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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1BACKGROUND

- REC-4881 is a novel, selective, allosteric inhibitor of mitogen-activated protein kinase (MEK1) and MEK2.
- 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.

2OBJECTIVES AND ENDPOINTS

Part 1

Primary: PK of REC-4881 after single and multiple doses: Cmax, Tmax, 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: Emax, TE, Emax, T1/2, 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 (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 or a change in desmoid disease in the abdomen
    - Time to first occurrence of an AEs-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

3STUDY 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

Enroll N = 29 per arm
- 6-month treatment period
- Extension study

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 enrolled in 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

4METHODS

5ELIGIBILITY CRITERIA

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<tr>
<th>Key Inclusion Criteria</th>
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<td>≥18 years old with FAP with duodenal polyps (including ampulla of Vater) or residual colon/rectum/pouch as primary site of disease</td>
<td>Treatment with other investigational agents within 4 weeks prior to study day 1 or other FAP-directed drug therapy within 8 weeks</td>
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<td>Genetic diagnosis of FAP with APC gene mutation (part 2 only)</td>
<td>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</td>
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<td>Has undergone resection or subtotal colectomy</td>
<td>Cancer in gastrointestinal tract on biopsy at screening endoscopy (part 2 only)</td>
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<td>No significant cardiovascular, hematopoietic, hepatic, or renal abnormalities at screening</td>
<td>History of eye abnormalities, active pancreatitis, or active gall bladder disease</td>
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<td>Willingness to discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) 6 weeks prior to study and remain off NSAIDs throughout remainder of study</td>
<td>Large polyp (&gt;1 cm) not amenable to complete removal (except ampulla adenoma)</td>
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6ENROLLMENT

- 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.

7SUMMARY

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.

8REFERENCES


9ACKNOWLEDGMENTS

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10DISCLOSURES

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