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RXC008 A Promising Potential New Gastrointestinal-Restricted ROCK Inhibitor Therapy for the Management of Fibrostenosis in Crohn's Disease

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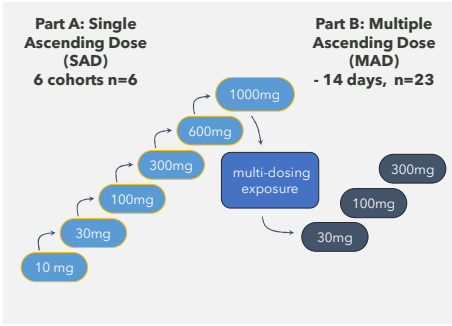
INTRODUCTION

- Rho-associated coiled-coil kinase (ROCK) is a biologically and clinically validated target. It sits at a nodal point in the fibrotic signalling pathway[1, 2]. ROCK 1/2 inhibition demonstrates robust anti-fibrotic activity in preclinical models. Systemic ROCK1/2 inhibition is known to result in hypotension which greatly limits the therapeutic utility[3].
- RXC008 is a highly selective and potent Rho-associated coiled kinase (ROCK) 1 and 2 (Pan ROCK) inhibitor in development for fibrostenotic Crohn's Disease. RXC008 is designed to be restricted to the gastrointestinal (GI) tract driven by low permeability and high efflux, rapid metabolism by plasma paraoxonase enzymes and rapid clearance by the liver.
- In experimental mouse fibrosis models RXC008 reduces extracellular matrix deposition and reverses fibrosis.
- Minimal systemic exposure has been confirmed in mouse, rat and dog, with high gut tissue exposure confirmed in mouse. ROCK target engagement was confirmed in mouse colon (suppression of myosin phosphatase target subunit 1(pMYPT1)).
- Here we present data from a phase 1 study in healthy participants, confirming tolerability, intestinal compound exposure and preliminary target engagement with minimal systemic exposure.

METHOD

- Single (SAD) and multiple (MAD) ascending dose design
- Healthy participants were randomised 2:1 to single doses of RXC008 (10 – 1000 mg) or placebo in the SAD part and 3:1 to once daily doses of RXC008 (30, 100 and 300 mg) or placebo in the MAD part
- Primary objective: safety and tolerability of orally administered single and multiple doses of RXC008
- Secondary objective: to characterize the PK of RXC008 in plasma and tissue
- Exploratory objective: potential effects of RXC008 on PD biomarkers
- Ambulatory blood pressure monitoring and telemetry for 24 hours post-dose on Day 1: all participants in SAD cohorts and in the 100mg MAD cohort
- Plasma PK sampling: pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12 and 24 hours post dose, on Day 1 in the SAD and on Day 1 and Day 11 in the MAD.
- Ileocolonoscopy: pre-dose and at Day 14 in all MAD participants to collect biopsies from the terminal ileum, ascending and descending colon to assess tissue concentrations of RXC008 and target engagement



Demographics

A total of 59 healthy participants were randomized and dosed.

Demographics	Part A (SAD) (N=36)	Part B (MAD) (N=23)
Sex, n (%)		
Male	36 (100.0)	23 (100.0)
Ethnicity, n (%)		
Not Hispanic or Latino	36 (100.0)	20 (87.0)
Hispanic or Latino	0	3 (13.0)
Race, n (%)		
White	31 (86.1)	16 (68.6)
Asian	1 (2.8)	1 (4.3)
Black or African American	2 (5.6)	3 (13.0)
Other	2 (5.6)	3 (13.0)
Age, yrs		
Median (Std Dev)	38.3 (7.67)	36.0 (8.57)

There were no relevant differences in either Part A (SAD) or B (MAD) between treatment cohorts in age, height, weight, BMI, ethnicity or race.

Safety

- No safety concerns at any doses
- No treatment emergent adverse events (TEAE) reported in SAD Cohorts
- No serious adverse events (SAEs) or discontinuations due to TEAEs
- All MAD TEAEs were mild or moderate
- No trends in TEAEs (SOC and PT)
- No cardiovascular effects were observed at any dose as determined by 24-hour blood pressure monitoring and telemetry
- There was one withdrawal in the MAD 30 mg cohort due to personal reasons

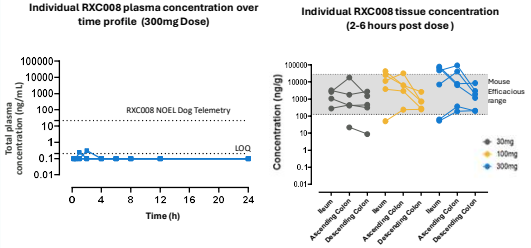
PT: Preferred Term; SOC: System Organ Class; TEAE: treatment emergent adverse event

	Part B (MAD) (N=23)
N (%) of Participants Reporting at Least One:	
TEAE	10 (43.5)
Study Procedure-Related AE	6 (26.1)
Serious TEAE	0
TEAE Leading to Withdrawal	0
TEAE Leading to Death	0
N (%) of Participants with TEAE by Severity:	
Mild	6 (26.1)
Moderate	4 (17.4)
Severe	0
N (%) of Participants with TEAE by Relationship to study drug:	
Definitely Related	0
Probably Related	0
Possibly Related	1 (4.3)*
Unlikely Related	0
Not Related	9 (39.1)

*1 participant reported decreased appetite following treatment with 30 mg RXC008 considered possibly related to study drug.

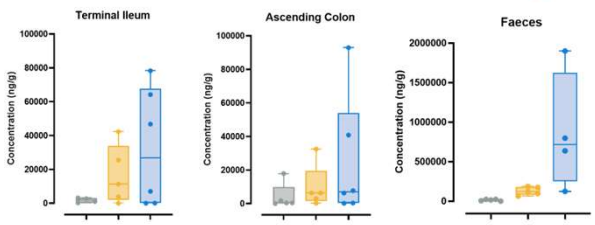
Pharmacokinetics

Clinical Data Confirms Lack of RXC008 Plasma Exposure with Tissue Exposure at Predicted Efficacious Concentrations



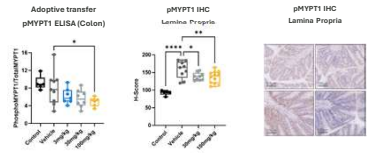
- In the MAD Cohorts, there was no measurable systemic exposure of RXC008 in plasma at 30mg and 100mg (data not shown), there was limited systemic exposure at the highest 300 mg dose up to 2 hours post dose, this exposure stayed below the pre-defined safety cut off. For graphical purposes below LOQ values are plotted as LOQ/2
- Robust exposure was noted in GI Tract biopsy tissue across all MAD doses
- This tissue exposure was within the efficacious ranges as extrapolated from murine disease models

Dose-Dependent Increase in RXC008 Concentration Observed in GI-tract Tissue Biopsies & Faeces



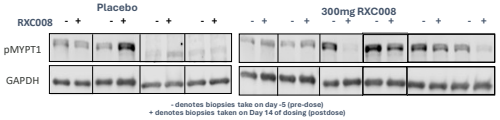
- In the MAD Cohorts, RXC008 GI tract tissue concentrations increased with dose
- A dose dependent increase in RXC008 concentration was also observed in faeces
- Faeces collected on Day 11/12

Target Engagement

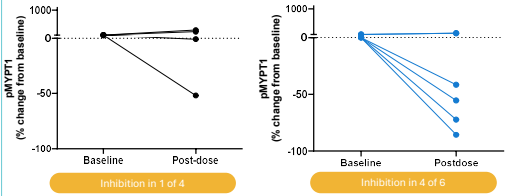


- MYPT1 is a downstream target of ROCK1/2.
- RXC008 reduces phospho-MYPT1 in an Adoptive T cell Transfer Mouse Model.
- Levels of phosphorylation were measured by ELISA assay and immunohistochemistry (IHC).
- Preclinical *In vivo* work has shown higher levels of pMYPT1 are detectable in a fibrotic disease setting.
- Despite low levels of pMYPT1 being predicted in Healthy Participants ileal biopsies from the MAD were assessed to validate pMYPT1 assays to take forward in to Phase 2.

Phosphorylated-MYPT1 in ileal biopsies detected by Western Blot



Phosphorylated-MYPT1 in ileal biopsies detected by ELISA



- Detection of pMYPT1 in biopsy tissue was feasible with good correlation between different assay formats
- In the highest dosed (300mg) group of the MAD, data is suggestive of target engagement in ~67% of volunteers
- As predicted, baseline pMYPT1 was not detectable in all healthy MAD participants

CONCLUSIONS

- Oral administration of RXC008 at single dose up to 1000mg and multiple doses up to 300mg over 14 days is well tolerated
- The GI restriction of the compound has been confirmed with limited systemic exposure, relevant exposure in tissue in the ileum and colon and clinically no evidence of hypotension
- pMYPT1 is a potential target engagement marker that can be further explored in patients in the planned phase 2 study
- RXC008 is an exciting potential new therapeutic option for fibrostenotic Crohn's disease which will be further explored in Phase 2

REFERENCES

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