



# 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

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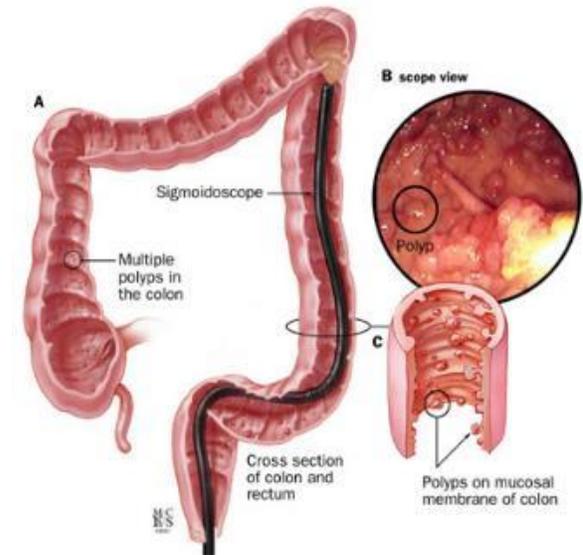
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# DISEASE CONTEXT

## 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

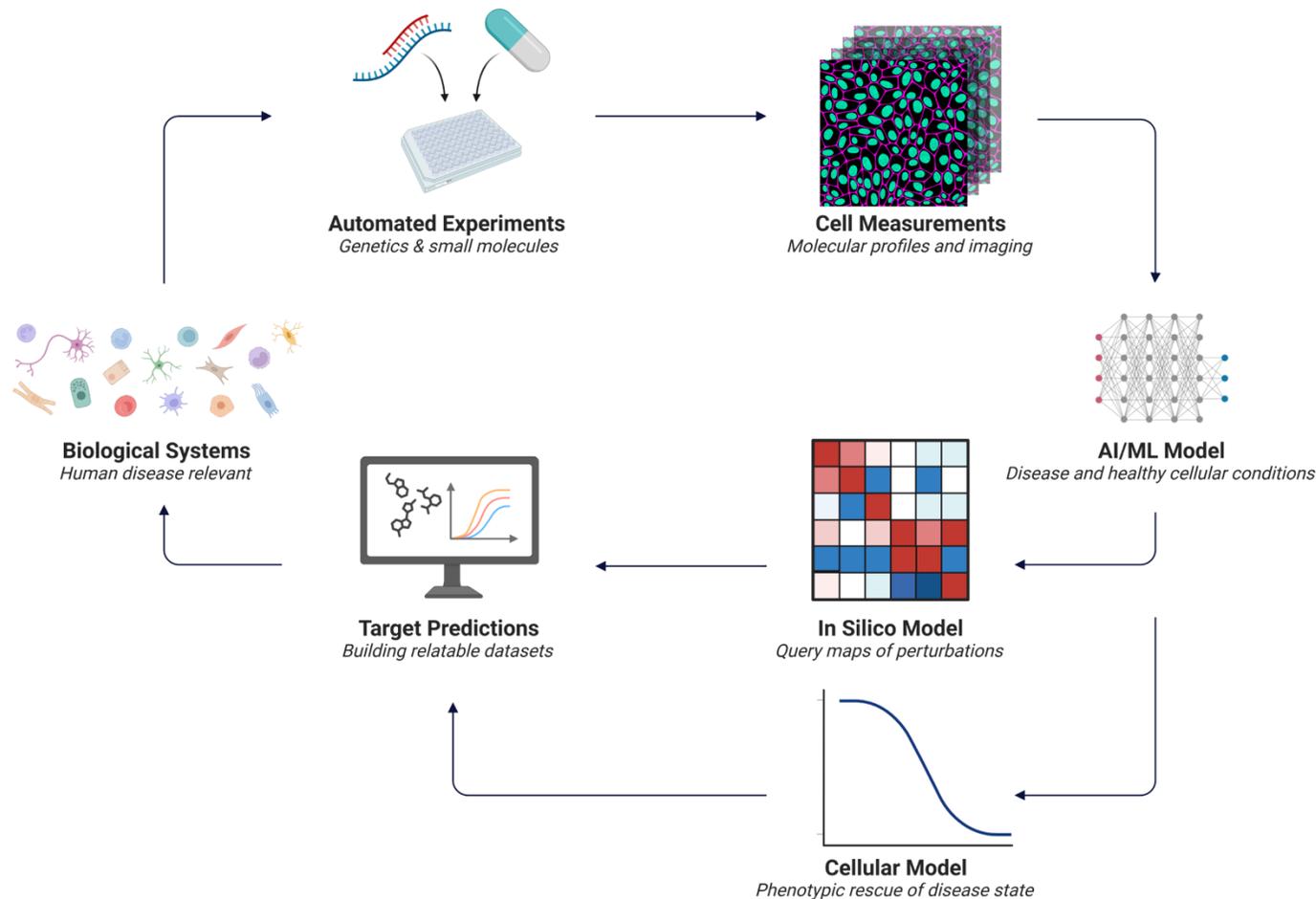
### HIGH UNMET NEED

- **~50,000** Diagnosed US + EU5<sup>1</sup>
- **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

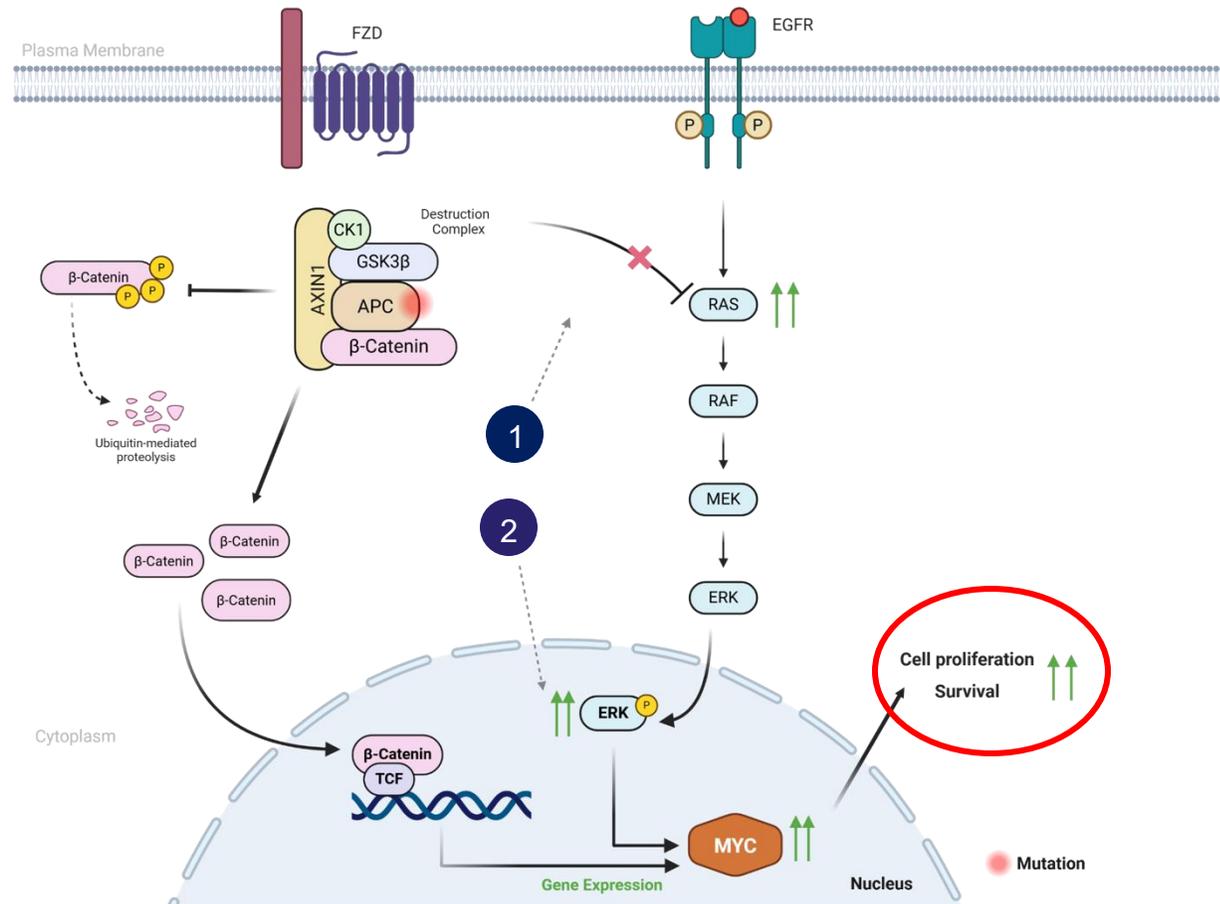


## METHODOLOGY

- 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

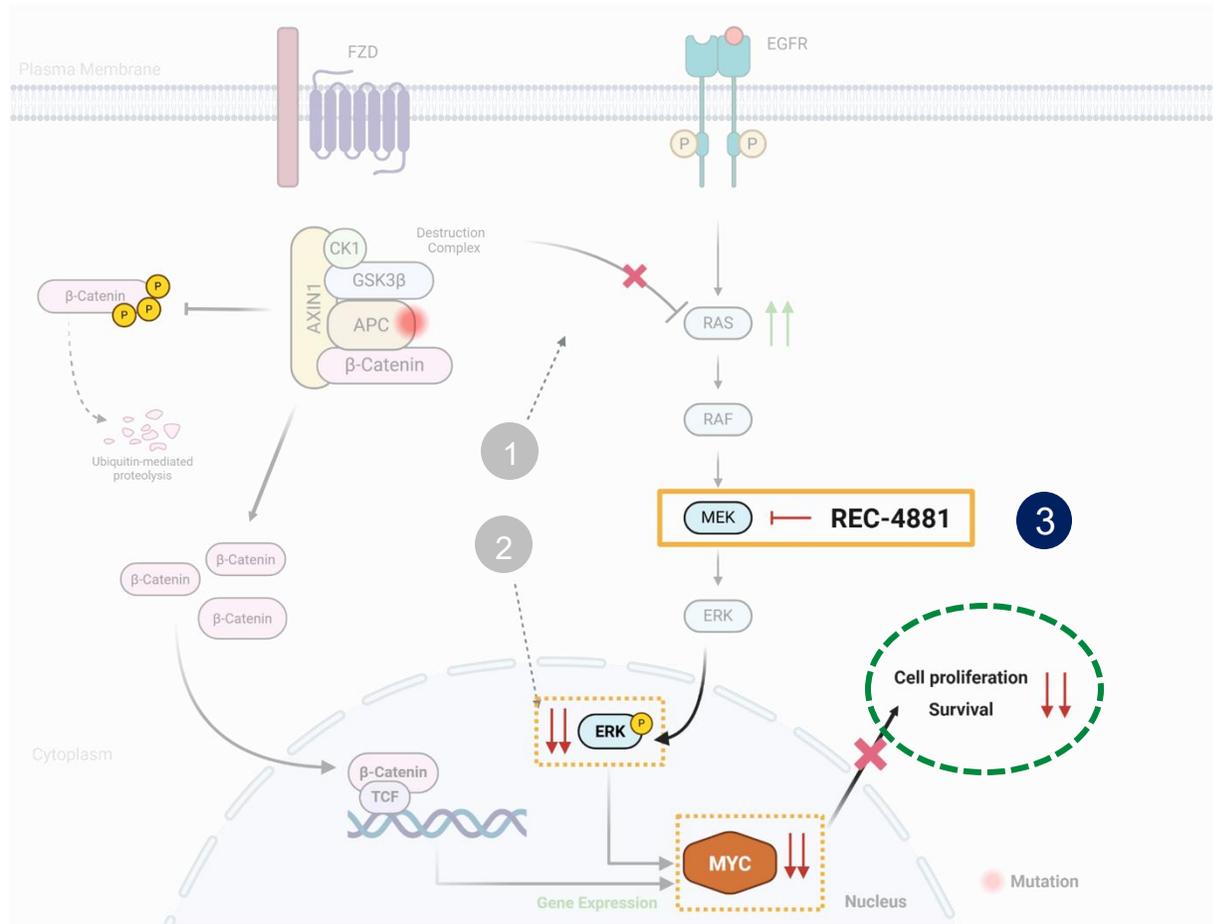


- 1 Inactivating mutations in *APC* mimic a Wnt-on state in the absence of Wnt ligands
- 2 This induces RAS stabilization and aberrant signaling through MEK to increase MYC gene expression

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

# MECHANISM OF ACTION

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



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

3

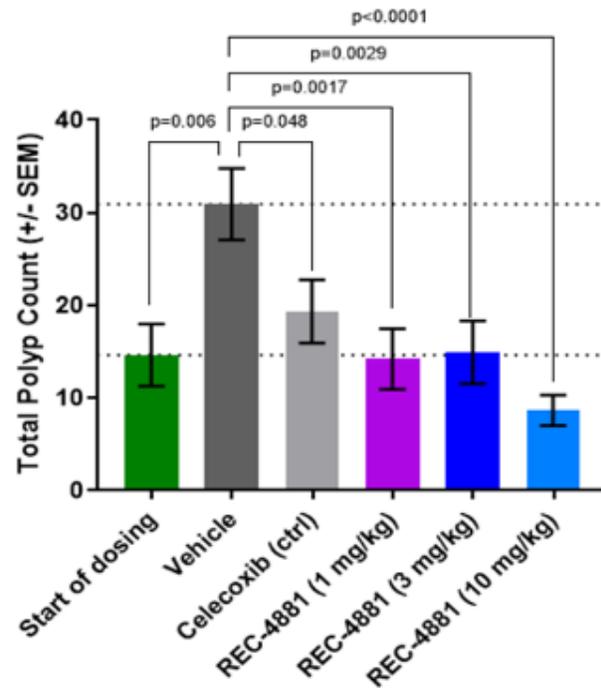
### REC-4881:

- Inhibits MEK 1/2 which is hypothesized to recover the destabilization of RAS by the  $\beta$ -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  $\mu$ M

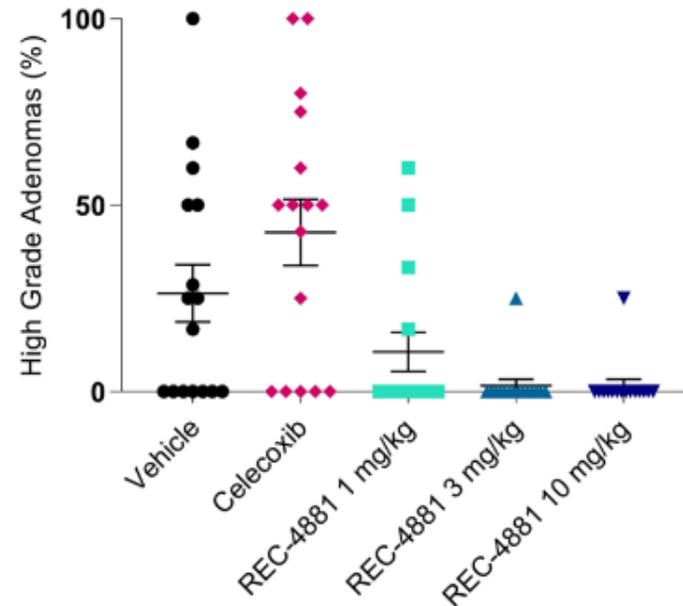
# PRE-CLINICAL DATA

## 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<sup>1</sup>

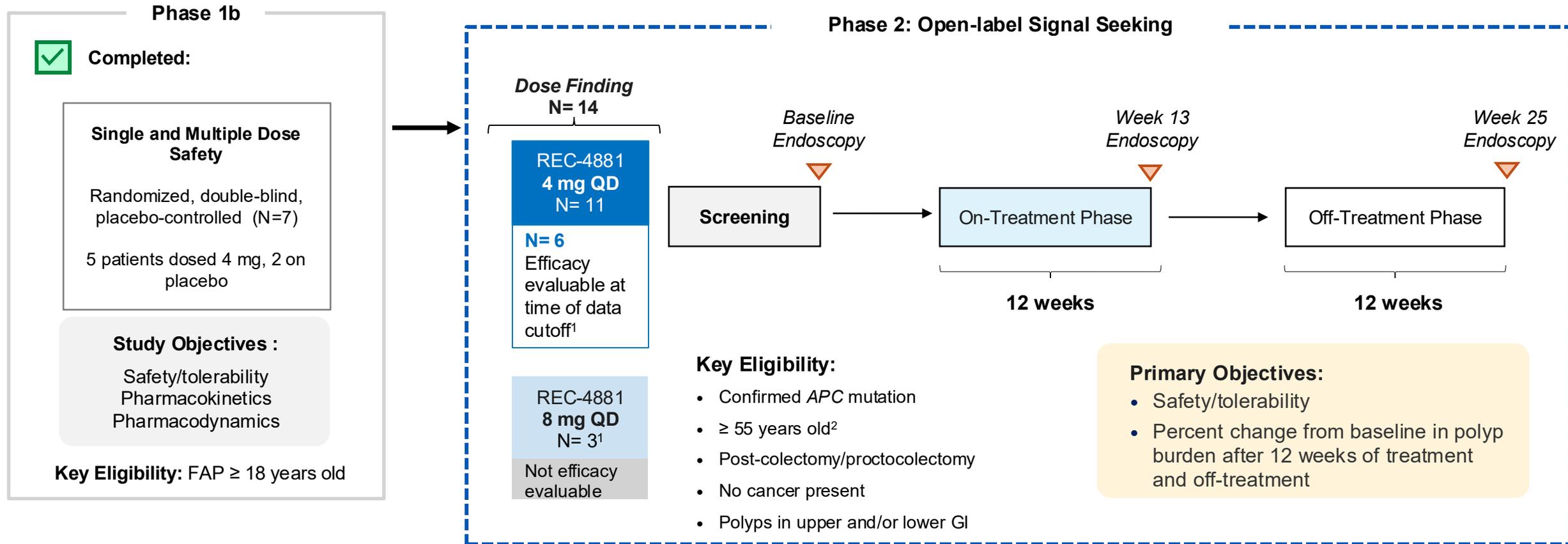
#### REC-4881:

- Reduces polyp count more effectively than celecoxib in APC<sup>min/-</sup> 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<sup>min</sup> 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**



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

# 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)
<b>Age, years</b>	62.2±5.2	63.7±9.0	62.5±5.8
<b>Sex, n (%)</b>			
Female	5 (45.5)	2 (66.7)	7 (50.0)
Male	6 (54.5)	1 (33.3)	7 (50.0)
<b>Race, n (%)</b>			
White	10 (90.9)	3 (100)	13 (92.9)
Black or African American	1 (9.1)	0	1 (7.1)
<b>FAP Disease Primary Site, n (%)</b>			
Duodenum	8 (72.7)	1 (33.3)	9 (64.3)
Rectum/Pouch	3 (27.3)	2 (66.7)	5 (35.7)
<b>Spigelman Stage at Baseline, n (%)</b>			
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)
<b>Total Polyp Burden at Baseline, mm</b>			
Median	78.7±76.3 45.0	0	61.9±74.8 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) <sup>3</sup>	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 <sup>2</sup>	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)<sup>1</sup>

#### 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



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**REC-4881:  
EFFICACY**

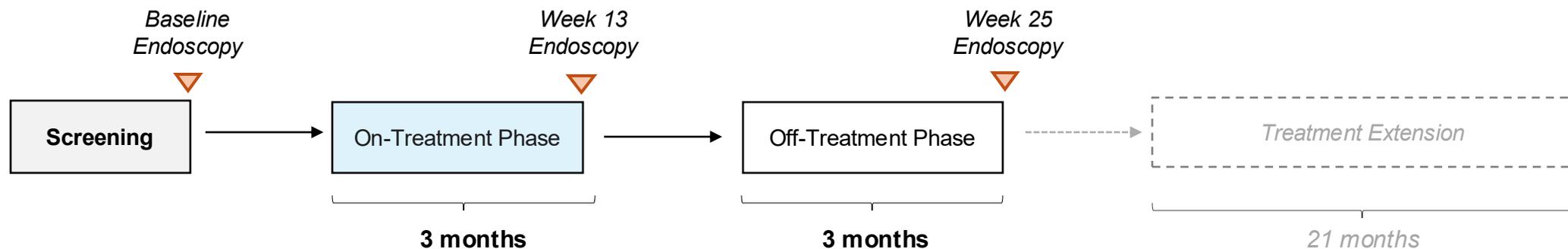
# PHASE 2

## 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.

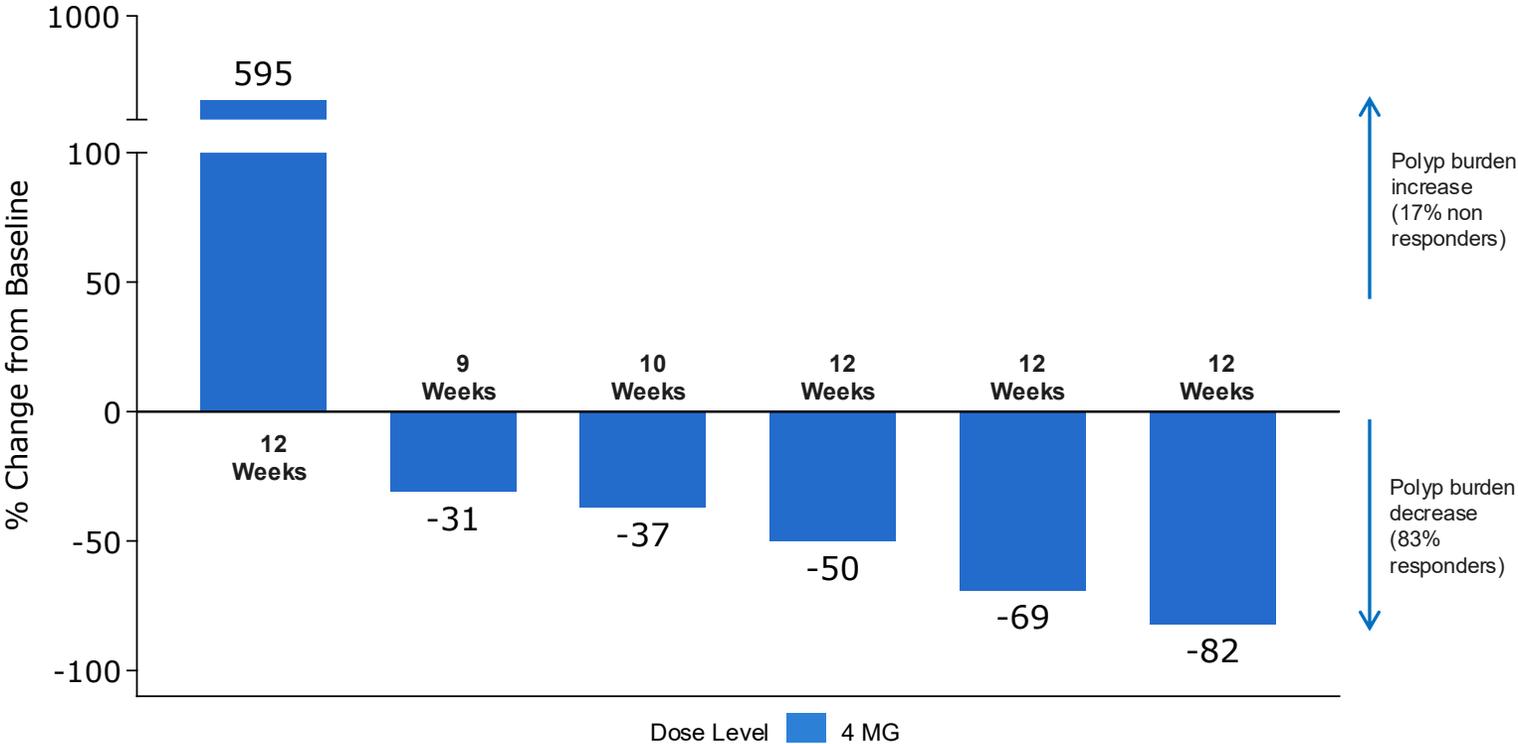
### Schedule of Assessments



# 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



### REC-4881 PRELIMINARY EFFICACY

- **6 patients** on 4 mg efficacy evaluable<sup>1</sup>
- **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**<sup>2</sup>

Data excludes one 4mg patient who received only 3 weeks of REC-4881 dosing and WK 13 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.

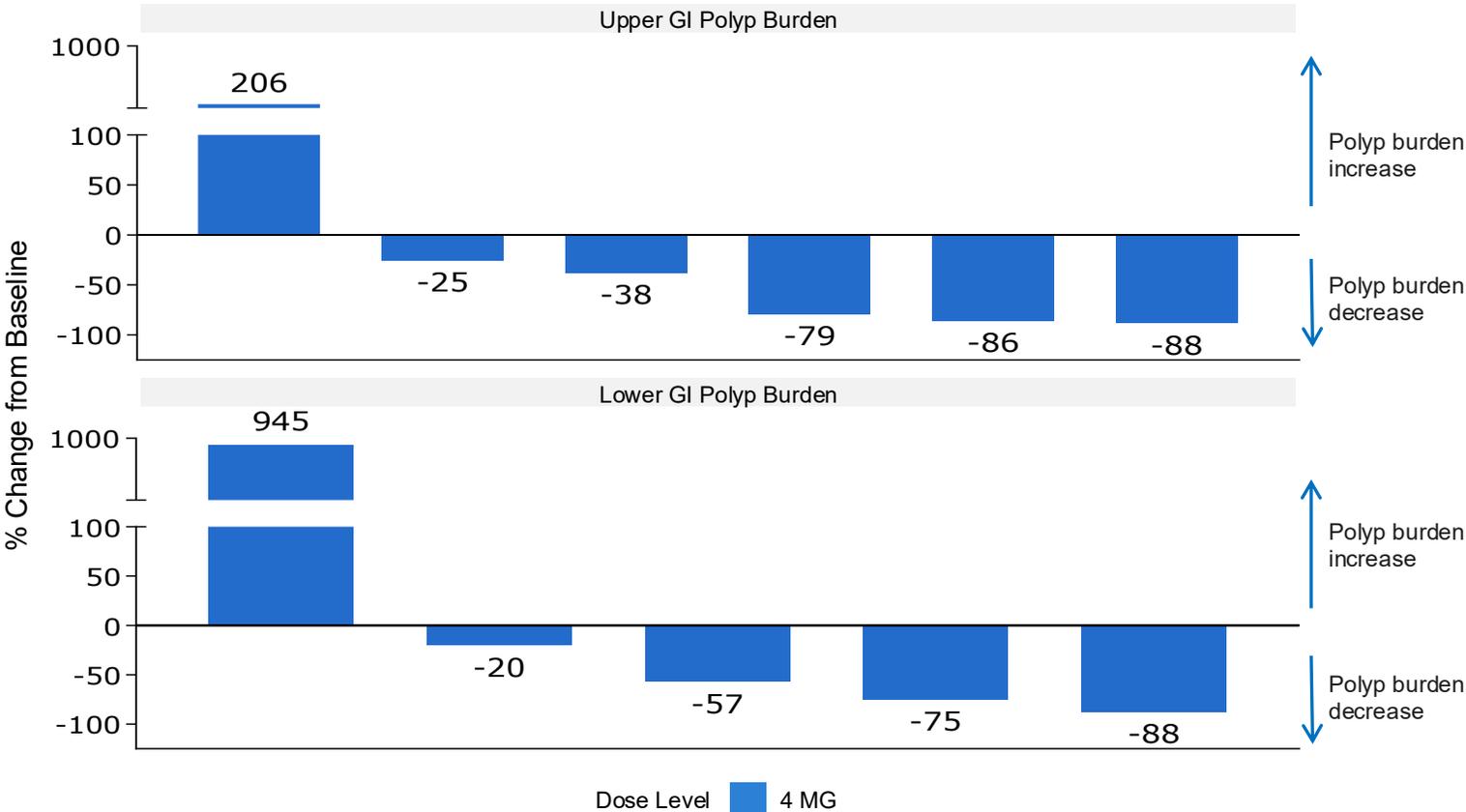
Data Snapshot Date: 2025-04-02; Data Cut-off Date: 2025-03-17; Report generated on: 2025-04-28

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

Waterfall Plot of % Change from Baseline in Upper or Lower 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 postresection 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<sup>1</sup>
- 58% median reduction in UGI polyp burden
- 50% patients with  $\geq 1$ -point decrease in Spigelman Stage

#### Lower GI Burden

- 5 patients efficacy evaluable<sup>1</sup>
- 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<sup>1</sup>** : 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  $\geq 1$  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<sup>2</sup>**.

**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

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<b>Dr. Boardman</b>	Mayo Clinic - Rochester
<b>Dr. Wise</b>	Washington University School of Medicine
<b>Dr. Engelking</b>	Genetic Cancer Prevention Clinic – UT Southwestern

**THANK YOU TO ALL THE TRIAL  
PATIENTS AND THEIR FAMILIES**

# Preliminary Results: 50% of patients on 4 mg REC-4881 demonstrated a reduction in Spigelman stage\*

Subject ID	Polyp Burden Screening -> W13 (CfB%)	Polyp Count Screening -> W13 (CfB%)	Spigelman Stage Screening ->W13
001-2001	-31%	-22%	NA-> II
016-2001	-50%	-56%	III -> I
016-2002	-69%	-78%	IV -> II
003-2001	-82%	-79%	III -> II
003-2002	-37%	-35%	II -> II
001-2003	+595%	+454%	II -> IV

>20% decrease	±20% increase/decrease	>20% increase
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## REC-4881 Preliminary Efficacy

- **Three patients** with a  $\geq 1$ -point change in Spigelman Stage
- **Effects in upper GI include** polyp burden reduction, polyp count, and Spigelman downstaging

\*Spigelman Stage can be confounded by sampling errors



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