RXC008, a first-in-class Gastrointestinal restricted pan-ROCK inhibitor developed for treatment of intestinal fibrosis shows GI restriction and tolerability: Results from the phase 1 program in healthy participants

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Potential Conflicts of Interest

Florian Rieder, Consulting or AdBoard:

- Adiso, Adnovate, Agomab, Allergan, AbbVie, Arena, Astra Zeneca, Bausch & Lomb, Boehringer-Ingelheim, Celgene/BMS, CelltrionCDISC, Celsius, Cowen, Eugit, Ferring, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, Guidepoint, Helmsley, Horizon Therapeutics, Image Analysis Limited, Index Pharma, Landos, Jannsen, Koutif, Mestag, Metacrine, Mirum, Mopac, Morphic, Myka Labs, Organovo, Origo, Palisade, Pfizer, Pliant, Prometheus Biosciences, Receptos, Redx, Roche, Samsung, Sanofi, Surmodics, Surrozen, Takeda, Techlab, Teva, Theravance, Thetis, Tr1x Bio, UCB, Ysios, 89Bio

Redx Pharma Ltd, Employees/Contractors:

- Amy Marshall, Kirsty Houslay, Elaine Kilgour, Tayeb Naveed, Silke Huettner, and Helen Timmis are employees / contractors of Redx Pharma Ltd

Simbec-Orion:

- Annelize Koch is employed by Simbec-Orion

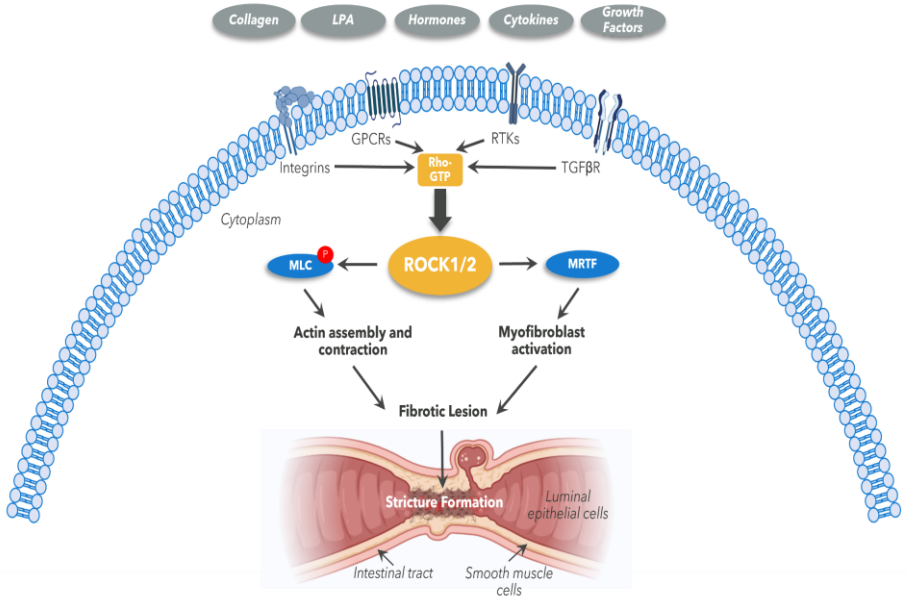
Medicines Evaluation Unit:

- Niamat Khan is an employee of MEU (Medicines Evaluation Unit)

Background

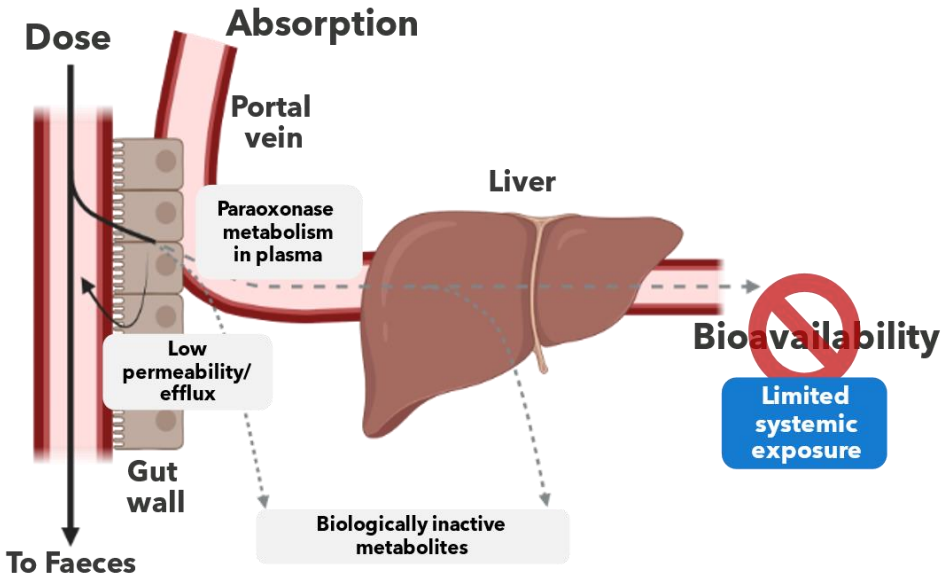
Rho-associated coiled kinase (ROCK) in Fibrotic Disease

- A biologically and clinically validated target
- A nodal point in the fibrotic signalling pathway[1,2]
- ROCK1/2 inhibition demonstrated robust anti-fibrotic activity in preclinical models
- Systemic ROCK1/2 inhibition is known to result in hypotension[3]



RXC008

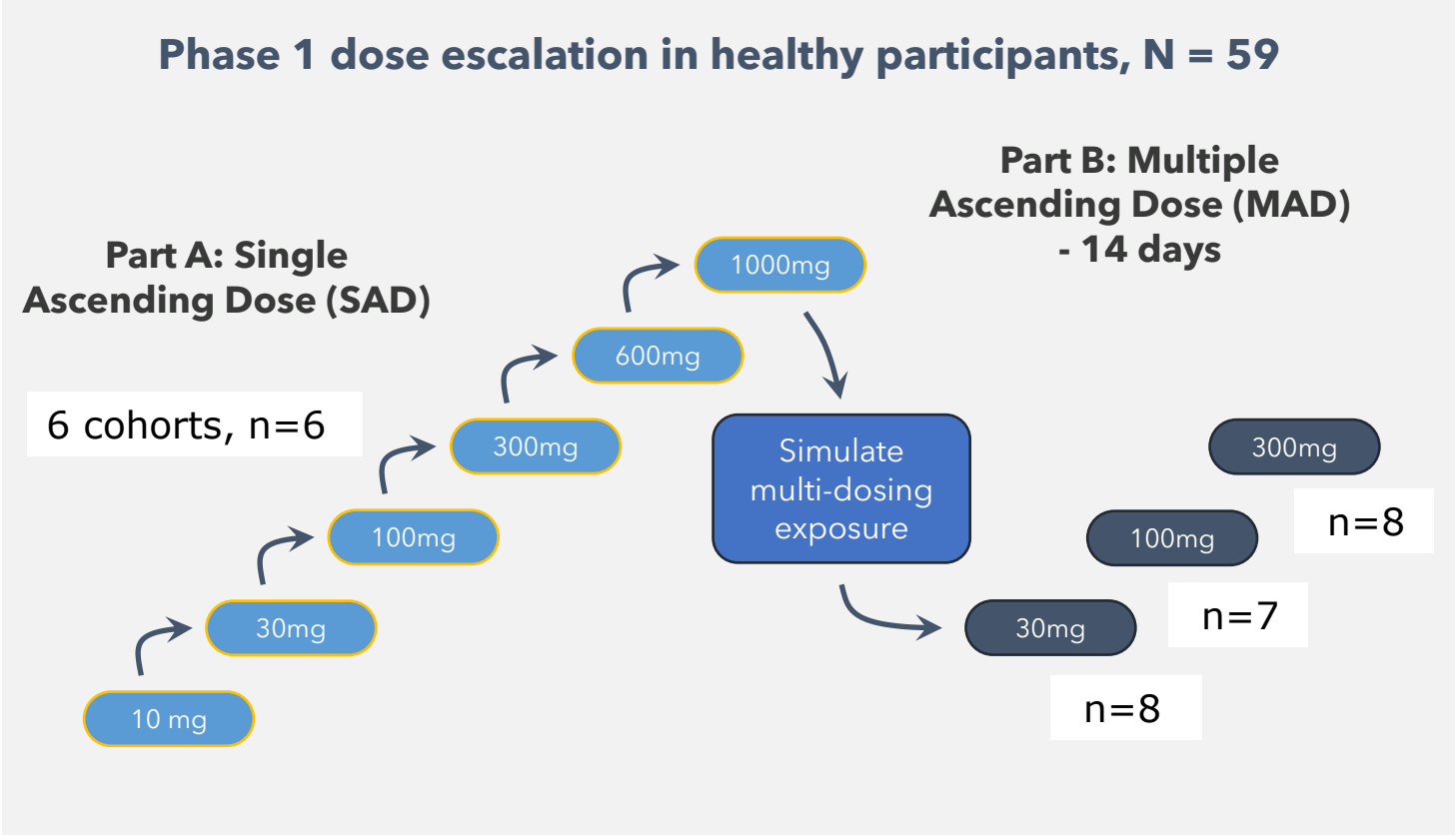
- A highly potent and selective gastrointestinal tract restricted ROCK1/2 inhibitor
- Gut restriction prevents systemic exposure and avoids hypotension, driven by:
  - low permeability and high efflux
  - Rapidly metabolised by paraoxonase enzymes
  - Rapidly cleared by the liver



1. Julian and Olson, 2014: Rho-associated coiled-coil containing kinases (ROCK): structure, regulation, and functions; 2. Knipe et al., 2015: The Rho kinases: critical mediators of multiple profibrotic processes and rational targets for new therapies for pulmonary fibrosis; 3. Noma et al 2006: Physiological role of ROCKs in the cardiovascular system. Am J Physiol Cell Physiol. 2006 Mar;290(3):C661-8. 3.

Methods

- Once daily oral dosing
- Safety, tolerability and systemic exposure assessed in both parts
- 24-hour blood pressure monitoring and telemetry were used to evaluate potential hypotensive effects in all SAD cohorts and the 100mg MAD cohort
- MAD participants underwent ileocolonoscopy on Day 14 to assess tissue compound concentrations in biopsies from the ileum and colon



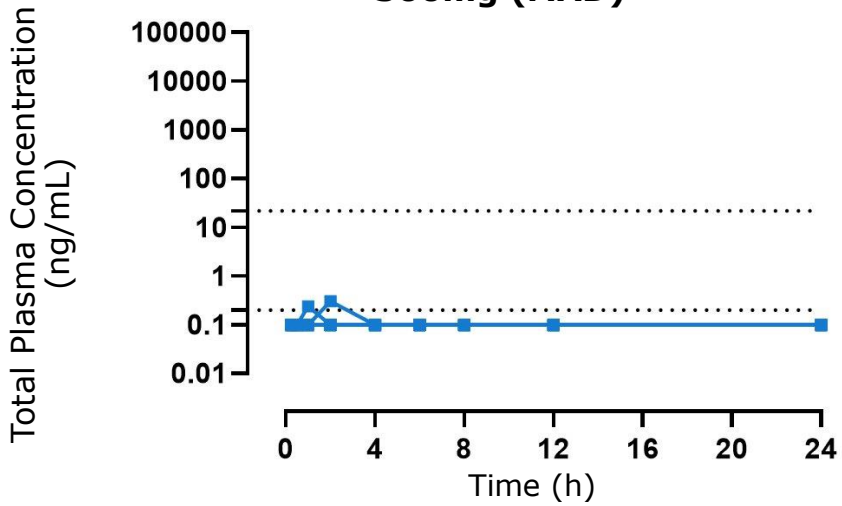
Results

SAFETY

- No SAEs and no AEs leading to treatment discontinuation
- Single TEAE, 30mg MAD cohort: reduced appetite, mild, onset Day 2 and resolved by Day 6
- No TEAEs in SAD cohorts
- All TEAEs mild or moderate with no trends and no observations of hypotension at any dose
- One discontinuation (30mg MAD participant) Day 11 due to personal reasons

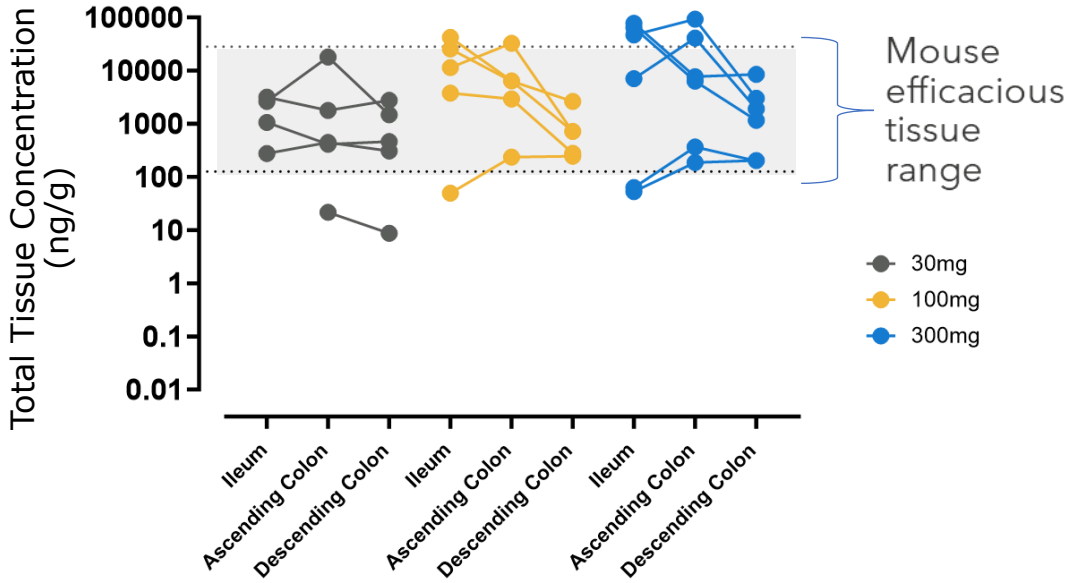
PHARMACOKINETICS

Individual Plasma Concentration (Day 11) 300mg (MAD)



- *For graphical purposes below LOQ values are plotted as LOQ/2*
- *All Plasma RXC008 concentrations at 30 mg and 100 mg were below LOQ (0.199 ng/mL) at all timepoints*

Individual Tissue Concentration (MAD)



- *Human HP Mean RXC008 GI tissue concentrations (Day 14 of dosing) are within mouse tissue efficacious concentration*

AE adverse event; GI Gastrointestinal; HP healthy participant; LOQ limit of quantification; MAD multiple ascending dose; SAD single ascending dose; SAE serious adverse event; TEAE treatment emergent adverse event

Conclusion

- Oral administration of RXC008 up to 1000mg as a single dose and up to 300mg once daily for 14 days was well tolerated with no safety signals
- GI restriction of the compound confirmed with no clinically relevant systemic exposure
- Robust tissue exposure in ileum and colon
- RXC008 is a promising treatment for patients with fibrostenotic Crohn’s disease