A phase 1/2 trial of FOG-001, a first-in-class direct β-catenin-TCF4 inhibitor: safety and preliminary antitumor activity in patients with desmoid tumors

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Declaration of Interests

Honorarium: Gilead

Advisory/consulting: C4 Therapeutics; Chordoma Foundation, Daiichi Sankyo, Inc; Ikena Oncology; Parabilis Medicines, PharmaMar

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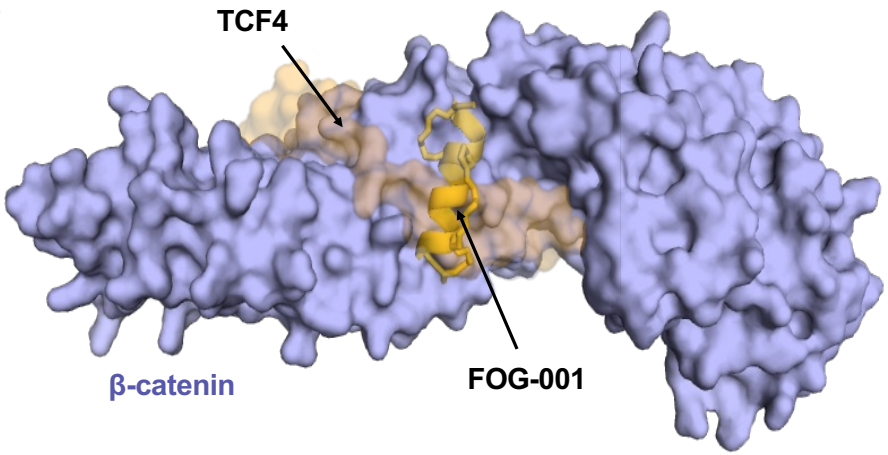
Background

- 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
- FOG-001 is a Helicon™ peptide that selectively inhibits β-catenin/TCF interaction with dose-proportional PK, ~1.5–2-day half-life with low variance, and offers a more direct disease-relevant approach than current options
- As of the data cut-off (11-Aug-2025), a total of N=12 patients with desmoid tumors have been enrolled across dose levels 2, 4 and 6



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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

Demographics and Baseline Characteristics

Characteristics	All patients (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)
Not available	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)

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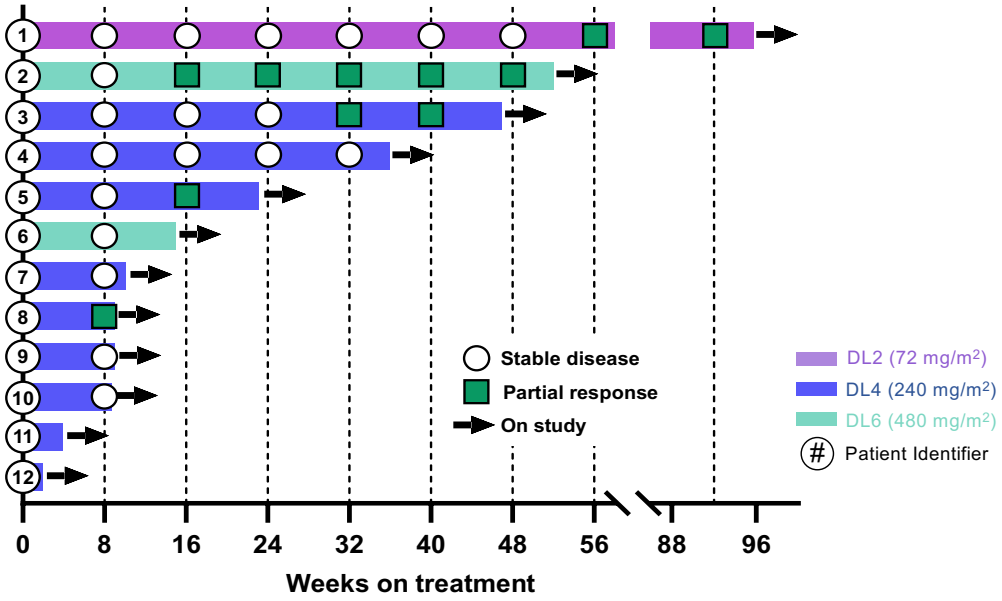
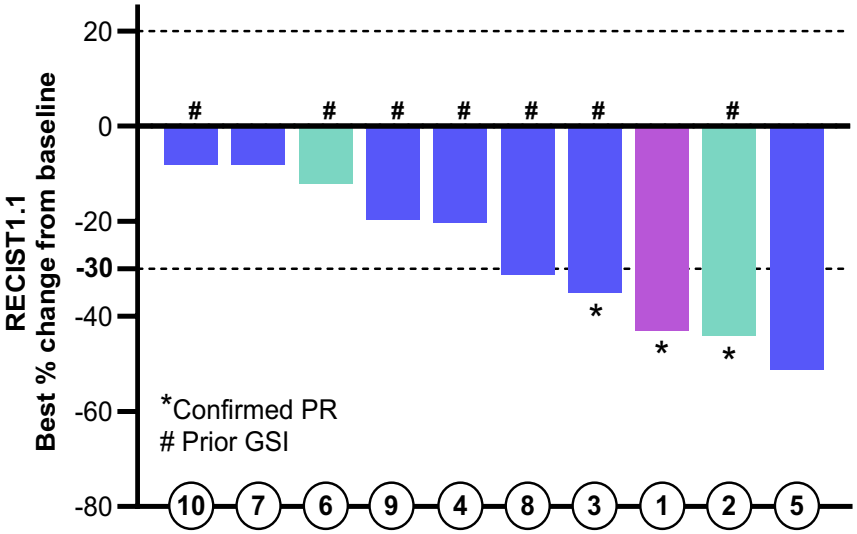
Data cutoff: 11-Aug-2025
[1]Includes clinical trial (n=2) and sulindac (n=1)

FOG-001: Preliminary Efficacy in Patients with Desmoid Tumors





- 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

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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

Safety Summary

TRAEs, n (%)	DL2 72 mg/m^2 (n=1)		DL4 240 mg/m^2 (n=9)		DL6 480 mg/m^2 (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	

- **Most commonly reported TRAEs are low-grade and reversible**
- **No Grade ≥3 TRAEs at DL4 and below**
- **No Grade 4 or 5, serious, or TRAEs resulting in treatment discontinuation**
- **No high-grade GI or skin toxicities**

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

Conclusions – FOG-001 in Desmoid Tumors

- FOG-001 is a Helicon™ peptide that selectively inhibits 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 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

Enrollment in a desmoid tumor-specific cohort is currently ongoing

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