MEK1/2 Inhibitor

REC-4881

May 2026

From platform discovery to positive clinical data: REC-4881's emerging potential for treatment of familial adenomatous polyposis

High Unmet Need in FAP

- **>50,000 patients** in US/EU5
- **Lifelong** surveillance and **life altering surgeries**
- **No approved** pharmacotherapy

Rapid Polyp Burden Reduction

- **Meaningful polyp reduction** at 4 mg in **majority of patients** after 12 weeks of treatment

Safety Data Update

- **Most common TRAEs in line with MEK1/2 class effect** (*incl. dermatitis acneiform, CPK increase, rash)*
- **Most Grade 1/2, low rates of Grade 3, no grade 4/5**

First Platform to Clinical Proof of Concept

- Recursion's **unbiased AI-driven phenotypic approach** uncovered MEK1/2i as a mechanism that rescues APC-deficient cells
- First to clinically investigate **MEK1/2 inhibition for FAP**

Durable Polyp Burden Reduction

- **Significant polyp burden reduction** maintained **in most patients** after 12 weeks off-treatment

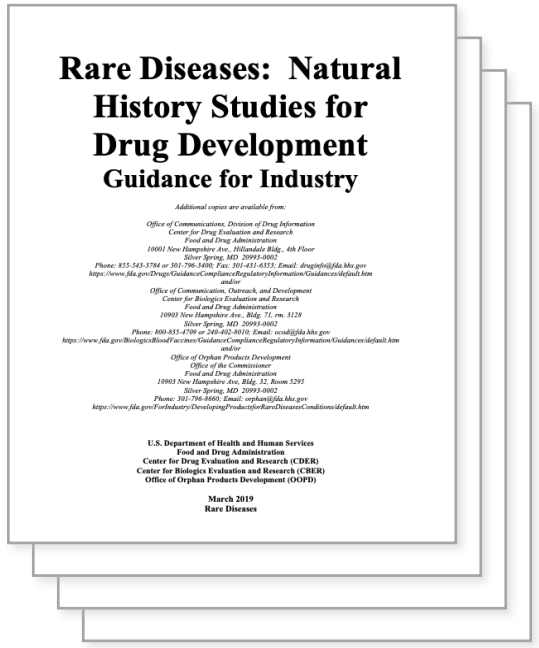
Path Forward

- **Update on FDA engagement** to define a potential registration path (2H26)
- Expand population from **≥55 to 18 years old** and further optimize **dosing** schedule

Recursion

Natural history RWE: Quantifying FAP disease progression to contextualize TUPELO program and inform regulatory path

Natural history data generation is critical in rare disease drug development, and noted by health authorities in numerous guidances[1]


Rare Diseases: Natural History Studies for Drug Development
Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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March 2019
Rare Diseases

Leveraged our ClinTech platform and academic partnerships to run **large-scale real-world evidence (RWE) analytics** to contextualize TUPELO program

1. Understand FAP burden in US and inform future trial design

- Analyzed more than 1,000 US FAP patients and 250,000 physician notes
- Custom LLM-based pipeline to assess disease progression and treatment patterns

1. Supported by multiple guidances including: U.S. Food and Drug Administration. Rare Diseases: Natural History Studies for Drug Development (Draft Guidance for Industry) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2019 Mar; U.S. Food and Drug Administration. Rare Diseases: Considerations for the Development of Drugs and Biological Products (Guidance for Industry) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2023 Dec; U.S. Food and Drug Administration. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (Guidance for Industry) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2023 Aug; and others

Recursion

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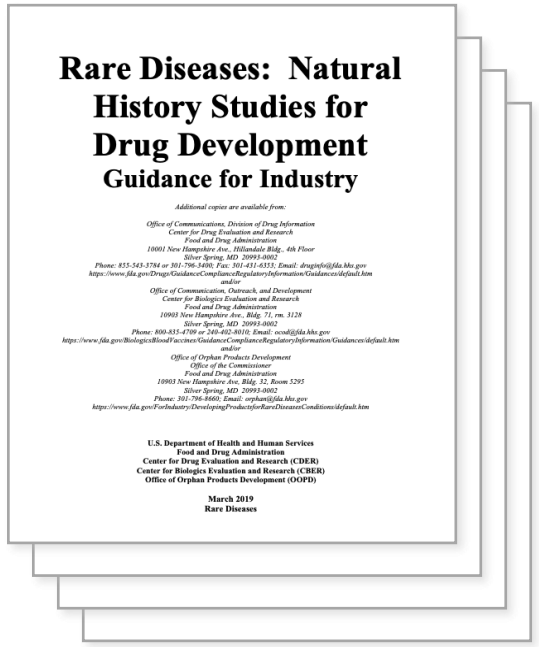
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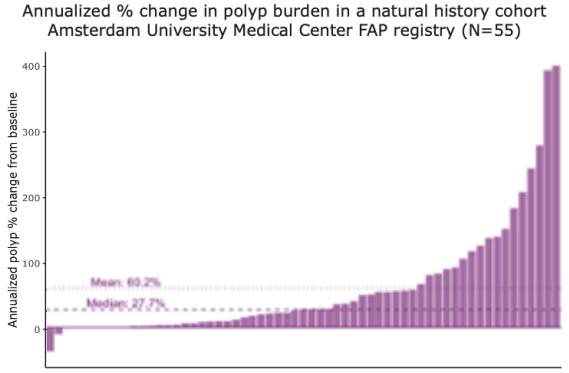
March 2019
Rare Diseases

Leveraged our ClinTech platform and academic partnerships to run **large-scale real-world evidence (RWE) analytics** to contextualize TUPELO program

2. Contextualize efficacy in TUPELO relevant population

- Registry from one of the largest and longest running real-world FAP cohorts with ~200 patients with ~20 years of follow up
- Quantify natural change in polyp burden



In collaboration with Amsterdam University Medical Center

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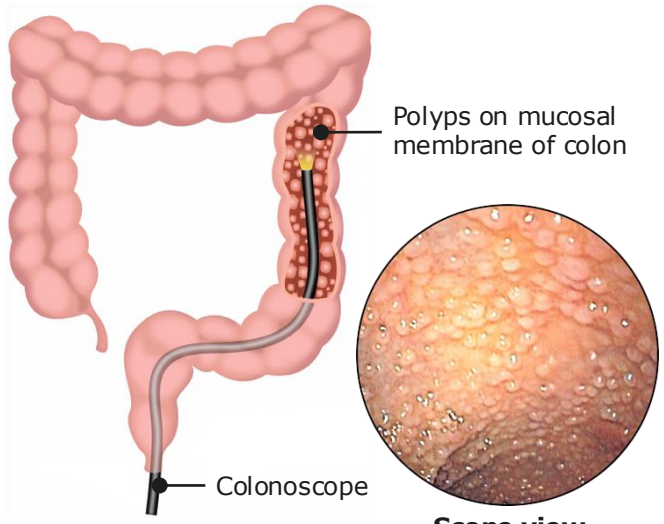
Recursion

Disease context: FAP is a rare disease characterized by extensive polyps in the GI tract, with no approved pharmacotherapies

Disease Background

- **Orphan disease** caused by autosomal dominant **inactivating mutations in *APC*[1]**
- **One of the most clinically significant hereditary colorectal cancer syndromes**
- Majority of patients will develop 100s-1000s of colorectal adenomas with **near-100% CRC risk** by age ~40 in absence of surgery or excisions
- Adenomas **progressively accumulate** with **limited evidence** of **spontaneous regression**, driving disease burden throughout life
- Lifetime of endoscopic surveillance, frequent excisional interventions, **life-altering surgeries**, and poor QoL, morbidity and mortality



Scope view source: Samir at the English-language Wikipedia, CC BY-SA 3.0, via Wikimedia Commons

High Unmet Need

- **>50,000** addressable patients in US + EU5[2]
- **Surgery** as the only standard-of-care
- Current medical therapies have **no impact on slowing disease progression**
- **REC-4881** may be positioned to fill a significant unmet need with **no approved pharmacotherapies**

1. 20-30% of FAP patients have de novo mutations with no family history. Half E et al, *Orphanet J Rar Dis.* 2009
2. Internal company estimates

Recursion

Patient journey: FAP is a lifelong continuum of disease progression and intervention, driven by chronic polyp growth

100s of polyps develop in adolescence; progress to CRC by age 40 if left untreated

Colectomy typically occurs in the early 20s to prevent malignant transformation[1]

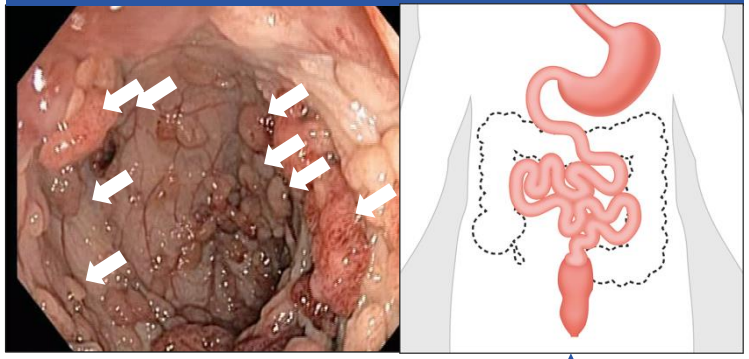
Retained rectum/neo-rectum continue to develop **progressive polyposis**

~50% of patients require rectum or pouch removal due to uncontrolled polyps, while others remain at high risk[2]

~90% of FAP patients develop **duodenal adenomas**, often progressive

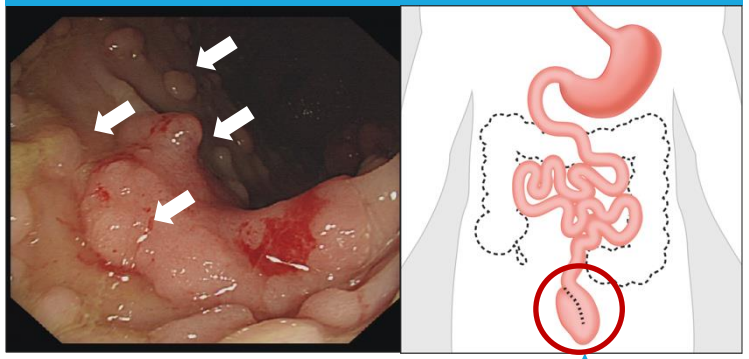
6% eventually undergo **duodenectomy** — one of the most complex GI surgeries[3]

Adolescence to early adulthood:
Colectomy: colon removal



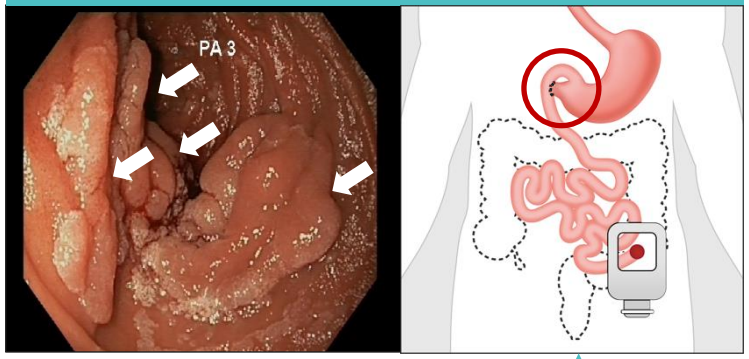
Eliminates immediate cancer risk in colon but does not stop ongoing polyp formation in the rectum/pouch or duodenum

Post colectomy disease:
Removal of rectum & high-risk polyps



Life-altering surgery that affects continence, fertility, and long-term GI function

Upper GI progression:
Duodenectomy: duodenum removal



High-morbidity intervention performed solely to control polyp growth

Note: There is a high degree of variability in SOC across practices and/or regions

1. Vasen HFA et al. Optimizing the timing of colorectal surgery in patients with Lynch syndrome: A review. Scand J Gastroenterol. 2019 May;54(5):541-8
2. Aziz O et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg. 2006 Apr;93(4):407–17.
3. Karstensen JG et al. Endoscopic indicators in patients with familial adenomatous polyposis undergoing duodenal resections – a nationwide Danish cohort study with long-term follow-up. Fam Cancer. 2024 Nov;23(4):607–615.

Recursion

ClinTech insights: Real-world US electronic health records and physician notes highlight disease progression in FAP patients

1,068 FAP patients and 256,000 physician notes were analyzed during period of 2017-2025[1]

> "No polyps were removed given there were an **innumerable amount (>300)** and removal would not be endoscopically feasible."

> "[they] had **greater than 10 surgeries and multiple revisions** of [their] colectomy and resection of [their] small bowel."

> "[they] underwent a Whipple procedure because the **duodenal and ampullary polyp burden was too high**."

- Patients commonly had disease **progression and continuous intervention**
  - Limited evidence of spontaneous polyp burden reduction in any FAP patient
- Frequent polypectomies with **at least 5 polyps removed per patient per year**[2]
  - Advanced excisions are associated with **risk of complications** such as perforation and bleeding[3,4]
- At least **75% of patients had a major FAP-related surgery** documented[5]

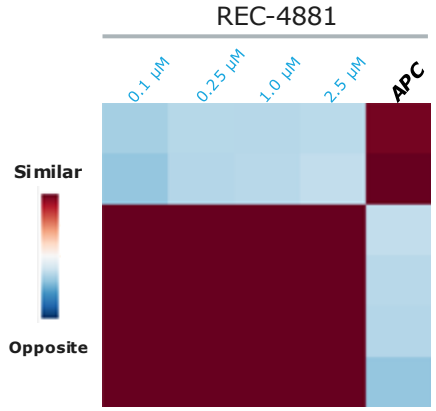
Note: all reported rates are adjusted for variable follow up time. Data analysis includes unstructured physician notes and structured components of EHRs such as billing codes for phenotype definitions.

1. Notes were processed using a custom NLP pipeline with Recursion-built and operated supercomputer, BioHive-2
2. Polypectomy rates are expected to be under-estimated due to documentation practices in routine clinical care
3. Amoyel M, Belle A, Dhooge M, et al. Outcomes of endoscopic mucosal resection for large superficial non-ampullary duodenal adenomas. Sci Rep. 2022;12:14592. doi:10.1038/s41598-022-18528-7
4. Lemos Garcia J, Rosa I, Pereira da Silva J, Lage P, Claro I. Endoscopic Approach to Duodenal Adenomas in Familial Adenomatous Polyposis: A Retrospective Cohort. GE Port J Gastroenterol. 2023;30:430-436. doi:10.1159/000527209
5. Major surgeries were defined as ileal pouch-anal anastomosis, colectomy, proctocolectomy, Whipple, ileostomy, and ampullectomy. Analysis captures documentation of "history of" such procedures. Major surgeries are expected to be underestimated due to limited follow up period and potential underreporting of patient medical history.

Recursion

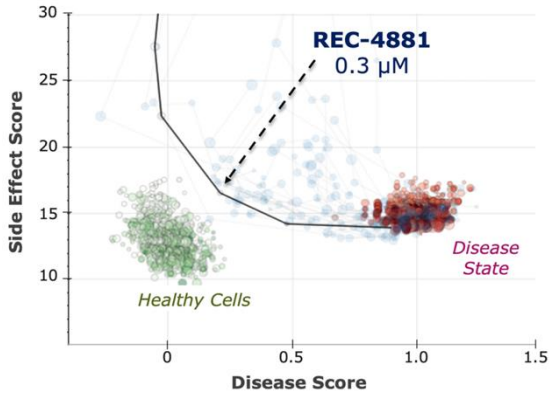
Platform insight: Unbiased AI-driven phenotypic discovery identified MEK1/2 inhibition as a novel APC-rescue mechanism, positioning REC-4881 for FAP

Identified by **phenotypic discovery** platform to rescue APC LoF



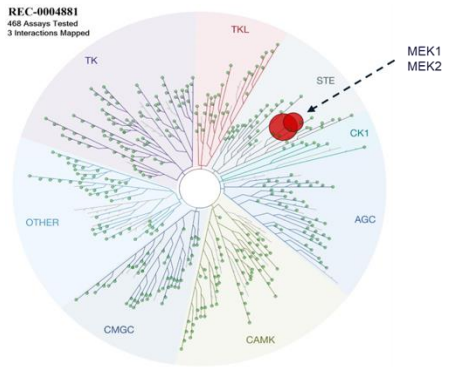
- Platform screened **thousands of compounds** in *APC* mutant rescue assays
- **REC-4881 strongly clusters with APC rescue signature**, indicating reversal of *APC* LoF induced phenotypes
- Identified a **novel, mechanistically grounded therapeutic entry point** for FAP; a disease driven by *APC* inactivation

REC-4881 **suppresses disease-inducing effect** of APC mutations



- In disease-model systems, **REC-4881 shifts *APC*-mutant cells toward healthy-state biology**
- Demonstrates **suppression of disease-inducing ERK/MAPK hyperactivation**
- **Precision mechanism aligned** with the underlying **genetics of FAP**

REC-4881 is a **potent and selective** allosteric MEK1/2 inhibitor



- From 468 kinases, **only 3 had inhibition >65% at 1 µM**
- **No significant binding inhibition** (>50%) across 71 **receptors or ion channels** at 10 µM
- Selectivity profile supports a **clean, targeted approach**

Guided by this novel insight, **Recursion in-licensed REC-4881 from a major pharmaceutical company[1] and redirected REC-4881** as a **mechanistically aligned therapeutic candidate for FAP**

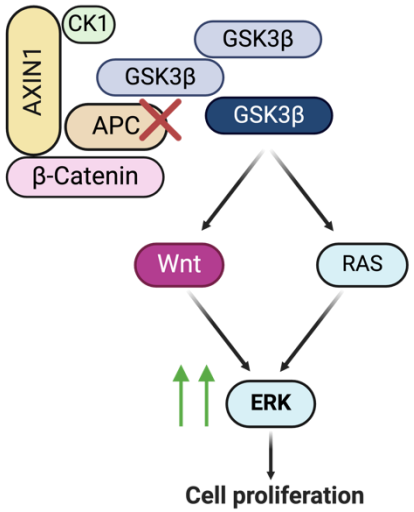
1. Recursion in-licensed REC-4881 from Takeda

Recursion

REC-4881 profile: A precision MEK1/2 inhibitor uniquely suited to the biology and anatomy of FAP

Mechanism of Action

- **APC loss-of-function drives FAP** through hyperactivation of Wnt/β-catenin and MAPK signaling, leading to uncontrolled adenoma formation
- **REC-4881 selectively blocks ERK activation (MAPK pathway)**—a key downstream consequence of APC inactivation and a driver of adenoma proliferation
- **Precision mechanism aligned with the underlying genetics** of FAP



Differentiation

- Potential **first-in-disease** and **best-in-class** for FAP
- **Potent, non-competitive, allosteric** MEK1/2 inhibitor
- Oral 4 mg dose is **pharmacologically active** with meaningful target engagement
- PK/PD profile supports **localized GI activity enriching at the disease site**

	REC-4881[1]
Half-Life (hr)	**48-60**
Dose Regimen	**4 mg QD**
COLO-205 Cells[2] In Vitro (nM)	**0.54**
MEK1 IC_{50} (nM)[3]	**3**
Mean Clinical Concentration (unbound nM)	**0.37**
Unchanged Fecal Percent of Dose (%)	**17**

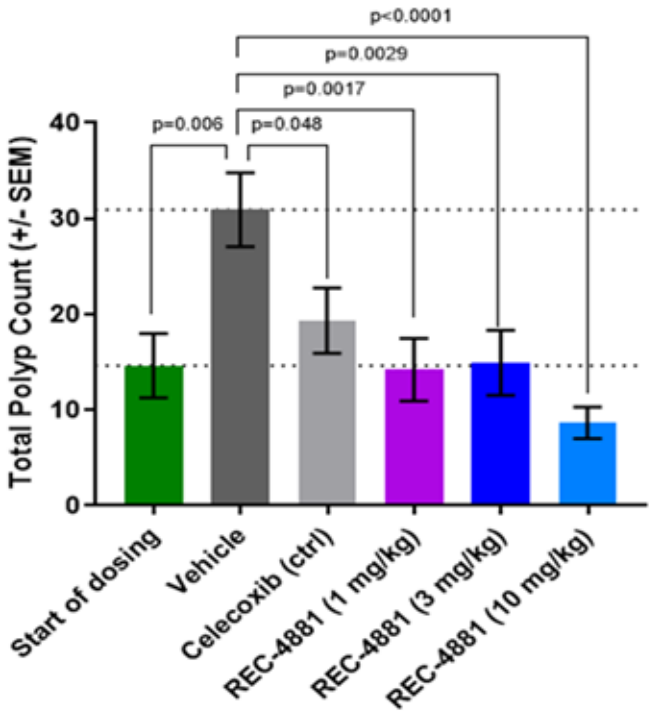
REC-4881's high GI excretion and long half-life supports targeted exposure at GI adenomas — the primary sites of disease in FAP

1. Data on File
2. COLO-205 is a cell line originated from the ascitic fluid of a 70-year-old Caucasian male with colon adenocarcinoma
3. Measured in a biochemical assay

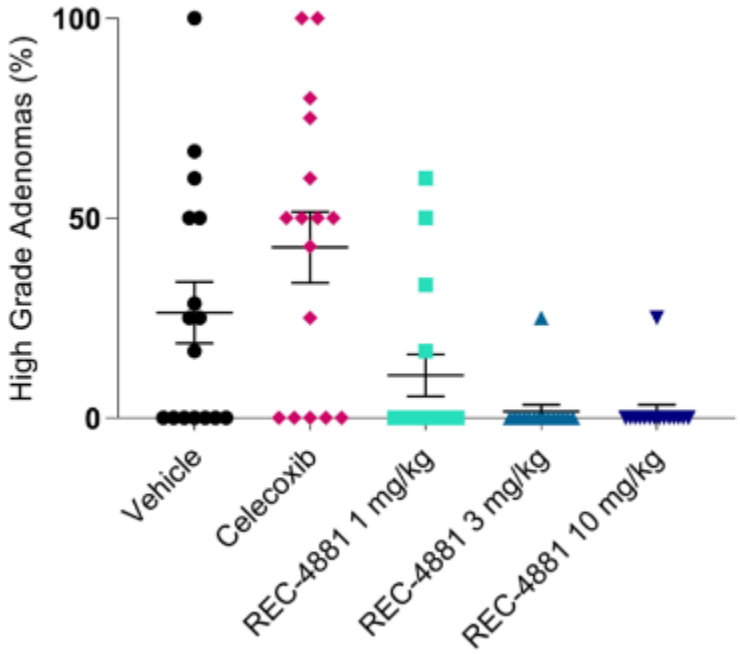
Recursion

Preclinical data: REC-4881 reduced total polyps and high-grade adenomas in APC$^{min/+}$ FAP models

Mean Polyps Per Group[1]



% Pre-Cancerous Polyps[2]



Preclinical Summary

APC$^{min/+}$ Mouse Model of FAP

- **Significant reduction in polyp count**, outperforming celecoxib at clinically relevant exposures[3]
- Decreases both **polyp number** and **pre-cancerous adenomas**

1. 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.
2. 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
3. Estimate celecoxib dose used equivalent to 400 mg BID human dose based on estimated water intake at 100mg/kg

Recursion

Phase 2: REC-4881-201 study design & objectives

Safety, tolerability, PK/PD, and efficacy of once-daily REC-4881 for 12 weeks in FAP

TUPELO

Screening

- Confirmed *APC* mutation
- ≥55 years old[1]
- Post-colectomy/ proctocolectomy
- No active cancer
- Polyps in upper and/ or lower GI tract

Baseline Endoscopy

Week 13 Endoscopy

Week 25 Endoscopy

12 week on-treatment phase
REC-4881 Ph 2: 4 mg QD
N=14 (safety evaluable)
N=12 efficacy evaluable[2]

12 week off-treatment phase

Primary Objectives

- Safety/tolerability
- Efficacy: Percent change from baseline in polyp burden (sum of polyp diameters, mm) after 12 weeks of treatment and 12 weeks off-treatment

*In parallel, **Natural History Study** conducted analyzing RWD from ~200 FAP patients with ~20 years of follow-up[3]*

Note: REC-4881 Ph 2 was also tested N=2 patients in 8 mg QD. One patient was excluded due to: less than 75% drug exposure (N=1) and the other patient was excluded due to having zero polyp burden at baseline (N=1)

1. After analysis in Phase 1b, the eligibility criteria was shifted to enroll only patients 55+ years of age to minimize TRAEs associated with MEK1/2 inhibition
2. 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. For 4 mg QD group, of 14 patients, 12 were efficacy-evaluable. Two were excluded due to: lack of Week 13 endoscopy and less than 75% drug exposure (N=1) and less than 75% drug exposure (N=1)
3. In collaboration with Amsterdam University Medical Center

Recursion

Phase 2: Baseline demographics and clinical characteristics

Study enrolled a clinically relevant FAP population with significant residual disease burden despite prior surgeries

Phase 2 patients in the safety evaluable population at baseline[1]

Characteristic	Ph 2 REC-4881 4 mg (N=14 safety evaluable)[2]
Age, years	61.9±4.8
Sex, n (%)	
Female	8 (57.1)
Male	6 (42.9)
Race, n (%)	
White	14 (100)
FAP Disease Primary Site, n (%)[3]	
Duodenum	11 (78.6)
Rectum/Pouch	3 (21.4)
Spigelman Stage at Baseline, n (%)[4]	
Stage 0	0
Stage I	1 (8.3)
Stage II	2 (16.7)
Stage III	7 (58.3)
Stage IV	2 (16.7)
Unknown	2 (16.7)
Total Polyp Burden at Baseline, mm	814.5±2376.7
Median	132.0

Note: Plus-minus values are means ± SD. Percentages may not total 100 due to rounding
1. Only patients from Phase 2 have FAP-related information since no endoscopy assessments were performed for Phase 1b participants
2. N=14 safety evaluable patients, N=12 efficacy evaluable patients in Phase 2
3. N=1 No LGI anatomy; N=2 No UGI anatomy
4. Spigelman Staging System is used to assess the severity of duodenal polyposis in patients with FAP. The stage is determined based on polyp number and size, histology, and dysplasia severity

Recursion

Phase 1b and Phase 2: REC-4881 summary of adverse events

REC-4881's safety profile is consistent with the MEK inhibitor class

Event, n (%)	**REC-4881 Ph 1b and 2 4 mg** (N=19 safety evaluable)[1]
Any TEAE related to study drug (TRAE)	**18** (94.7)
Grade 4/5 TRAE	**0**
Grade 3 TRAE	**3** (15.8)
Discontinuation due to TRAE	**4** (21.1)
Dose interruption due to TRAE	**2** (10.5)
Dose modification due to TRAE	**0**

REC-4881 Safety

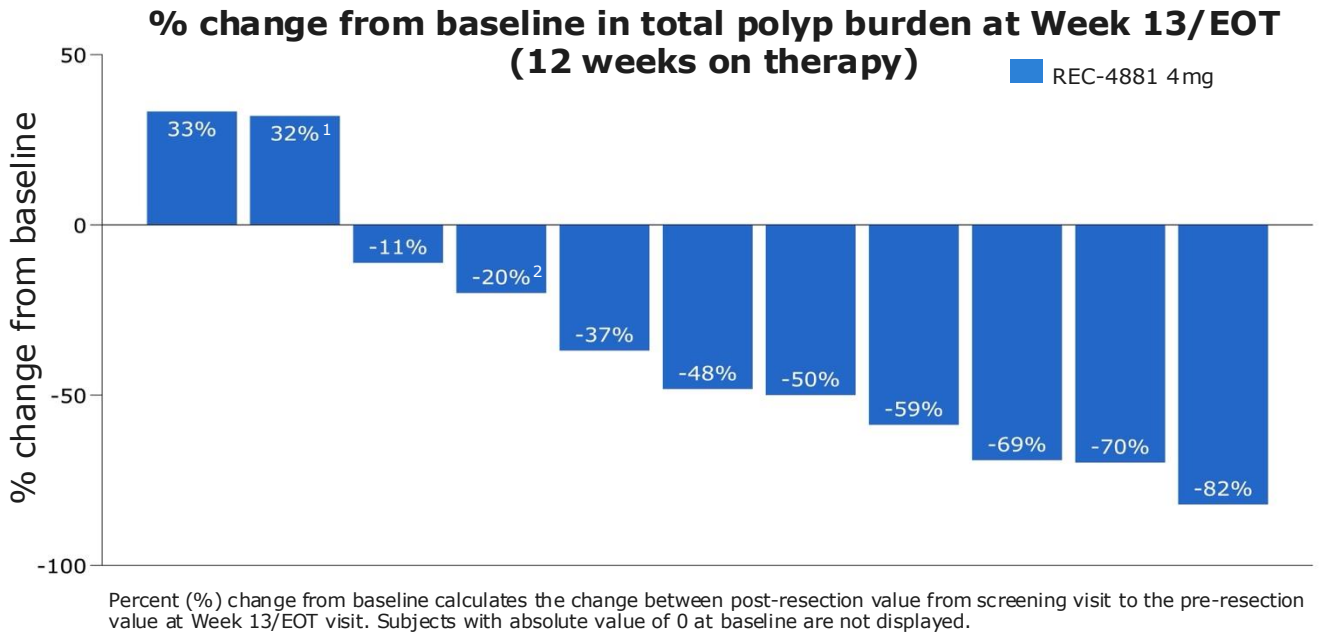
4 mg dose: Safety profile **consistent with MEK1/2 inhibition**

- **Most common TRAEs Grade 1/2:**
  - Dermatitis acneiform (57.9%; 52.6% Grade 1/2, 5.3% Grade 3)
  - Blood CPK increase (36.8%; 26.3% Grade 1/2, 10.5% Grade 3)
  - Rash (31.6%; all Grade 1/2)
  - Diarrhea (26.3%; all Grade 1/2)
  - LVEF decrease (10.5%; Grade 2)[2]
- **Low rates of Grade 3 TRAEs, no Grade 4/5 events:**
  - Grade 3 (n=3): Dermatitis acneiform (5.3%, n=1), blood CPK increase (10.5%, n=2)
- **Discontinuations (n=4) due to:**
  - Grade 1 (n=1): 1 diarrhea
  - Grade 2 (n=3): 1 retinopathy, 1 rash, 1 hypertension
- **92% common TRAEs are Grade 1/2**
- 72% common TRAEs resolved within 12 weeks[3]

Note: For 8 mg (N=2, only 1 efficacy evaluable), N=1 (50%) exhibited Grade 2 TRAEs (rash), no Grade 3 TRAEs

1. For 4 mg, N=5 patients in Phase 1b and N=14 patients in Phase 2 were dosed; safety data cutoff date of 2025-11-25
2. Decrease was transient, patients were asymptomatic and 1 recovered following drug withdrawal. Based on using absolute percent change in LVEF, which is the widely used approach to measure changes in trials, for MEK inhibitors, etc.
3. Resolved: 96% Grade 1/2, 4% Grade 3; Unresolved: 71% Grade 1/2, 29% Grade 3 (e.g., CPK, Dermatitis Acneiform, rash)

Safety & efficacy: Rapid reductions in polyp burden with 4mg dose of REC-4881 and safety profile consistent with class effects



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.

On Treatment Phase | Week 13

75% evaluable patients responded

- **Polyp burden reduction[3]: 43% median**

Summary of Adverse Events

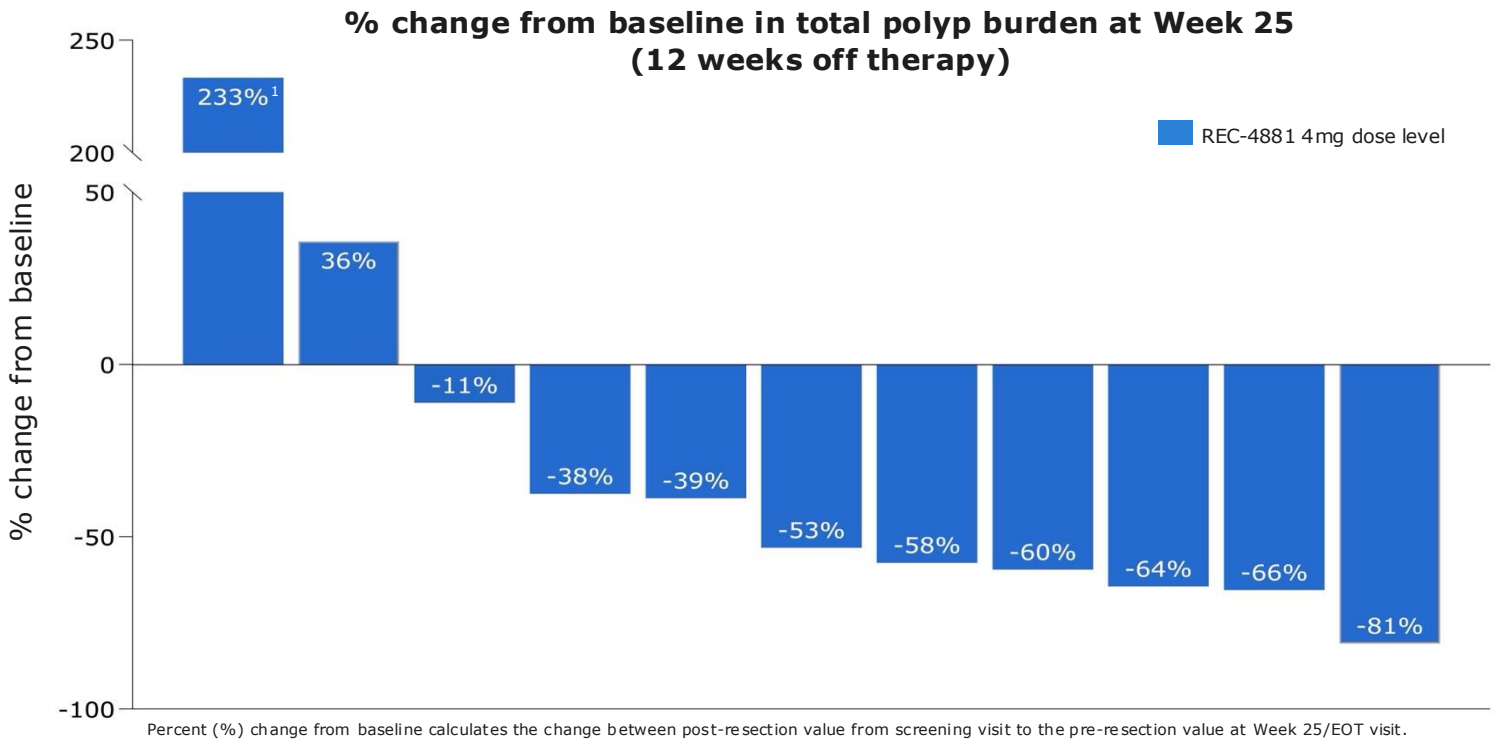
Safety profile **consistent with MEK1/2 inhibition**

- **18 TRAE events with majority Grade 1/2**:
  - E.g., Dermatitis acneiform, CPK increases, rash, diarrhea, LVEF decrease
- **Low rates of Grade 3 TRAEs (n=3)**
- **No Grade 4/5 events**
- **Discontinuations (n=4)[4]**

Note: Polyp burden defined as the sum of all diameters of polyps in the GI

1. Following the March data cut, a quality review identified suboptimal bowel preparation at baseline. To ensure an accurate, like-for-like assessment, polyp burden was re-evaluated using video review restricted to the clean distal LGI segments matched to the same anatomical regions at Weeks 13 and 25
2. Patient reached W25 but did not perform W25 Assessment
3. Efficacy Evaluable Population (n=12): 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 was efficacy evaluable after completion of W25 assessment but did not complete W13 assessment, baseline measurement carried forward for W13 assessment per SAP for missing data. Therefore, this patient contributed 0% polyp burden reduction at W13 and not shown in figure.
4. Discontinuations: Grade 1 (n=1): 1 diarrhea, Grade 2 (n=3): 1 retinopathy, 1 rash, 1 hypertension

Durability: Durable reductions in polyp burden maintained with 4mg dose of REC-4881



Off Treatment Phase | Week 25

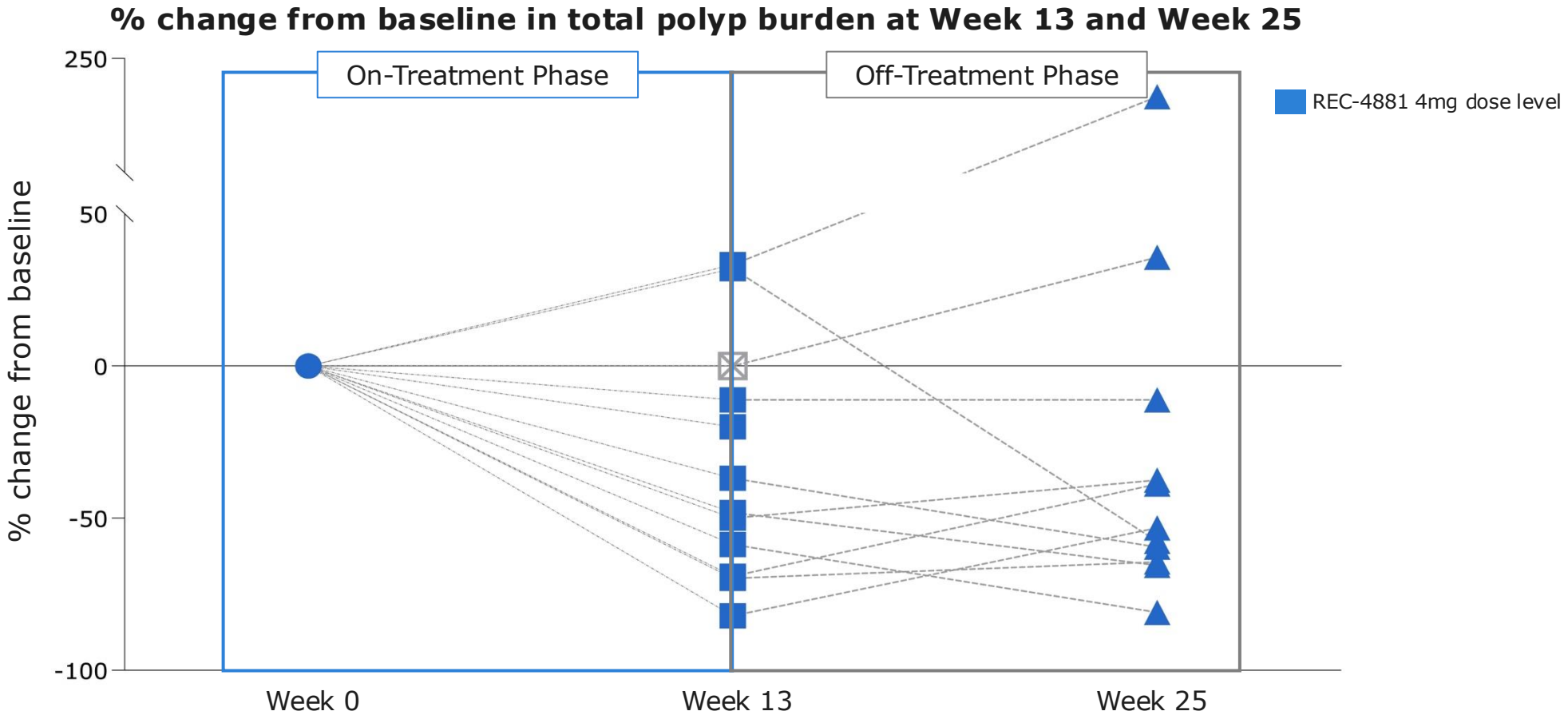
- **82% of evaluable patients responded**
- **73% achieved durable ≥30% reductions**
- **Polyp burden reduction: 53% median**

Note: Polyp burden defined as the sum of all diameters of polyps in the GI

1. Non-responder with 233% increase – polyp burden increased from 3mm to 10mm due to one polyp growth at Week 25
2. 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 who had a week 13 endoscopy did not have a Week 25 endoscopy

Recursion

3 months on and 3 months off-treatment: REC-4881 produces durable reductions in polyp burden through Week 25



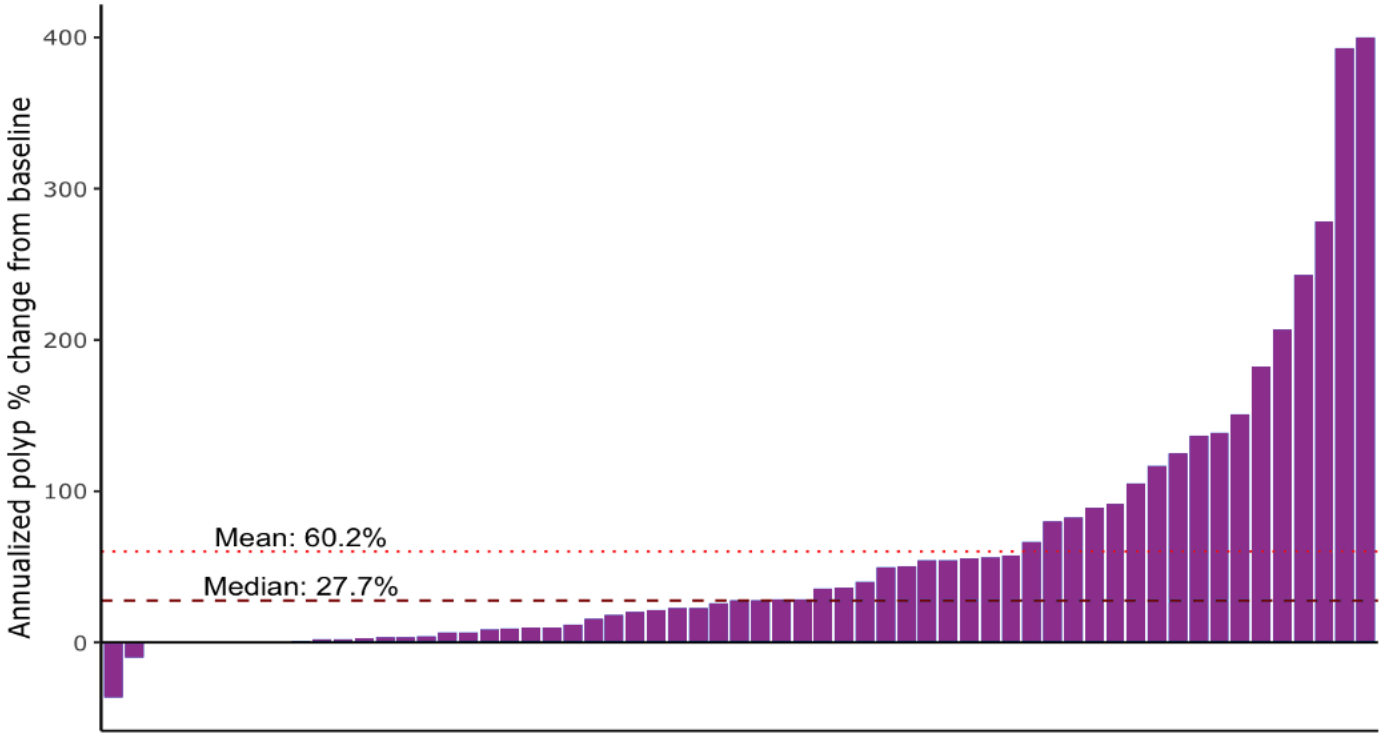
Week 25 results show that REC-4881's biological effect persists after dosing ends, with most patients maintaining meaningful reductions in polyp burden

Note: Percent (%) change from baseline calculates the change between post-resection value from screening visit to the pre-resection value at Week 13/EOT visit and Week 25/EOT. 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 was efficacy evaluable after completion of W25 assessment but did not complete W13 assessment, baseline measurement carried forward for W13 assessment per SAP for missing data (X box at W13)

Recursion

Natural history analysis: ~87% show polyp burden increase, while ~10% remained stable, highlighting the disease progression of FAP

Annualized % change in polyp burden in a natural history cohort
Amsterdam University Medical Center FAP registry (N=55)



Each bar represents one patient. Data includes 55 patients aged ≥55 with history of colectomy and measurable polyp burden at baseline endoscopy. In routine care, endoscopies for lower and upper GI are performed annually with variability. Therefore, polyp burden percent change was annualized. 52 (97%) of the 55 patients had an increase or stable polyp burden. 6 patients had separate endoscopic evaluations for upper and lower GI involvement and have repeated bars.

Natural History Study Summary

- **Key inclusion criteria of the TUPELO trial were applied** to select natural history cohort
- **Natural history** analysis showed:
  - **87% of untreated FAP patients had annual** polyp-burden increase
  - **10%** remained **stable**
  - **3% showed modest decrease**—showing spontaneous regression is rare
  - **Average of 60% polyp burden increase annually**
- Rates were annualized because **endoscopies are administered annually in routine care**
- These data are **not intended for direct comparison** with clinical trial data

Note: Natural History Analysis evaluated data from ~200 FAP patients; analysis shown represents a subset of patients who satisfy key inclusion criteria of TUPELO. Study is intended to Contextualize the TUPELO single arm data, better understand background natural history of FAP disease progression. Study limitations include: potential variability in polyp count estimation between endoscopies; endoscopies are typically conducted annually in routine care, while the TUPELO data represent polyp burden at Week 13

Week 13 Spigelman stage: REC-4881 produced Spigelman downstaging in 40% of patients, reflecting UGI disease improvement

Patient	Spigelman Stage Initial screening –> WK13 –> WK25
1	III -> III -> III
2	I -> NA[1] -> II
3	III -> II -> II
4	II -> II -> II
5	III -> II -> II
6	IV -> IV -> IV
7	III -> III -> III
8	III -> III -> NA[2]
8	III -> I -> I
10	IV -> II -> III

REC-4881 Efficacy

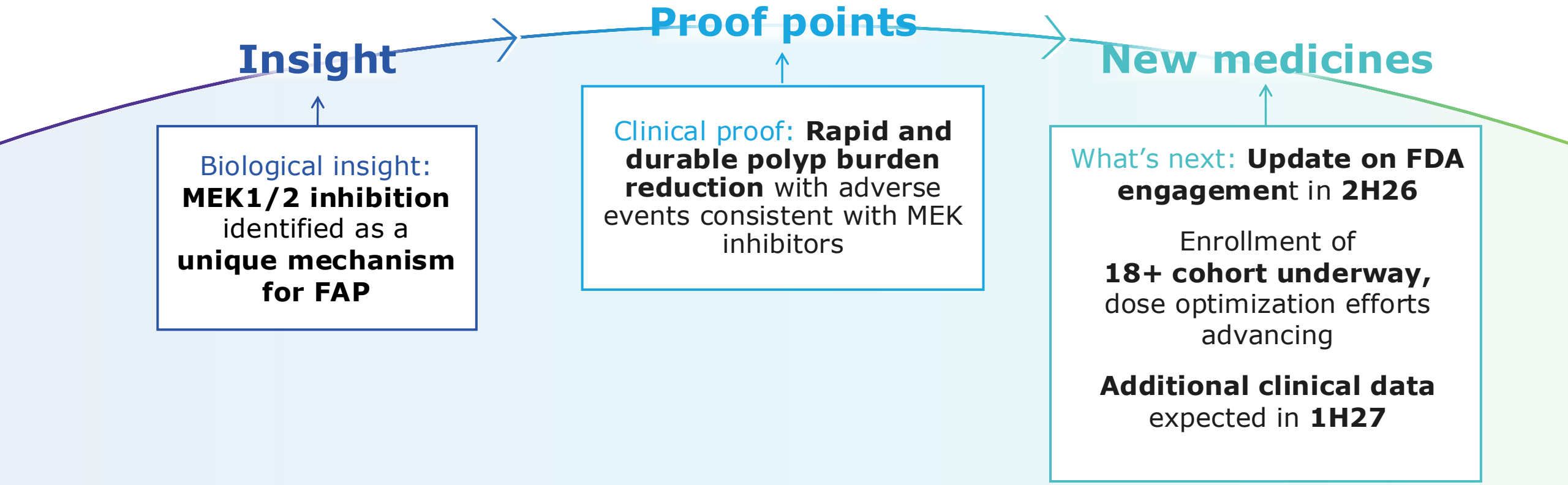
Improvements reflect **concordant reductions in the upper GI including** polyp burden reduction, polyp count, and Spigelman downstaging

- **WK13:**
  - **4/10 (40%) patients** achieved a ≥1-point change in Spigelman Stage
  - Spigelman **downstaging reflects improvement in duodenal polyposis severity** — a major unmet need with limited therapeutic options.
- **WK25:**
  - **4/10 patients maintained a** ≥1-point change in Spigelman Stage
  - 1 patient had a 1-point increase
  - 1 patient did not have Week 25 endoscopy

Natural history RWD analysis showed **20% of patients experienced an increase in Spigelman stage** between annual endoscopies in routine care. No decrease in Spigelman stage was observed.

AUMC: Amsterdam University Medical Center
Note: N=10 efficacy evaluable for UGI; 2 patients lacked UGI anatomy. Spigelman Stage can be confounded by sampling errors
1. Patient did not perform WK13 endoscopy and so no biopsy collected
2. No biopsy sample collected at WK25 to calculate Spigelman Score

REC-4881 (MEK1/2): First clinical validation of Recursion's platform – disease with no approved pharmacotherapies



Recursion