ONGOING PHASE 1B/2 TRIAL OF THE ALLOSTERIC MEK1/2 INHIBITOR REC-4881 AS MONOTHERAPY IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

PRELIMINARY SAFETY AND EFFICACY DATA

Jewel Samadder, M.D.

May 4, 2025

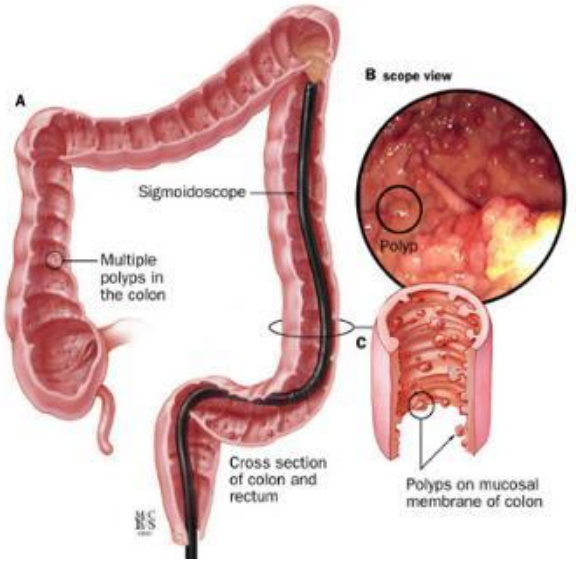
N Jewel Samadder, Gautam Mankaney, Jessica Stout, Reid Ness, Ziad Younes, Harinath Sheela, Bryson W. Katona, Bahar Shamloo, Kasra Yousefi, Johnny Viscusi, Ying Su

DISEASE CONTEXT

FAP IS A RARE DISEASE CHARACTERIZED BY POLYPS IN THE GI TRACT, WITH NO APPROVED THERAPIES

DISEASE BACKGROUND

- FAP is an **orphan disease** caused by autosomal dominant **inactivating mutations in *APC***
- FAP patients develop 100s of colorectal adenomas with a **nearly 100% risk of CRC** in absence of colectomy
- Duodenal neoplasia develops **in >50% of FAP patients including 10-15% risk of duodenal and ampullary cancers**
- Lifetime of surveillance and surgical/excisional interventions



Source : Johns Hopkins

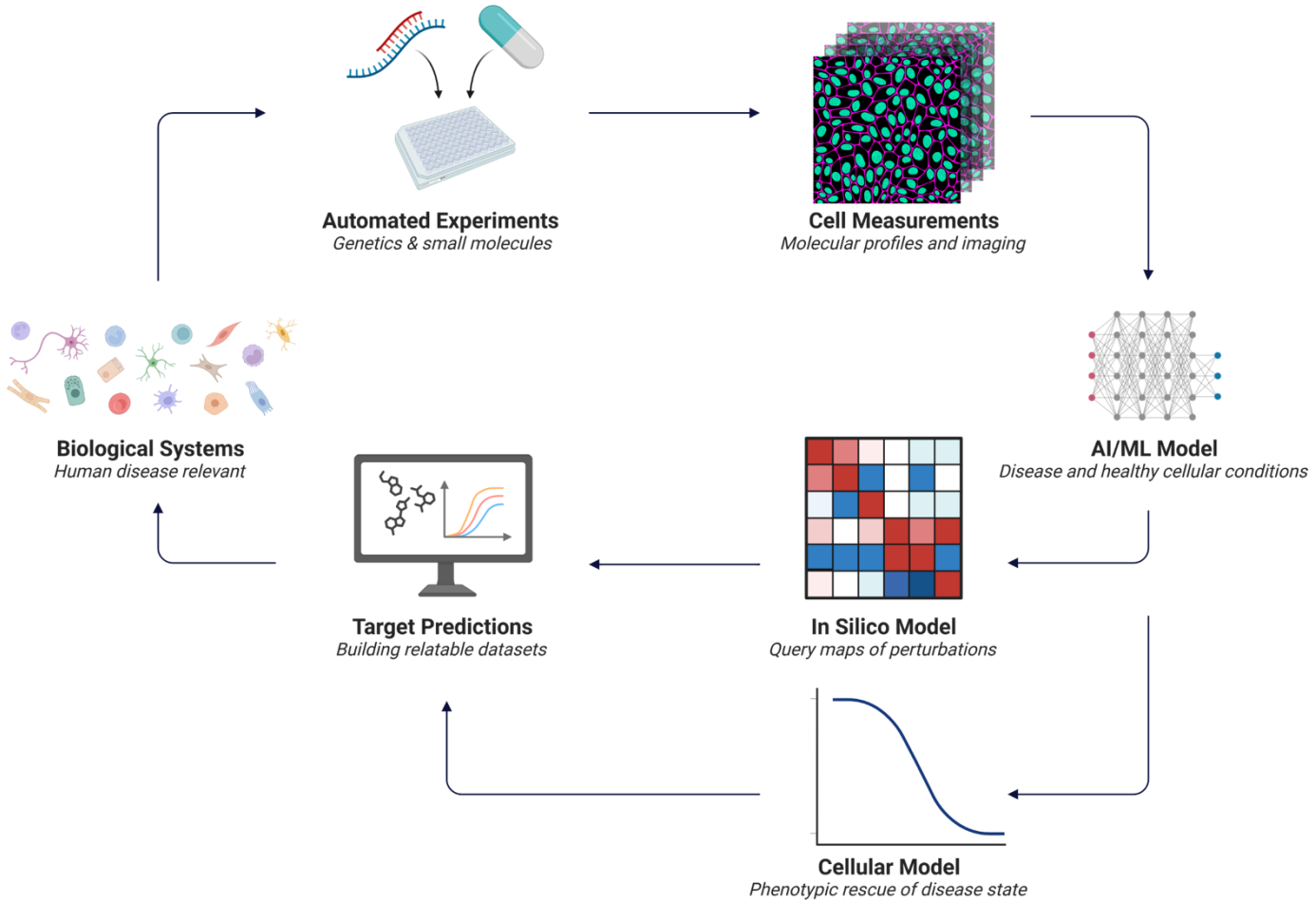
HIGH UNMET NEED

- **~50,000** Diagnosed US + EU5[1]
- **Colectomy with upper GI surveillance** is the standard-of-care for GI neoplasia risk reduction
- Current medical therapies have **no impact** on slowing **disease progression and/or need for surgery**
- **REC-4881** may be positioned to fill a significant unmet need with **no approved pharmacotherapies**

1. Prevalence for adult and pediatric population, internal company estimates.

PLATFORM

THE AI-POWERED RECURSION OPERATING SYSTEM (OS) WAS LEVERAGED TO UNCOVER NOVEL THERAPEUTIC MECHANISMS RELEVANT FOR FAP

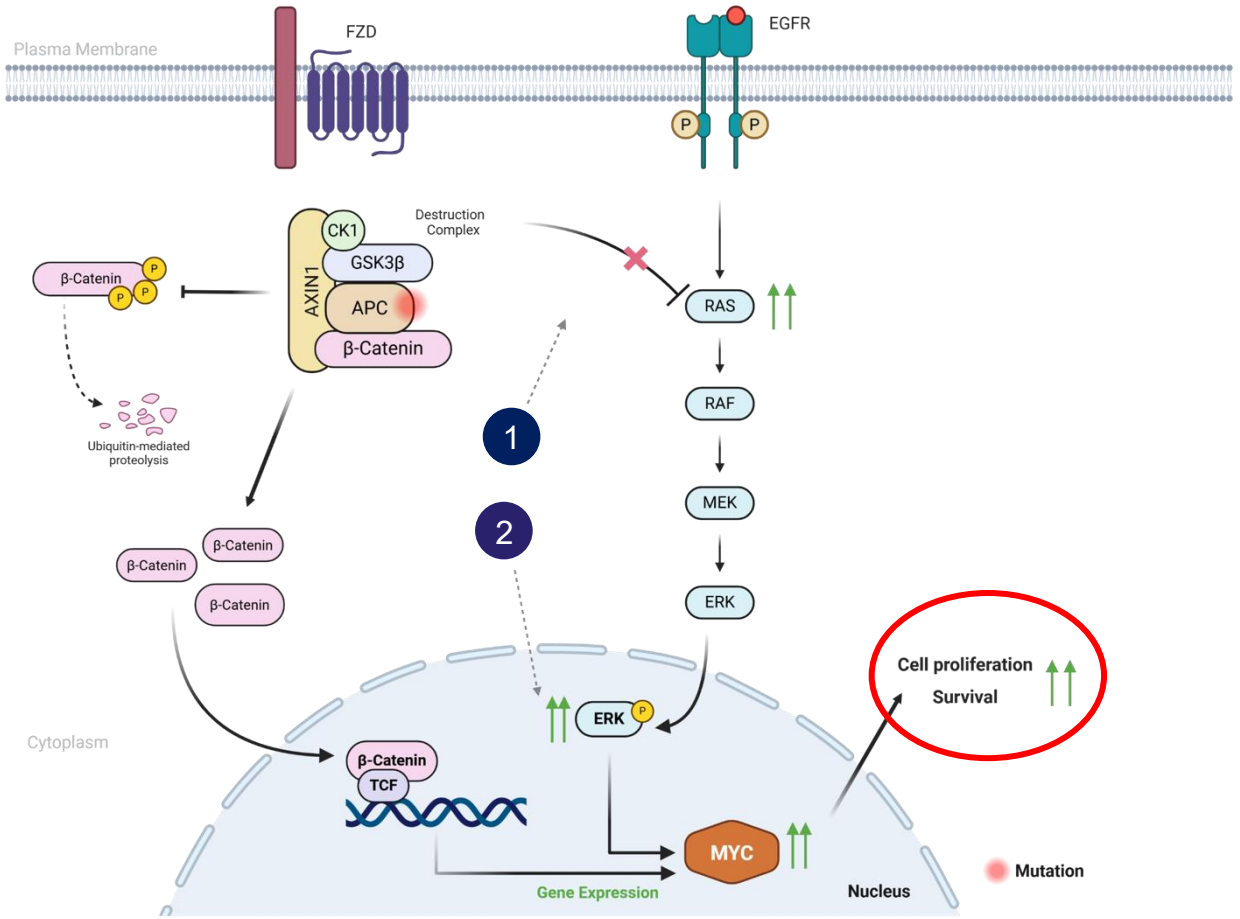


METHODOLOGY

- The platform analyzed cellular models of APC gene loss—the root cause of FAP
- **AI/ML** extracts morphological features to **distinguish "diseased" vs. "healthy" states**
- Numerous compounds screened to identify therapeutic mechanisms that **reverse disease state back to healthy** in a concentration-dependent manner
- **REC-4881 (an allosteric MEK 1/2 inhibitor)** demonstrated **potent and concentration dependent rescue**

MECHANISM OF DISEASE

APC LOSS OF FUNCTION MUTATIONS LEAD TO DYSREGULATION OF SEVERAL KEY PATHWAYS



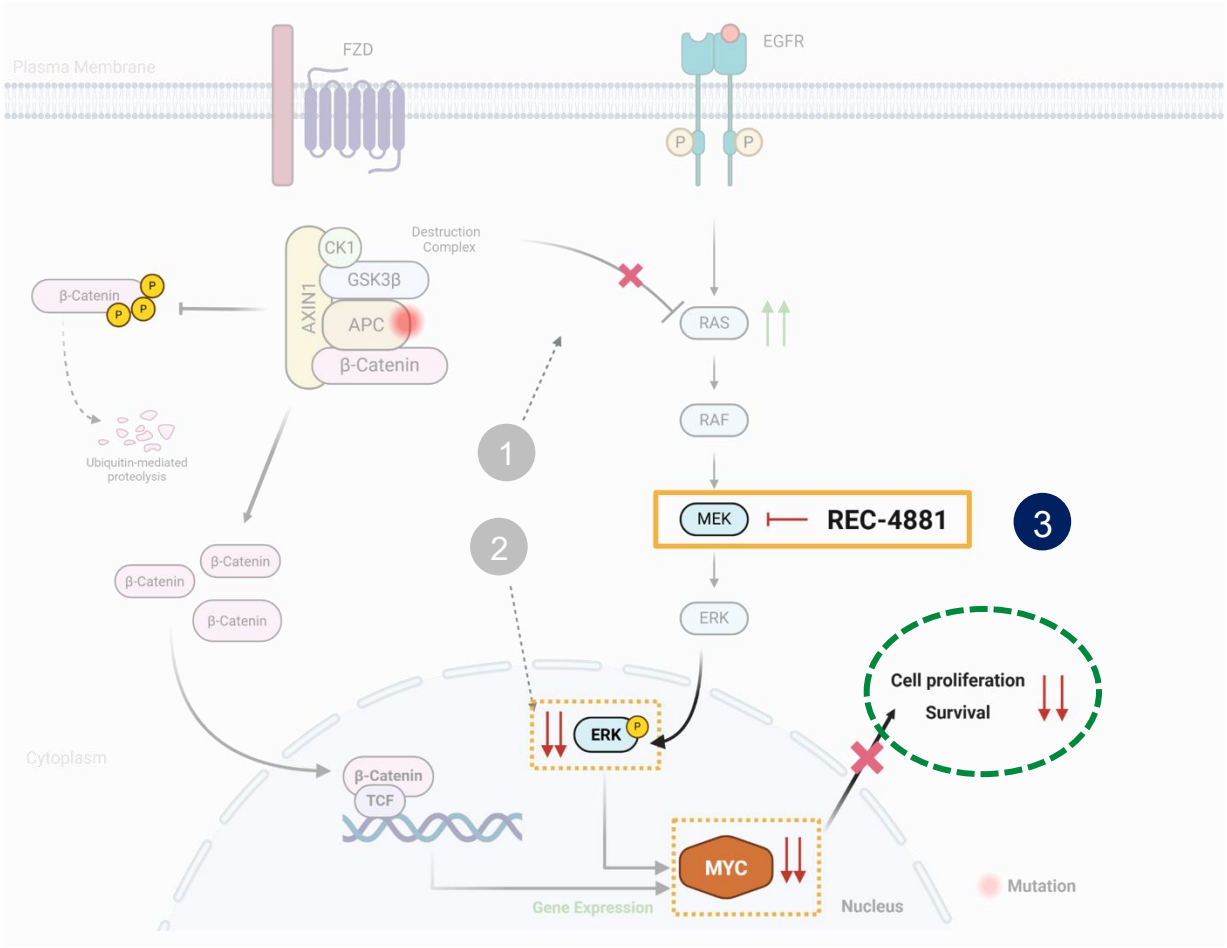
S.K. Lee et al, Adv. Biol. Regulat. (2018)

1. Inactivating mutations in *APC* mimic a Wnt-on state in the absence of Wnt ligands

2. This induces RAS stabilization and aberrant signaling through MEK to increase MYC gene expression

MECHANISM OF ACTION

REC-4881 MAY RESTORE PATHWAY DYSREGULATION CAUSED BY *APC* LOSS OF FUNCTION MUTATIONS



S.K. Lee et al, Adv. Biol. Regulat. (2018)

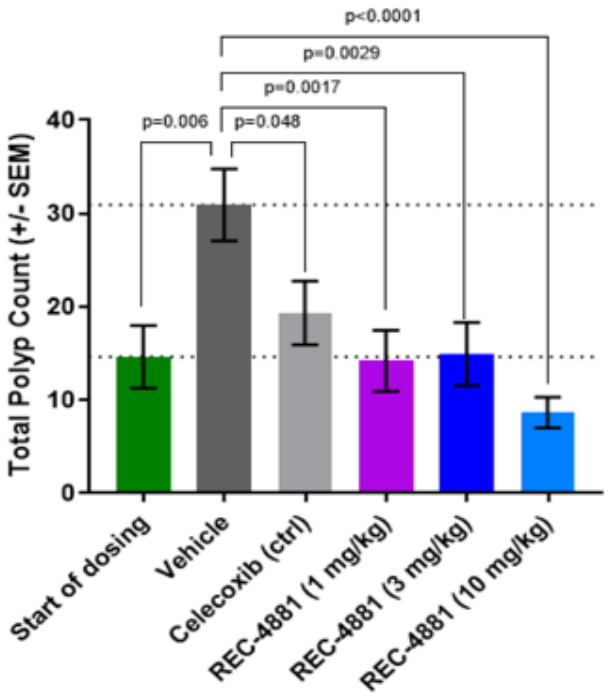
3 **REC-4881**:

- **Inhibits MEK 1/2** which is **hypothesized to recover** the **destabilization of RAS** by the β-Catenin destruction complex
- **Indirectly** acts **downstream** to **restore** the cell back to a **Wnt-off like state**
- **Differentiated ADME profile** may enhance exposures in the GI tract
- No significant binding inhibition (>50%) across 71 receptors or ion channels at 10 μM

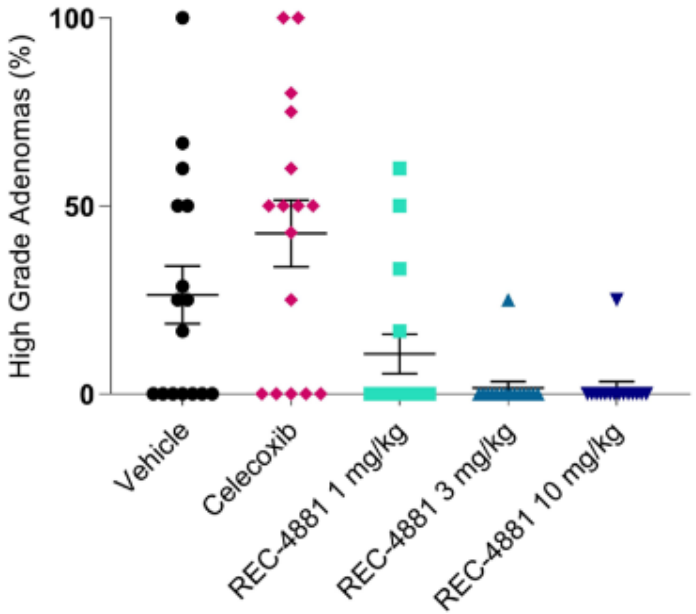
PRE-CLINICAL DATA

REC-4881 SIGNIFICANTLY DECREASED POLYPS AND HIGH-GRADE ADENOMAS IN FAP MOUSE MODELS

A) Mean Polyps Per Group



B) % Pre-Cancerous Polyps



PRE-CLINICAL SUMMARY[1]

REC-4881:

- **Reduces polyp count more effectively** than **celecoxib** in $APC^{min/-}$ mice
- **Decreases** both **polyp number and high-grade adenoma** percentage, unlike celecoxib

1. *REC-4881 reduces polyp count and eliminates high grade adenomas in Apc^{min} mouse model of FAP. A) Mean GI polyp count after oral administration of indicated dose of REC-4881, celecoxib or vehicle control for 8 weeks. Polyp count at start of dosing reflects animals sacrificed at the start of study (15 weeks of age). P < 0.001 for all REC-4881 treatment groups versus vehicle control. B) Same data displayed in A shown for individual animals on study suggests that at lowest dose tested (1 mg/kg) REC-4881 demonstrates maximum efficacy*

PHASE 1B AND PHASE 2: REC-4881-201 STUDY DESIGN & OBJECTIVES

- Two stage study designed to assess safety, tolerability, PK/PD and **preliminary efficacy of REC-4881 in FAP**
- Phase 1b (safety run-in) followed by Phase 2 (open-label) evaluating once-daily **REC-4881 for 12 weeks**

Phase 1b

Completed:

Single and Multiple Dose Safety

Randomized, double-blind, placebo-controlled (N=7)

5 patients dosed 4 mg, 2 on placebo

Study Objectives :

Safety/tolerability
Pharmacokinetics
Pharmacodynamics

Key Eligibility: FAP ≥ 18 years old

Phase 2: Open-label Signal Seeking

Dose Finding
N= 14

REC-4881
4 mg QD
N= 11

N= 6
Efficacy evaluable at time of data cutoff[1]

REC-4881
8 mg QD
N= 3[1]

Not efficacy evaluable

Baseline Endoscopy → **Screening** → On-Treatment Phase (*Week 13 Endoscopy*) → Off-Treatment Phase (*Week 25 Endoscopy*)

12 weeks | **12 weeks**

Key Eligibility:

- Confirmed *APC* mutation
- ≥ 55 years old[2]
- Post-colectomy/proctocolectomy
- No cancer present
- Polyps in upper and/or lower GI

Primary Objectives:

- Safety/tolerability
- Percent change from baseline in polyp burden after 12 weeks of treatment and off-treatment

1. *Efficacy Evaluable Population: Defined as all participants who have measurable disease (non-zero polyp burden) at end of baseline endoscopy, received at least 75% of study drug, and have at least one post-baseline on study endoscopic assessment*
2. *After analysis in Phase 1b, in an effort to minimize observed TRAEs, the eligibility criteria was shifted to enroll only patients 55+ years of age*
3. *Participants from RP2D in Dose Finding will Contribute to the sample size in Cohort Expansion*

TUPELO

PHASE 2

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Patients in the safety evaluable population at baseline*

Characteristic	REC-4881 4 mg (N=11)	REC-4881 8 mg (N=3)* Note: NOT efficacy evaluable	Total (N=14)
Age, years	62.2±5.2	63.7±9.0	62.5±5.8
Sex, n (%)			
Female	5 (45.5)	2 (66.7)	7 (50.0)
Male	6 (54.5)	1 (33.3)	7 (50.0)
Race, n (%)			
White	10 (90.9)	3 (100)	13 (92.9)
Black or African American	1 (9.1)	0	1 (7.1)
FAP Disease Primary Site, n (%)			
Duodenum	8 (72.7)	1 (33.3)	9 (64.3)
Rectum/Pouch	3 (27.3)	2 (66.7)	5 (35.7)
Spigelman Stage at Baseline, n (%)			
Stage 0	0	1 (33.3)	1 (7.1)
Stage I	1 (9.1)	2 (66.7)	3 (21.4)
Stage II	3 (27.3)	0	3 (21.4)
Stage III	5 (45.5)	0	5 (35.7)
Stage IV	1 (9.1)	0	1 (7.1)
Unknown	1 (9.1)	0	1 (7.1)
Total Polyp Burden at Baseline, mm	78.7±76.3	0	61.9±74.8
Median	45.0	0	27.0

Plus-minus values are means ±SD. Percentages may not total 100 due to rounding
**Only patients from Phase 2 have FAP-related information since no endoscopy assessments were performed for Phase 1b participants.*

1 REC-4881: SAFETY

PHASE 1B AND PHASE 2

REC-4881 SUMMARY OF ADVERSE EVENTS

Event, n (%)	Placebo (N=2)	REC-4881 4 mg (N=16)[3]	REC-4881 8 mg (N=3)	REC-4881 Total (N=19)
Any Treatment Emergent Adverse Event (TEAE)	**2** (100)	**13** (81.2)	**3** (100)	**16** (84.2)
TEAEs Grade ≥3	**0**	**5** (31.2)	**0**	**5** (26.3)
Any TEAE related to study drug (TRAE)	**1** (50.0)	**13** (81.2)	**2** (66.7)	**15** (78.9)
Grade ≥3 TRAE	**0**	**3** (18.8)	**0**	**3** (15.8)
Discontinuation due to Related-TEAE	**0**	**3** (18.8)	**0**	**3** (15.8)
Dose interruption due to Related-TEAE	**0**	**1** (6.20)	**0**	**1** (5.3)
Dose modification due to Related-TEAE	**NA**	**0**[2]	**1** (33.3)	**1** (5.3)

REC-4881 PRELIMINARY SAFETY

4 mg dose:

- **Most common TRAEs**: dermatitis acneiform (50%; All G1/2), rash (31.2%; 25% G1/2 and 6% G3), diarrhea (31.2%; All G1/2), blood CPK increase (25%; All G1/2), and LVEF decrease (25%; 19% G1/2, 6% G3)
- **Grade 3 TRAEs:** Rash (6%, n=1), CRP increase (6%, n=1), LVEF Decrease (6%, n=1)[1]

8 mg dose:

- **No Grade 3 TRAEs**
- **Grade 2 TRAEs:** Rash (33%, n=1)

1. *LVEF decrease was transient, and patient recovered following drug withdrawal*
2. *4 mg is the lowest dose available in this Study*
3. *For 4mg, N=5 patients in Phase 1b and N=11 patients in Phase 2 were dosed*

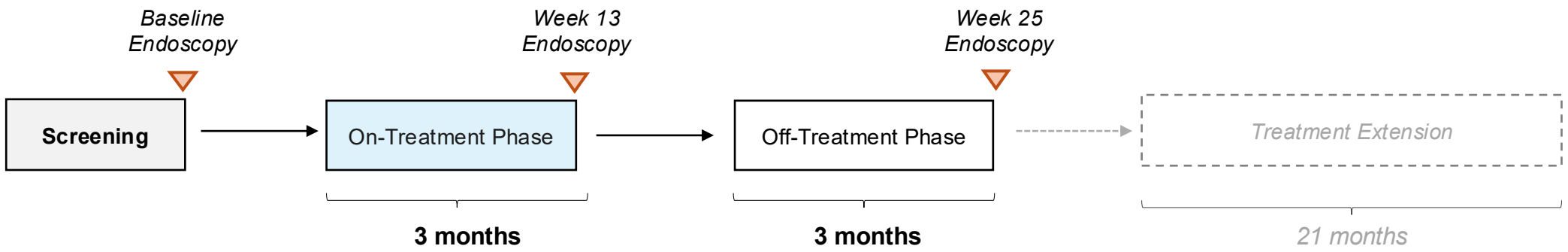
2 REC-4881: EFFICACY

PHASE 2
EFFICACY ASSESSMENTS

EFFICACY ASSESSMENTS

- Preliminary efficacy was assessed as **percent change in polyp burden** by comparing Week 13 and Week 25 to baseline polyp burden
  - Upper and lower endoscopies were performed at screening, Week 13, and Week 25
  - Polyp burden based on total polyp number and diameter
- Clinical intervention and management staging systems used:
  - InSiGHT staging system - lower GI
  - Spigelman staging system - upper GI
- **Efficacy Evaluable Population:** Defined as all participants who have measurable disease (non-zero polyp burden) at end of baseline endoscopy, received at least 75% of study drug, and have at least one post-baseline on study endoscopic assessment.

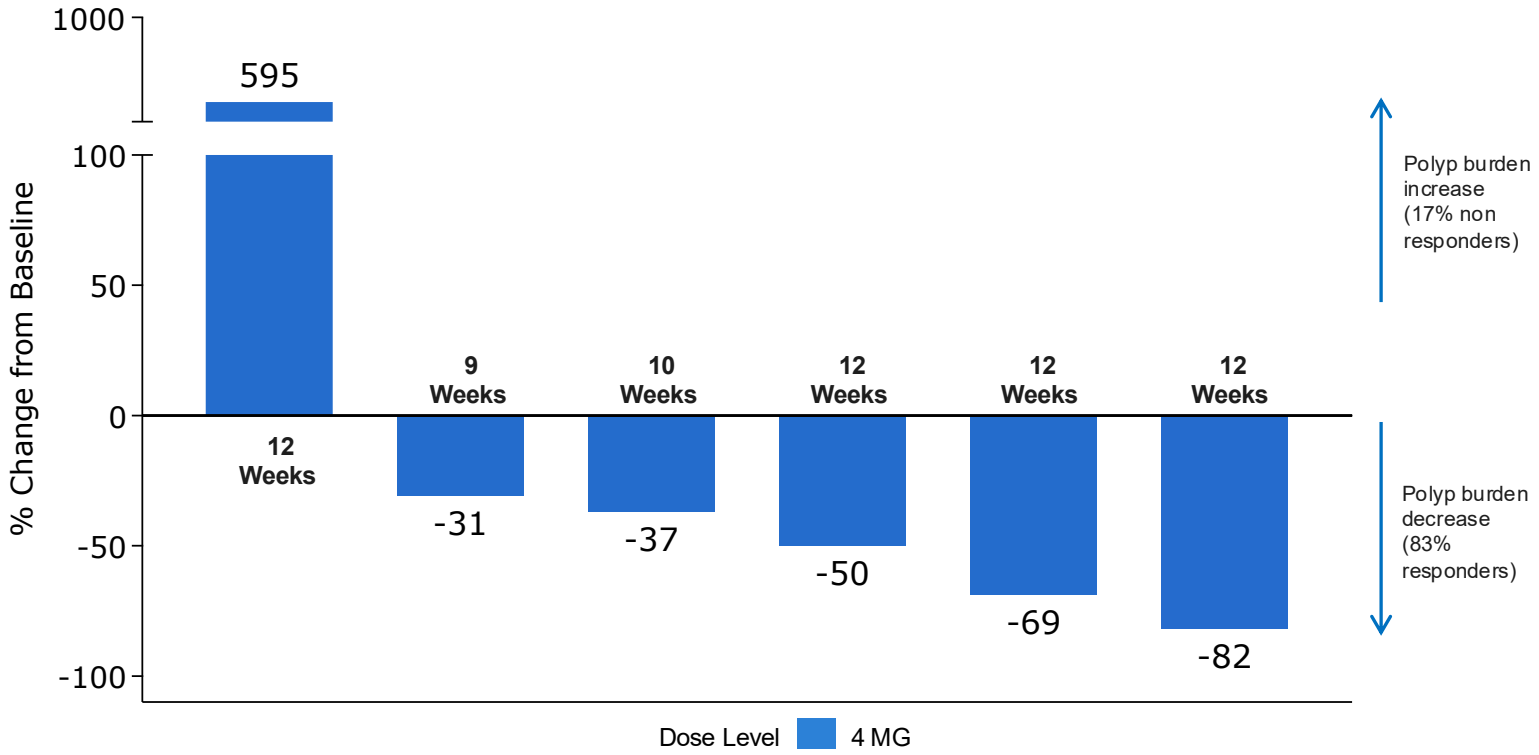
Schedule of Assessments



PRELIMINARY RESULTS

43% MEDIAN REDUCTION IN TOTAL POLYP BURDEN ON 4 MG REC-4881

Waterfall Plot of % Change from Baseline in Total Polyp Burden at Week 13/EOT



Data excludes one 4mg patient who received only 3 weeks of REC-4881 dosing and WK13 endoscopy was performed 10 weeks post last dose.
Percent (%) change from baseline calculates the change between post-resection value from screening visit to the pre-resection value at Week 13/EOT visit. Subjects with absolute value of 0 at baseline are not displayed.
Data Snapshot Date: 2025-04-02; Data Cut-off Date: 2025-03-17; Report generated on: 2025-04-28

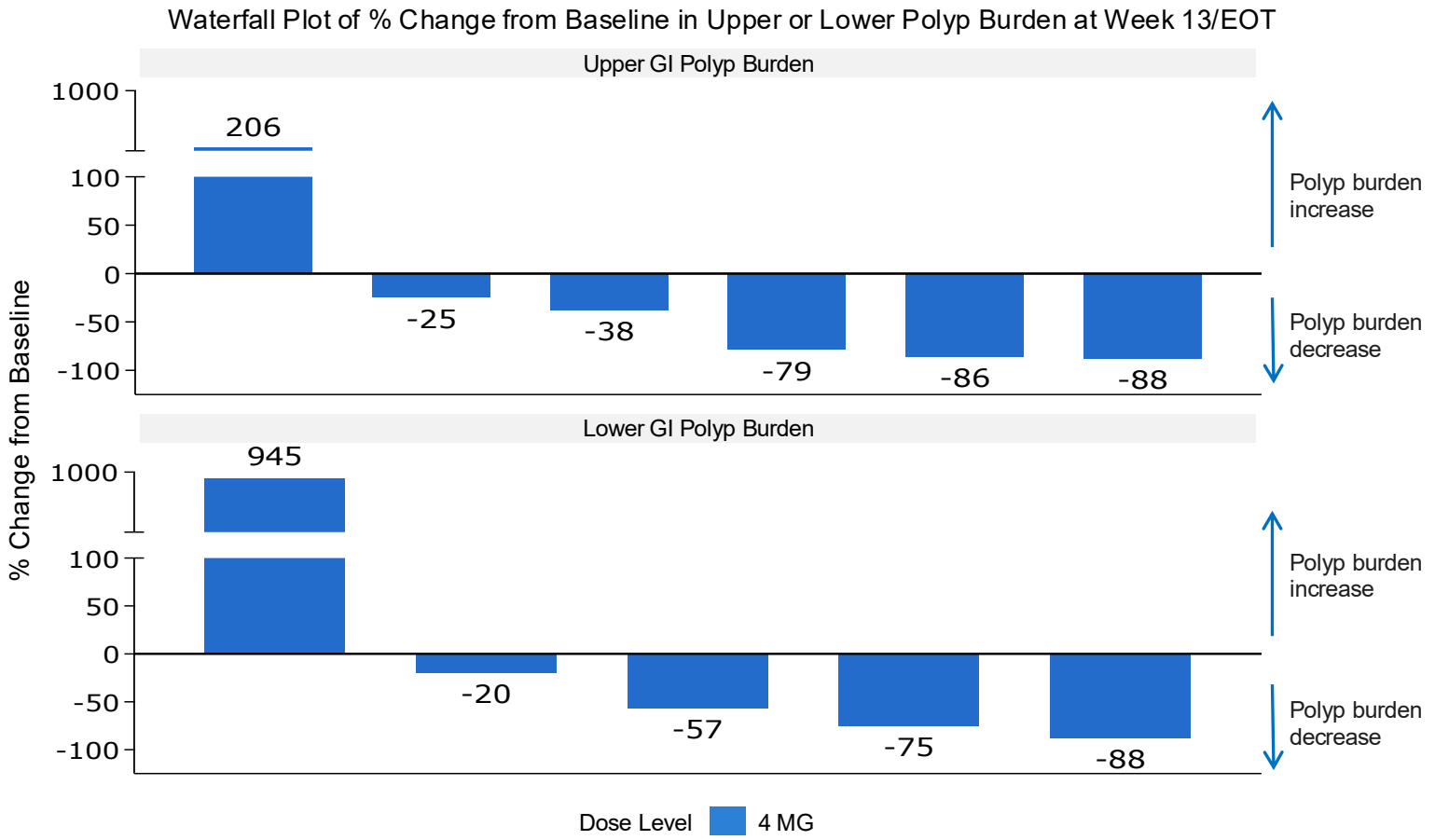
REC-4881 PRELIMINARY EFFICACY

- **6 patients** on 4 mg efficacy evaluable[1]
- **100% (n=6)** received at **least 75% of treatment**
- **43% median reduction** in total polyp burden (sum of polyp diameters) at week 13 assessment
- **At week 25, 2 out of 2 patients** on the 12-week on/12-week off regimen **maintained a durable >30% reduction**[2]

1. Efficacy Evaluable Population: Defined as all participants who have measurable disease (non-zero polyp burden) at end of baseline endoscopy, received at least 75% of study drug, and have at least one post-baseline on study endoscopic assessment.
2. A third patient, Patient 001-2001, who reached W25, did not perform W25 Assessment

PRELIMINARY RESULTS

REDUCTIONS IN POLYP BURDEN SEEN ACROSS UPPER AND LOWER GI TRACT



Data excludes one 4mg patient who received only 3 weeks of REC-4881 dosing and WK13 endoscopy was performed 10 weeks post last dose.
Percent (%) change from baseline calculates the change between post-resection value from screening visit to the pre-resection value at Week 13/EOT visit. Subjects with absolute value of 0 at baseline are not displayed.
Data Snapshot Date: 2025-04-02; Data Cut-off Date: 2025-03-17; Report generated on: 2025-04-28

REC-4881 PRELIMINARY EFFICACY

Upper GI Burden

- **6 patients** efficacy evaluable[1]
- **58% median reduction** in UGI polyp burden
- **50% patients with ≥1-point decrease** in Spigelman Stage

Lower GI Burden

- **5 patients** efficacy evaluable[1]
- **57% median reduction** in LGI polyp burden

1. *Efficacy Evaluable Population: Defined as all participants who have measurable disease (non-zero polyp burden) at end of baseline endoscopy, received at least 75% of study drug, and have at least one post-baseline on study endoscopic assessment. One patient does not have LGI anatomy.*

SUMMARY

PRELIMINARY RESULTS AND NEXT STEPS

Proof of Concept of an AI based target selection and drug development in a rare disease with unmet need

Preliminary REC-4881 safety

- **Generally well-tolerated in early analysis**
- **TRAEs in 4 mg patients**[1] : rash (45.5%), dermatitis acneiform (45.5%), blood CPK increase (36.4%), diarrhea (27.3%)
- Limited cardiac toxicity concern in Phase 2: 18% (N=2) patients reported G2 LVEF decrease

Promising early efficacy results for 4 mg REC-4881 QD for 12 weeks showed:

- **43% preliminary median total polyp burden reduction** over 3 months
  - **LGI polyp burden: 57% median reduction of**
  - **UGI polyp burden: 58% median reduction**
  - **50%** (N=3) **reduced Spigelman stage by ≥1** point at **Week 13**
- Preliminary REC-4881 data suggests a **high polyp burden reduction** in a short timeframe (3 months). Other **investigational agents have reported 20-30% reduction in 6 months**[2].

Upcoming:

- Continued enrollment across US centers with additional efficacy and safety analyses planned for H2, 2025

1. Phase 2 portion, N=11; Data cutoff 2025-03-17
2. *Steinberg et al 2000 NEJM and Burke et al 2024 Gastroenterology*

INVESTIGATORS & CLINICAL SITES

Dr. Stout	Huntsman Cancer Institute at University of Utah
Dr. Katona	University of Pennsylvania Perelman Center for Advanced Medicine
Dr. Samadder	Mayo Clinic - Scottsdale
Dr. Reiss	Tandem Clinical Research
Dr. Ogilvie	Corewell Health (Spectrum Health Hospitals)
Dr. Ness	Vanderbilt University Medical Center
Dr. Mankaney	Benaroya Research Institute at Virginia Mason
Dr. Sheela	Digestive & Liver Center of Florida
Dr. Younes	GastroOne
Dr. Vilar-Sanchez	MD Anderson Cancer Center
Dr. Boardman	Mayo Clinic - Rochester
Dr. Wise	Washington University School of Medicine
Dr. Engelking	Genetic Cancer Prevention Clinic – UT Southwestern

THANK YOU TO ALL THE TRIAL PATIENTS AND THEIR FAMILIES

