Zolucatetide (FOG-001), a first-in-class direct β-catenin:TCF inhibitor, exhibits activity in a familial adenomatous polyposis (FAP) patient with desmoid tumor (DT) and in a preclinical FAP model

Samuel J. Klempner[1], Gregory M. Cote[2], Kyriakos P. Papadopoulos[2], Meredith Pelster[3], Jordi Rodon[4], Michael Cecchini[5], Rona Yaeger[6], Moh'd Kushman[7], Sunil Sharma[8], Shivaani Kummar[9], David Bajor[10], Brandon Nicolay[11], Jorge Ramos[11], Marie Nguyen[11], Megan Tipps[11], Jonathan Hurov[11], Daniel C. Chung[12]

[1]Mass General Brigham Cancer Institute, Boston, MA, USA; [2]START San Antonio, San Antonio, TX, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Yale University School of Medicine, New Haven, CT, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Washington University, St, Louis, MO, USA; [8]HonorHealth, Scottsdale, AZ, USA; [9]Oregon Health & Science University, Portland, OR, USA; [10]University Hospitals – Case Western Reserve University, Cleveland, OH, USA; [11]Parabilis Medicines, Cambridge, MA, USA; [12]Mass General Brigham Division of Gastroenterology, Boston, MA, USA

Poster #78

Short Summary

Familial adenomatous polyposis (FAP) arises from inherited *APC* loss-of-function mutations, which promote constitutive Wnt/β-catenin signaling and early development of numerous colorectal adenomas that, if left untreated, have near-certain risk of progression to colorectal cancer. Given the absence of approved systemic therapies for FAP, targeting the earliest drivers of tumor development presents a key opportunity for early intervention. Zolucatetide, a first-in-class and only direct inhibitor of β-catenin is currently being evaluated in a Phase 1/2 trial (NCT05919264). Herein, zolucatetide demonstrated encouraging preliminary activity in a patient with FAP, with a reduction in duodenal polyps and co-existing desmoid tumor driven by a germline *APC* loss of function mutation. This clinical observation was supported in a mouse model of FAP where zolucatetide inhibited β-catenin transcriptional activity in tumor cells and blocked disease progression as measured by polyp formation and survival, at doses and exposures relevant to the ongoing Phase 1/2 clinical trial. Taken together, these data support that zolucatetide intercedes at a critical pathogenic node in FAP, offering a potential disease-modifying therapeutic approach for chemoprevention of both colonic and duodenal polyposis and merits further evaluation. Enrollment in a desmoid-specific cohort, including patients with FAP and desmoid tumors, is ongoing.

Background

- Mutations that lead to dysregulation of the Wnt/β-catenin signaling pathway and accumulation of β-catenin in the nucleus play a critical role in driving tumorigenesis in ~11% of all cancers[1]
- FAP is caused by germline LoF mutations in the *APC* gene, leading to activation of the Wnt/β-catenin signaling and development of numerous colorectal adenomas with a near-inevitable progression to CRC[2]
- Despite prophylactic total colectomy, patients with FAP have an increased risk for other cancers, including desmoid tumors[3,4]
- Currently, no systemic treatment options are approved for FAP, with prior approaches mainly focused on polyp size reduction rather than preventing their initiation. Addressing the earliest drivers of tumor formation represents a significant unmet need and a key opportunity for early intervention[2]
- Zolucatetide is a first-in-class and only direct inhibitor of β-catenin that competitively inhibits the interaction between β-catenin and the TCF family of transcription factors (**Figure 1**), the most downstream node in the Wnt/β-catenin pathway (**Figure 2**)
- Zolucatetide is currently being evaluated in a Phase 1/2 trial (NCT05919264)[5]

Figure 1. Zolucatetide, a novel β-catenin:TCF inhibitor

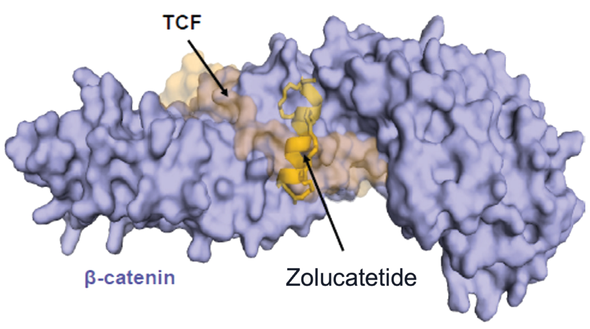
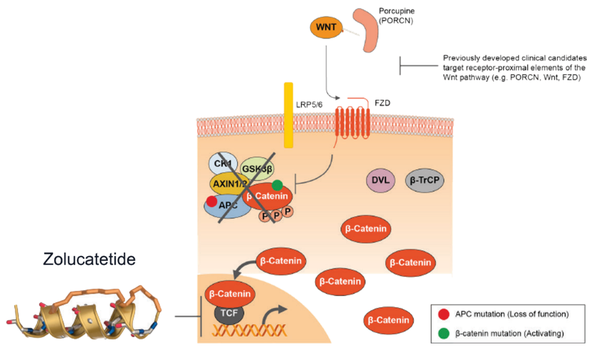


Figure 2. Zolucatetide mechanism of action



Objectives

Here we present both clinical and preclinical evidence supporting zolucatetide as a potential treatment option for FAP and desmoid tumors.

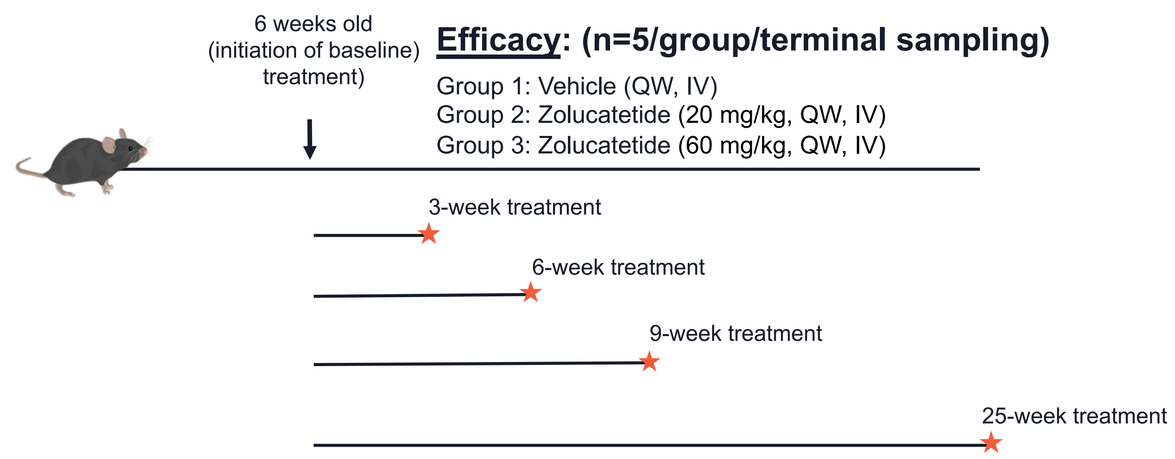
Preclinical

Methods

The FAP *APC*$^{Exon16\Delta/+}$ Mouse Model

- To support the clinical development of zolucatetide for FAP, we used the CyaGen C001511 (C57BL/6JCya-Apc^em3Cya) mouse model, a genetically engineered germline *APC* knockout LoF mutation (exon 16) homozygous lethal model developed on a C57BL/6 background
- Exon 16 deletion mutation in the *APC* gene leads to truncation in the *APC* gene that extends into the mutation cluster region of the APC protein
- This model was used to measure the dose- and time-dependent effects of zolucatetide on the inhibition of β-catenin transcriptional activity and survival
- Heterozygous animals are viable and develop spontaneous intestinal adenomas under normal dietary conditions
- Consistent with alternative germline *APC* deficient models, adenoma formation occurs predominantly in the small intestine
- The formed adenomas model key aspects of dysregulated Wnt/β-catenin signaling phenotypically are similar to human FAP
- This model provides a genetically defined platform for evaluating Wnt/β-catenin pathway directed pharmacologic interventions for treatment of FAP pathology in mice (**Figure 3**)
- Mice were treated with either vehicle control or zolucatetide for 3 to 25 weeks

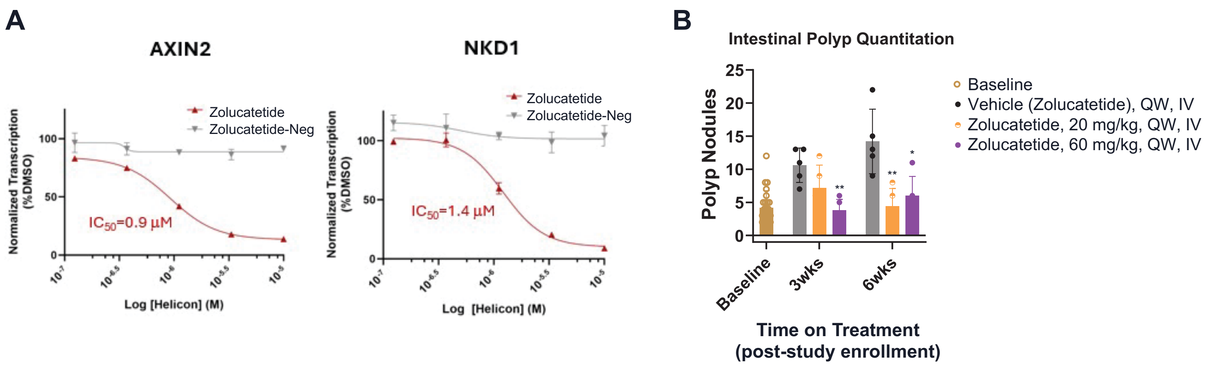
Figure 3. Study Design Schema of *APC*$^{Exon16\Delta/+}$



- Zolucatetide treatment was administered once weekly
- At predetermined time points (red star), animals were sacrificed and polyps were quantified within the small intestine and colon
- Animals were tested for up to 25 weeks
- Zolucatetide effects on overall survival as related to disease burden were evaluated as well as effects on disease control

Results

Figure 4. Zolucatetide inhibited β-catenin dependent transcription and treatment demonstrated dose-dependent reduction in polyps in a mouse FAP model



Unpaired t-test comparing the effect size between vehicle and zolucatetide: **P*<0.02; ***P*<0.01

- Transcription assay was run in 4% FBS
- Mouse plasma protein binding is 98.5% (1.5% free)
- IC_{50} for inhibition of β-catenin:TCF interaction in cells using Nanobret assay in serum-free medium is 100nM
- Inhibition of β-catenin dependent AXIN2 and NKD1 mRNA transcript levels using RT-qPCR in the ECC10 gastric cancer cell line (bearing an *APC* p.Thr1556Asnfs*3 mutation). Cells were treated for 48 hours with zolucatetide and a zolucatetide negative control Helicon (zolucatetide-Neg, with reduced affinity for β-catenin). Data are representative of multiple experimental runs and individual points are plotted ± SD values from biological triplicates (**Figure 4A**)
- Interim data reveals zolucatetide dose-dependent reduction of polyps within the small intestine of *APC*$^{Exon16\Delta/+}$ animals through 6 weeks of treatment.
- This study is ongoing and will continue to evaluate depth and durability of anti-polyp and transcriptional effects observed through 25 weeks (**Figure 4B**)

Clinical

Methods

Figure 5. Study Design

Monotherapy cohorts

Parts 1a, 1c and 1d are open for enrollment
Parts 1a and 1d are the focus of this presentation

Part 1a: Zolucatetide monotherapy dose escalation (MSS CRC and WPAM+ solid tumors, including desmoid tumors)[a]

Part 1c: Zolucatetide monotherapy dose optimization (HCC)

Part 1d: Zolucatetide monotherapy dose optimization (desmoid tumors)

Zolucatetide PD biomarker cohort
(MSS CRC; patients with WPAM– tumors are not eligible)

Combination cohorts

Zolucatetide + FOLFOX + bevacizumab
(1L MSS CRC)

Zolucatetide + nivolumab
(3L MSS CRC, with and without liver metastases)

Zolucatetide + trifluridine/tipiracil + bevacizumab
(3L MSS CRC)

Key inclusion criteria for patients with desmoid tumors

- Aged ≥18 years
- ECOG PS score of 0-1
- Histologically confirmed desmoid tumor (**Parts 1a and 1d**)
- ≥10% tumor growth within 12 months prior to first dose (**Part 1d only**)
- Adequate organ and marrow function

Key exclusion criteria for patient with desmoid tumors

- Bone metastases
- Osteoporosis
- Major surgery within 6 weeks of first dose

Key objectives

Part 1a

- Evaluate safety and tolerability zolucatetide in patients with MSS CRC and WPAM+ solid tumors
- Select pRP2D

Part 1d

- Evaluate safety and tolerability of zolucatetide in patients with active desmoid tumors

Parts 1a and 1d

- Define PK profile of zolucatetide
- Evaluate preliminary antitumor activity

NCT05919264

[a]Part 1a includes dose levels 1-6 (36-480 mg/m²). Participants with desmoid tumors have been enrolled in Part 1a and 1d at dose levels 2, 4, and 6 (72, 240, and 480 mg/m²).

Results

Case: Patient with Desmoid Tumor

Baseline Characteristics

- Male patient
- Aged 23 years
- Abdominal wall desmoid tumor (115 mm per RECIST; diagnosed in 2023) in the context of known FAP (germline *APC* p.Y935*; diagnosed in 2022)
- The patient underwent total proctocolectomy

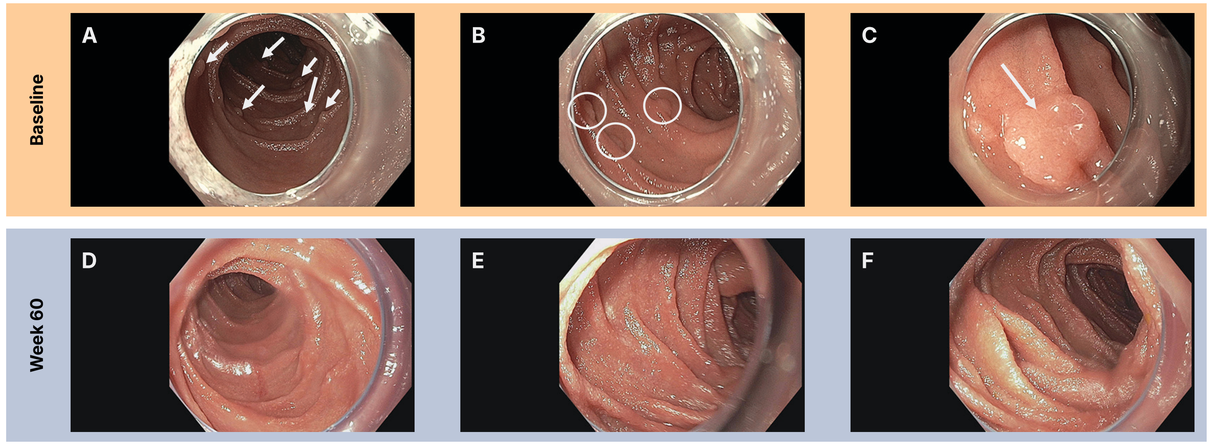
Treatment

- Patient began therapy on August 13, 2024 and had received 62.8 weeks of treatment as of October 27, 2025
- The patient remains on study as of today

Efficacy

- The patient achieved a partial response beginning at 16 weeks (-33.9% vs baseline) which has been sustained throughout treatment (-52.2% at last assessment [60 weeks])
- For surveillance of his FAP, a routine endoscopy performed at 60 weeks (October 2025) showed an improvement in the duodenal polyp burden
- Compared to 2 years ago before initiation of zolucatetide treatment (baseline, July 2023; **Figures 6A-C**), there appeared to be a clear reduction in polyp number and size in the duodenum consistent with downstaging from Spigelman stage 2 polyposis to stage 1 disease (**Figures 6D-F**)
- There were no polyps in the rectal pouch at either the baseline or at 60 weeks (**Figure 6**)
- This was unexpected given what is known of the constant growth pattern of polyps in FAP[6]

Figure 6. Endoscopy evaluations



Conclusions

- Zolucatetide demonstrated encouraging preliminary activity in a patient with FAP, showing reduction in duodenal polyps and co-existing desmoid tumor driven by a germline *APC* LOF mutation
- This clinical observation was supported using zolucatetide in a mouse model of FAP confirming blockade of disease progression as measured by polyp formation at doses and exposures relevant to the ongoing Phase 1/2 clinical trial
- Taken together, these data highlight that by directly targeting dysregulated Wnt/β-catenin signaling, zolucatetide intercedes at a critical pathogenic node in FAP, offering a potential disease-modifying therapeutic approach for chemoprevention of both colonic and duodenal polyposis and merits further evaluation for this disease

Current Status

Enrollment in a desmoid-specific cohort, including patients with FAP and desmoid fibromatosis, is currently ongoing (NCT5919264).

Abbreviations

3L, third line; CRC, colorectal cancer; DMSO, dimethyl sulfoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; FBS, fetal bovine serum; FAP, familial adenomatous polyposis; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HCC, hepatocellular carcinoma; IC_{50}, half-maximal inhibitory concentration; IV, intravenous; LOF, loss of function; mRNA, messenger RNA; MSS, microsatellite stable; Neg, negative; PD, pharmacodynamics; PK, pharmacokinetics; pRP2D, preliminary recommended Phase 2 dose; QW, weekly; QR, quick response; RECIST, Response Evaluation Criteria in Solid Tumors; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SD, standard deviation; TCF, T-cell factor; wk, week; WPAM, Wnt pathway activating mutation.

Additional Information

Scan the QR code for additional information about this clinical trial (NCT05919264)

References

1. Shang S, et al. *Oncotarget*. 2017;8(20):33972-33989. doi:10.18632/oncotarget.15687.
2. Ferrandon S, et al. *Fam Cancer*. 2025;24(2):52. doi: 10.1007/s10689-025-00479-3.
3. Rausa E, et al. *BJS Open*. 2024;9(1). zrae148. doi:10.1093/bjsopen/zrae148.
4. Aoun RJN, et al. *Fam Cancer*. 2025;24(3):56. doi: 10.1007/s10689-025-00481-9.
5. https://clinicaltrials.gov/study/NCT05919264.
6. Sarvepalli S, et al. *Gastrointest Endosc*. 2018;88(4):726-733. doi: 10.1016/j.gie.2018.05.021.

Acknowledgments

- Parabilis and the authors would like to thank all the patients and their families, as well as all the investigators, clinical trial researchers, personnel and staff who contributed to or participated in the trial
- Medical writing and editorial assistance were provided by Second City Science, funded by Parabilis Medicines, Inc.

Disclosures

The presenter has indicated that they have a relationship that, within the context of this presentation, could be perceived as a real or apparent conflict of interest. However, they do not consider this will influence the content of their presentation. The nature of the conflict is as follows:

Affiliation/Financial interest	Commercial Company
Grants/Research Support:	None
Honoraria or Consultation Fees:	Amgen, Astellas, AstraZeneca, BeiGene, BMS, Boehringer-Ingelheim, DaiichiSankyo, Eisai, Elevation Oncology, EsoBiotec, Gilead, I-Mab, Merck, Signet Therapeutics, Taiho Oncology (past 36 months; Gastric Cancer Advisory Board) Merck (Gastric Cancer Lecture in 2023)
Participation in a Company Sponsored Bureau:	Sanofi-Aventis (Data Safety Monitoring Board or Advisory Board, ongoing, no compensation)
Stock Shareholder:	MBrace Therapeutics (stock options, no value, private company)
Spouse/Partner:	None
Other Support/Potential Conflict of Interest:	NCCN (NCCN Guidelines® panel member, no compensation), Research to Practice (CME participation, compensation), Debbies Dream Foundation (medical advisory board member, no compensation), Hope for Stomach Cancer (medical advisory board member, no compensation)

The presenter has clarified that the upcoming presentation will NOT include any discussion of commercial products or services. They also declared that they have no affiliations with any tobacco companies or commercial entities.

Presented at the InSiGHT Biennial Meeting, 4–7 March, 2026, Singapore