Impact of Nirogacestat on Pain, a Key Symptom in Patients With Desmoid Tumors: Results From the Phase 3 DeFi Study

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INTRODUCTION

- Desmoid tumors (aggressive fibromatosis) are rare, locally invasive, soft-tissue tumors that can result in severe pain, functional impairment, and other complications[1–9]
  - Pain is the most debilitating symptom reported by patients with desmoid tumors, and the potential for dependency on narcotics is a substantial concern[2,9]
  - As many as 60% of patients with desmoid tumors experience chronic pain, and pain may indicate desmoid tumor progression[5,9]
  - Pain reduction is a key treatment goal for patients with desmoid tumors[1,2,5,9]
- Nirogacestat is an investigational, oral, small-molecule, selective gamma-secretase inhibitor evaluated for the treatment of desmoid tumors in the international phase 3 Desmoid Fibromatosis (DeFi) study (NCT03785964)[8]
  - In DeFi, nirogacestat (n=70) significantly improved progression-free survival (the primary endpoint) compared with placebo (n=72) in patients with progressing desmoid tumors (hazard ratio: 0.29 [95% CI, 0.15–0.55]; two-sided *P*<0.001)[8]
  - Nirogacestat also achieved a significant and clinically meaningful reduction in pain severity by 1.51 points (on a 10-point scale) compared with placebo at cycle 10 (*P*<0.001) per the prespecified secondary endpoint of "worst pain" from the Brief Pain Inventory–Short Form (BPI-SF)
- Additional assessment tools, which included pain measurements, were reported by patients in DeFi to further characterize treatment impact on this key symptom

OBJECTIVE

- To evaluate the impact of nirogacestat on desmoid tumor pain (secondary and exploratory study endpoints) in the phase 3 DeFi study

METHODS

- DeFi was a phase 3, global, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of nirogacestat in patients aged 18 years or older with a histologically confirmed diagnosis of progressing desmoid tumors[8]
  - 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[8]
- During the DeFi study, patients completed three assessment tools (including pain measurements) at home using electronic devices; readouts were taken each cycle and assessed at the prespecified cycle 10
  - The BPI-SF,[10] which includes assessment of average "worst pain" intensity scored between 0 (no pain) and 10 (pain as bad as you can imagine)
  - The GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom Scale (GODDESS-DTSS) pain domain,[4] which includes questions about worst "pain," "dull pain," and "shooting pain," and is scored between 0 (no pain) and 10 (pain as bad as you can imagine)
  - The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) two-item pain subscale,[11] which captures "pain" and "pain interference with daily activities" and is scored between 0 and 100, with higher scores denoting worse pain or more interference
- Change from baseline in pain scores was compared between treatment arms at cycle 10 and overall, using mixed-models repeated measures (MMRM) analyses with visit as a fixed effect, and baseline score and stratification factor (primary tumor location) as fixed-effects covariates. The proportions of patients with clinically meaningful pain reduction (defined using prespecified thresholds) were compared between treatment arms using a stratified Cochran–Mantel–Haenszel test at cycle 10
- Cycle 10 was prespecified as the post-treatment time point for between-arm comparisons to allow adequate time for a treatment effect to be observed

RESULTS

BASELINE CHARACTERISTICS

- From May 2019 through August 2020, a total of 142 patients were randomized (70 to the nirogacestat group and 72 to the placebo group) across 37 sites in the United States, Canada, and Europe[8]
- Baseline patient characteristics **(Table 1)** were generally similar between groups and representative of the general patient population with desmoid tumors[8]

Table 1. Baseline patient characteristics

CHARACTERISTICS	NIROGACESTAT (n=70)	PLACEBO (n=72)
Median age (range), years	33.5 (18–73)	34.5 (18–76)
Sex, n (%)		
Female	45 (64)	47 (65)
Male	25 (36)	25 (35)
Target tumor location, n (%)		
Intra-abdominal	17 (24)	18 (25)
Extra-abdominal	53 (76)	54 (75)
Focal category, n (%)		
Single	43 (61)	41 (57)
Multifocal	27 (39)	31 (43)
Median target tumor size[‡] per RECIST (IQR), mm	91.6 (64.7–134.1)	115.7 (73.5–161.7)
BPI-SF uncontrolled pain, n (%)[†]	27 (39)	31 (43)
BPI-SF "worst pain" score		
Mean (SD)	3.2 (3.23)	3.3 (3.31)
GODDESS-DTSS pain score		
Mean (SD)	3.6 (2.57)	3.9 (2.80)
EORTC QLQ-C30 pain domain		
Mean (SD)	46.7 (30.77)	47.9 (32.71)

[‡]Sum of the longest diameters for target tumors.

[†]Uncontrolled pain was defined as a BPI-SF average worst pain-intensity score of more than 4 (range, 0 to 10, with higher scores indicating worse pain). Scores were calculated as the average of the daily scores for worst pain during the 7-day period before the baseline visit.

BPI-SF, Brief Pain Inventory–Short Form; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GODDESS-DTSS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom Scale; IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation.

Figure 1. Change from baseline in BPI-SF "worst pain" intensity score

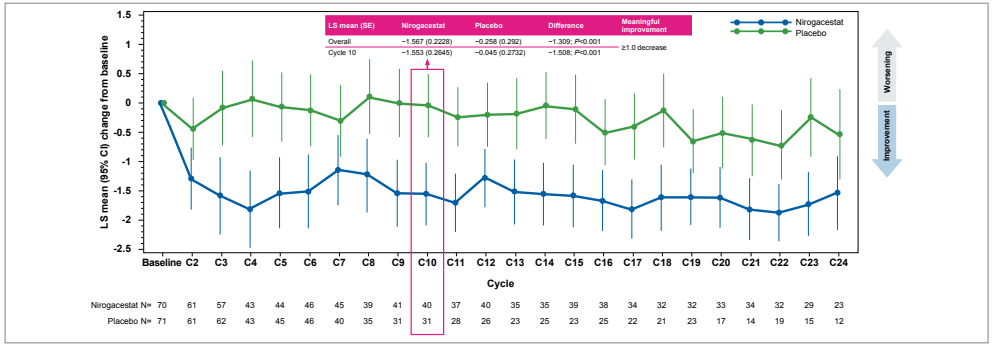
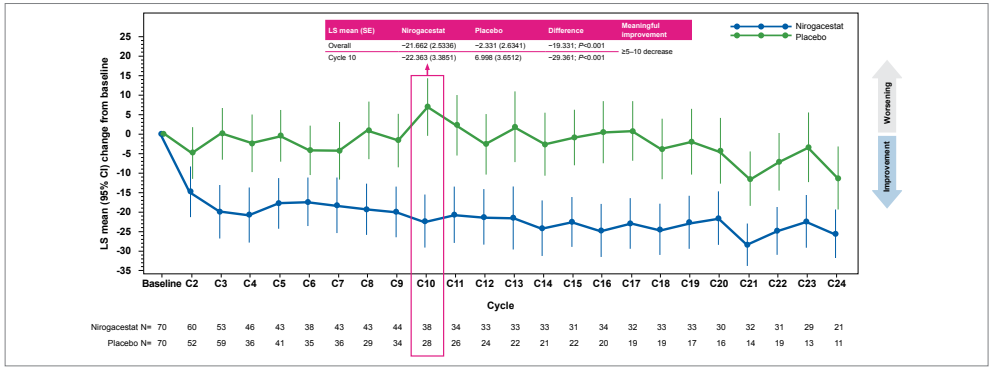


Figure 2. Change from baseline in GODDESS-DTSS pain score

Figure 3. Change from baseline in EORTC QLQ-C30 pain subscale



C, cycle; CI, confidence interval; LS mean, least-squares mean; SE, standard error.

PAIN ASSESSMENTS

- Statistically significant and clinically meaningful pain reduction was observed with nirogacestat compared with placebo at cycle 10 across all three assessment tools evaluated in DeFi; exploratory analyses show that those receiving nirogacestat quickly improved, with separation between treatment arms observed as early as cycle 2 and sustained throughout treatment

BPI-SF

- At cycle 10, nirogacestat significantly reduced pain severity per the BPI-SF "worst pain" score (0–10 range) by 1.55 points (SE=0.26) compared with 0.05 points (SE=0.27) with placebo (one-sided *P*<0.001) **(Figure 1)**

GODDESS-DTSS

- At cycle 10, nirogacestat significantly reduced mean baseline pain per the GODDESS-DTSS pain score (0–10 range) by 1.78 points (SE=0.27) compared with an increase in pain by 0.34 points (SE=0.28) with placebo (one-sided *P*<0.001) **(Figure 2)**

EORTC QLQ-C30

- At cycle 10, nirogacestat significantly reduced mean baseline pain per the EORTC QLQ-C30 pain subscale (0–100 range) by 22.36 points (SE=3.39) compared with an increase in pain by 7.00 points (SE=3.65) with placebo (one-sided *P*<0.001) **(Figure 3)**

CLINICALLY MEANINGFUL PAIN REDUCTION FROM BASELINE (RESPONDER ANALYSIS)

- Per the BPI-SF "worst pain" score (0–10 range), a statistically significant greater proportion of patients achieved a clinically meaningful within-patient pain reduction from baseline (of ≥2.0 points) with nirogacestat (68.2%) than with placebo (26.3%) at cycle 10 (one-sided *P*=0.001) **(Table 2)**
- Per the GODDESS-DTSS pain score (0–10 range), a statistically significant greater proportion of patients achieved a clinically meaningful within-patient pain reduction (of ≥1.9 points) with nirogacestat (58.7%) than with placebo (18.9%) at cycle 10 (one-sided *P*<0.001) **(Table 2)**

Table 2. Proportion of patients with clinically meaningful pain reduction from baseline at cycle 10

		Responder (%)[‡]		Odds ratio		
Measure	**Response threshold[†]**	**Nirogacestat (n=70)**	**Placebo (n=72)**	**Value**	**95% CI**	***P* (one-sided)**
BPI-SF "worst pain" score	2.0 points	68.2	26.3	6.08	1.95–18.98	0.001
GODDESS-DTSS pain score	1.9 points	58.7	18.9	6.24	2.16–17.99	<0.001

Note: analysis is based on a multiple imputation model and the denominator is ITT population.

[†]For the BPI-SF "worst pain" responder analysis, the value of 2 points was used as the threshold to determine clinically meaningful improvement. Threshold values of 30% or greater change, or 2-point or greater change in numerical rating of BPI-SF scores, have been proposed in the literature to detect clinically important improvements in cancer-related breakthrough pain and chronic pain states[12,13]

[‡]Within-patient clinically meaningful response threshold.

BPI-SF, Brief Pain Inventory–Short Form; CI, confidence interval; GODDESS-DTSS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom Scale; ITT, intent-to-treat.

CONCLUSIONS

- In the phase 3 DeFi study, patients with progressing desmoid tumors who received nirogacestat achieved a rapid, sustained, and consistent reduction in different aspects of pain (e.g. worst pain, dull pain, shooting pain, pain interference with daily activities) compared with those who received placebo
- Significantly greater proportions of patients achieved clinically meaningful reduction in pain with nirogacestat compared with placebo
- The benefit of nirogacestat versus placebo in reducing pain was consistent across multiple patient-completed assessment tools, which included pain measurements
- As pain is the most commonly reported symptom by patients with desmoid tumors, pain reduction should be a key clinical study endpoint and treatment goal

ACKNOWLEDGMENTS: *This presentation was supported by SpringWorks Therapeutics, Inc. Writing and editing support was provided by Jeffrey Walter and Daria Renshaw of IQVIA with funding from SpringWorks Therapeutics, Inc.*

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Originally presented at the American Society for Clinical Oncology (ASCO) Annual Meeting 2023. Encore presentation at the National Community Oncology Dispensing Association (NCODA) International Fall Summit • October 25–27, 2023 • Orlando, FL, USA