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

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally invasive, soft-tissue tumors that can result in severe pain, functional morbidity, and quality of life impairment[1,2]
- DT symptoms, particularly chronic pain, are well documented to negatively impact patients' quality of life, 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 DT 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 patient-reported outcomes (PRO), including DT-related pain intensity, compared with placebo[5]
- While assessments of PRO 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 PRO and their correlation with pain in patients with DT assigned to nirogacestat or placebo in the DeFi trial

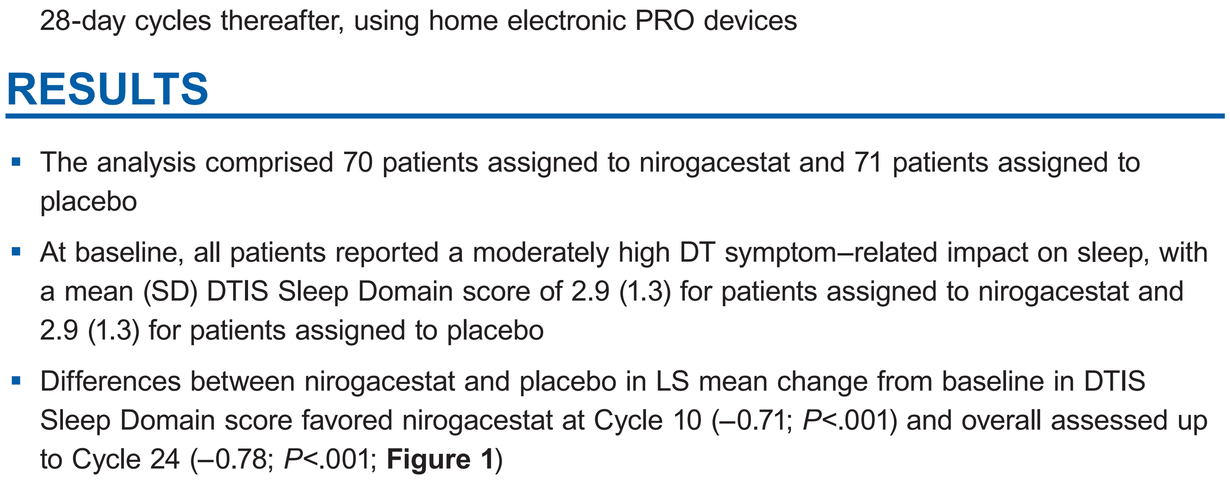
METHODS

- This post hoc analysis of the DeFi double-blind phase (final database lock 19 December 2024) evaluated sleep outcomes using Sleep Domain and sleep-related item PRO scores:
  - Sleep Domain scores from the Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS) DT Impact Scale (DTIS)[6]
    - > The GODDESS DTIS Sleep Domain is scored on a 5-point Likert scale, with higher scores indicating greater negative impact on sleep
  - Individual sleep-related item scores from 3 PRO assessment tools:
    - > GODDESS DTIS items, which include questions related to "Being Comfortable in Bed," "Falling Asleep," and "Staying Asleep," scored on a 5-point Likert scale with higher scores indicating greater negative impact on sleep
    - > The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) item "Having Trouble Sleeping," scored between 0 and 100; item scores were calculated as ([raw score - 1] / range) x 100, with higher scores denoting greater negative impact on sleep
    - > The Brief Pain Inventory–Short Form (BPI-SF) item "Pain Interfered With Sleep," scored between 0 and 10, with higher scores denoting greater sleep interference
- Least squares (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 PRO[5]
  - Baseline for DTIS and EORTC QLQ-C30 assessments was defined as the most recent measurement prior to the first administration of study treatment
  - Treatment and visit were used as factors, with corresponding baseline score and primary tumor location (intra-abdominal or extra-abdominal) used as covariates, and included baseline-by-visit and treatment-by-visit interactions
  - Only patients with a baseline measurement and ≥1 postbaseline PRO score were included in each analysis; scheduled visits with <10 patients in the arm and unscheduled visits were not included
- Correlation between the change from baseline in DTIS Sleep Domain scores and the change from baseline in average pain intensity (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 for BPI-SF assessments was defined as the weekly average of the baseline period (study days -7 through -1); if there were <4 days of assessments during this period, the weekly average of the screening visit assessments was used, provided there were ≥4 days of assessments during that period
- All PRO measures were completed by patients at screening, baseline (ie, Cycle 1), and then in 28-day cycles thereafter, using home electronic PRO devices

RESULTS

- The analysis comprised 70 patients assigned to nirogacestat and 71 patients assigned to placebo
- 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 assigned to nirogacestat and 2.9 (1.3) for patients assigned to placebo
- 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; **Figure 1**)
- 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)

Figure 1. Change From Baseline in DTIS Sleep Domain Score by Visit

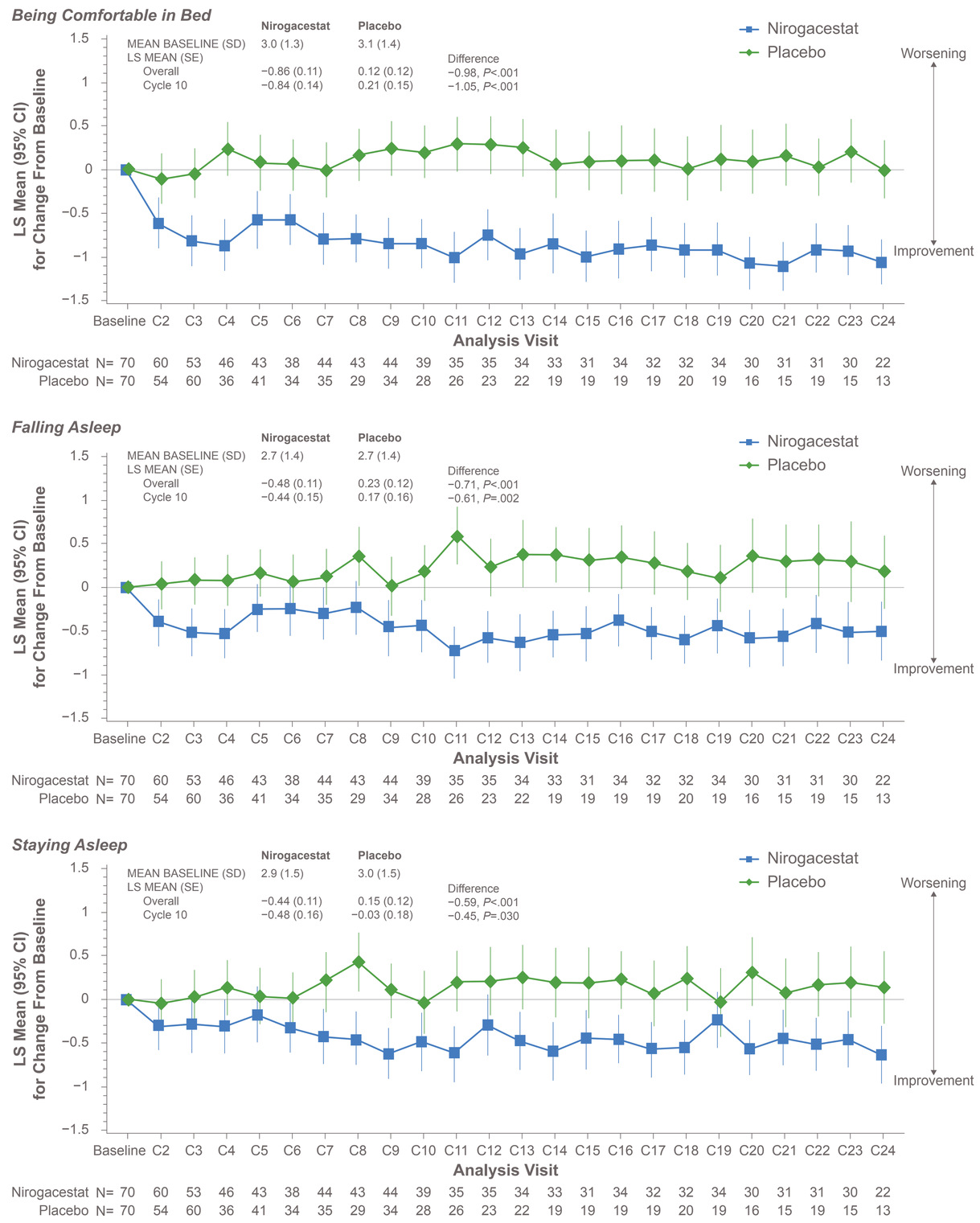


A positive change from baseline indicates worsening impact; a negative change from baseline indicates an improvement. A negative LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo.
One patient assigned to receive placebo did not have data at baseline and was not included in this analysis.
DTIS, Desmoid Tumor Impact Scale; LS, least squares.

RESULTS (CONT.)

- Differences in LS mean change from baseline favored nirogacestat for DTIS Sleep Domain individual items "Being Comfortable in Bed," "Fallling Asleep," and "Staying Asleep"; placebo showed worsening from baseline or no impact in all individual item scores (**Figure 2**)

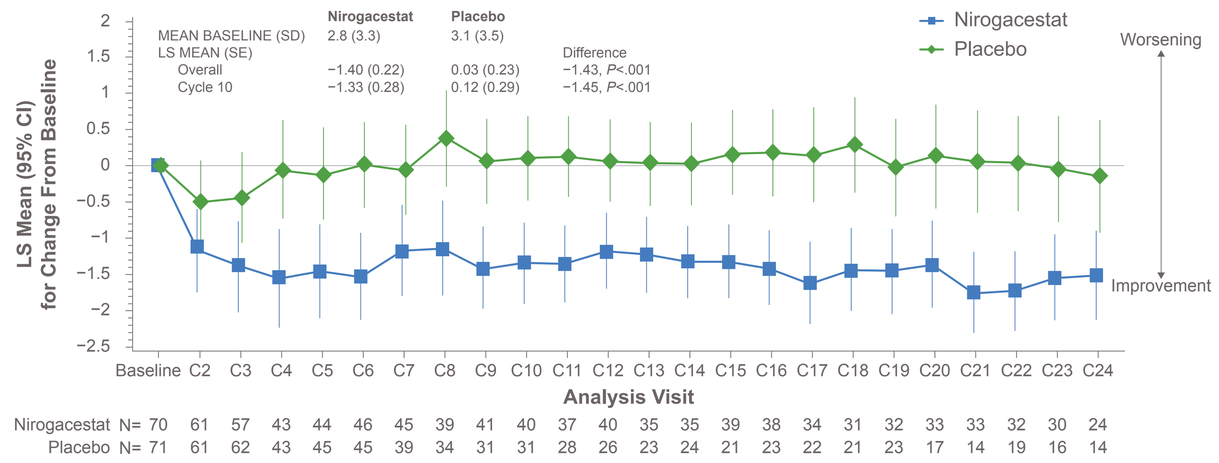
Figure 2. Change From Baseline in DTIS Sleep Domain Individual Item Scores by Visit



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

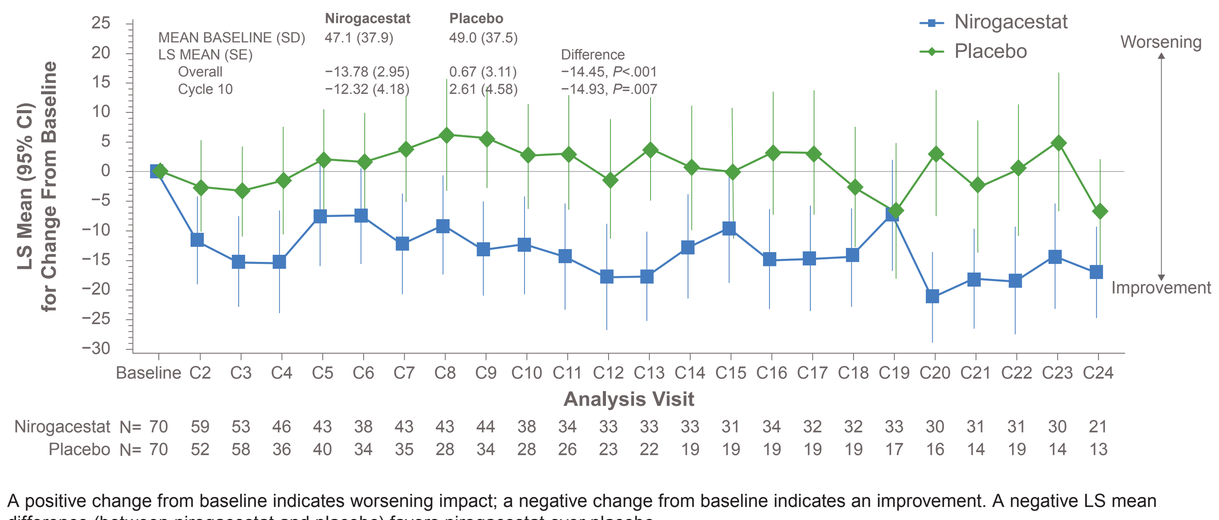
- Nirogacestat also had a positive effect on sleep-related individual item scores for BPI-SF item "Pain Interfering with Sleep" and EORTC QLQ-C30 item "Have Trouble Sleeping"; placebo showed worsening from baseline or no impact (**Figures 3 and 4**)

Figure 3. Change From Baseline in Individual Sleep-Related BPI-SF Score for "Pain Interfered With Sleep" Item by Visit



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.
BPI-SF, Brief Pain Inventory–Short Form; LS, least squares.

Figure 4. Change From Baseline in Sleep-Related EORTC QLQ-C30 Score for "Have Trouble Sleeping" Item by Visit



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.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, least squares.

CONCLUSIONS

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

DISCLOSURES: *BK has served on an advisory board for Ayala, Bayer, Boehringer Ingelheim, PharmaMar, and SpringWorks Therapeutics Inc.; as a local PI for Cogent and a coordinating PI for Immunome, PharmaMar, and SpringWorks Therapeutics Inc.; and served 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).*

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