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

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Disclosures

I, ***Bernd Kasper***, declare financial interests (eg, honoraria, funding, etc) with the following:

- Ayala Pharmaceuticals; Bayer; Boehringer Ingelheim; Cogent Medicine; GlaxoSmithKline; Immunome; PharmaMar; Pharmamar-zeltia; SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany

I have also served:

- On an advisory board for Ayala, Bayer, Boehringer Ingelheim, PharmaMar, and SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany
- As a local principal investigator for Cogent and a coordinating PI for Immunome, PharmaMar, and SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany
- In a leadership role for the European Organisation for Research and Treatment of Cancer (EORTC) and as a past-chair of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG)

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[1–3]
- DT symptoms, particularly chronic pain, are known to negatively impact patients' QoL, with pain directly leading to sleep disturbances in most patients[3,4]
- 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[5]
- While assessments of PROs have demonstrated the negative impact of DT symptoms on sleep, **the effect of DT treatment on patients' sleep has not been explored**

Objective

To evaluate the impact of DT treatment on sleep using sleep-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.** Penel N, et al. *Curr Opin Oncol*. 2017;29(4):268–274. **3.** Lucas A, et al. *Orphanet J Rare Dis*. 2025;20(1):515. **4.** Bektas M, et al. *Adv Ther.* 2023;40(9):3697–3722. **5.** 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

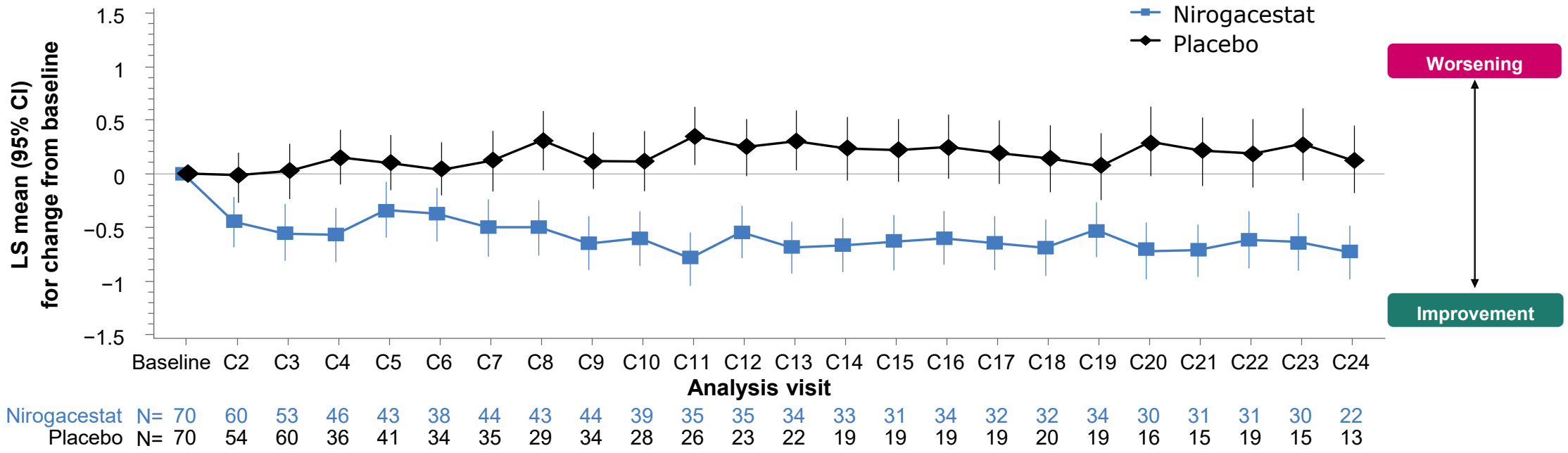
- This post hoc analysis of the DeFi double-blind phase 3 trial evaluated sleep outcomes using the following PROs, with higher scores indicating greater negative impact or interference on sleep:
  - **GODDESS DTIS Sleep Domain PRO scores[1]**
  - **Individual sleep-related item PRO scores (from GODDESS DTIS, EORTC QLQ-C30, and BPI-SF)**
- LS mean change from baseline in sleep 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 Sleep Domain scores and the change from baseline in API was 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 assessments 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 Sleep Domain Score by Visit

At baseline, all patients reported a moderately high DT symptom–related impact on sleep, with a mean (SD) DTIS Sleep Domain score of 2.9 (1.3) for patients on nirogacestat and 2.9 (1.3) for patients on placebo, on a 5-point Likert scale[a]



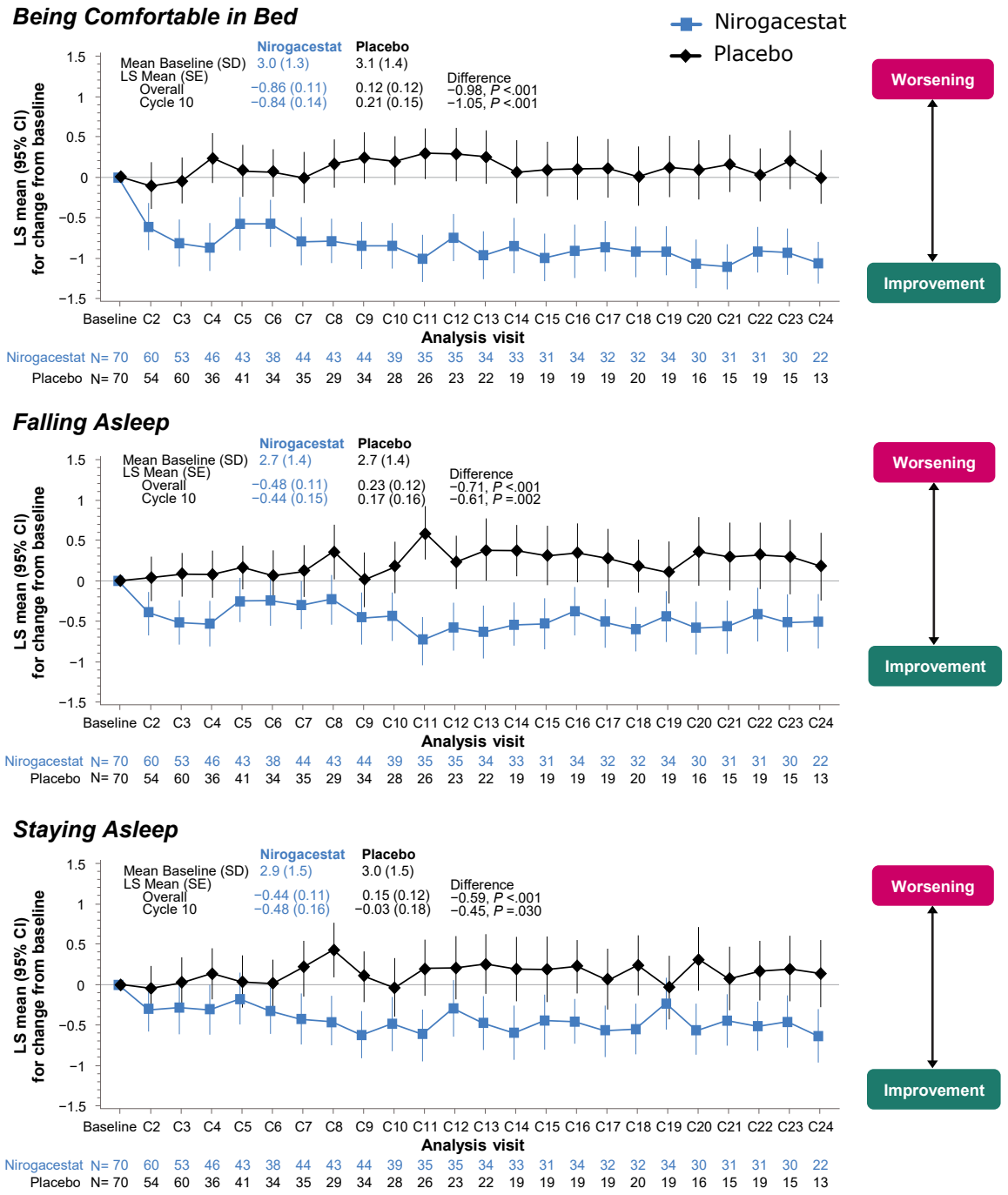
Differences between nirogacestat and placebo in LS mean change from baseline in DTIS Sleep Domain score favored nirogacestat at Cycle 10 (**–0.71; *P*<.001**) and overall assessed up to Cycle 24 (**–0.78; *P*<.001**)

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. One patient assigned to receive placebo did not have data at baseline and was not included in this analysis.
[a]Higher scores indicate greater negative impact on sleep.
C, cycle; DT, desmoid tumor; DTIS, Desmoid Tumor Impact Scale; LS, least squares.

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Change From Baseline in DTIS Sleep Domain Individual Item Scores by Visit

- For patients with pain at baseline (API>0) treated with nirogacestat (n=24), **API reduction showed a moderate correlation to improvement** in DTIS Sleep Domain score at Cycle 10 (r=0.62; *P*<.01)
- Differences in LS mean change from baseline favored nirogacestat for DTIS Sleep Domain individual items (5-point Likert scale)
  - "Being Comfortable in Bed"
  - "Falling Asleep"
  - "Staying Asleep"
- Placebo showed worsening from baseline or no impact in all individual item scores



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.
One patient assigned to receive placebo did not have data at baseline and was not included in this analysis.
API, average pain intensity; C, cycle; DTIS, Desmoid Tumor Impact Scale; LS, least squares.

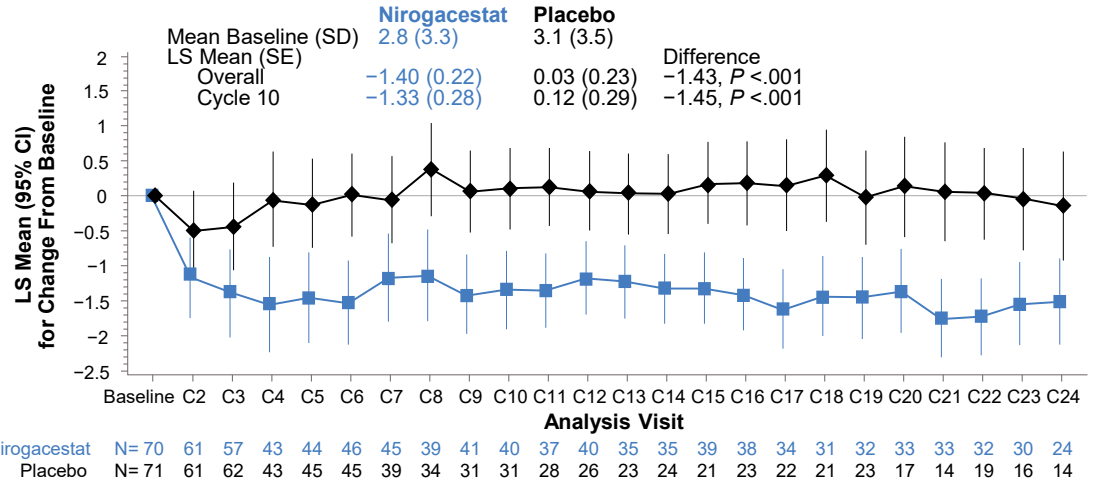
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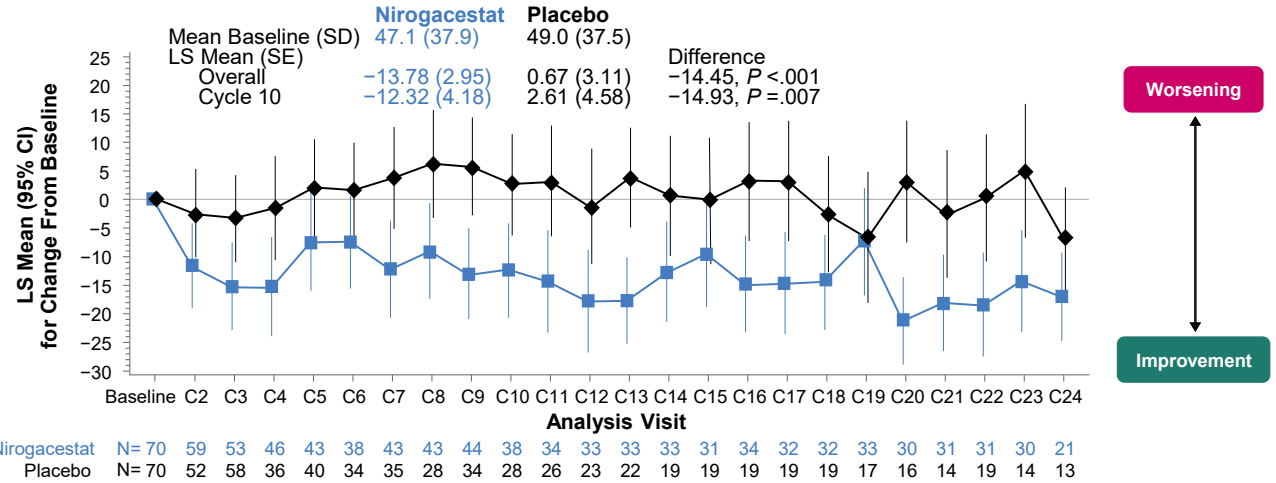
Changes From Baseline in Individual Sleep-Related BPI-SF Score and EORTC QLQ-C30 Item Score by Visit

Nirogacestat Placebo

Sleep-Related BPI-SF Score for "Pain Interfered With Sleep" (scored between 0 and 10)



Sleep-Related EORTC QLQ-C30 Score for "Have Trouble Sleeping"[a] (scored between 0 and 100)



Nirogacestat had a positive effect on sleep-related individual item scores for BPI-SF item "Pain Interfered with Sleep" and EORTC QLQ-C30 item "Have Trouble Sleeping"; placebo showed worsening from baseline or no impact

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.
[a]One patient assigned to receive placebo did not have data at baseline and was not included in this analysis.
BPI-SF, Brief Pain Inventory–Short Form; C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, least squares.

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Conclusions



Baseline sleep scores indicate that patients in the DeFi trial with progressing DTs experienced significant sleep burden owing to DT-related symptoms, suggesting an unaddressed need in patients with DTs



Treatment of DTs with nirogacestat led to improvements in various patient-reported sleep outcomes, including falling asleep, sleep comfort, and staying asleep; these improvements emerged early and were sustained over time



Patient-reported improvement in sleep with nirogacestat treatment was positively correlated with reductions in pain intensity

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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.