Trial in Progress: A Single-Arm, Open-Label Phase 4 Trial of Nirogacestat in Adult Premenopausal Females With Desmoid Tumors

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally aggressive soft tissue neoplasms that do not metastasize[1]
  - DT tumor formation and growth are unpredictable and associated with morbidity, pain, and functional limitation[1,2]
  - Prevalence is highest in young females who are usually of reproductive age[3,4]
- Gamma-secretase inhibitors (GSIs) can cause ovarian toxicity (OT) in females of reproductive potential (FORP), characterized by abnormal reproductive hormone levels, perimenopausal symptoms such as menstrual irregularities or amenorrhea, or both[5]
- Nirogacestat is an oral, targeted GSI and the only US FDA- and European Commission-approved treatment for adults with progressing DT who require systemic treatment
- The DeFi trial was a randomized, double-blind, placebo-controlled phase 3 study designed to evaluate the efficacy and safety of nirogacestat in adult patients with progressing DT[6]
- In the DeFi trial, nirogacestat treatment had a manageable safety profile and led to clinically significant improvement vs placebo in progression-free survival, objective response rate, and patient-reported outcomes of pain, symptom burden, physical and role functioning, and health-related quality of life[6]
  - OT was identified by investigators based on abnormal reproductive hormone values, perimenopausal symptoms, or both[5]
  - OT events were identified in 75% (27/36) of FORP treated with nirogacestat, compared to no events identified in the 37 FORP treated with placebo[5]
  - Off-treatment resolution of OT was reported by investigators in all (100%; 11/11) FORP who discontinued nirogacestat for any reason; 2 patients were lost to follow-up[5]

OBJECTIVE

- To further characterize the incidence and recovery rate of OT events in FORP with DT treated with nirogacestat

TRIAL OVERVIEW

STUDY DESIGN

- This is a single-arm, open-label, phase 4 study of postpubertal and premenopausal females with DT receiving nirogacestat
  - NCT07176689
  - EudraCT 2024-515215-21-00
- Key inclusion and exclusion criteria for patient eligibility are shown in **Table 1**

Table 1. Key eligibility criteria

Inclusion Criteria	Exclusion Criteria
▪ Female ▪ Aged 18–40 years ▪ Premenopausal at baseline: – Estradiol >30 pg/mL – FSH <40 IU/L – Regular menses for ≥3 menstrual cycles ▪ Histologically confirmed, symptomatic/progressive DT requiring systemic treatment ▪ Adequate organ function ▪ Eastern Cooperative Oncology Group performance status ≤2 at screening ▪ Negative pregnancy test result at screening and at the baseline visit before the first dose of nirogacestat ▪ Has not harvested or donated eggs (ova, oocytes) for the purpose of reproduction for at least 90 days prior to the first dose of nirogacestat and agrees to not harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment and clinical follow-up periods	▪ Breastfeeding ▪ Currently using or has used hormonal contraception or ovarian suppression within 90 days of the first dose of nirogacestat ▪ Currently receiving or has previously received GSIs or anti-Notch antibody therapy ▪ Currently receiving any treatment for DT, including TKIs or any investigational treatment, within 28 days of the first dose of nirogacestat ▪ A history of polycystic ovary syndrome, hypothalamic amenorrhea, or severe endometriosis involving ovaries ▪ A family history of primary ovarian insufficiency ▪ Any chromosomal abnormality, mutation, gene variant, or medical condition associated with early/premature menopause, including a history of OT while on a TKI

DT, desmoid tumor; FSH, follicle-stimulating hormone; GSI, gamma-secretase inhibitor; OT, ovarian toxicity; TKI, tyrosine kinase inhibitor.

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TRIAL OVERVIEW (CONT.)

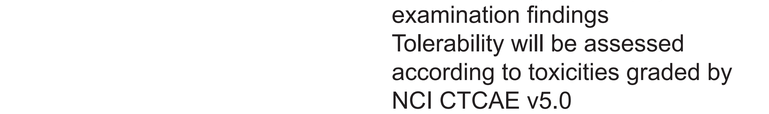
TREATMENT PERIOD

- Following a screening period of ≤28 days, patients will receive nirogacestat 150 mg twice daily for ≤24 cycles (**Figure 1**)

CLINICAL FOLLOW-UP PERIOD

- After discontinuation of nirogacestat treatment, patients will be followed for 12 months or until a new treatment for DT is initiated, whichever occurs first (**Figure 1**)
  - A safety follow-up visit will occur 30 days after the last dose of nirogacestat

Figure 1. Study schema



[a]If a patient reports a TEAE of OT and ovarian function recovery is not confirmed by Day 365 post-treatment, follow-up to confirm ovarian function recovery may continue for up to 12 additional months (up to 24 months total) or until new treatment for DT is initiated.
BID, twice daily; DT, desmoid tumor; niro, nirogacestat; OT, ovarian toxicity; TEAE, treatment-emergent adverse event.

ENDPOINTS

- The primary objective of the study is to determine the ovarian function recovery rate in patients reporting a treatment-emergent adverse event (TEAE) of OT (**Table 2**)
  - Ovarian function recovery is defined as:
    - > Resumption of ≥2 consecutive menstrual periods and a follicle-stimulating hormone (FSH) level <30 mIU/mL with concomitant estradiol <80 pg/mL; OR
    - > A positive serum β-human chorionic gonadotropin (β-HCG) pregnancy test
  - OT is defined as new onset amenorrhea lasting ≥3 consecutive menstrual periods, FSH level ≥30 mIU/mL, and a negative serum β-HCG pregnancy test
- Secondary objectives are described in **Table 2**
- Exploratory objectives are described in **Table 3**

Table 2. Primary and secondary objectives and endpoints

Primary Objectives	Primary Endpoints
Determine the ovarian function recovery rate	Ovarian function recovery rate of OT TEAEs
Secondary Objectives	**Secondary Endpoints**
Determine the incidence of OT	Incidence of OT TEAEs
Determine the timing of ovarian function recovery	Time to ovarian function recovery in patients with a TEAE of OT
Evaluate the safety and tolerability of nirogacestat	Safety endpoints include incidence of TEAEs, changes in hormone levels, vital signs, and physical examination findings Tolerability will be assessed according to toxicities graded by NCI CTCAE v5.0

OT, ovarian toxicity; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

RECRUITMENT

- Approximately 50 eligible patients with progressing DT will be enrolled and receive nirogacestat to yield a sample size of approximately 40 patients treated with nirogacestat for ≥12 cycles
- This trial is planned for Belgium, Germany, Italy, the Netherlands, Spain, and the UK (**Figure 2**)

Table 3. Exploratory objectives and endpoints

Exploratory Objectives	Exploratory Endpoints
Determine the objective response rate (ORR)	The proportion of patients with CR + PR using RECIST v1.1 criteria
Determine the duration of response (DoR)	DoR for patients whose best response is CR or PR
Determine the disease control rate (DCR)	DCR for patients whose best response is CR, PR, or SD
Determine the duration of disease control (DoDC)	DoDC for patients whose best response is CR, PR, or SD
Determine progression-free survival (PFS)	PFS, defined as the time from the start of study treatment until the date of assessment of progression[a] or death by any cause
Determine changes in tumor volume	Change in tumor volume from baseline as assessed by MRI volumetric analysis
Determine changes in T2 hyperintensity	Change in T2 hyperintensity from baseline as assessed by MRI analysis
Characterize serum nirogacestat concentrations	Trough and 1-hour post-dose serum nirogacestat concentrations
Evaluate pain severity	Pain severity assessed during the first 2 treatment cycles by evaluating change from baseline in BPI-SF scores
Understand patient experience	Qualitative patient interviews performed at the end of treatment and the end of the clinical follow-up
Identify surrogate pharmacodynamic biomarkers	Changes from baseline in surrogate biomarkers and their correlation with DT disease status and/or OT onset and recovery

[a]Progression will be determined radiographically using RECIST v1.1 performed by a local radiologist.
BPI-SF, Brief Pain Inventory–Short Form; CR, complete response; DT, desmoid tumor; OT, ovarian toxicity; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 2. Countries participating in the trial