Impact of Nirogacestat on Functional Status in Patients with Desmoid Tumors: Results From the Phase 3 DeFi Study

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INTRODUCTION

- Desmoid tumors (DT; aggressive fibromatosis) are rare, locally aggressive, and invasive soft-tissue tumors that can cause severe pain and functional impairment[1,2]
  - Functional impairment can be either physical (eg, difficulty walking, lifting heavy objects, or carrying out daily tasks) or role-related (eg, relationship problems, difficulty caring for children, or unemployment)[1]
- Treatment goals for patients with DT often focus on clinical markers, such as progression-free survival, but should also consider pain reduction and improvements in DT symptoms, physical functioning, role functioning, and overall quality of life[3]
- Nirogacestat is an investigational, oral, small-molecule, selective gamma secretase inhibitor evaluated for the treatment of DT in the phase 3 Desmoid Fibromatosis (DeFi) study (NCT03785964)[4]
  - Nirogacestat (n=70) significantly improved the primary endpoint of progression-free survival compared with placebo (n=72) in patients with progressing DT (hazard ratio: 0.29 [95% CI, 0.15–0.55]; two-sided *P*<0.001)[4]
- Secondary and exploratory DeFi endpoints included different aspects of patient-relevant outcomes, such as pain and functional status, to further characterize the treatment effect of nirogacestat
  - Patients who received nirogacestat achieved statistically significant and clinically meaningful improvements in physical functioning and role functioning compared with placebo at cycle 10, including improvements in disease-specific physical functioning[4]

OBJECTIVE

- To further evaluate the impact of nirogacestat on physical functioning and role functioning (secondary and exploratory study endpoints) in the phase 3 DeFi study

METHODS

- DeFi was a phase 3, international, double-blind, randomized, placebo-controlled study that evaluated the efficacy and safety of nirogacestat in patients aged 18 years or older with a histologically confirmed diagnosis of progressing DT[4]
  - Patients received oral nirogacestat (150 mg) or placebo twice daily, taken continuously in 28-day cycles until trial completion, disease progression, death, or trial discontinuation due to other reasons
- During the DeFi study, patients completed three prespecified functional status assessment tools at home, using electronic devices **(Table 1)**:
  - The GOunder/Desmoid Tumor Research Foundation DEsmoid Impact Scale (GODDESS DTIS) Physical Functioning (PF) domain, which captures the concepts of moving, reaching, vigorous activity, moderate activity, and accomplishing less daily[4,5]
  - The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) PF domain, which captures the concepts of strenuous activities, taking a long walk, taking a short walk, need to stay in a bed or chair, and help with eating/dressing/washing/using the toilet[4,6]
  - The EORTC QLQ-C30 Role Functioning (RF) domain, which captures the concepts of work/other daily activities and hobbies/leisure activities[4,6]
  - The Patient-Reported Outcomes Measurement Information System Physical Function Short Form 10a (PROMIS PF10a) tool, which captures the concepts of dexterity (upper extremities), walking/mobility (lower extremities), neck/back, and daily activities such as errands[7]

Table 1. Score ranges and direction of improvement

FUNCTIONING DOMAIN	SCORE RANGE	DIRECTION OF IMPROVEMENT
GODDESS DTIS Physical Functioning[5]	5-point Likert scale	↓
EORTC QLQ-C30 Physical Functioning[4]	0–100	↑
EORTC QLQ-C30 Role Functioning[4]	0–100	↑
PROMIS PF10a[4]	13.5–61.9	↑

- PROMIS measures are scored on the T-score metric, where a score of 50 is equivalent to the average score across the general US population and 10 is the standard deviation of that population.[8] It was used in this analysis to assess return to normal functional status in patients with DT
- Cycle 10 was prespecified as the posttreatment time point for between-arm comparisons of patient-relevant endpoints to allow adequate time for a treatment effect to be observed
- Changes from baseline in functional status scores were compared between treatment arms at cycle 10; least-squares (LS) mean differences, standard error (SE), and *P*-values were calculated using a mixed model with repeated measures, with treatment and visit as factors and the corresponding baseline score and primary tumor location (intra-abdominal or extra-abdominal) as covariates; baseline by visit and treatment by visit interactions were also included
  - Some baseline values were missing from the placebo arm for each measure
- The proportions of "responders" were compared between treatment arms at cycle 10 using a stratified Cochran–Mantel–Haenszel test
  - "Responders" were characterized as patients with clinically meaningful functional improvement, defined using prespecified within-patient meaningful change thresholds (MCT) for each tool (≥0.8 for GODDESS DTIS PF and ≥10 for both the EORTC QLQ-C30 PF and RF)[9]
  - For responder analysis, there is a prerequisite for patients at baseline to have a minimum score to allow observation of a clinically meaningful change based on the within-patient MCT; therefore, the sample sizes and score distribution may be smaller at baseline for these analyses
  - Missing values were imputed using multiple imputation

RESULTS

BASELINE CHARACTERISTICS

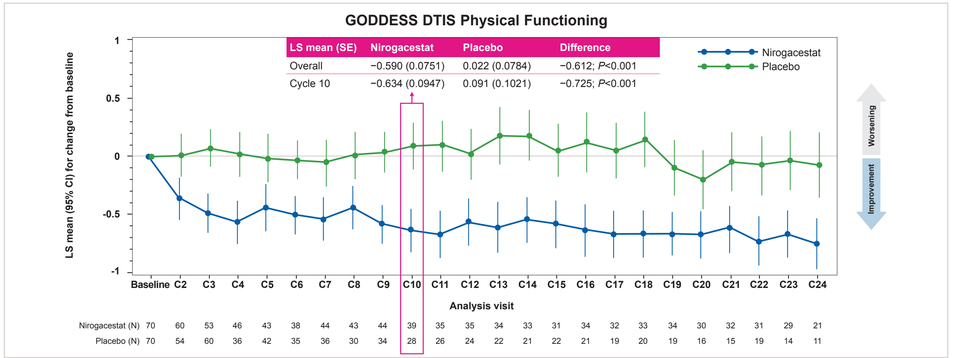
- From May 2019 through August 2020, a total of 142 patients were randomized across 37 sites in North America and Europe
- Baseline patient characteristics were generally similar between groups and representative of the general patient population with DT,[4] including baseline functioning scores (data not shown)

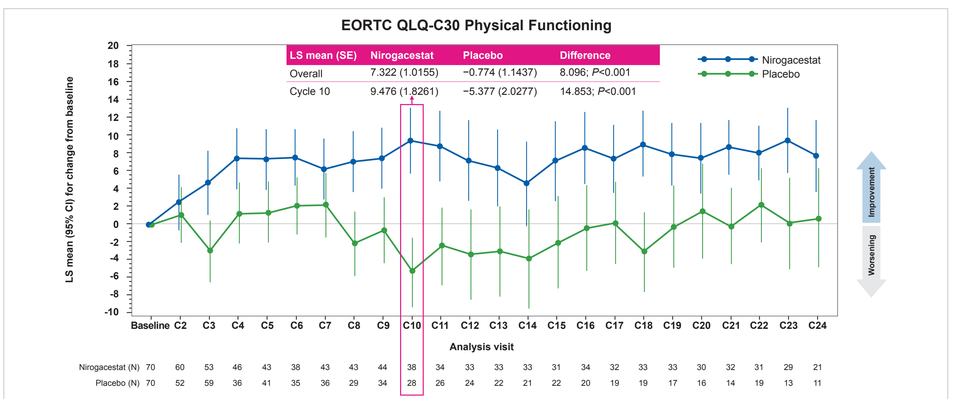
CHANGE IN FUNCTIONING SCORES OVER TIME

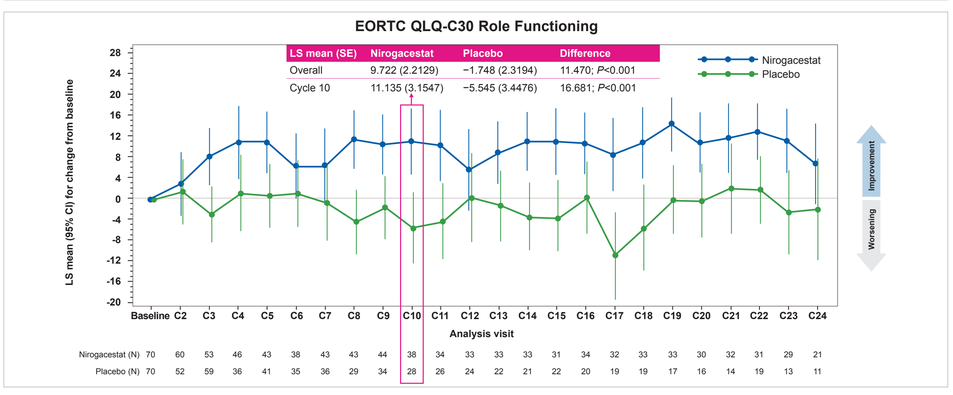
- Statistically significant and clinically meaningful improvements from baseline in physical functioning and role functioning were observed with nirogacestat compared with placebo at cycle 10 across GODDESS DTIS PF, and EORTC QLQ-C30 PF and RF **(Figure 1)**
- Improvement with nirogacestat, compared with placebo, emerged as early as cycle 2 for some aspects of patient-reported functional status and were sustained through cycle 24 **(Figure 1)**

RESULTS

Figure 1. Change in functioning from baseline to cycle 24



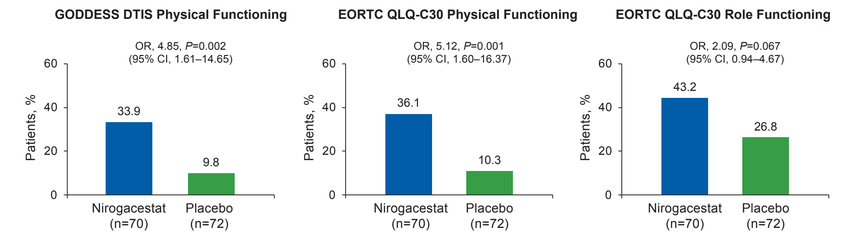




CLINICALLY MEANINGFUL FUNCTIONING IMPROVEMENT FROM BASELINE (RESPONDER ANALYSIS)

- At cycle 10, a greater proportion of patients achieved a clinically meaningful within-patient improvement from baseline in GODDESS DTIS PF, and EORTC QLQ-C30 PF and RF scores with nirogacestat versus placebo **(Figure 2)**. The improvement was statistically significant for both physical functioning measures, but not for role functioning
- At cycle 10, patients receiving nirogacestat were 5 times more likely to have a clinically meaningful improvement in physical functioning and 2 times more likely to have a clinically meaningful improvement in role functioning than those receiving placebo

Figure 2. Patients with clinically meaningful functioning improvement from baseline at cycle 10

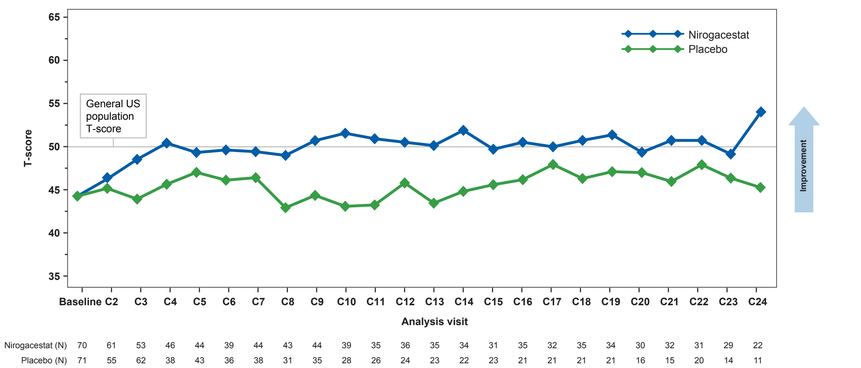


Note: The analysis was limited to patients with baseline values that could improve by at least the MCT for each measure. Missing values were imputed using multiple imputation. A total of 50 datasets were produced.
CI, confidence interval; OR, odds ratio.

PROMIS PF10a PHYSICAL FUNCTIONING COMPARED WITH THE GENERAL US POPULATION AVERAGE

- By cycle 4, the PROMIS PF10a score of the nirogacestat arm reached the average score observed in the general US population (T-score, 50), whereas the score of the placebo arm did not **(Figure 3)**

Figure 3. Mean PROMIS PF10a T-score through cycle 24



CONCLUSION

- In the phase 3 DeFi study, at cycle 10, patients with progressing DT who received nirogacestat achieved a statistically significant and clinically meaningful improvement in different assessments of functional status compared with those who received placebo
  - These improvements emerged as early as cycle 2 (the first assessment period) and were sustained through cycle 24 (final assessment)
- A greater proportion of patients achieved a clinically meaningful improvement in functioning from baseline with nirogacestat versus placebo at cycle 10 according to GODDESS DTIS PF, and EORTC QLQ-C30 PF and RF assessments, with the improvement being statistically significant for both physical functioning measures, but not for role functioning
- Improvements in functioning were consistent with improvements in pain measures, disease-related symptoms, and overall health-related quality of life previously observed with nirogacestat[4]
- By cycle 4, the nirogacestat arm reached the average score observed in the general US population for physical functioning (T-score, 50), according to PROMIS PF10a (while the placebo arm did not), and this was maintained through cycle 24
- This analysis suggests that patients with DT can experience meaningful improvement in functioning with nirogacestat; therefore, this outcome could be an important treatment goal for people with DT

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