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

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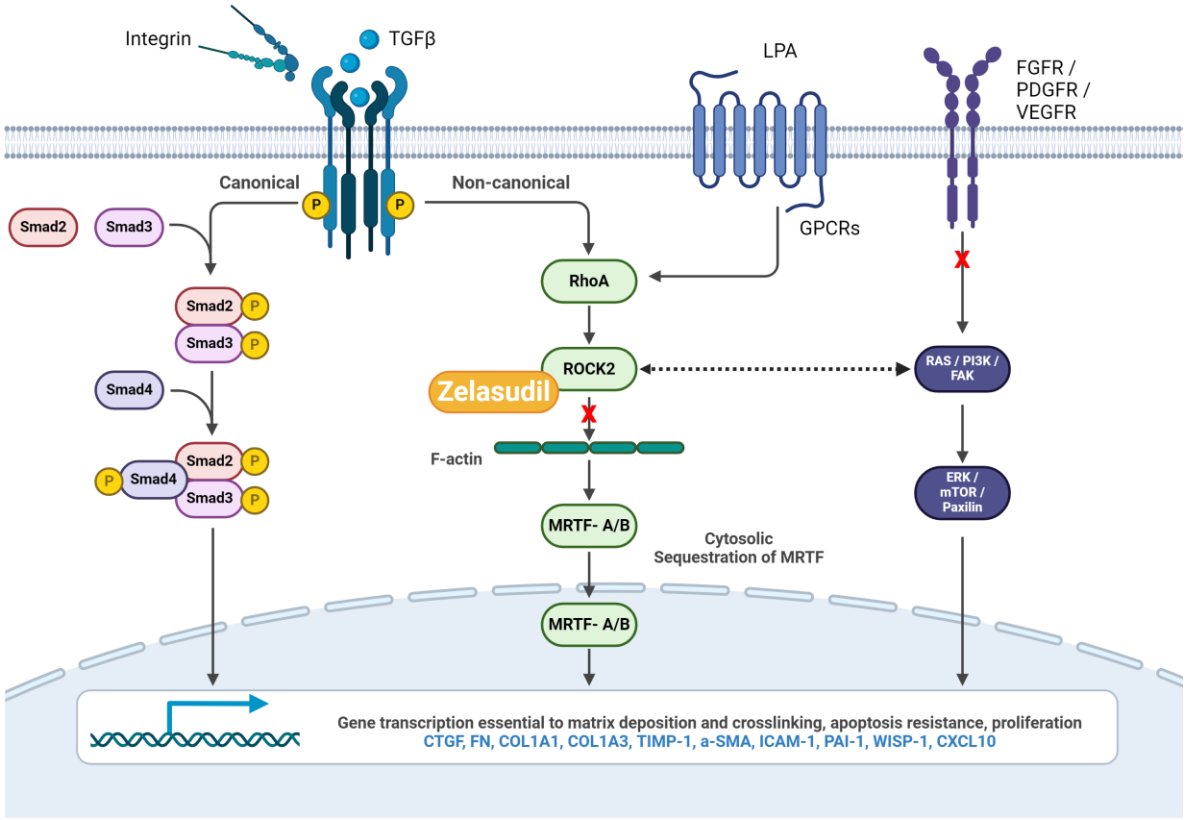
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Zelasudil is a Best in Class, Potent, Selective ROCK2 Inhibitor

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Potential of selective ROCK2 inhibition

- ROCK sits at a nodal position in fibrotic signaling pathways
- Pan-ROCK inhibition shows robust anti-fibrotic activity in preclinical models
- Systemic pan-ROCK inhibition results in hypotension. This does not happen with selective ROCK2 inhibition
- ROCK2 inhibition alone is sufficient to drive anti-fibrotic efficacy in multiple preclinical fibrosis models

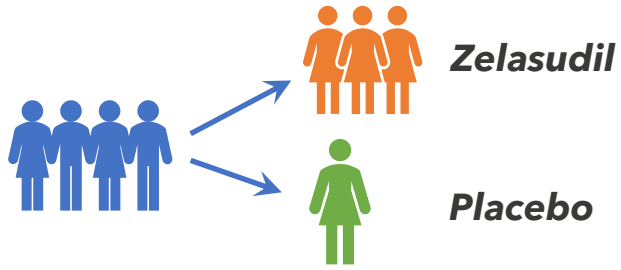


Selective ROCK2 inhibitors hold great treatment potential in fibrotic disease

ROCK: Rho-associated protein kinase

Phase 2a Study to Assess Safety, Tolerability, PK and Initial Efficacy in IPF patients

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Double Blind Dosing period 12 weeks

Zelasudil 20mg BID (n=18)

Zelasudil 50mg BID (n=18)

Placebo (pooled) (n=12)

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

Study end

Optional OLE 12 weeks
(placebo crossover to zelasudil)

Key endpoints:

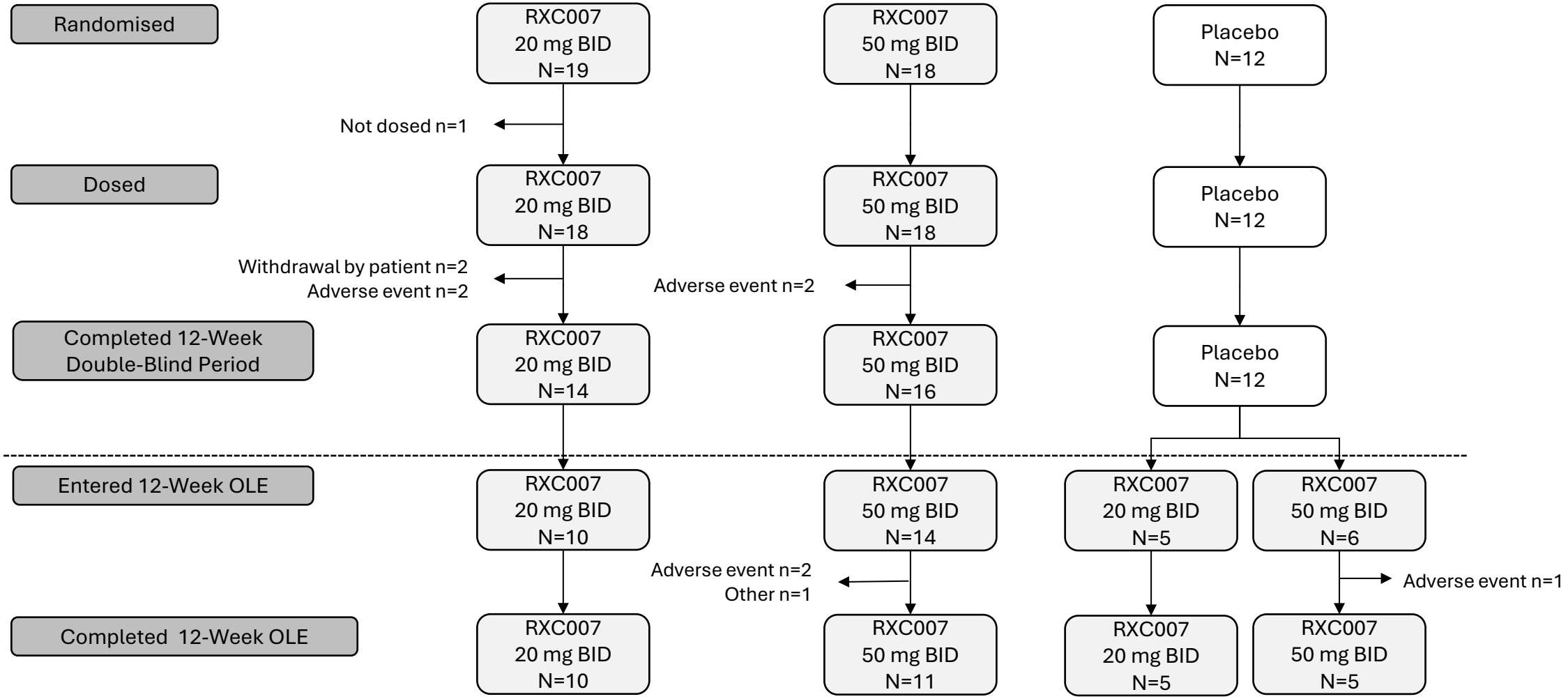
- Safety and tolerability; PK Profile
- Efficacy:
  - FVC
  - HRCT imaging - QLF Score
- Translational Science: Changes from baseline in blood biomarkers e.g. Pro-C3

- Recruitment in 9 Countries (UK + 8 EU countries) approved with 31 sites
- 35 patients entered the open label extension

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

Study Disposition

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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/m^2)			
- Mean	29.5	28.3	27.5
- Min/Max	26.1, 40.3	24.3, 35.8	21.1, 31.9

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

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)

Zelasudil is Well Tolerated With and Without Background Antifibrotic Therapy

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- No deaths and no treatment related SAE
- No evidence of hypotension
- No GI signal
- No ECG or vital sign safety concerns, including QTcF
- No significant changes in Karnofsky score
- Potential signal on ALT/AST observed – monitorable and reversible
- No other clinically significant lab abnormalities / trends in any other lab parameter
- No differences in safety by dose, duration of treatment (12 / 24 weeks) or background 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

n= number of patients; E = number of events

SAE: serious adverse event; TEAE: treatment emergent adverse event; TREAE: treatment related emergent adverse event

Most Common Treatment Related Adverse Event: Reversible ALT/AST Increases

All patients N=48

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

*Patients with ALT increases also had AST increases

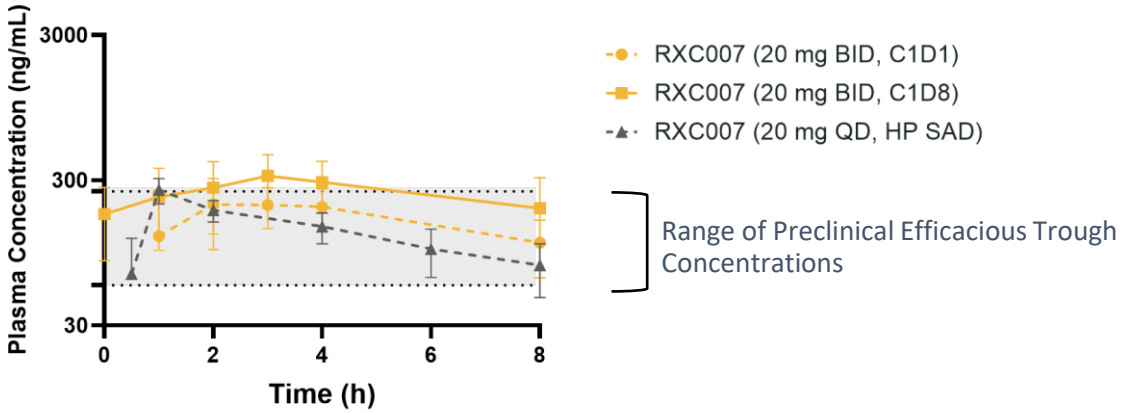
- ALT/AST increases were most common TREAE and occurred in 7 patients in total
  - 5 during 12-week double blind period
  - 2 during OLE
- Asymptomatic
- Resolved on treatment interruption
- No associated bilirubin increases
- No cases of Hy's law
- No dose modifications were permitted in this study (will be further explored in future studies)

ALT: Alanine aminotransferase; AST: Aspartate transaminase; TREAE: Treatment related emergent adverse event

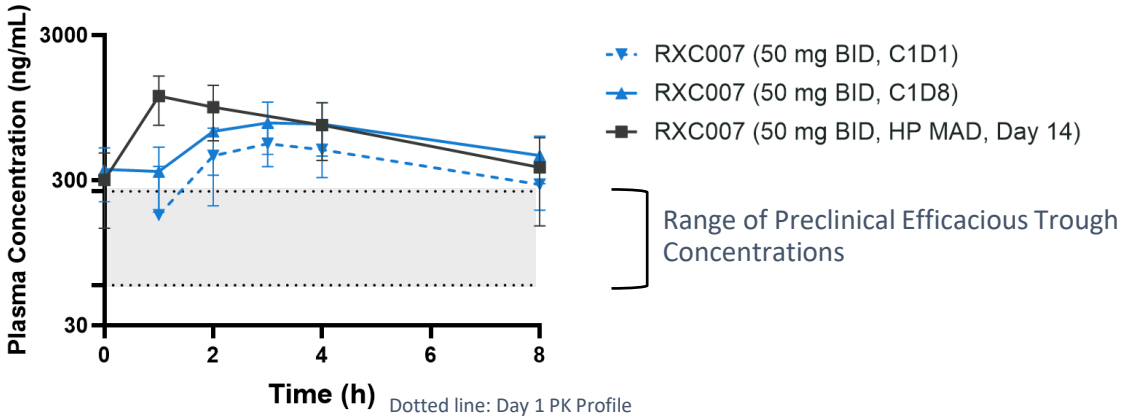
Zelasudil Exposure Above Preclinical Efficacious Trough Concentration at Both Clinical Doses

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RXC007 20 mg BID Dose Covers Lowest Trough Efficacious Concentration



RXC007 50 mg BID Dose Covers Highest Trough Efficacious Concentration



Dotted line: Day 1 PK Profile
Continuous line Steady-state PK Profile
No Steady-state data generated in HV at 20 mg BID (MAD HV was 50 and 70 mg BID)

PK Data Consistent with Phase 1 HV and PBPK

- C_{max} 50 mg ~ 2-fold C_{max} 20 mg as anticipated
- A 50 mg BID dose covers highest preclinical efficacious trough concentration
- A 20 mg BID dose covers lowest preclinical efficacious trough concentration

No clinically relevant interactions observed to date with nintedanib and pirfenidone

- No significant change of exposure of standard of care following administration of zelasudil

BID: Twice daily; HV: Healthy volunteers; MAD: Multiple ascending dose; PBPK: Physiologically-based pharmacokinetic; PK: Pharmacokinetics; QD: Once daily; SAD: Single ascending dose

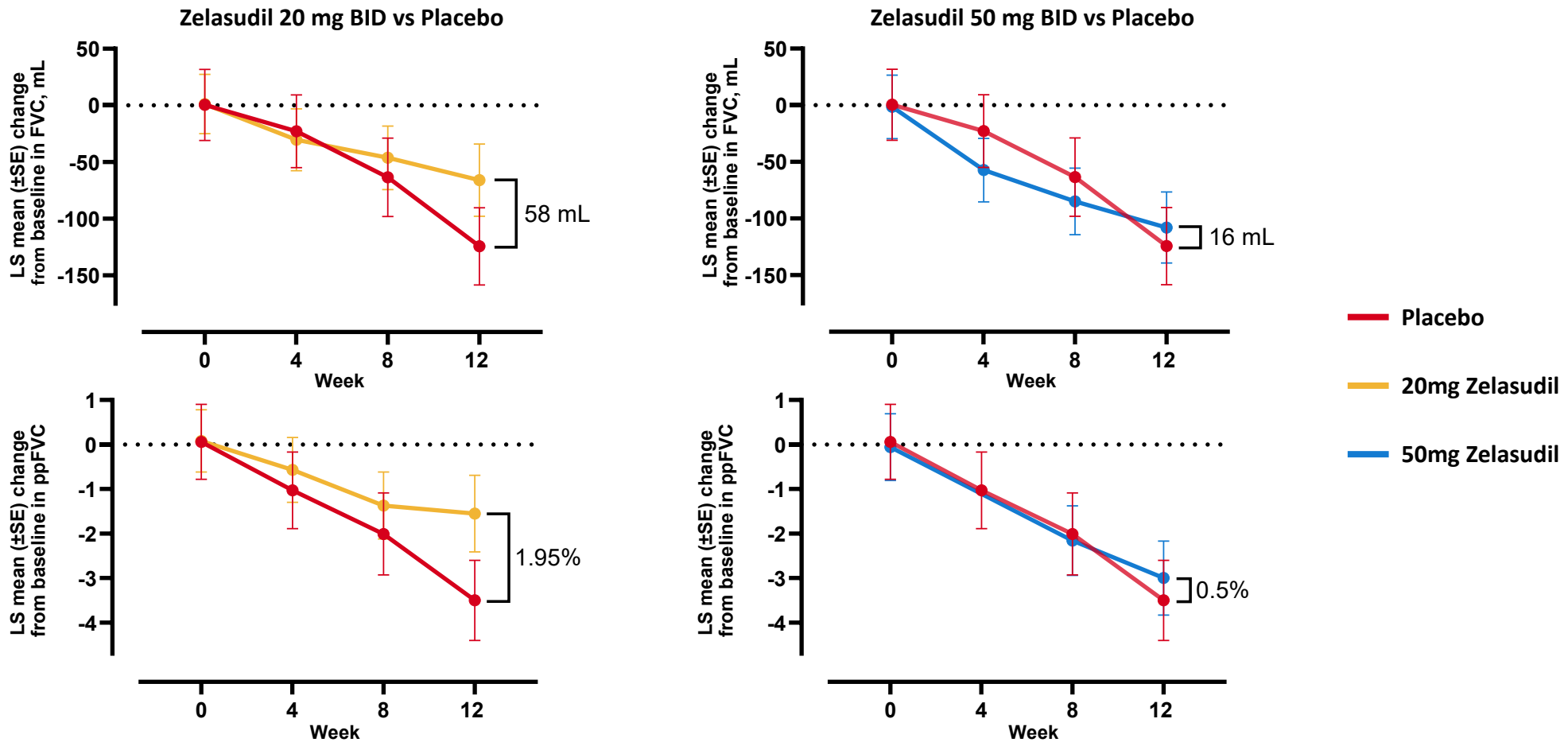
Zelasudil Reduces FVC Decline Numerically at 12 Weeks in IPF Patients

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Zelasudil reduces FVC decline in mL

Zelasudil reduces ppFVC decline

Lung Function
All patients



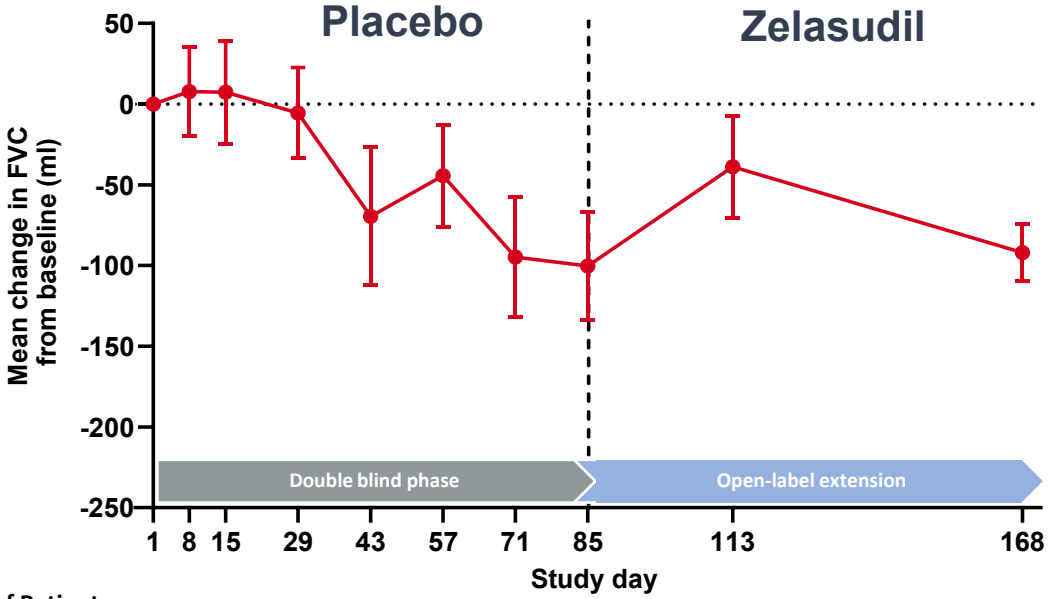
Efficacy evaluable data set (46 patients; 50mg=17, 20mg=17, pbo=12)

BID: Twice daily; FVC: Forced Vital Capacity; IPF: Idiopathic pulmonary fibrosis, ppFVC: Percentage predicted forced vital capacity

In The OLE FVC Continues to Stabilize

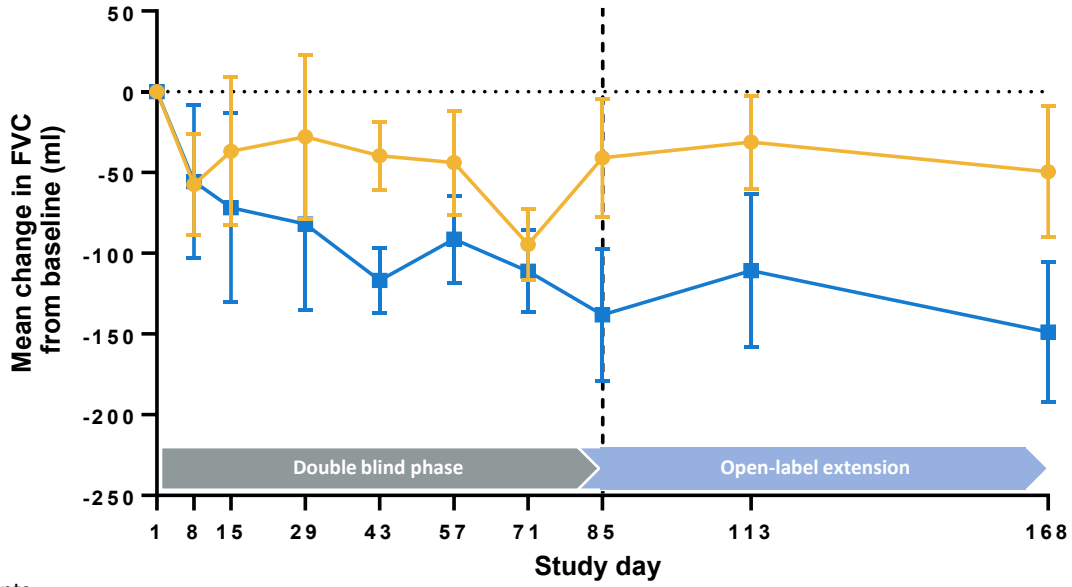
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In the OLE, Lung Function is Stabilised in Placebo Patients who Switch to Zelasudil during Open Label Extension



No. of Patients										
Placebo	11	11	9	10	9	10	10	10	8	9

In the OLE, Patients Continue to Benefit from Zelasudil For Entire 6-month Treatment Period



No. of Patients										
Zelasudil 20mg	10	9	8	9	9	10	9	7	5	8
Zelasudil 50mg	11	9	9	11	10	10	10	8	9	8

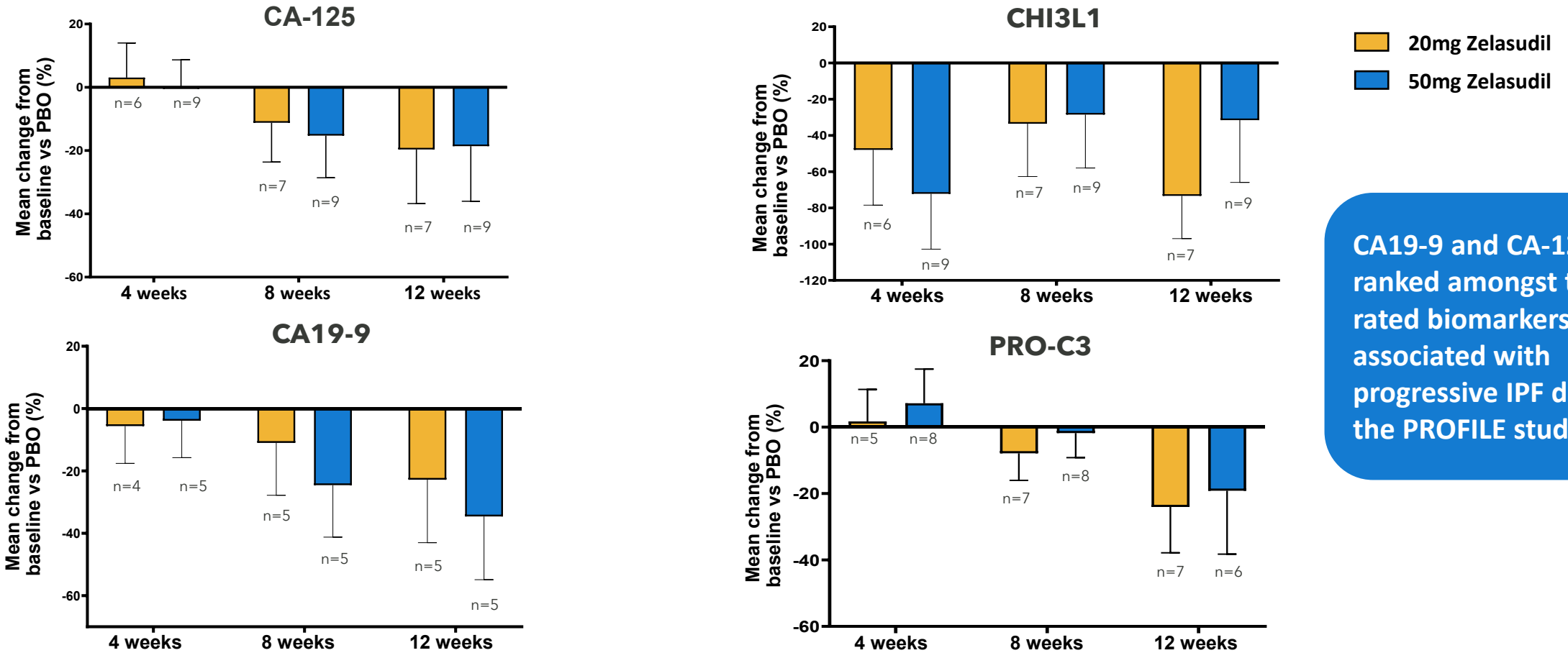
Δ values are mean FVC change from baseline

Placebo **20mg Zelasudil** **50mg Zelasudil**

Zelasudil Reduces Circulating Markers Associated with Progressive IPF Disease

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Zelasudil modulates markers of different disease associated pathways: CA 19-9/CA-125 (epithelial), PRO-C3 (collagen fragment), CHI3L1 (macrophage)



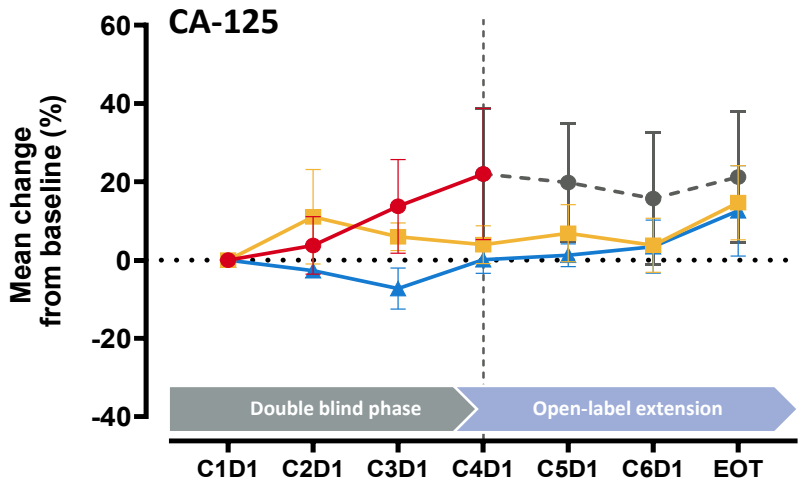
CA19-9 and CA-125: ranked amongst the top-rated biomarkers associated with progressive IPF disease in the PROFILE study

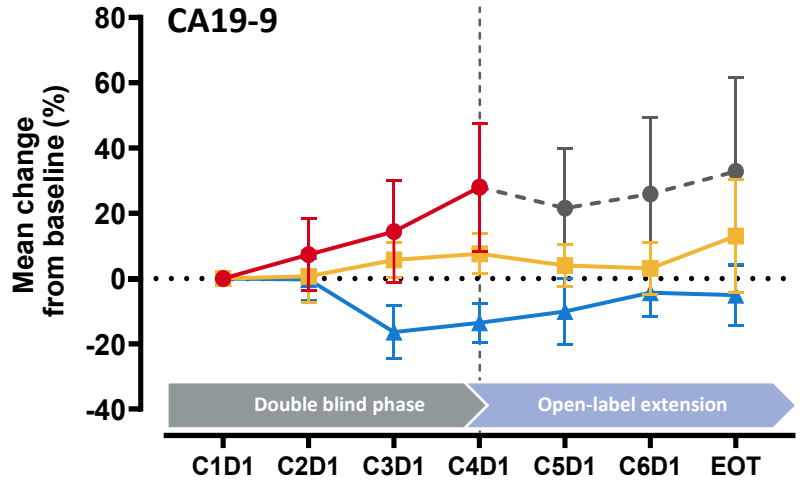
Data is mean ± SEM. Cohort: background therapy. CA19-9: only patients with CA19-9 detectable at baseline included.
Selected references: Zhou et al (2014), Jessen et al (2021), Maher et al (2017), Fainberg et al (2024)

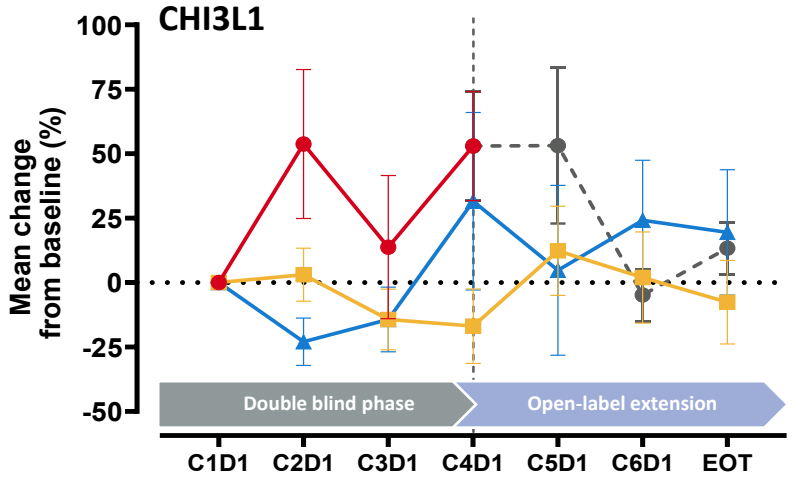
Zelasudil Induces Longitudinal Reductions in Circulating Markers Associated with Progressive IPF Disease

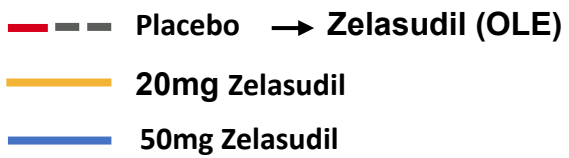
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Patients on background therapy, who entered OLE









Mean ± SEM. One cycle is 4 weeks. Cohort: background therapy and entered OLE, CA19-9 detectable at baseline

C: Cycle; D: Day; EOT: End of treatment;
IPF: Idiopathic pulmonary fibrosis

Conclusions

- IPF remains an area of high unmet need with limited therapeutic options
- ROCK sits at a nodal position in fibrotic signaling pathways
- Zelasudil is a best-in-class ROCK 2 inhibitor
- Zelasudil is well tolerated both with and without background antifibrotic therapy
- Pharmacokinetics in-line with predictions and Zelasudil can be combined with other antifibrotic therapies (nintedanib and pirfenidone)
- In this Phase 2a study, antifibrotic activity has been demonstrated which is supported by circulating biomarker data
- Further investigation in IPF / ILD is warranted