INTRODUCTION

Desmoid tumors (DT, aggressive fibromatoses) are rare, locally aggressive, and invasive soft-tissue tumors that can cause severe pain and functional impairment.1

- Functional impairment can be either physical (e.g., difficulty walking, lifting heavy objects, or moving out of bed), or nonphysical-related (e.g., relationship problems, difficulty caring for others, or unemployment).

- Treatment goals for patients with DT often focus in clinical markers, such as progression-free survival, but should also consider pain reduction and improvements in quality of life.2

Nirogacestat is an investigational, oral, small-molecule selective GPER agonist evaluated for the treatment of DT in the phase 3 Desmoid Fibromatoses (DeFi) study (NCT03728596).3

- Nirogacestat (n=70) significantly improved the primary endpoint of progression-free survival compared with placebo (n=72) in patients with progressing DT (median time to progression [TTTP]: 5.2 months [95% CI, 1.7–10.5] vs 1.7 months [95% CI, 0.9–3.0]).

- Secondary and exploratory endpoint endpoints included different aspects of patient-reported outcomes, as well as physical 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.

OBJECTIVE

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

RESULTS

BASELINE CHARACTERISTICS

- From May 2019 through August 2020, a total of 142 patients were randomized across 37 sites in North America and Europe to receive oral nirogacestat (150 mg) or placebo twice daily, taken with food, for up to 48 weeks. The ratio of patients with intra-abdominal tumor location compared with extra-abdominal represents the general patient population with DT, 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 at cycle 12 across GODDESS DTIS, EORTC QLQ-C30, and PROMIS PF10a scores for both the physical and role functioning measures, but not for the PROMIS RP10a score.

- 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.

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 RP (Figure 2).

- The improvement was statistically significant for both physical functioning and role functioning measures, but not for the PROMIS RP10a score.

- 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.

Table 1. Score ranges and direction of improvement

<table>
<thead>
<tr>
<th>FUNCTIONING DOMIAN</th>
<th>SCORE RANGE</th>
<th>DIRECTION OF IMPROVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GODDESS DTIS Physical Functioning</td>
<td>0–100</td>
<td>Increase</td>
</tr>
<tr>
<td>EORTC QLQ-C30 Physical Functioning</td>
<td>0–100</td>
<td>Increase</td>
</tr>
<tr>
<td>PROMIS PF10a</td>
<td>5.0–70.0</td>
<td>Increase</td>
</tr>
</tbody>
</table>

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 methods. Only patients with complete data were included.

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 assessment of functional status compared with those who received placebo.

- Improvements in functioning were consistent with improvements in pain measures, disease-related symptoms, and overall health-related quality of life previously observed with nirogacestat.

- By cycle 10, the nirogacestat arm reached the minimal clinically important change in the general US population for physical functioning (T-score, 9.0), 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 patients with DT.