TUPELO Trial: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of REC-4881 in Subjects With Familial Adenomatous Polyposis (FAP): Study Design

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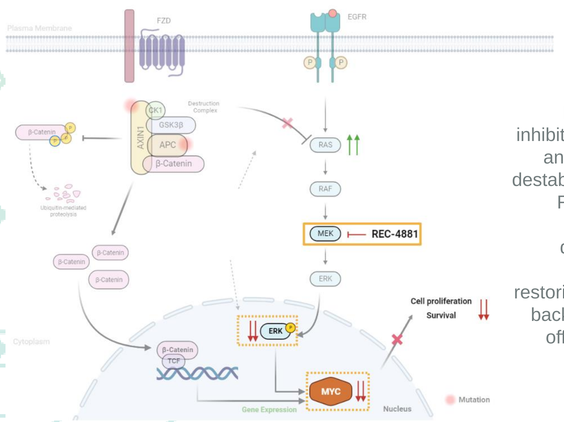
1 BACKGROUND

- Recursion is a clinical stage TechBio company leading the space by decoding biology to industrialize drug discovery.
- REC-4881 is a novel, selective, allosteric inhibitor of mitogen-activated protein kinase (MEK)1 and MEK2.[1]
- TUPELO is a phase 2, randomized, multicenter trial to investigate the pharmacokinetics (PK), pharmacodynamics (PDs), safety, and efficacy of REC-4881, including effects on duodenal and rectal/pouch polyp burden in patients with familial adenomatous polyposis (FAP) who have had a colectomy or proctocolectomy.[2]

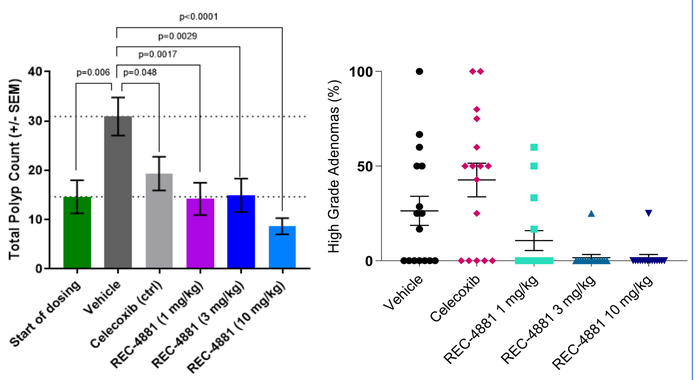
REC-4881 Blocks Wnt Mutation–Induced MAPK Signaling



REC-4881 inhibits MEK 1/2 and recovers destabilization of RAS by the β-catenin destruction complex, restoring the cell back to a Wnt-off-like state.

APC, adenomatous polyposis coli; CK1, casein kinase 1; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FZD, frizzled; GSK3β, glycogen synthase kinase-3β; MAPK, mitogen-activated protein kinase pathway; P, phosphate; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma.

REC-4881 Reduced Polyp Count and High-Grade Dysplasia in *APC*^{min} Mouse Model



SEM, standard error of the mean.

2 OBJECTIVES AND ENDPOINTS

Part 1

Primary: PK of REC-4881 after single and multiple doses: C_{max}, T_{max}, AUC

Secondary: Safety and tolerability of REC-4881: clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, vital signs, and ongoing assessment of AEs

Exploratory: PD of REC-4881
- Percent inhibition of pERK in PBMCs
- PD parameters: E_{max}, TE_{max}, E_{av}, AUEC

Part 2

Primary: Mean percent change in polyp burden after 6 months of treatment with REC-4881

Secondary
- Characterize PK and PD after 2 weeks of daily REC-4881 (PK/PD subset only)
- Safety and tolerability of REC-4881: incidence of AEs after 6 months and change from baseline in clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis), 12-lead ECGs, assessment of ventricular function, and vital sign measurements
- Effect of REC-4881 on polyp number, histologic grade, and disease score (Spigelman classification and InSiGHT staging)

Exploratory
- Effect of REC-4881 QD for 6 months on
  - Development of or a change in desmoid disease in the abdomen
  - Time to first occurrence of any FAP-related event at any disease site
  - Molecular and genomic biomarkers associated with polyp proliferation, FAP disease progression, and the Wnt/β-catenin signaling and MAPK pathways
- Evaluate the relationship between the nature/location of *APC* gene mutation(s) and REC-4881 efficacy

AEs, adverse event; AUC, area under the curve; AUEC, area under the effect curve; C_{max}, maximum plasma drug concentration; E_{av}, average effect over the dosing interval; E_{max}, maximum observed effect; PBMCs, peripheral blood mononuclear cells; pERK, phosphorylated ERK; QD, once daily; TE_{max}, time to E_{max}; T_{max}, time to maximum concentration.

3 STUDY DESIGN

Part 1

Enroll N = up to 7 (5:2 active/placebo)

Single dose (4 mg or placebo) → *Multiple dose (4 mg or placebo QD for 14 days)*

Option to roll into Part 2…

Part 2

Screening and randomization 1:1:1	Treatment	Follow-up

Enroll N = 29 per arm → 8 mg / 12 mg / Placebo → **6-month treatment period** → **Extension study**

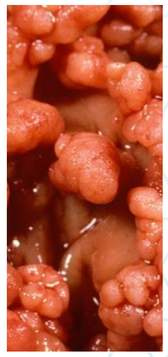
4 METHODS

Part 1: Single-Dose and Multiple-Dose PK/PD Study
- Up to 7 participants with FAP post-colectomy/proctocolectomy.
- REC-4881 4 mg or placebo single-dose administration with a 14- to 28-day washout period followed by QD oral dosing of REC-4881 4 mg or placebo for 14 days.
- All participants will complete a safety follow-up visit.

Part 2: Randomized Placebo-Controlled Treatment Study
- FAP participants with a confirmed germline *APC* mutation, post-colectomy/proctocolectomy and a primary disease site of either the duodenum (including ampulla of Vater) or the rectum/pouch.
- Part 1 participants who are rolled over into part 2 of the study will be randomized 1:1 to receive either REC-4881 8 mg or 12 mg for 6 months.
- The first 15 participants (not including part 1 rollover participants) for part 2 will undergo additional PK/PD assessments.

Long-term Extension (LTE) Study
- Part 2 participants who complete the end-of-treatment visit may enter an LTE study (REC-4881-202).

Follow-up Period (Part 2 Only)
- Part 2 participants not continuing in the LTE will return for a follow-up/end-of-study visit 30 days following completion of the treatment period.

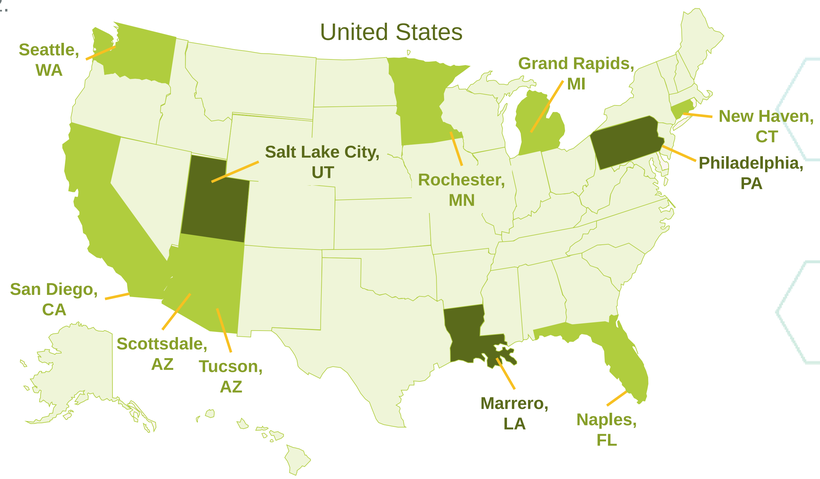


5 ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
≥18 years old with FAP with duodenal polyps (including ampulla of Vater) or residual colon/rectum/pouch as primary site of disease	Treatment with other investigational agents within 4 weeks prior to study day 1 or other FAP-directed drug therapy within 8 weeks
Genetic diagnosis of FAP with *APC* gene mutation (part 2 only)	Use of omega-3 fatty acids or oral corticosteroids within 30 days, or use of strong cytochrome P450 enzyme inhibitors or inducers within 14 days
Has undergone colectomy or subtotal colectomy	Cancer in gastrointestinal tract on biopsy at screening endoscopy (part 2 only)
No significant cardiovascular, hematopoietic, hepatic, or renal abnormalities at screening	History of eye abnormalities, active pancreatitis, or active gall bladder disease
Willingness to discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) 6 weeks prior to study and remain off NSAIDs throughout remainder of study	Large polyp (>1 cm) not amenable to complete removal (except ampullary adenoma)

6 ENROLLMENT

- Up to 7 participants will be enrolled in part 1 of the study, and approximately 87 participants (29 per arm) will be enrolled in part 2.



- Additional information is available at https://clinicaltrials.gov/ct2/show/NCT05552755 and https://www.tupelostudy.com/tupelo-study.

7 SUMMARY

TUPELO is designed to investigate the safety, efficacy, PK, and PD of REC-4881, representing a potential new pharmacologic treatment for patients with FAP. Enrollment is ongoing.

8 REFERENCES

1. Chernick A. A one-size-fits-all path to precision medicines. *J Precision Med.* 2021;7(1):68-71.
2. ClinicalTrial.gov identifier: NCT05552755. Accessed April 11, 2023. https://clinicaltrials.gov/ct2/show/NCT05552755.

9 ACKNOWLEDGMENTS

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10 DISCLOSURES

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TUPELO

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