 (65.6)
Race n(%):							
Asian	2(33.3)	1 (16.7)	2 (33.3)	2 (33.3)	7 (29.2)	4 (50)	11 (34.4)
White	3 (50.0)	4 (66.7)	4 (66.7)	4 (66.7)	15 (62.5)	4 (50)	19 (59.4)
Other	1 (16.7)	1 (16.7)	0	0	2 (8.3)	0	2 (6.3)
Mean BMI (kg/m²)±SD	24.75±4.50	25.32±3.65	23.08±2.53	25.68±3.50	24.71±3.52	25.24±3.20	24.84±3.40

Table 2. Summary of Treatment-Emergent Adverse Events - SAD

	ORJ-001					Placebo	Overall
	100mg N=6 n (%)	200mg N=6 n (%)	300mg N=6 n (%)	400mg N=6 n (%)	Pooled N=24 n (%)	N=8 n (%)	N=32 n (%)
Number of Participants Reporting at least one:							
TEAE	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	5 (62.5)	29 (90.6)
Serious TEAE	0	0	0	0	0	0	0
Severe (≥ Grade 3)	0	0	0	1 (16.7)	1 (4.2)	0	1 (3.1)
TEAE related to study drug	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	5 (62.5)	0
TEAE leading to study drug discontinuation	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0

The most commonly reported TEAEs by SOC were General disorders and administration site conditions of which there were 53 events in 24/24 (100%) ORJ-001 participants and 6 events in 5/8 (62.5%) participants in placebo group. The most common by PT were:
- Injection site erythema: 22/24 (91.7%) ORJ-001 groups and none in placebo.
- Injection site pain: 12/24 (50.0%) ORJ-001 groups and 4/8 (50.0%) in placebo.
- Injection site pruritus: 8/24 (33.3%) ORJ-001 groups and none in placebo.
- Injection site oedema: 7/24 (29.2%) ORJ-001 groups and none in placebo.

The remaining events occurred in < 10% of participants.

Table 3. Baseline characteristics- MAD

	ORJ-001					Placebo	Overall
	200mg n=7	300mg n=6	400mg 5D n=6	400mg 4W n=6	Pooled n=25	n=8	n=33
Mean Age (years)±SD	30.3±11.8	32.8±7.4	29.5±4.0	43.2±12.3	33.8±10.6	33.4±9.4	33.7±10.2
Sex n(%):							
Female	4 (57.1)	3 (50.0)	3 (50.0)	3 (50.0)	13 (52.0)	3 (37.5)	11 (34.4)
Male	2 (42.9)	3 (50.0)	3 (50.0)	3 (50.0)	12 (48.0)	5 (62.5)	21 (65.6)
Race n(%):							
American Indian or Alaska Native	0	0	1 (16.7)	0	1 (4.0)	0	1 (3.0)
Asian	1(14.3)	2 (33.3)	2 (33.3)	1 (16.7)	6 (24.0)	1 (12.5)	7 (21.2)
Black	1 (14.3)	1 (16.7)	1 (16.7)	0	3 (12.0)	0	3 (9.1)
White	5 (71.4)	3 (50.0)	2 (33.3)	5 (83.3)	15 (60.0)	7 (87.5%)	22 (66.7)
Mean BMI (kg/m²)±SD	22.56±3.00	26.27±4.04	27.80±3.48	26.90±2.45	25.75±3.72	25.55±3.60	25.70±3.64

Table 4. Summary of Treatment-Emergent Adverse Events - MAD

	ORJ-001					Placebo	Overall
	200mg N=7 n (%)	300mg N=6 n (%)	400mg 5D N=6 n (%)	400mg QW N=6 n (%)	Pooled N=25 n (%)	N=8 n (%)	N=33 n (%)
Number of Participants Reporting at least one:							
TEAE	7 (100)	5 (83.3)	6 (100)	6 (100)	24 (96)	6 (75.0)	30 (90.9)
Serious TEAE	0	0	0	0	0	0	0
Severe (≥ Grade 3)	0	0	0	0	0	0	0
TEAE related to study drug	7 (100)	5 (83.3)	6 (100)	6 (100)	24 (96)	5 (62.5)	29 (87.9)
TEAE related to Injection Site Reactions	7 (100)	5 (83.3)	6 (100)	6 (100)	24 (96)	5 (62.5)	29 (87.9)
TEAE leading to study drug discontinuation	2 (28.6)	0	0	0	2 (8.0)	0	2 (6.1)
TEAE leading to death	0	0	0	0	0	0	0

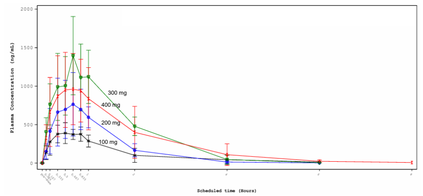
Of theTEAEs **not associated with Injection Site Reactions** (ISRs), the most common reported TEAEs by PT were headache (28% and 25% in ORJ-001 and placebo participants, respectively), followed by vascular access site pain (16.0% and 25% ORJ-001 and placebo participants, respectively), nausea (8.0% participants on ORJ-001) and flushing (8.0% participants on ORJ-001). All other TEAEs by PT occurred in only 1 participant each.

Summary of Pharmacokinetic and Immunogenicity Results

- ORJ-001 and a single metabolite (M1) rapidly appeared in the systemic circulation at the earliest calculated timepoint of 5 -10 minutes.
- Maximum plasma concentrations ($C_{max,l}$) of ORJ-001 occurred between 40 minutes and 1 hour post dose, after which ORJ-001 plasma concentrations declined rapidly in a monophasic manner, with an apparent terminal elimination half-life ($t_{1/2}$) ranging from 0.440 to 0.595 hours.
- Median T_{max} and mean $t_{1/2}$ values were similar across the dose range in both analytes.
- Exposure to ORJ-001 (C_{max} and AUC) increased with increasing dose, albeit Cohort SAD 400mg and MAD 300 mg showed lower AUC and C_{max} compared to other doses; the inter patient variability detected is likely owing to the small sample size within the cohorts.
- ADA assays demonstrated negative results for all participants.

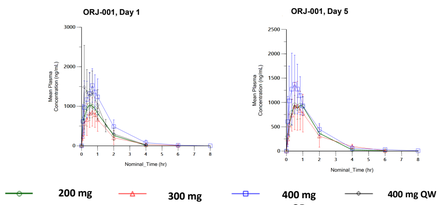
Pharmacokinetics

SAD: Mean ± SD Plasma ORJ-001 Concentrations

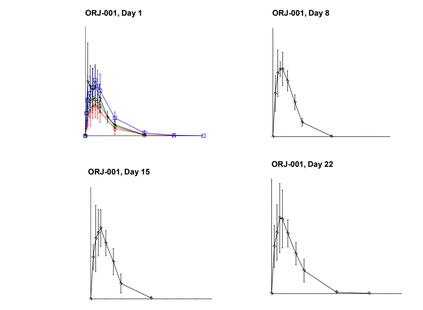


MAD: Mean ± SD Plasma ORJ-001 Concentrations

Daily dosing cohorts, 5 days



Weekly dosing cohort, 4 weeks



Dose estimation for Phase 2

A Physiologically-Based Pharmacokinetic (PBPK) model compared the plasma concentrations in mice (PAD range) and in human healthy volunteers (SAD + MAD)
Exposures in the PAD in mice are achievable in humans in the dose range between 200 mg and 400 mg.

PAD mice (mg/kg)	AUC mean (h*ng/mL)	Estimated HED (60kg human)	Dose in SAD and MAD (mg)	Calculated AUC (h*ng/mL)
30	6.8	146 mg (2.44 mg/kg)	200	15.6
60	17.2	293 mg (4.9 mg/kg)	300	32.0
90	29.7	439 mg (7.3 mg/kg)	400	27.0

Conclusions:

ORJ-001 was well tolerated in Human healthy volunteers
Exposures in the efficacy range in the bleomycin model of pulmonary fibrosis are achievable in humans in the dose tested in the Phase 1, justifying dose selection for future studies in IPF.

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