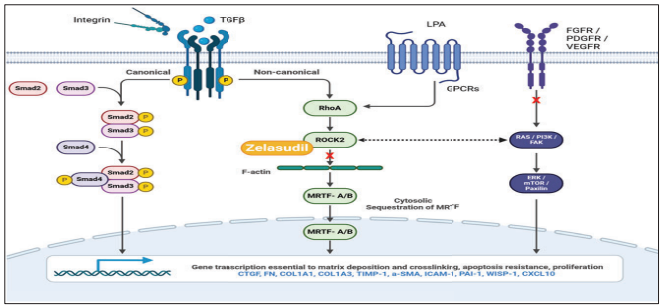
Phase 2a signal searching study with zelasudil in idiopathic pulmonary fibrosis (IPF)

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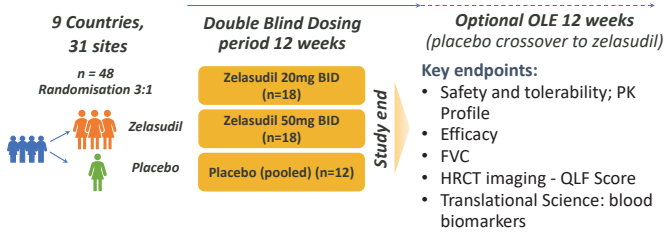
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Introduction and Potential of selective ROCK2 inhibition

IPF has a poor prognosis, with an average life expectancy of only 3 to 4 years in patients not receiving antifibrotic therapy[1,2]. The median survival of patients with IPF who experience an acute exacerbation is only approximately 3 to 4 months[3]. Therefore, new treatments are needed to reduce or reverse fibrosis, improve outcomes and provide better quality of life for IPF patients. Rho-Coiled kinase (ROCK) sits at a nodal position in antifibrotic signaling pathways. Pan-ROCK inhibition shows robust anti-fibrotic activity in preclinical models but use of this is hampered systemically by hypotension. Selective inhibition of ROCK2 alone is sufficient to drive anti-fibrotic efficacy in multiple preclinical fibrosis models and holds great treatment potential in fibrotic disease. Here we present data from a Phase 2a study in patients with IPF.



Phase 2a Study to Assess Initial Efficacy in IPF patients



Key endpoints:

- Safety and tolerability; PK Profile
- Efficacy
- FVC
- HRCT imaging - QLF Score
- Translational Science: blood biomarkers

Each dose cohort includes patients on background pirfenidone and nintedanib as well as monotherapy zelasudil

NCT05570058 - Study Details | Assess the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of RXC007 in Idiopathic Pulmonary Fibrosis | ClinicalTrials.gov

Baseline Demographics and Disease Characteristics Similar Across Treatment Groups

	RXC007 20mg BID N=18	RXC007 50mg BID N=18	Overall Placebo N=12
Age (years)			
- Mean	69.4	69.0	70.8
- Min/Max	56, 78	57, 78	60, 79
Gender			
- Male (n, %)	15 (83.3)	15 (83.3)	7 (58.3)
- Female (n, %)	3 (16.7)	3 (16.7)	5 (41.7)
BMI (kg/m²)			
- Mean	29.531	28.327	27.489
- Min/Max	26.06, 40.29	24.28, 35.79	21.07, 31.94

Full Analysis Set, N=48	RXC007 20mg BID N=18	RXC007 50mg BID N=18	Overall Placebo N=12
FVC (mL)			
- Mean	2980.4	3176.5	2813.6
- Median	3049.0	3378.0	2911.5
- Range	1667-4508	1531-4161	1456-4580
- % predicted, mean	80.4	83.4	79.9
DLCO			
• Mean	4.18	4.25	4.27
• Median	4.26	4.31	3.97
• Range	2.60-6.79	1.99-6.73	2.31-8.23
Background antifibrotic			
- None, n (%)	7 (38.9)	5 (27.8)	4 (33.3)
- Nintedanib, n (%)	6 (33.3)	9 (50.0)	4 (33.3)
- Pirfenidone, n (%)	5 (27.8)	4 (22.2)	4 (33.3)

- All patients were white
- There were no women of child-bearing potential

Zelasudil is Well Tolerated With and Without Background Antifibrotic Therapy

All patients: Main study, N=48	Overall RXC007 12 weeks N = 36 n (%) E	Overall Placebo 12 weeks N=12 n (%) E
Any TEAE	30 (83.3) 122	7 (58.3) 50
Any TREAE	13 (36.1) 28	5 (41.7) 20
Any SAE	1 (2.8) 2	0
Any treatment related SAE	0	0
Any TEAE leading to discontinuation	6 (16.7) 10	0
Any TREAE leading to discontinuation	5 (13.9) 9	0
Any TEAE leading to interruption	5 (13.9) 10	1 (8.3) 2
Any TREAE leading to interruption	5 (13.9) 7	1 (8.3) 2

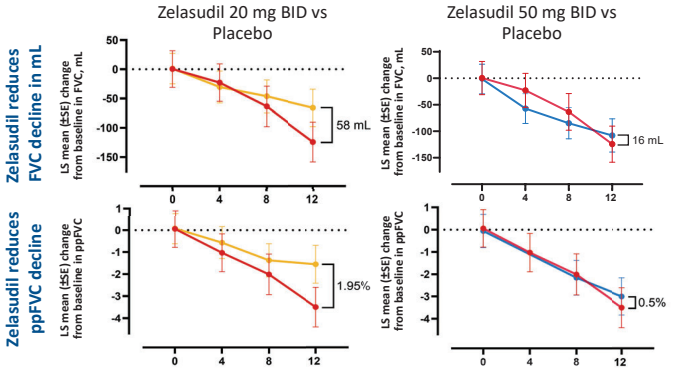
Common TREAE (≥2 patients) summary	Main Study		
	20mg BID (12 weeks on drug) N=18	50mg BID (12 weeks on drug) N=18	Placebo N=12
Abdominal pain upper	0	0	2 (16.7%)
ALT increased*	2 (11.1%)	3 (16.7%)	0
AST increased*	2 (11.1%)	3 (16.7%)	0

- No deaths or treatment related SAEs
- No hypotension or GI signal
- No differences in safety by dose, duration of treatment (12 / 24 weeks) or background therapy
- Most common TREAE asymptomatic ALT/AST increases
  - No associated bilirubin increases
  - Reversible on treatment interruption
  - No Hy's Law cases

Main Conclusions

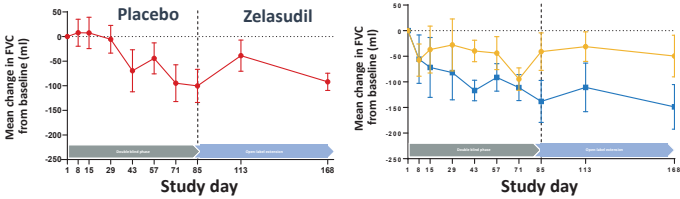
- Zelasudil is a best-in-class ROCK 2 inhibitor
- Zelasudil is well tolerated both with and without background antifibrotic therapy
- Further investigation in IPF / ILD is warranted

Zelasudil Reduces FVC Decline Numerically at 12 Weeks in IPF Patients



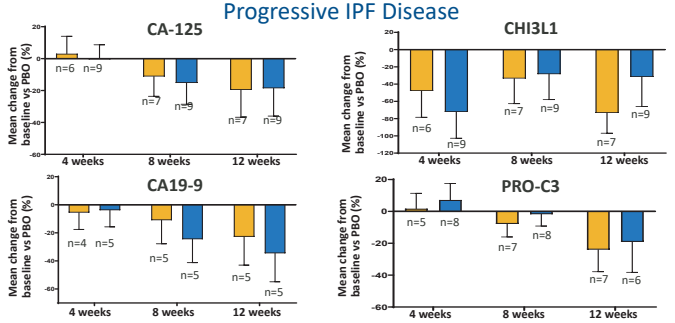
Efficacy evaluable data set (46 patients; 50mg=17, 20mg=17, pbo=12)

OLE: Lung Function Stabilised in Placebo Patients who Switch to Zelasudil, with Patients Continuing to Benefit from Zelasudil for Entire 6-month Treatment Period



Δ values are mean FVC change from baseline

Zelasudil Reduces Circulating Markers Associated with Progressive IPF Disease



Data is mean ± SEM. Cohort: background therapy. CA19-9: only patients with CA19-9 detectable at baseline included.

1. Maher, 2019. 2. Strek 2019, 3. Collard, 2016.

Placebo
20mg Zelasudil
50mg Zelasudil