Patient-Reported Outcomes (PROs) with Varegacestat Versus Placebo in Progressing Desmoid Tumors: Results from RINGSIDE Part B

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Renumerated conflict of interest 2024-2026

- Research grant from Eli Lilly (to the institute)
- Advisory: Immunome (to the Institute)
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- Local PI Boehringer Ingelheim (inst.)
- Local PI Springworks (inst.)
- local PI Immunome (inst)

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Non-renumerated conflicts of interest (2024-2026)

- President/Board member of the European Organisation for Research and Treatment of Cancer (EORTC)
- Co-chair of the EORTC Taskforce Rare Cancers
- Chair of the Board of the Dutch AYA care network
- Board Member of European Cancer Organisation
- Member of ESMO Sarcoma Faculty
- PI of STRONG AYA (Horizon EU)
- PI of COMPRAYA (KWF)
- PI of GEN-AYA (KWF)
- Member of Scientific Council KiKa (Children with Cancer)
- Member Leadership Group Common Sense Oncology
- Member Trial Steering Committee of rEECur study
- Member Trial Steering Committee InterEwing-1 study
- Member Trial Steering Committee Fa-RMS study
- Member Advisory Committee HEROES AYA
- Member Advisory Committee Lancet Oncology
- Co-chair of Lancet Commission AYA Oncology
- Co-chair of Lancet Commission Independent Clinical Research in Oncology

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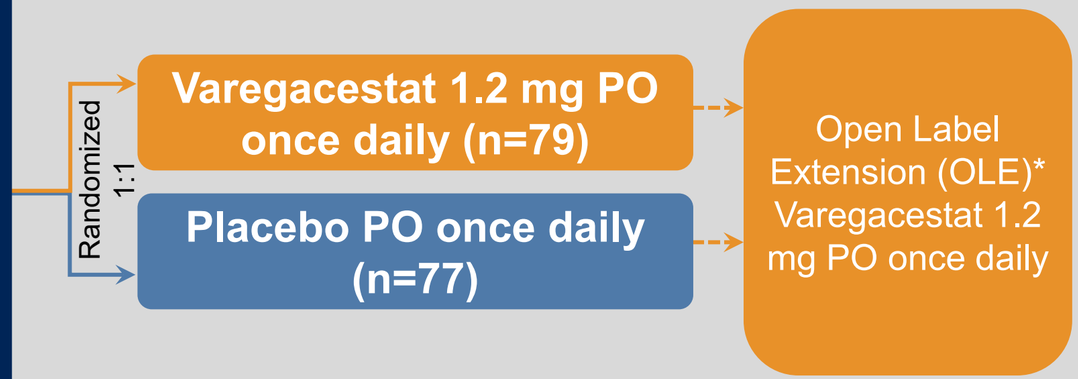
RINGSIDE: A Phase 3, Randomized Trial of Varegacestat for Treatment of Progressing Desmoid Tumors (DT)

- DTs are rare, locally aggressive soft tissue tumors associated with substantial pain and functional impairment.
- Varegacestat is a once-daily oral gamma-secretase inhibitor (GSI) developed to provide meaningful clinical benefit for patients with progressing DT.

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 are eligible



Primary Endpoint: PFS by Blinded Independent Central Review (BICR)

Key Secondary Endpoints:

- ORR
- Change from baseline in tumor volume
- Change from baseline in worst pain intensity (WPI)

Select PRO Exploratory Endpoints:

- Change from baseline in pain and DT symptoms (GODDESS)
- Change from baseline in Physical Functioning (PROMIS Physical Functioning 10a)

Abbreviations: GODDESS, GOunder/Desmoid Tumor Research Tumor Foundation DEsmoid Symptom Scale and Impact Scale; DTSS, Desmoid Tumor Symptom Scale; PROMIS, Patient-Reported Outcome Measurement Information System.

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RINGSIDE Met all Primary and Key Secondary Endpoints

Primary Endpoint

84% reduction in the risk of radiographic disease progression or death with Varegacestat vs. Placebo

Hazard ratio: 0.16, p-value <0.0001

Key Secondary Endpoint

−2.24 point reduction in WPI with Varegacestat vs +0.18 point increase with Placebo at Week 12

Difference: -2.42, p-value <0.0001

Key Secondary Endpoints

55.7% ORR in Varegacestat vs 9.1% with Placebo

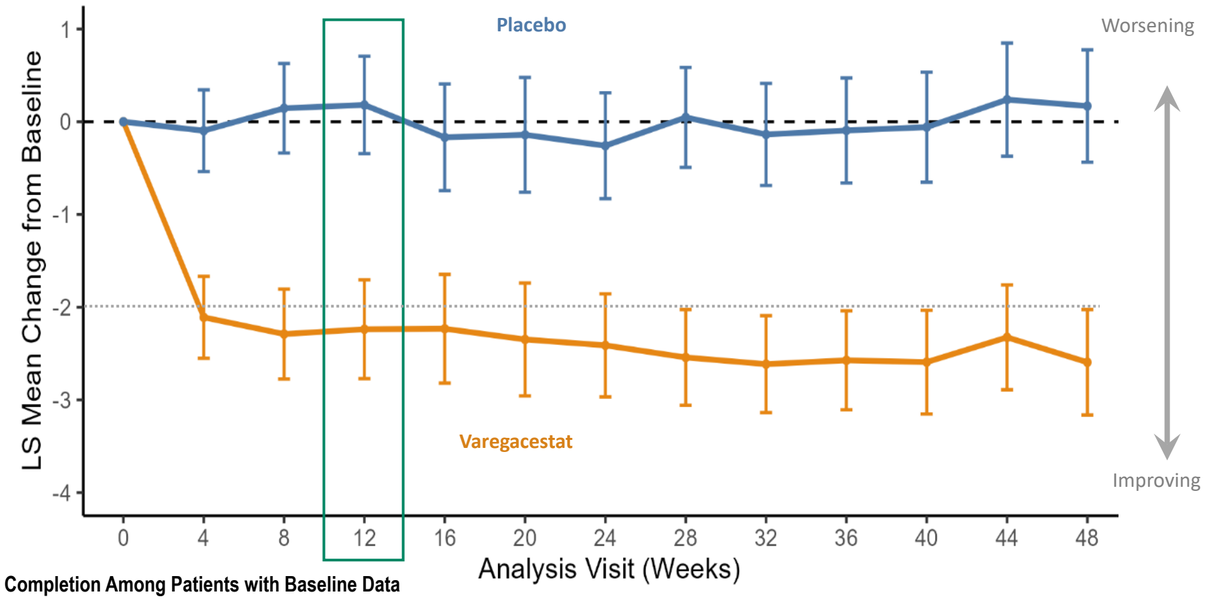
p-value <0.0001

−109.6 cm^3 reduction in tumor volume with Varegacestat vs +122.8 cm^3 increase with Placebo at Week 24

−83% best percent change in tumor volume

Difference: -232.4, p-value <0.0001

Change in Worst Pain Intensity Score



PRO Completion Among Patients with Baseline Data

Varegacestat	72	64	61	52	46	48	47	46	42	45	41	38	37
Placebo	71	62	58	55	50	42	43	35	33	31	29	28	27

As measured by LS mean in WPI as measured by item 1 in GODDESS DTSS

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PRO Analyses of GODDESS DTSS and PROMIS Physical Function

GODDESS DTSS

Completed as a daily diary for 7 days (scores averaged over the 7 days), at baseline and every 4 weeks

Pain Domain	1	WPI
	2	Dull pain
	3	Shooting pain
—	4	Fatigue
Extra-abdominal domain	5	Swelling
	6	Muscle weakness
	7	Difficulty moving
—	8	Tumor location
Intra-abdominal domain	9	Abdominal pain
	10	Nausea
	11	Fullness

Items in Total Symptom Score -5 (TSS-5)domain

Higher Scores = Worse Symptoms; scored on 0 to 10 scale

Domains and Items scored 0 (no symptoms) to 10 (worse symptoms imaginable)

PROMIS Physical Function 10a

Completed once at baseline and every 4 weeks

1. Vigorous activity (running, sports)
2. Walking more than 1 mile
3. Climbing one flight of stairs
4. Lifting or carrying groceries
5. Bending, kneeling, or stooping
6. Chores (vacuuming, yard work)
7. Dressing (shoelaces, buttons)
8. Shampooing your hair
9. Washing and drying your body
10. Sitting on / rising from the toilet

Higher Scores = Better Function

Items scored on a scale of 1 (cannot do) to 5 (can do without any difficulty/ not impacted)

- Analyses on ITT population; symptoms at baseline were not an enrollment criterion
- Clinically meaningful thresholds were derived from the RINGSIDE population

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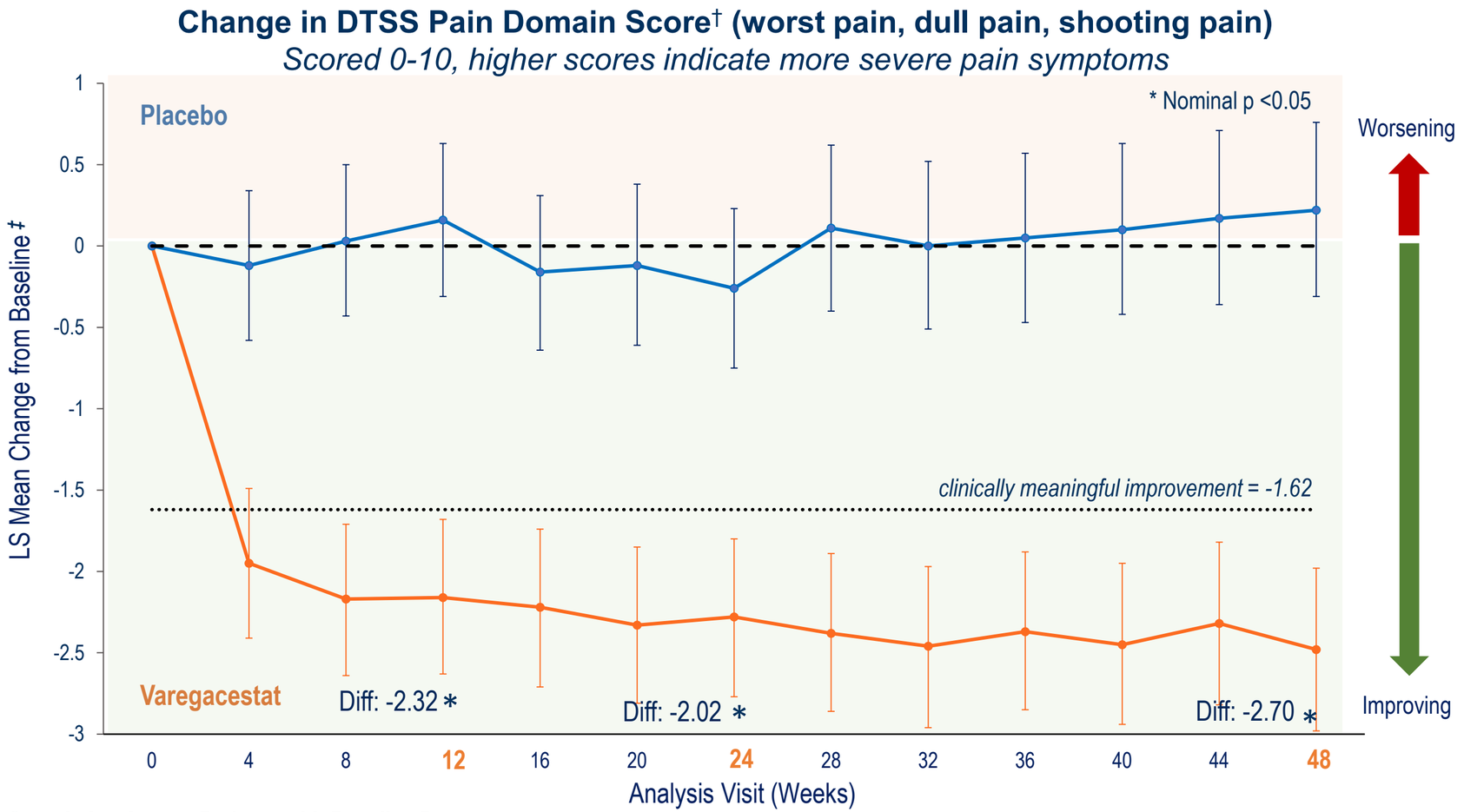
Varegacestat Reduces Pain as Early as First Assessment



PRO Completion Among Patients with Baseline Data

Varegacestat	72	64	61	52	46	48	47	46	42	45	41	38	37
Placebo	71	62	58	55	50	42	43	35	33	31	29	28	27

- At baseline, the mean WPI score was 4.43 for varegacestat and 4.94 for placebo. Approximately 80% had a score of ≥ 2.
- At all prespecified timepoints, results were in favor of varegacestat

† Least-square (LS) means derived from mixed model for repeated measures (MMRM)

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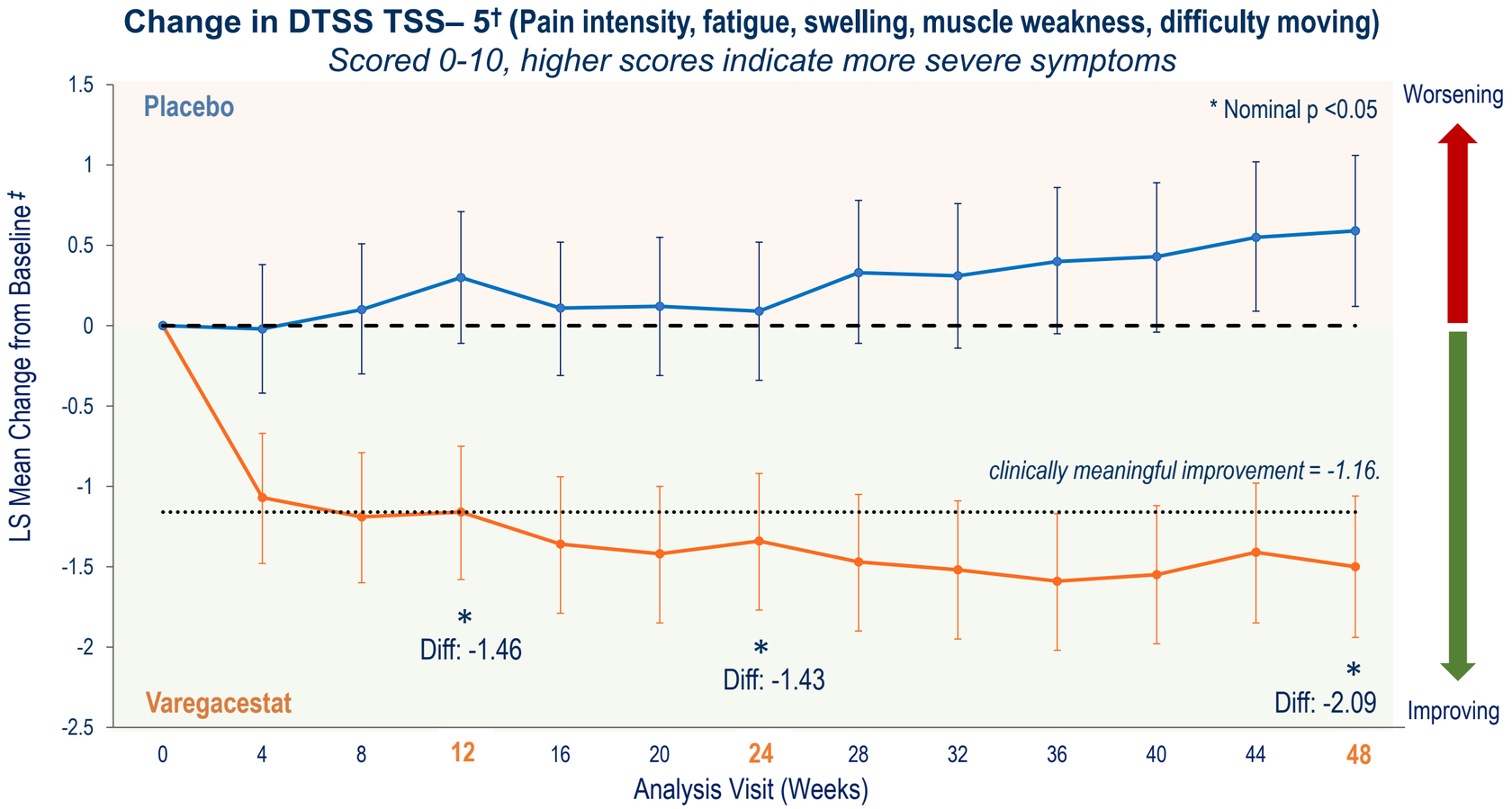
Varegacestat Improves DT Symptoms



PRO Completion Among Patients with Baseline Data

Varegacestat	72	64	61	52	46	48	47	46	42	45	41	38	37
Placebo	71	62	58	55	50	42	43	35	33	31	29	28	27

- Average baseline score across arms was approximately 4 indicating moderate symptom burden.
- At all prespecified timepoints, results were in favor of varegacestat

† Least-square (LS) means derived from mixed model for repeated measures (MMRM)

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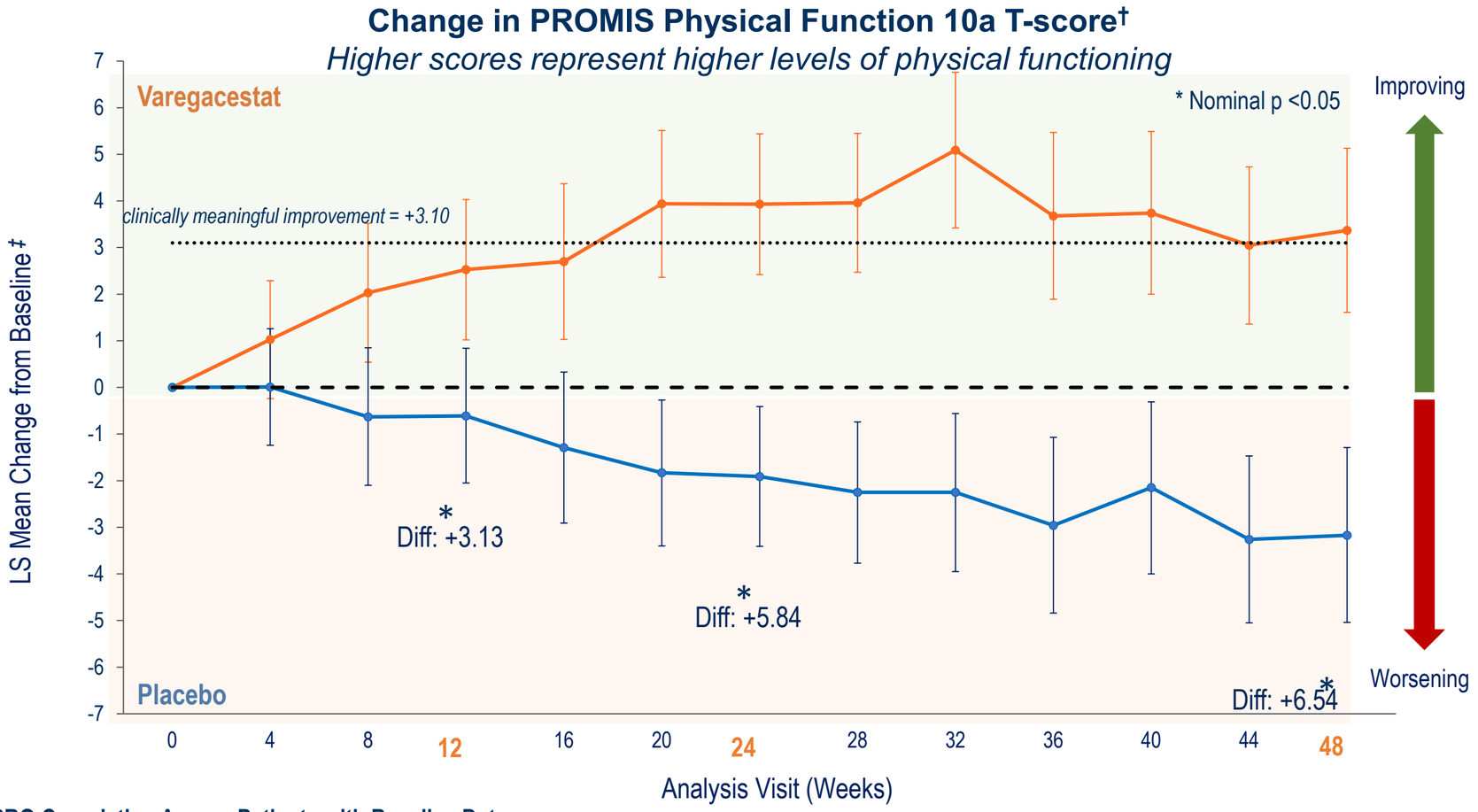
Varegacestat Improves Physical Functioning



PRO Completion Among Patients with Baseline Data

Varegacestat	71	66	62	54	49	51	47	44	42	42	40	42	37
Placebo	73	64	60	60	53	47	45	39	37	33	33	29	26

- A T-score of 50 reflects the average level of physical functioning in a general population; average baseline score across arms was approximately 45, indicating mild functional impairment.
- At all prespecified timepoints, results were in favor of varegacestat

‡ Baseline was originally defined as the last assessment before randomization and was redefined post hoc to include PRO assessments completed on or before first dose. Results shown use this updated baseline definition and remained consistent with the primary week 12, 24, and 48 findings.

† Least-square (LS) means derived from mixed model for repeated measures (MMRM)

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CONCLUSION

In RINGSIDE, varegacestat met all primary and key secondary endpoints

In patients on the varegacestat arm, exploratory PRO analyses demonstrated fast, sustained, and clinically meaningful improvements in patient-reported:

- **Pain**
- **DT symptoms**
- **Physical functioning**

These results support the primary outcomes of the RINGSIDE trial and underscore the potential of varegacestat as a standard of care option for patients with DT

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Thank you!

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