2026 CGA-IGC Annual Meeting

The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer



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The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer
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Updated Safety and Efficacy Data of REC-4881 Monotherapy in Familial Adenomatous Polyposis: Phase 1b/2 Trial Results Contextualized With Real-World Registry Data

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Relevant disclosures

- L Boardman: Site PI for clinical trials for Recursion and Adela
- N J Samadder: Consultation for Recursion Pharmaceuticals, Parabilis Pharmaceuticals
- T Ly, J Viscusi, R Gan, H Kananamedala, E Bruckheimer: Real or option ownership interest in Recursion Pharmaceuticals
- All other authors declare no conflicts of interest

Recursion's platform uncovered a novel therapeutic opportunity in FAP

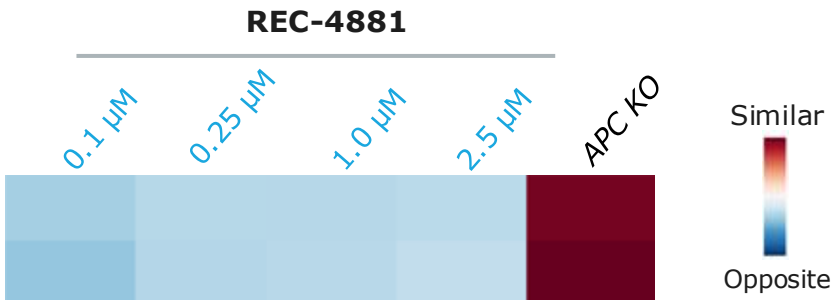
Novel insight uncovered by platform

Unbiased phenotypic screening

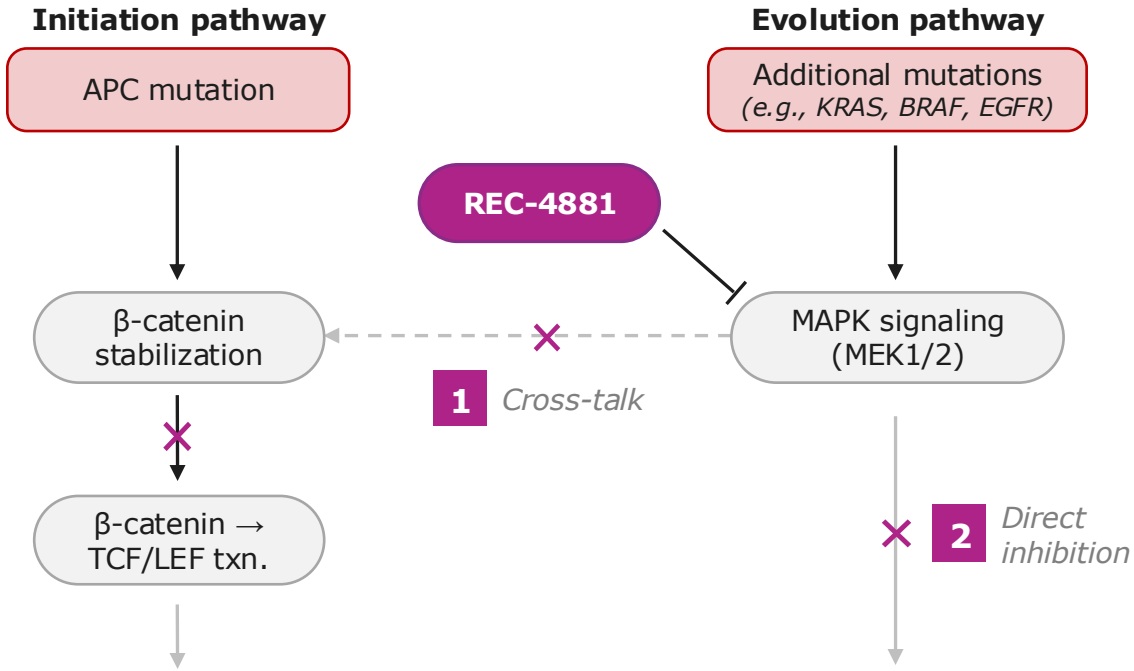
Proprietary AI foundation models analyzed cellular images to identify relationships between genetic and compound perturbations

Unexpected biological insight

MEK1/2 inhibition emerged as a potential way to reverse cellular phenotypes associated with APC loss – unappreciated synthetic rescue relationship



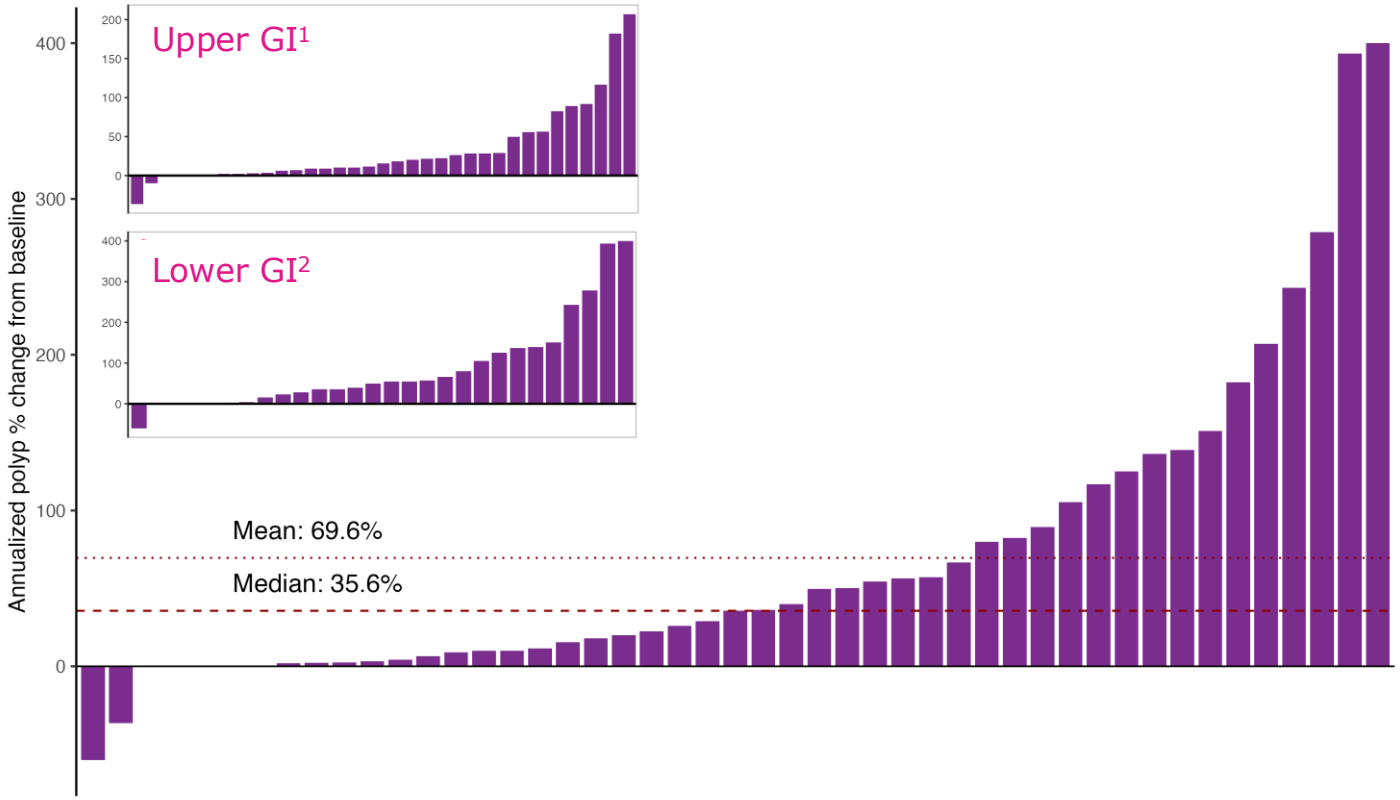
Mechanistic rationale for REC-4881



Sources: Fujishita T, et al. Cancer Sci. 2015;106(6):692–699; Blaj C, et al. Cancer Res. 2017;77(7):1763–1774; Guardavaccaro D, Clevers H. Sci Signal. 2012;5(219):pe15; Cheng YT, et al. Part Fibre Toxicol. 2026;23:4; Georgopoulos NT, et al. J Cell Sci. 2014;127(13):2967–2982.

Real world data show persistent polyp growth over time

Annualized change in total polyp burden (n=47)
Amsterdam UMC registry



- Natural history study of FAP patients 55 years and older conducted using Amsterdam UMC registry data
- 85% of evaluated post-colectomy patients had annual polyp burden increases
- Annualized increases in polyp burden observed in patients with both Upper[1] and Lower[2] GI involvement
- Findings underscore the need for pharmacologic treatment options for post-colectomy FAP patients

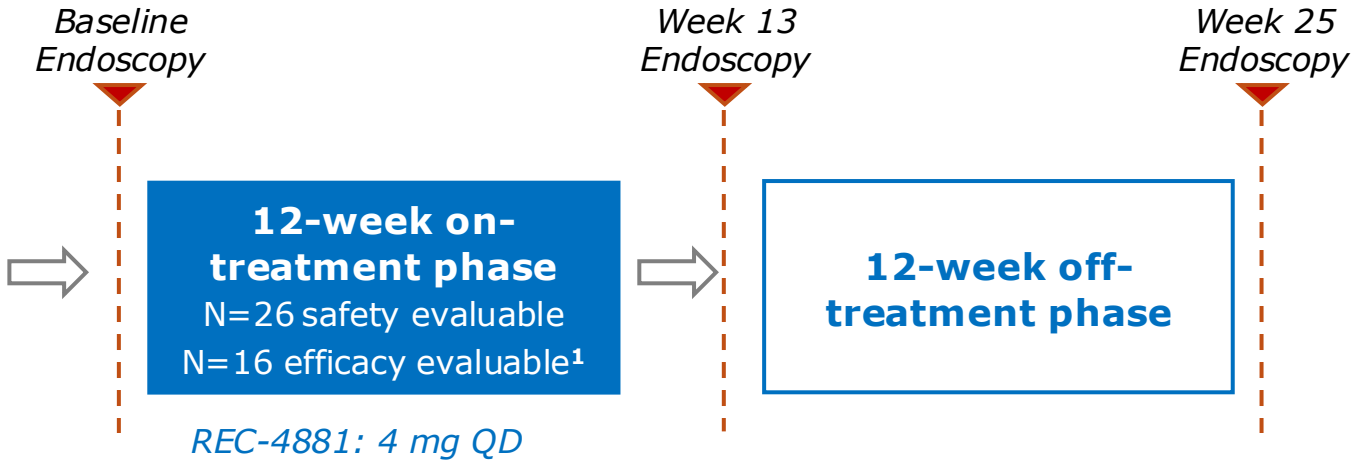
1. Mean and median annualized polyp change from baseline for patients with Upper GI involvement is 33.3% and 15.4%, respectively
2. Mean and median annualized polyp change from baseline for patients with Lower GI involvement is 87.8% and 52.2%, respectively

Note: Natural History Analysis evaluated data from ~200 FAP patients. The analysis shown is a subset of 47 patients aged ≥55 with a history of colectomy and measurable polyp burden at baseline endoscopy, matching TUPELO's original eligibility criteria. Each bar represents one patient. The analysis is intended to contextualize the TUPELO single-arm data and to better understand the background natural history of FAP disease progression. 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. These data are not intended for direct comparison with clinical trial data

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

Screening

- Confirmed *APC* mutation
- ***≥18 years old***
- Post-colectomy/ proctocolectomy
- No active cancer
- Polyps in upper and/ or lower GI tract



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 analysis of RWD from ~200 FAP patients with ~20 years of follow-up[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. For 4 mg QD group, of 21 patients, 16 were efficacy-evaluable. Three were excluded due to lack of post baseline endoscopy and two were excluded due to less than 75% drug exposure (N=2).
2. In collaboration with Amsterdam University Medical Center

Note: REC-4881 Ph 2 was also tested in N=2 patients in 8 mg QD. One patient was not efficacy evaluable due to less than 75% drug exposure (N=1)

REC-4881-201: Patient demographics

Characteristic	REC-4881 4 mg QD (N=26 safety evaluable)[1]
Age, years	54.7±12.3
Sex, n (%)	
Female	14 (53.8)
Male	12 (46.2)
Race, n (%)	
White	24 (92.3)
Not Reported	2 (7.7)
FAP Disease Primary Site, n (%)[2]	
n[3]	21
Duodenum	16 (76.2)
Rectum/Pouch	5 (23.8)
Spigelman Stage at Baseline, n (%)[4]	
n[5]	19
Stage 0	0
Stage I	1 (5.3)
Stage II	5 (26.3)
Stage III	11 (57.9)
Stage IV	2 (10.5)

1. Of 26 safety evaluable, 5 patients came from Phase 1b and 21 from Phase 2; of the 21 patients from Phase 2, 16 patients were efficacy evaluable at the time of the data cut: 2 patients were on-study at the time of the 10-Sep-26 data cut
2. N=1 No LGI anatomy; N=1 all LGI burden excised at baseline and remained 0 at week 13, N=2 No UGI anatomy
3. Only patients from Phase 2 have FAP disease information since no endoscopy assessments were performed for Phase 1b participants (n=5)
4. Spigelman Staging System is used to assess the severity of duodenal polyposis in patients with FAP. The stage is determinedbased on polyp number and size, histology, and dysplasia severity.
5. Spigelman assessment was not performed for two patients from Phase 2 lacking UGI anatomy

Favorable safety profile supports potential for chronic dosing

Event, n (%)	REC-4881 4 mg QD (N=26 safety evaluable)[1]
Any TEAE related to study drug (TRAE)	**25** (96.2)
Grade 1/2 TRAE	**21** (80.8)
Grade 3 TRAE	**4** (15.4)
Grade 4/5 TRAE	**0** (0)
Discontinuation due to TRAE	**4** (15.4)
Dose interruption due to TRAE	**2** (7.7)

80.8% patients had TRAEs ≤ Grade 2 consistent with mechanism of MEK1/2 inhibition

Most common TRAEs Grade 1/2

- Dermatitis acneiform (57.7%)
- Blood CPK increase (26.9%)
- Rash (23.1%)
- Diarrhea (19.2%)
- LVEF decrease (11.5%)[2]

Low rates of Grade 3 TRAEs, no TRAEs >Grade 3:

- Blood CPK increase (7.7%, n=2)
- Dermatitis acneiform (3.8%, n=1)
- Rash (3.8%, n=1)

Discontinuations (n=4) due to:

- Grade 1 (n=2): 1 diarrhea, 1 left atrial enlargement (pre-existing)[3]
- Grade 2 (n=2): 1 retinopathy (pre-existing ocular condition)[4], 1 rash

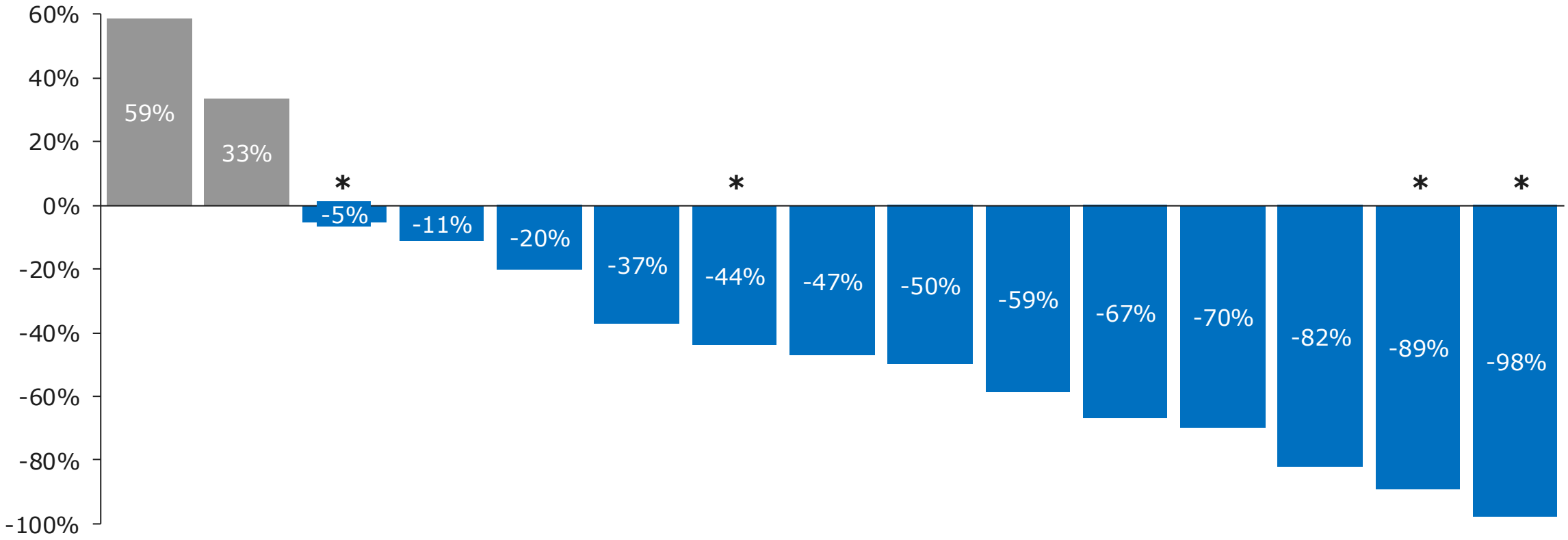
AEs were manageable and most resolved within 12 weeks off treatment

1. For 4 mg, N=5 patients in Phase 1b and N=21 patients in the 12 weeks on/12 weeks off QD arm of the Phase 2 were dosed; safety data cutoff date of 2026-09-10
2. Occurred in N=3 patients. Patients were asymptomatic and 2 returned to >50% (the 3rd patient was 49% at the end of follow-up). Based on absolute percent change in LVEF and CTCAE v5.0, the approach widely used to measure LVEF changes in trials, including for MEK inhibitors.
3. Patient had pre-existing left atrial enlargement. Protocol was subsequently amended to exclude this condition
4. Patient had pre-existing ocular condition which worsened during treatment

REC-4881 drives significant reductions in total polyp burden after 12 weeks of treatment, with 87% of patients responding

1 in 3 patients had ≥65% polyp burden reduction from baseline

Week 13 total polyp burden reduction (n=15[1])



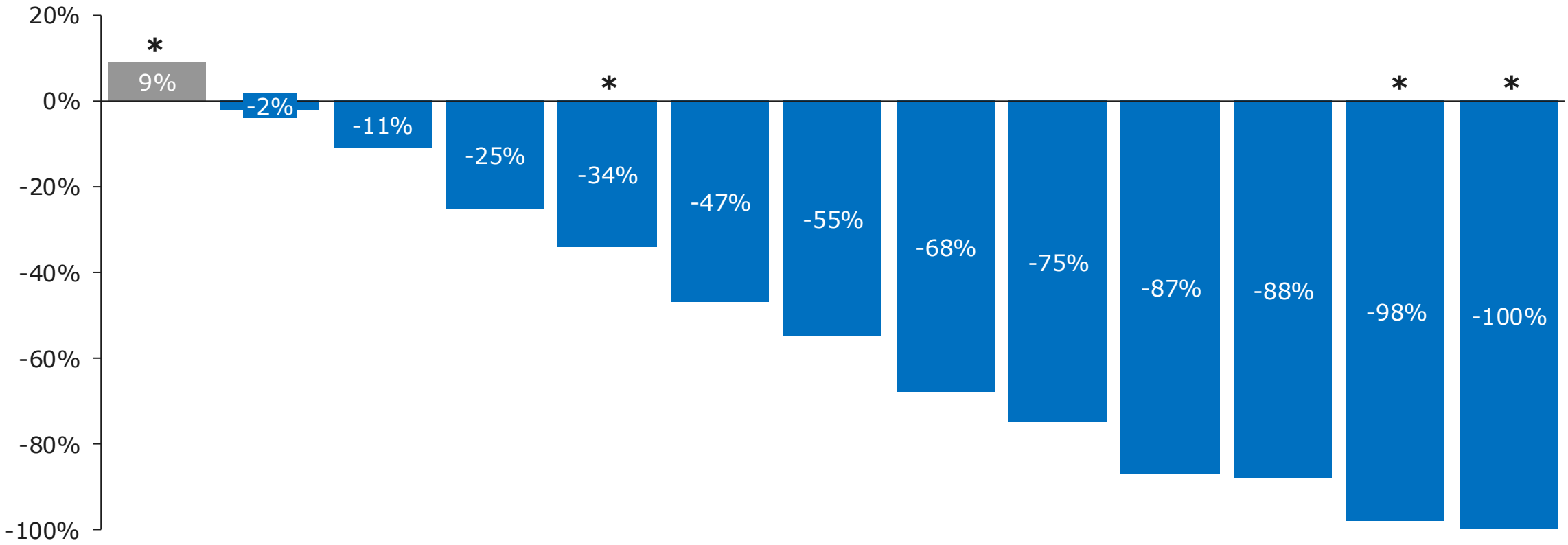
*Additional patients since previously reported data cutoff (November 25, 2025)

1. 15 of 16 efficacy evaluable patients are shown, as 1 patient did not have a Week 13 endoscopy
Note: Efficacy Evaluable (n=16); Efficacy-evaluable population defined as patients with measurable baseline polyp burden, ≥75% study drug exposure, and ≥1 post-baseline endoscopic assessment
Note: Results reflect the 10-Sep-2026 data cutoff. Data review since the last presentation also updated 2 patients after minor corrections of <5mm: -48% to -47% and -69% to -67%

Upper GI | 92% of patients had reductions in polyp burden from baseline after 12 weeks of treatment

~1 in 2 patients with ≥65% polyp burden reduction from baseline[1]

Week 13 Upper GI polyp burden reduction (n=13[2])



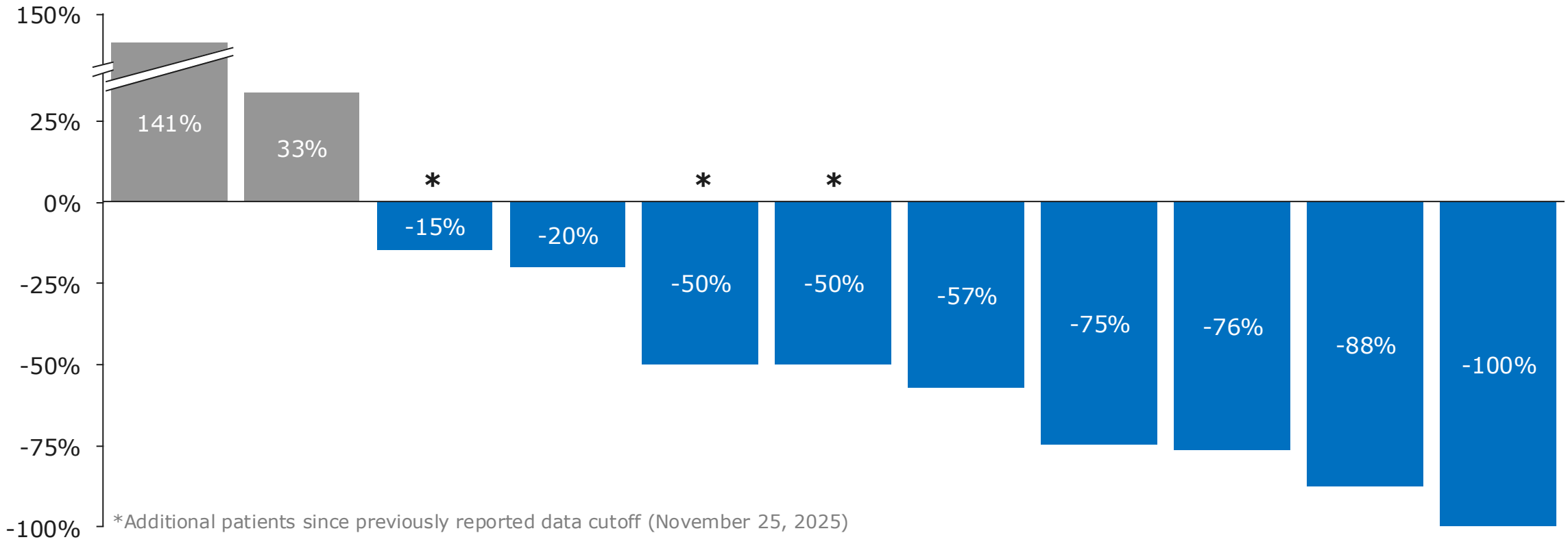
*Additional patients since previously reported data cutoff (November 25, 2025)

1. 6 of 13 (46%) patients had polyp burden reduction ≥65% at Week 13
2. Upper GI evaluable at week 13: n=13 of 16 efficacy evaluable patients; 2 patients had no upper GI anatomy and 1 did not have a Week 13 endoscopy

Lower GI | 82% of patients had reductions in polyp burden from baseline after 12 weeks of treatment

~1 in 3 patients with ≥65% polyp burden reduction from baseline[1]

Week 13 Lower GI polyp burden reduction (n=11[2])



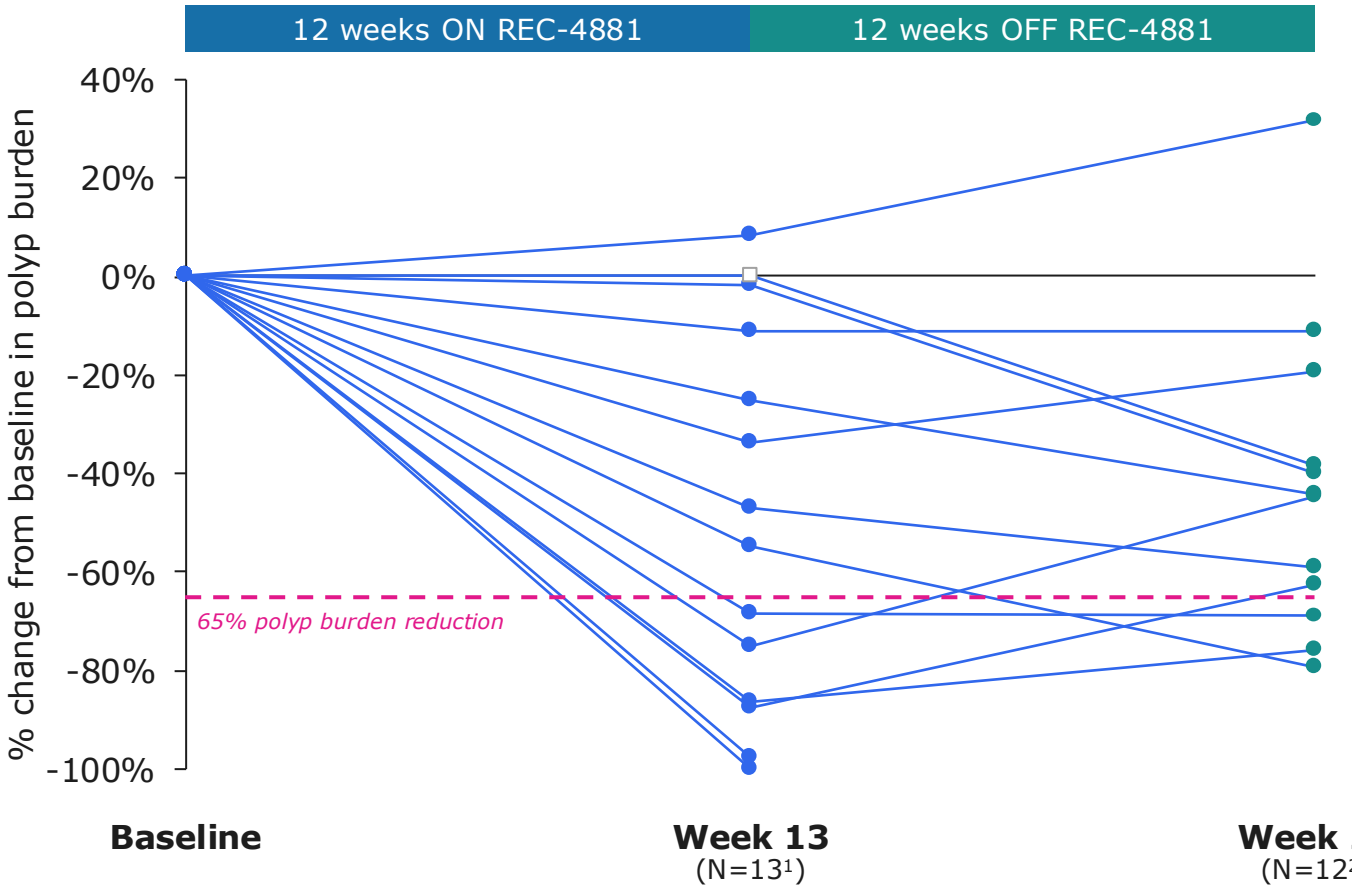
*Additional patients since previously reported data cutoff (November 25, 2025)

Not shown: Two patients with no lower GI polyp burden at baseline but non-zero lower GI polyp burden at Week 13 so % change cannot be calculated[3]

1. 4 of 11 (36%) patients had ≥65% polyp burden reduction from baseline
2. Of the full set of 16 efficacy evaluable patients, 11 patients are shown: 1 patient had no lower GI anatomy, 1 patient missed their Week 13 visit, and 3 patients had no polyp burden at baseline
3. One patient had an increase in polyp burden of 0 mm to 1 mm; the second patient had an increase in polyp burden of 0 mm to 6 mm

Upper GI | Polyp burden in the Upper GI remained below baseline in 92% of patients 12 weeks after stopping REC-4881

Upper GI polyp burden reduction
Week 13 & Week 25



Key findings

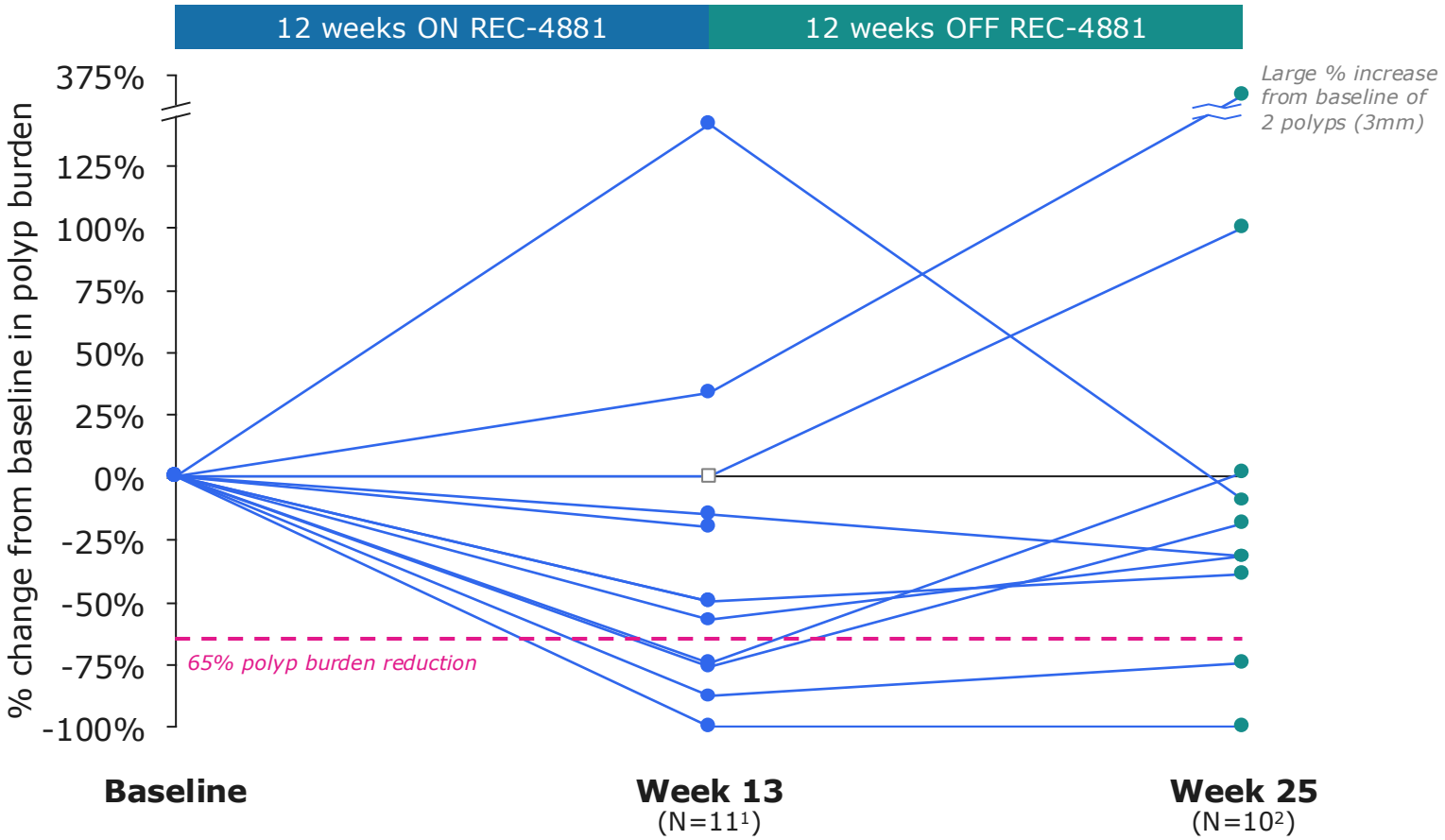
- **6 of 13 patients** at Week 13 with Upper GI polyp burden **reduction ≥65%**
- **11 of 12 patients** with Upper GI polyp burden below baseline at Week 25, after 12 weeks off drug

1. Upper GI evaluable at week 13: n=13 of 16 efficacy evaluable patients; 2 patients had no upper GI anatomy and 1 did not have a Week 13 endoscopy (shown at Wk. 13 as an open square)
2. Upper GI evaluable at week 25: n=12 of 16 efficacy evaluable patients; 2 patients had no upper GI anatomy and 2 did not have Week 25 results at the data cutoff
Note: For any excisions at the week 13 endoscopy, the excised polyp burden was added back to the week 25 polyp burden before calculating the change from baseline.

Lower GI | Polyp burden in the Lower GI remained below baseline in 70% of patients 12 weeks after stopping REC-4881

Lower GI polyp burden reduction

Week 13 & Week 25



Key findings

- **4 of 11 patients** at Week 13 with Lower GI polyp burden **reduction ≥65%**
- **7 of 10 patients** with Lower GI polyp burden below baseline at Week 25, after 12 weeks off drug

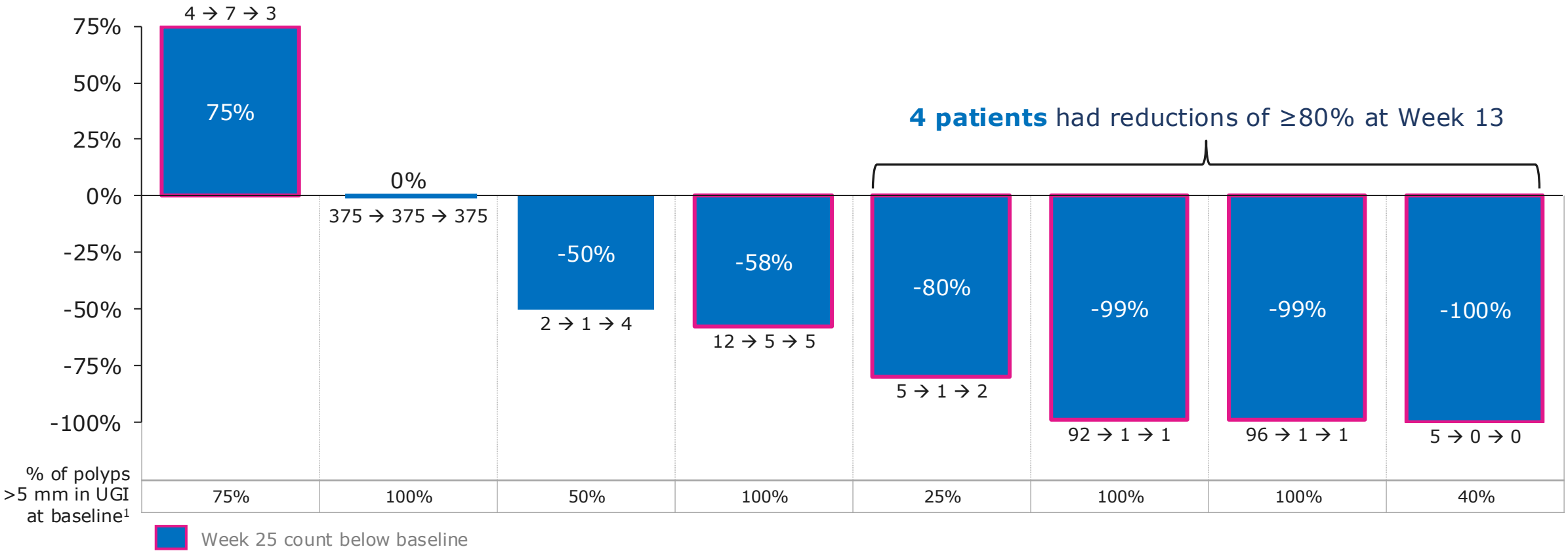
1. Lower GI evaluable at Week 13: n=11 of 16 efficacy-evaluable pts; 3 had no lower GI polyps at baseline, 1 had no Lower GI anatomy, and 1 did not have a Week 13 endoscopy (shown at Wk. 13 as an open square)
2. Lower GI evaluable at Week 25: n=10; 3 had no lower GI polyps at baseline, 1 had no Lower GI anatomy, 1 patient discontinued the study after Week 13, and 1 did not have Week 25 results at the data cutoff

Note: For any excisions at the week 13 endoscopy, the excised polyp burden was added back to the week 25 polyp burden before calculating the change from baseline

REC-4881 reduced number of >5 mm polyps in 6 of 8 patients (75%)

% change from baseline to Week 13 in count of polyps >5 mm across entire GI tract (n=8)

Patients with at least one polyp >5 mm at baseline



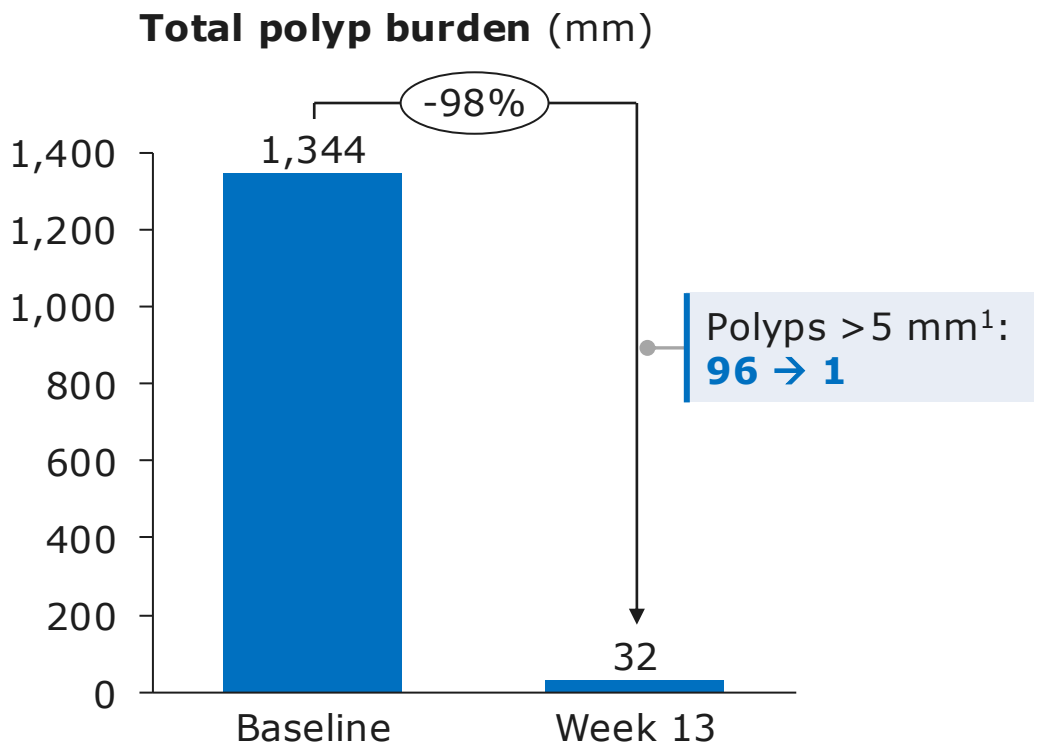
Baseline → Wk13 → Wk25: Absolute counts of polyps >5 mm shown above each bar

Not shown: 1 patient with no polyps >5 mm at baseline had 4 polyps >5 mm at Week 13 and 2 polyps >5 mm at Week 25

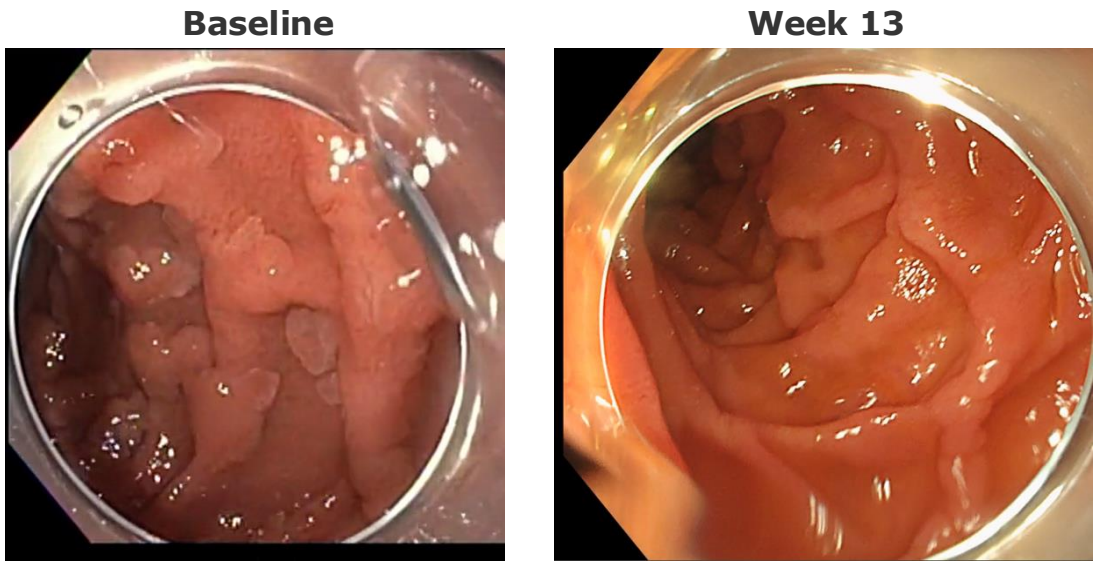
1. Proportion of total polyps >5 mm found in the Upper GI at baseline
Note: Polyps >10 mm were not separately measured and are included in the totals for polyps >5 mm

Additional detail on highest Week 13 responder

The result presented here is only for one out of the 16 total efficacy evaluable patient population; this result is not representative of the overall efficacy of the evaluable patient population to date



Images taken from the 2nd portion of the duodenum of highest responder



1. Patient had 96 polyps >5 mm at baseline which were reduced to 1 polyp >5 mm at Week 13

Conclusions

Natural history analysis demonstrates consistent progression in polyp burden over time, contextualizing polyp burden reductions driven by REC-4881

REC-4881 safety

- Favorable safety profile; AEs consistent with the MEK1/2 inhibitor class
- Treatment-related AEs mostly Grade 1/2; Grade 3 (15%) and no Grade 4/5

REC-4881 polyp burden reduction

- Polyp burden reduction observed across both upper and lower GI, in 92% and 82% of evaluable patients, respectively
- Durability demonstrated in both upper and lower GI, with 92% and 70% of evaluable patients, respectively, remaining below baseline at Week 25
- 75% of patients evaluated with polyps >5 mm had reductions, which is important for endoscopic excisional management

Results to be further investigated in a registrational study anticipated to begin 2H 2027[1]

1. Pending outcome of ongoing FDA discussions

Thank you *to all the trial participants and their families*

and to the investigators and study teams at each trial site

Dr. Stout	Dr. Katona	Dr. Boardman (Rochester) Dr. Samadder (Scottsdale)	Dr. Ricciardiello Dr. Vilar-Sanchez
Dr. Ness	Dr. Mankaney	Dr. Reiss	Dr. Younes
Dr. Ogilvie	Dr. Wise	Dr. Engelking	Dr. Aelvoet Dr. de Haan Dr. Dekker