Detailed Safety Analysis of Varegacestat Treatment for Desmoid Tumors in the RINGSIDE Phase 3 Trial

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BACKGROUND

- Gamma secretase inhibitors (GSIs) target cellular proliferation in desmoid tumors, providing a mechanistic rationale for GSI therapy.[1]
- Strong clinical evidence supports the role of GSIs in treating desmoid tumors.[2,3,4]
- Common GSI adverse events include diarrhea (84%), nausea (54%), fatigue (51%), hypophosphatemia (42%) and ovarian toxicity events (75% of women of childbearing potential).[2]
- The RINGSIDE Phase 3 trial investigating once-daily varegacestat vs placebo for desmoid tumors met all primary and key secondary endpoints and showed overall safety consistent with the GSI class.[3]
- We report detailed safety analyses of varegacestat in RINGSIDE Phase 3.

RINGSIDE Met All Primary and Key Secondary Endpoints[3]

Risk of Radiographic Disease Progression or Death
84% reduction with varegacestat vs placebo (HR: 0.16, P<0.0001) — Primary endpoint

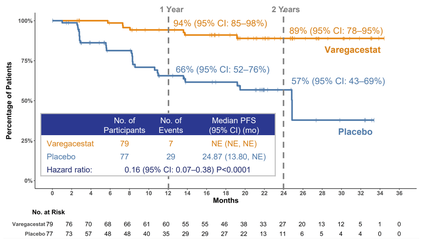
Change in Worst Pain Intensity at Week 12
−2.24 point mean* reduction with varegacestat vs +0.18 point increase with placebo (P<0.0001)

Objective Response Rate
55.7% for varegacestat vs 9.1% for placebo (P<0.0001)

Change in Tumor Volume at Week 24
−109.6 cm³ mean* reduction with varegacestat vs +122.8 cm³ increase with placebo (P<0.0001)

*Least-squares mean

Varegacestat Demonstrated Significant Improvement in PFS[3]



METHODS

Phase 3 Randomized, Double-Blind Placebo-Controlled Trial

Key Eligibility Criteria
- Adults with histologically confirmed DT that has progressed in the past 12 months per RECIST 1.1
- Treatment-naïve and previously treated patients
- Measurable disease
- ECOG PS score 0-2

Randomized 1:1
- Varegacestat 1.2 mg PO once daily (n=79)
- Placebo PO once daily (n=77)

Open Label Extension (OLE)*: Varegacestat 1.2 mg PO once daily

Stratification factor: Tumor location (intra- vs. extra-abdominal)

Enrollment: Nov 15, 2022 – Feb 14, 2024
Data-cutoff date: October 7, 2025

Endpoints
Primary: PFS by BICR
Key Secondary:
- ORR by BICR
- Change in tumor volume from baseline at Week 24 by BICR
- Change in GODDESS patient-reported worst pain intensity (WPI) from baseline at Week 12

Safety Analyses
- Treatment-emergent AEs (TEAEs)
- Grade ≥3 AEs & serious AEs (SAEs)
- AEs of interest
- Dose modifications due to AEs
- Time to AE onset

*crossover to OLE from either arm allowed if progressive disease. BICR: Blinded independent central review; DT: Desmoid tumors; ECOG PS: Eastern Cooperative Oncology Group performance status; GODDESS: GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; ORR: objective response rate; PFS: progression free survival.

RESULTS

Participant Characteristics

Characteristic, n (%)		Varegacestat (n=79)	Placebo (n=77)
Median age (range), years		42.0 (18–66)	39.0 (20–69)
Sex	Male	26 (32.9)	29 (37.7)
	Female	53 (67.1)	48 (62.3)
	Premenopausal	36/53 (67.9)	38/48 (79.2)
Target tumor location†	Extra-abdominal	60 (75.9)	49 (63.6)
	Intra-abdominal	19 (24.1)	28 (36.4)
Medical history of FAP		7 (8.9)	8 (10.4)
Median target tumor size per RECIST (range), mm		75.1 (18.0, 244.9)	84.8 (21.3, 666.3)
Prior therapies	Any prior therapy	52 (65.8)	60 (77.9)
	Surgery	24 (30.4)	33 (42.9)
	Radiation therapy	8 (10.1)	12 (15.6)
	Systemic therapy‡	43 (54.4)	46 (59.7)
Prior systemic therapies	0 lines	36 (45.6)	31 (40.3)
	1 line	25 (31.6)	22 (28.6)
	≥2 lines	18 (22.8)	24 (31.2)

RECIST Response Evaluation Criteria in Solid Tumors | † Per electronic data capture system | ‡ Includes chemotherapy, tyrosine kinase inhibitors, and hormonal therapy | Percentages may not total 100 because of rounding.

Varegacestat Safety Profile

- No deaths due to adverse events
- Serious adverse events: Varegacestat: 25 pts (32%) | Placebo: 7 pts (9%)

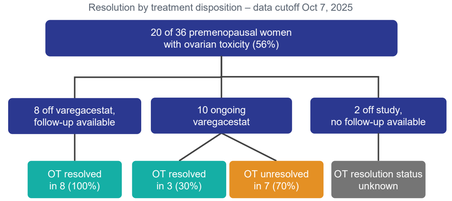
Most Common Treatment-Emergent Adverse Events, n (%)	Varegacestat (n=79) Any grade	Varegacestat (n=79) Grade ≥3	Placebo (n=77) Any grade	Placebo (n=77) Grade ≥3
Any adverse event	79 (100)	45 (57)	70 (91)	13 (17)
Reported in ≥20% in either arm*				
Diarrhea	65 (82)	8 (10)	21 (27)	0
Fatigue	35 (44)	1 (1)	18 (23)	2 (2.6)
Rash	34 (43)	2 (3)	9 (12)	0
Nausea	28 (35)	0	20 (26)	0
Cough	27 (34)	0	4 (5)	0
Hypophosphatemia	27 (34)	1 (1)	2 (3)	0
Alopecia	26 (33)	0	3 (4)	0
Dry mouth	24 (30)	0	5 (7)	0
Hair color changes	20 (25)	0	0	0
Pruritus	20 (25)	0	4 (5)	0
Rash maculo-papular	20 (25)	1 (1)	1 (1)	0
ALT increase	18 (23)	3 (4)	4 (5)	0
AST increase	18 (23)	2 (3)	2 (3)	0
Amenorrhea	17 (22)	0	2 (3)	0
Upper respiratory tract infection	17 (22)	0	5 (7)	0
Vomiting	16 (20)	0	6 (8)	0

*MedDRA preferred terms. ALT, alanine aminotransferase; AST, aspartate aminotransferase
Population: all participants who received ≥1 dose of study drug (i.e., the intention-to-treat population).

Ovarian Toxicity

- A known class effect of GSI
- Varegacestat 56% | Placebo 5% of premenopausal women
- No women discontinued varegacestat due to ovarian toxicity
- Ovarian toxicity resolved in all participants with follow-up data after stopping treatment

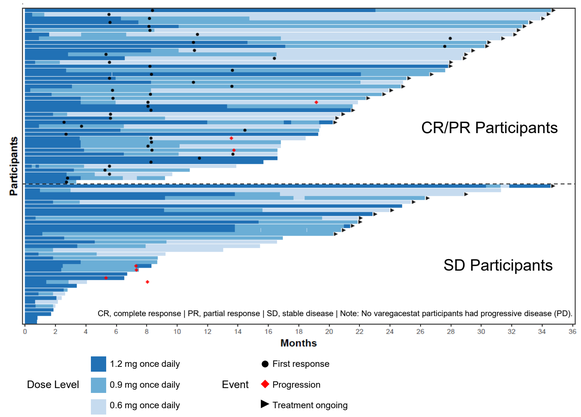
RINGSIDE Varegacestat Group
Resolution by treatment disposition – data cutoff Oct 7, 2025



Ovarian toxicity includes the MedDRA preferred terms amenorrhea, premature menopause, menopause, ovarian failure.

Varegacestat Dose Modifications According to Response Status

Median treatment duration: 20 months



Median Time to First Dose Reduction*

Varegacestat
↓ to 0.9 mg (n=60): 3.7 (IQR 1.8, 8.3) months
↓ to 0.6 mg (n=36): 7.3 (IQR 3.0, 12.5) months

Placebo
↓ to 0.9 mg (n=7): 5.6 (IQR 2.1, 16.1) months
↓ to 0.6 mg (n=2): 10.7 (IQR 4.9, 16.6) months

Median Time to First Dose Interruption*

Varegacestat (n=63): 2.5 (IQR 1.0, 5.7) months

Placebo (n=29): 3.4 (IQR 1.9, 7.3) months

*Time to dose reduction or dose interruption is defined as the duration from the date of the first dose to the start date of the first dose reduction (to either dose) or dose interruption. IQR, interquartile range

Dose Modifications Due to Adverse Events

Dose Reduction
Varegacestat 80% | Placebo 9%

Most common AEs leading to dose reduction

Preferred Term, n (%)	Varegacestat (n=79)	Placebo (n=77)
Diarrhea	15 (19.0)	0
Fatigue	7 (8.9)	1 (1.3)
Rash	7 (8.9)	0
Rash maculo-papular	6 (7.6)	0
Folliculitis	4 (5.1)	0
Hidradenitis	4 (5.1)	0
ALT increased	3 (3.8)	0
Cough	3 (3.8)	1 (1.3)

ALT, alanine aminotransferase

Dose Interruption
Varegacestat 65% | Placebo 14%

Most common AEs leading to dose interruption

Preferred Term, n (%)	Varegacestat (n=79)	Placebo (n=77)
Diarrhea	9 (11.4)	1 (1.3)
Fatigue	6 (7.6)	0
Rash	6 (7.6)	0
Vomiting	5 (6.3)	1 (1.3)
ALT increased	4 (5.1)	2 (2.6)
Pyrexia	4 (5.1)	1 (1.3)

Discontinuation
Varegacestat 20% | Placebo 7%

Most common AEs leading to discontinuation

Preferred Term, n (%)	Varegacestat (n=79)	Placebo (n=77)
Fatigue	2 (2.5)	1 (1.3)
Hidradenitis	2 (2.5)	0
Hyperthyroidism	2 (2.5)	0

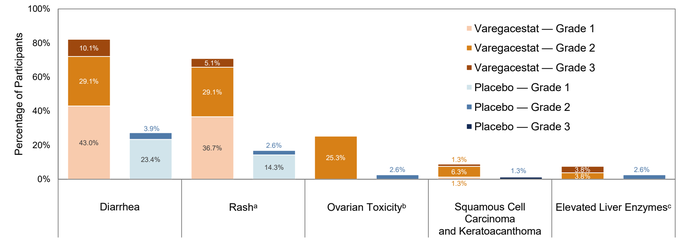
Time to First Onset of Frequently Reported Adverse Events with Varegacestat

	Varegacestat (N=79)				Placebo (N=77)			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
Adverse Events (AE)	n (%)	Median Time to Onset (days)	n (%)	Median Time to Onset (days)	n (%)	Median Time to Onset (days)	n (%)	Median Time to Onset (days)
Diarrhea	65 (82.3)	14.0	8 (10.1)	110.0	21 (27.3)	21.0	0	-
Rash*	56 (70.9)	24.0	4 (5.1)	33.5	13 (16.9)	69.0	0	—
Fatigue*	46 (58.2)	27.5	1 (1.3)	73.0	24 (31.2)	19.0	2 (2.6)	48.5
Hair follicle AEs*	32 (40.5)	59.0	2 (2.5)	164.5	3 (3.9)	70.0	0	—
Cough*	31 (39.2)	16.0	1 (1.3)	166.0	5 (6.5)	198.0	0	—
Nausea	28 (35.4)	8.0	0	—	20 (26.0)	7.5	0	—
Hypophosphatemia	27 (34.2)	29.0	1 (1.3)	58.0	2 (2.6)	49.5	0	—
Upper respiratory infection*	27 (34.2)	46.0	0	—	6 (7.8)	136.5	0	—
Dry mouth	24 (30.4)	13.0	0	—	5 (6.5)	8.0	0	—
Hair color changes	20 (25.3)	60.5	0	—	0	—	0	—
Ovarian toxicity*	20 (25.3)†	56.5	0	—	2 (2.6)	41.5	0	—

* denotes grouped terms comprising multiple clinically related MedDRA preferred terms
† calculated as a percentage of the whole population – see Ovarian Toxicity section for more details

Select Adverse Events of Interest by Grade

- Among these AEs, the most frequently reported were diarrhea and rash, which were primarily grade 1-2



a. Denotes grouped terms comprising multiple clinically related MedDRA preferred terms
b. Ovarian toxicity includes the MedDRA preferred terms amenorrhea, premature menopause, menopause, ovarian failure.
c. Defined as alanine aminotransferase or aspartate aminotransferase with grade ≥2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0

CONCLUSIONS

- In the Phase 3 RINGSIDE trial, varegacestat 1.2 mg once daily demonstrated clinically meaningful benefit in adults with desmoid tumors with a safety profile consistent with known GSI class effects.
- While dose modifications were common, discontinuations were infrequent, making it possible for patients to remain on treatment and achieve continued efficacy benefit.
- These results support the use of varegacestat as a potential systemic treatment option for patients with desmoid tumors.

References: **1.** Ungerbäck J, et al. PLoS One. 2011;6(3):e17957. | **2.** Gounder M, et al. N Engl J Med. 2023;388(10):898-912. | **3.** Gounder M, et al. 2026 ASCO Annual Meeting. Abstract #11506. https://ascopubs.org/doi/10.1200/JCO.2026.44.16_suppl.11506 | **4.** Kasper B, et al. JAMA Oncol. 2024;10(8):1121–1128.

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