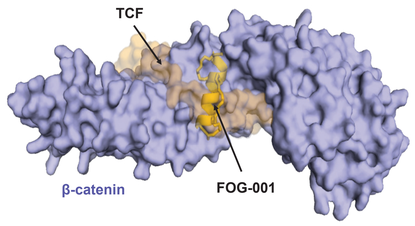
A phase 1/2 trial of FOG-001, a first-in-class direct β-catenin:TCF inhibitor Safety and preliminary antitumor activity in patients with desmoid tumors

Gregory M. Cote[1], Michael Cecchini[2], Kyriakos P. Papadopoulos[3], Moh'd Khushman[4], Meredith Pelster[5], Jordi Rodon[6], Shivaani Kummar[7], Rona Yaeger[8], Sunil Sharma[9], Amber L. Wells[10], Megan Tipps[10], Jonathan Rojo[10], Amanda Garofalo[10], Lalith Akella[10], Ziyang Yu[10], Xinwei Han[10], Laura Strong[10], Jorge D. Ramos[10], Marie Huong Nguyen[10], Keith Orford[11], Samuel J. Klempner[1]

[1]Massachusetts General Cancer Center, Boston, MA, USA; [2]Yale University School of Medicine, New Haven, CT, USA; [3]START San Antonio, San Antonio, TX, USA; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Oregon Health and Science University, Portland, OR, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Honor Health, Scottsdale, AZ, USA; [10]Parabilis Medicines, Cambridge, MA, USA; [11]Tagworks Pharmaceuticals, Doylestown, PA, USA

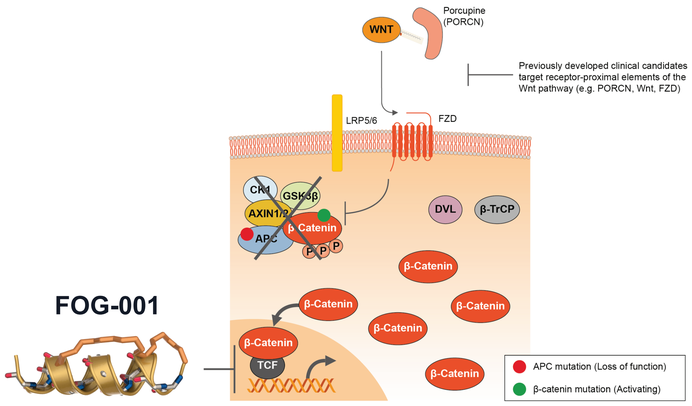
Background

Figure 1. FOG-001 – A novel β-catenin:TCF inhibitor



- Desmoid tumors are non-malignant, intermediate grade tumors with potential for locally aggressive behavior and significant morbidity.[1]
- Wnt/β-catenin pathway activating mutations are highly prevalent in desmoid tumors, with nearly all harboring a mutation in either CTNNB1 or APC.[2–3]
- Currently available systemic therapy options indirectly target the WNT/B-catenin pathway.
- As of the data cut-off (11-Aug-2025), a total of 12 patients with desmoid tumors have been enrolled across dose levels 2, 4 and 6.

Figure 2. FOG-001 – mechanism of action



- FOG-001 is a first-in-class and only direct inhibitor of β-catenin that competitively inhibits the interaction between β-catenin and the T-cell factor (TCF) family of transcription factors, the most downstream node in the Wnt pathway.
- By directly targeting the β-catenin:TCF protein–protein interaction, FOG-001 is downstream of, and thereby targets, virtually all mutations that activate canonical Wnt signaling.
- Preclinical data demonstrate good tolerability of FOG-001 with a clear therapeutic window.

Objectives

- In this poster we present safety, efficacy, and pharmacokinetic / pharmacodynamic results from the FOG-001-101 study of FOG-001 in patients with desmoid tumors.

Methods

Figure 3. FOG-001-101 trial schema (NCT05919264)

Key inclusion and exclusion criteria for participants with desmoid tumors[a]

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

Key exclusion criteria
- Bone metastasis
- Vertebral compression fracture or non-traumatic bone fracture in past 12 months and not receiving antiresorptive therapy
- Osteoporosis
- Inflammatory bowel disease

Monotherapy cohorts

Part 1a: FOG-001 monotherapy dose escalation (MSS CRC and WPAM+ solid tumors, including desmoid tumors)[b]

Part 1d: FOG-001 monotherapy dose optimization (desmoid tumors)

FOG-001 PD biomarker cohort
(MSS CRC; patients with WPAM– tumors are not eligible)

Combination cohorts

FOG-001 + FOLFOX + bevacizumab
(1L MSS CRC)

FOG-001 + nivolumab
(3L MSS CRC, with and without liver metastases)

FOG-001 + trifluridine/tipiracil + bevacizumab
(3L MSS CRC)

Key objectives:

Part 1a:
- Evaluate safety and tolerability of FOG-001 in patients with MSS CRC and WPAM+ solid tumors
- Select preliminary recommended Phase 2 dose (pRP2D)

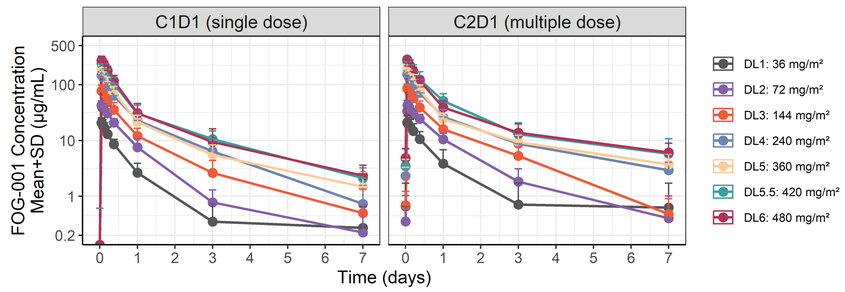
Part 1d:
- Evaluate safety and tolerability of FOG-001 in patients with active desmoid tumors

Parts 1a and 1d:
- Define PK profile of FOG-001
- Evaluate preliminary anti-tumor activity

[a]Please refer to QR code for full eligibility criteria, objectives, and outcomes. Additional planned cohorts not currently enrolling are not shown
[b]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)

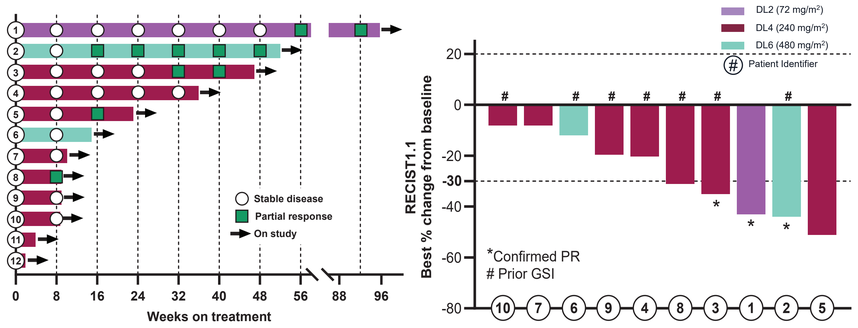
Results

Figure 4. FOG-001 pharmacokinetic characteristics



- FOG-001 has favorable pharmacokinetic characteristics:
  - Extensive distribution.
  - Dose-proportional exposure.
  - Low inter-patient variability.

Figure 5. FOG-001: Preliminary efficacy in patients with desmoid tumors



Data cutoff: 11-Aug-2025
DCR - Disease control rate; DL - Dose level; GSI – Gamma secretase inhibitor
PR – Partial response; RECIST – Response Evaluation Criteria in Solid Tumors

Table 1. Demographics and baseline disease characteristics

Characteristics	Patients with desmoid tumors (N=12)
Median age, years (range)	32.5 (20–53)
Sex, n (%)	
Female	10 (83.3)
Male	2 (16.7)
Wnt pathway activating mutation, n (%)	
APC	1 (8.3)
CTNNB1	10 (83.3)
Pending	1 (8.3)
Tumor location, n (%)	
Intra-abdominal	1 (8.3)
Extra-abdominal	11 (91.7)
Median number of prior therapies (range)	2 (0–6)
Prior therapies, n (%)	
Surgery	2 (16.7)
Radiation	1 (8.3)
Systemic	11 (91.7)
Median number of prior systemic therapies (range)	1.5 (0–5)
Prior systemic therapies, n (%)	
Nirogacestat	9 (75.0)
Sorafenib	6 (50.0)
Cytotoxic chemotherapy	5 (41.7)
Other[1]	3 (25.0)
Median target lesion size per RECIST, mm (range)	95.5 (37–250)

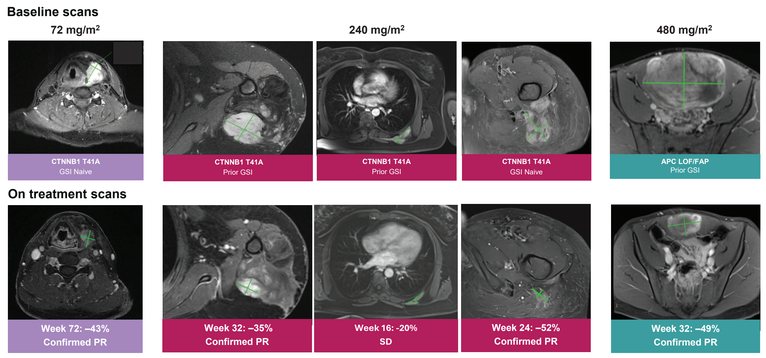
Data cutoff: 11-Aug-2025
[1]Includes clinical trial (n=2) and sulindac (n=1)

Table 2. Treatment-related adverse events by dose level

TRAEs, n (%)	DL2 72 mg/m² (n=1)		DL4 240 mg/m² (n=9)		DL6 480 mg/m² (n=2)		All patients (N=12)	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Any TRAE	1 (100)	0	7 (77.8)	0	2 (100)	2 (100)	10 (83.3)	2 (16.7)
TRAEs (any grade) in ≥25% of patients								
Fatigue	0	0	5 (55.6)	0	2 (100)	0	7 (58.3)	0
Alopecia	1 (100)	0	3 (33.3)	0	2 (100)	0	6 (50.0)	0
AST increased	0	0	3 (33.3)	0	2 (100)	1 (50.0)	5 (41.7)	1 (8.3)
Nausea	0	0	4 (44.4)	0	1 (50.0)	0	5 (41.7)	0
ALT increased	0	0	2 (22.2)	0	2 (100)	0	4 (33.3)	0
Blood bilirubin increased	0	0	2 (22.2)	0	2 (100)	1 (50.0)	4 (33.3)	1 (8.3)
Epistaxis	0	0	4 (44.4)	0	0	0	4 (33.3)	0
Hypoaldosteronism	0	0	1 (11.1)	0	2 (100)	0	3 (25.0)	0
Any serious TRAE							0	
TRAE leading to discontinuation of treatment							0	
TRAEs leading to death (Grade 5)							0	

Data cutoff: 11-Aug-2025
ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; DL – Dose level GI – Gastrointestinal; TRAE – Treatment-related adverse event (n=1)

Figure 6. Patient cases: Tumor reductions seen in patients with desmoid tumors at all dose levels, irrespective of tumor locations or genetic mutation profiles



FOG-001 efficacy

- All patients remain on study treatment.
- 10 patients are response-evaluable (≥1 post-baseline scan):
  - Patients across all dose levels have had tumor reductions; DCR 100% at first scan.
  - Of the 5 patients with >1 post-baseline scan, 4 (80%) have had an objective response per RECIST 1.1.
  - Responses seen in patients that are both GSI-naive and post GSI.
  - Anti-tumor activity seen with pathogenic mutations in both CTNNB1 and APC.

FOG-001 safety

- The most commonly reported TRAEs were low-grade and reversible.
- There were no Grade ≥3 TRAEs at dose level 4 and below.
- There were also no Grade 4 or 5, serious, or TRAEs resulting in treatment discontinuation.
- Patients did not experience high-grade gastrointestinal or skin toxicities.

Conclusions – FOG-001 in desmoid tumors

- FOG-001 is a Helicon™ peptide that selectively inhibits the β-catenin / TCF interaction.
- Preliminary data suggests that FOG-001 has clinically meaningful anti-tumor activity:
  - Tumor reductions seen in all patients.
  - Objective responses in 4 out of 5 patients with more than one post-baseline scan.
    - Irrespective of prior exposure to gamma secretase inhibitors, tumor location or mutations in CTNNB1 or APC.
- FOG-001 has a well-managed safety and tolerability profile.
- These data support further development of FOG-001 in patients with desmoid tumors and suggest that FOG-001 directly addresses the underlying mechanism of disease through inhibition of β-catenin.

FOG-001 101 sites open for enrollment

- Massachusetts General Cancer Center
- START – San Antonio
- Sarah Cannon Research Institute
- University of Texas – MD Anderson Cancer Center
- Yale School of Medicine
- Memorial Sloan Kettering Cancer Center
- Washington University School of Medicine
- Honor Health
- University of Minnesota
- Oregon Health & Science University
- Stanford Cancer Center
- University of Pittsburgh Hillman Cancer Center
- University of Wisconsin
- Johns Hopkins
- University Hospitals Seidman Cancer Center
- Florida Cancer Specialists
- University of California San Francisco

Acknowledgements

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

References

1. Penel N, et al. Curr Opin Oncol 2017;29:268–274.
2. Timbergen MJM et al. Front Oncol 2019;9:397.
3. Federman N. NPJ Precis Oncol 2022;6:62.

Presented at the CTOS Annual Meeting, Boca Raton, FL, USA, 12–15 November 2025