Efficacy of Nirogacestat in Improving Emotional Impact Outcomes in Adults With Desmoid Tumors: Post Hoc Analysis From the DeFi Trial

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Disclosures

I, ***Mrinal Gounder***, declare financial interests (eg, funding, royalties, and/or advisory board membership, etc) with the following:

- Avacta; Bristol Myers Squibb International; Erasca; Ikena Oncology; Immunome; Kura Oncology; Neok Bio; Orion; Parabilis; SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany; Tango; Vivace Therapeutics

I also hold nonfinancial positions including advisory roles for Chordoma Foundation and Liposarcoma Support Network and a leadership role as a Scientific Director of the Desmoid Tumor Research Foundation

Memorial Sloan Kettering owns the licensing agreement for the **GODDESS PRO Instrument**

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Introduction

- DTs are rare, locally invasive, soft-tissue tumors that can result in severe pain, functional morbidity, and QoL impairment[1,2]
- Impaired QoL due to DT symptoms—especially pain—is known to contribute toward persistent emotional distress, such as feelings of anxiety and depression[3–5]
- Nirogacestat is an oral, targeted gamma secretase inhibitor and the only US Food and Drug Administration–, European Commission–, and UK Medicines and Healthcare Product Regulatory Agency–approved treatment for adults with progressing DTs who require systemic treatment
- In DeFi (NCT03785964), a global, randomized, placebo-controlled, multicenter, phase 3 trial evaluating the efficacy and safety of nirogacestat, treatment with nirogacestat resulted in a significant and clinically meaningful reduction in all prespecified assessments of PROs, including DT-related pain intensity, compared with placebo[6]
- PRO assessments have demonstrated the high emotional and psychological burden of DTs, with patients experiencing fear, frustration, and hopelessness related to their condition; however, **the effect of DT treatment on patients' emotional well-being has not been explored**

Objective

To evaluate the emotional impact of DT treatment via emotion-related PROs and their correlation with pain in patients with DTs treated with nirogacestat or placebo in the DeFi trial

DT, desmoid tumor; PRO, patient-reported outcome; QoL, quality of life.

1. Riedel RF, Agulnik M. *Cancer*. 2022;128(16):3027–3040. **2.** Kasper B, et al. *Ann Oncol*. 2017;28(10):2399–2408. **3.** Lucas A, et al. *Orphanet J Rare Dis*. 2025;20(1):515. **4.** Timbergen MJM, et al. *Qual Life Res*. 2018;27(12):3097–3111. **5.** Bektas M, et al. *Adv Ther*. 2023;40(9):3697–3722. **6.** Gounder MM, et al. *N Engl J Med*. 2023;388(10):898–912.

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Post Hoc Analysis of Phase 3 DeFi Trial: Assessment Tools and Methods

- This post hoc analysis of the DeFi double-blind phase 3 trial evaluated emotional outcomes using emotion-related item scores from two PRO assessment tools:
  - **Emotional Domain scores from the GODDESS DTIS[1]**
  - **Emotional Functioning scores from the EORTC QLQ-C30**
- LS mean change from baseline in emotional outcome scores was compared between treatment arms at Cycle 10 and overall (up to Cycle 24) using mixed model with repeated measures, per published DeFi methods demonstrating the effect of nirogacestat on PROs[2]
  - Baseline for DTIS and EORTC QLQ-C30 assessments was defined as the most recent measurement prior to the first administration of study treatment
- Correlation between the change from baseline in DTIS Emotional Domain/EORTC QLQ-C30 Emotional Functioning scores and the change from baseline in API were assessed at Cycle 10 for patients assigned to nirogacestat
  - API was calculated using the BPI-SF item 3 (worst pain in the past 24 hours; 0–10 scale)
  - Baseline BPI-SF API was defined as the weekly average of the baseline period (study days −7 through −1)
- **All PRO measures were completed by patients at screening, baseline (ie, Cycle 1), and in 28-day cycles thereafter, using home electronic PRO devices**

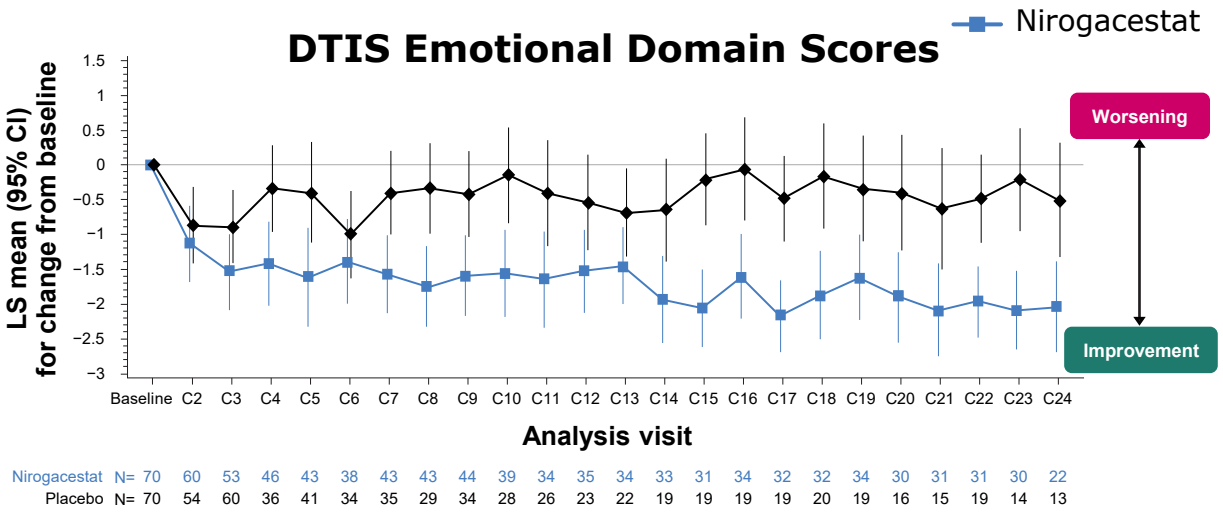
Final database lock 19 December 2024.
API, average pain intensity; BPI-SF, Brief Pain Inventory–Short Form; DTIS, Desmoid Tumor Impact Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GODDESS, Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; LS, least squares; PRO, patient-reported outcome.
1. Gounder MM, et al. *Qual Life Res*. 2023;32(10):2861–2873. **2.** Gounder MM, et al. *N Engl J Med*. 2023;388(10):898–912.

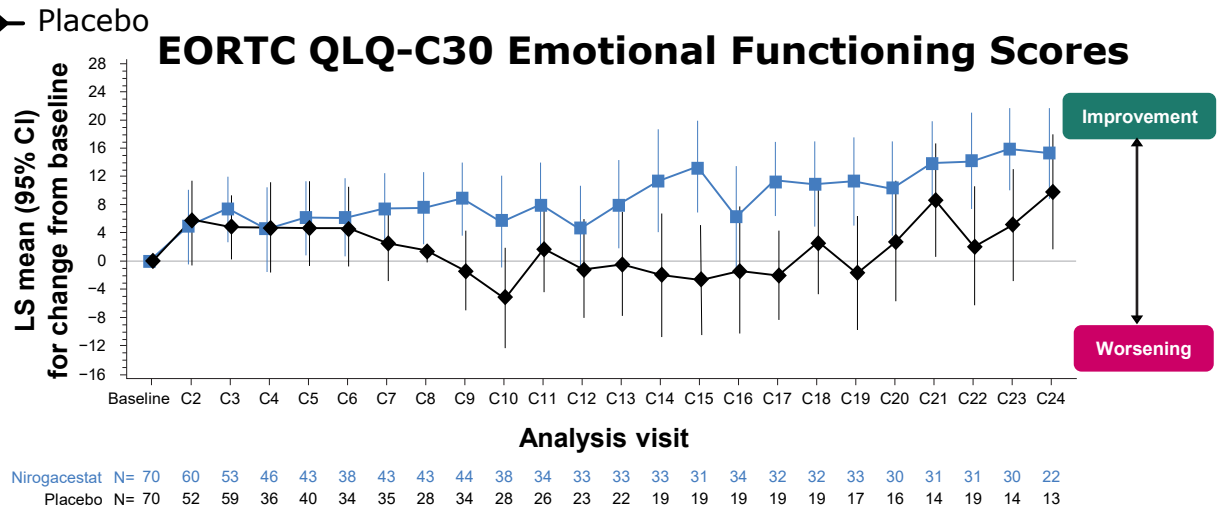
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Change From Baseline in DTIS Emotion Domain Score and EORTC QLQ-C30 Emotional Functioning Score by Visit

- At baseline, all patients reported a moderately high DT symptom–related emotional impact
- Mean (SD) baseline scores for patients treated with nirogacestat and placebo were 4.6 (2.7) and 4.7 (2.9) for DTIS Emotional Domain (scored between 0–10),[a] respectively, and 63.6 (22.3) and 66.0 (24.7) for EORTC QLQ-C30 Emotional Functioning (scored between 0 to 100),[b] respectively





Differences between nirogacestat and placebo in LS mean change from baseline for DTIS Emotional Domain scores favored nirogacestat at Cycle 10 (**−1.4; *P*=.001**) and overall up to Cycle 24 (**−1.26; *P*<.001**)[c]

Differences between nirogacestat and placebo in LS mean change from baseline for EORTC QLQ-C30 Emotional Functioning scores favored nirogacestat at Cycle 10 (**10.80; *P*<.05**) and overall up to Cycle 24 **(7.29; *P*<.01**)[d]

[a]Higher scores indicate more severe negative emotional impact overall. [b]Higher scores denote improvement in overall emotional well-being. [c]A positive change from baseline indicates worsening impact; a negative change from baseline indicates an improvement. A negative LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo. [d]A positive change from baseline indicates improvement of functioning; a negative change from baseline indicates a worsening of function. A positive LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo.
C, cycle; DT, desmoid tumor; DTIS, Desmoid Tumor Impact Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, least squares.

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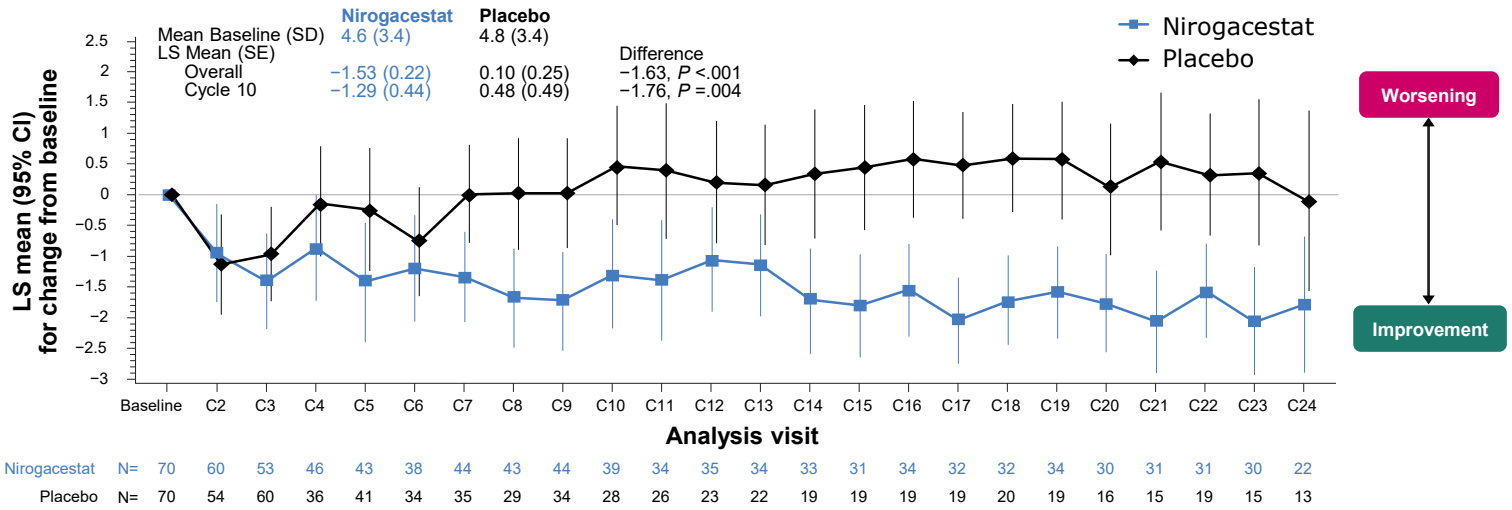
Change From Baseline in Individual Emotion-Related Item Scores

- For patients with pain at baseline (BPI-SF API>0) treated with nirogacestat (n=24), **API reduction did not correlate with improvements** in DTIS Emotion Domain or EORTC QLQ-C30 Emotional Functioning scores at Cycle 10
- Compared to placebo, nirogacestat had a positive impact on individual emotion-related item scores in DTIS and EORTC QLQ-C30 based on LS mean change from baseline
  - Placebo showed worsening from baseline or no impact
- **Improvement with nirogacestat vs placebo was seen in the individual DTIS Emotion Domain items "Fear of Future Diagnostic Tests" and "Fear of Desmoid Tumor Recurrence/Growth"**

API, average pain intensity; BPI-SF, Brief Pain Inventory–Short Form; C, cycle; DTIS, Desmoid Tumor Impact Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, least squares.

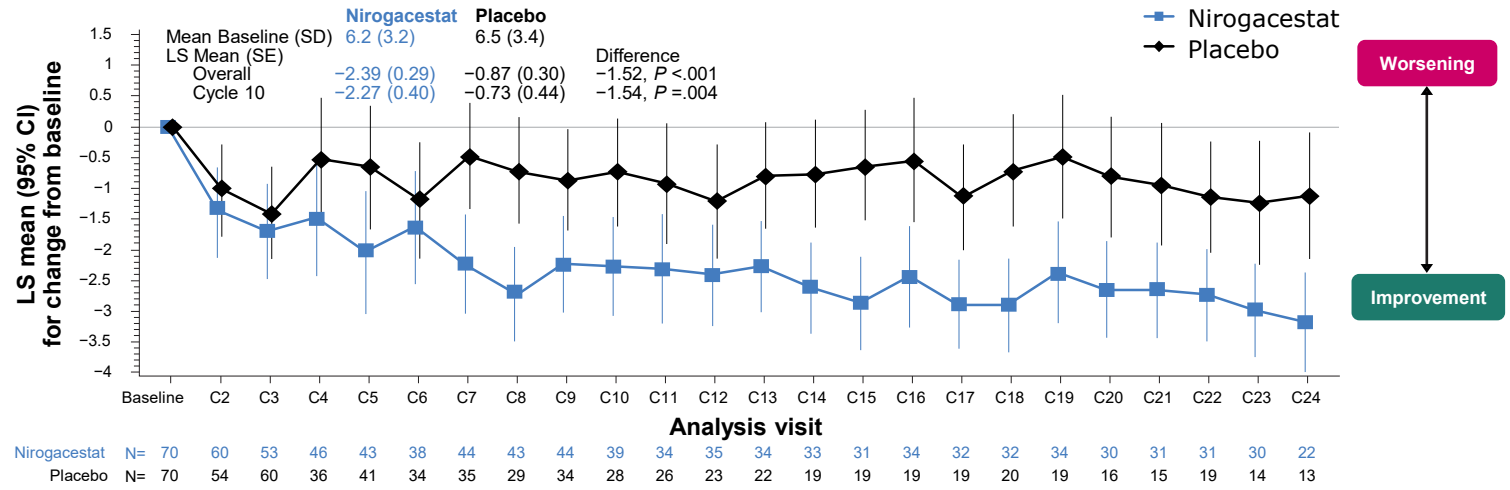
Change From Baseline in DTIS Emotional Domain Items by Visit

Fear of Future Diagnostic Tests



Nirogacestat	N=	70	60	53	46	43	38	44	43	44	39	34	35	34	33	31	34	32	32	34	30	31	31	30	22
Placebo	N=	70	54	60	36	41	34	35	29	34	28	26	23	22	19	19	19	19	20	19	16	15	19	15	13

Fear of Desmoid Tumor Recurrence/Growth



Nirogacestat	N=	70	60	53	46	43	38	44	43	44	39	34	35	34	33	31	34	32	32	34	30	31	31	30	22
Placebo	N=	70	54	60	36	41	34	35	29	34	28	26	23	22	19	19	19	19	20	19	16	15	19	14	13

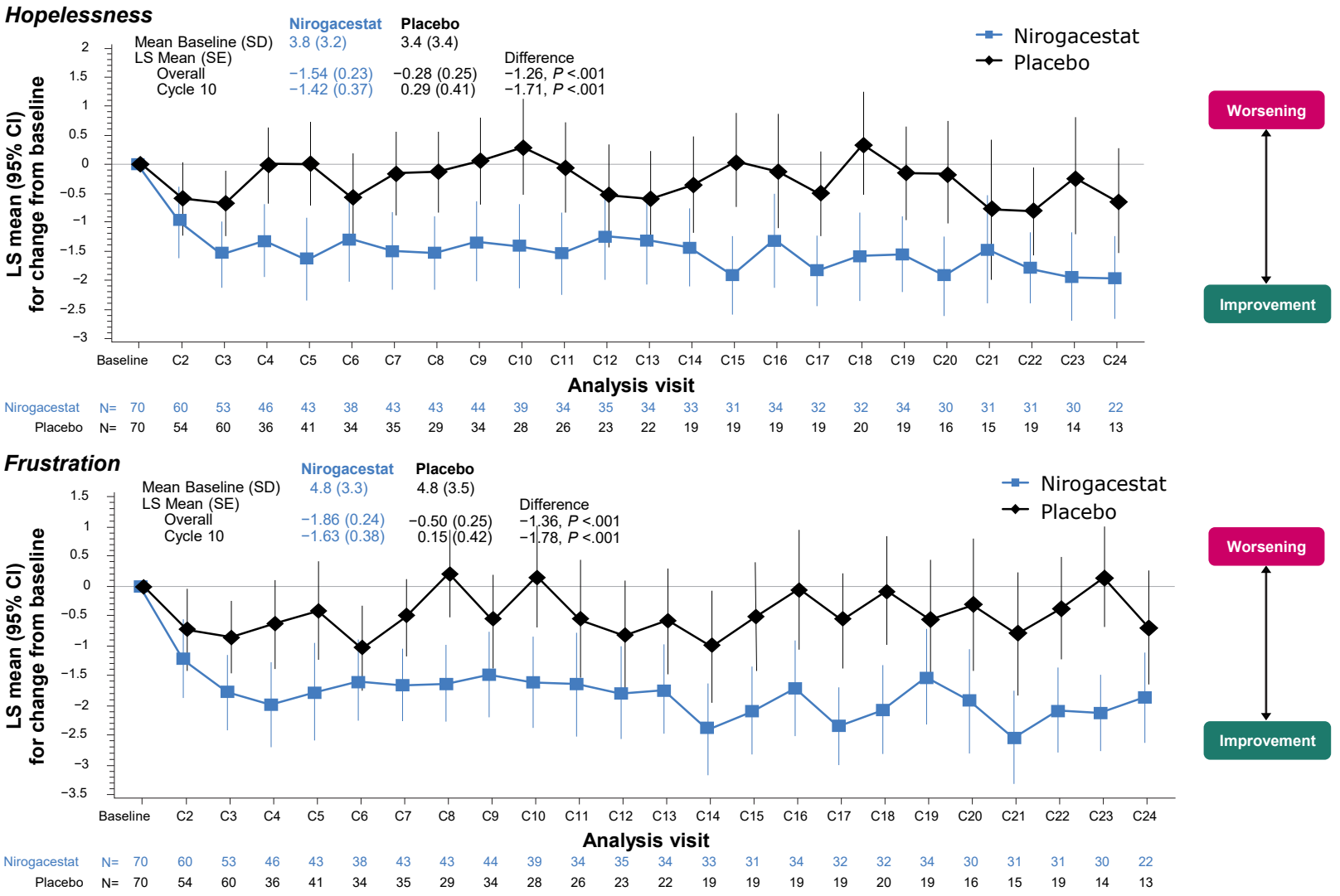
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Change From Baseline in Individual Emotion-Related Item Scores

- **Improvement with nirogacestat vs placebo was seen in the individual DTIS Emotion Domain items "Hopelessness" and "Frustration"**

Change From Baseline in DTIS Emotional Domain Items by Visit



C, cycle; DTIS, Desmoid Tumor Impact Scale; LS, least squares.

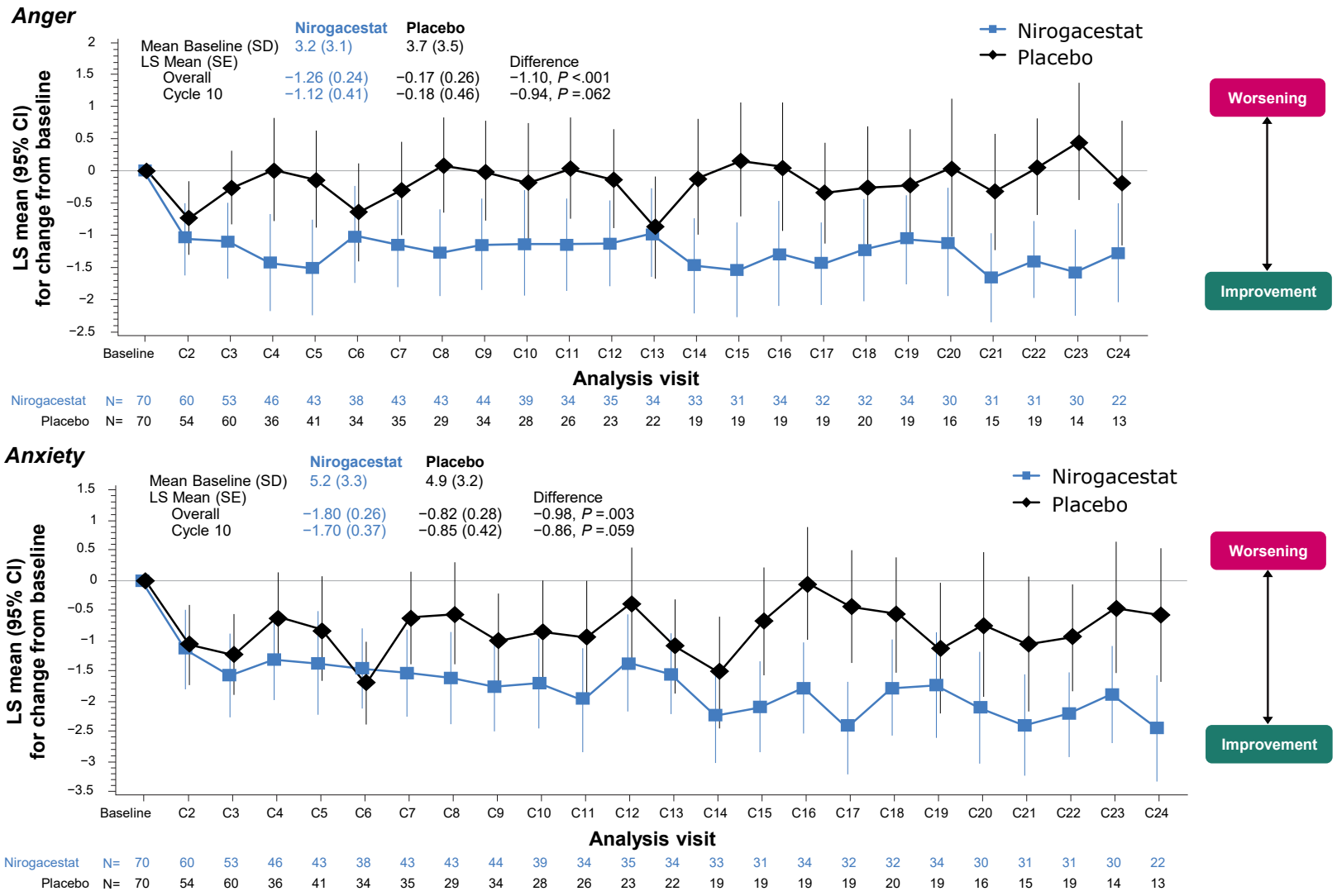
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Change From Baseline in Individual Emotion-Related Item Scores

- **Improvement with nirogacestat vs placebo was seen in the individual DTIS Emotion Domain items "Anger" and "Anxiety"**

Change From Baseline in DTIS Emotional Domain Items by Visit



C, cycle; DTIS, Desmoid Tumor Impact Scale; LS, least squares.

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Change From Baseline in Individual Emotion-Related Item Scores

- Improvement with nirogacestat was also seen with the individual *(data not shown)*:
  - **DTIS items:**
    - People Avoidance Due to Appearance
    - Dissatisfaction About Appearance
  - **EORTC QLQ-C30 items:**
    - Feel Tense
    - Worry
    - Feel Irritable
    - Feel Depressed

DTIS, Desmoid Tumor Impact Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

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Conclusions



Baseline emotion scores indicate that patients in the DeFi trial with progressing DTs experienced a significant level of DT symptom-related emotional burden, suggesting the need for proactive assessment and management



Treatment of DTs with nirogacestat led to improvement in patient-reported emotional burden; this improvement emerged early and was sustained over time



Patient-reported improvement in pain intensity did not correlate with changes in emotional health, suggesting potential multifactorial drivers of emotional burden in patients with progressing DTs

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DT, desmoid tumor.

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*Note that **CBh, TB,** and **RC** were employees at the time of the analysis and are now former employees.