Report OGSIVEO® - Nirogacestat

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Nirogacestat **Brand Name:** Ogsiveo **Originator/licensee:** SpringWorks Therapeutics Ireland Limited **Classification:** NCE **ATC code:** L01XX **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** Nirogacestat, an antineoplastic agent, is an inhibitor of gamma secretase. By blocking gamma secretase, it inhibits the Notch signalling pathway, thereby preventing tumour growth [1].	**Authorized Indication:** **EMA**: Nirogacestat as monotherapy is indicated for the treatment of adults with progressing DT who require systemic treatment [1]. **FDA:** Nirogacestat is indicated for adults with progressing DT who require systemic treatment [2]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 19/06/2025 **FDA M.A. date:** 27/11/2023 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **AE**: Adverse Event **BICR**: Blinded independent central review **BID:** Twice daily **BPI-SF**: Brief Pain Inventory–Short Form **CHMP**: Committee for Medicinal Products for Human Use **CI**: Confidential Interval **DT**: Desmoid tumour **DTSS**: Desmoid Tumour Symptom Scale **ECOG**: Eastern Cooperative Oncology Group **EORTC QLQ-C30**: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 **FAP**: Familial Adenomatous Polyposis **GODDESS**: Gounder–Desmoid Tumour Research Foundation Desmoid Symptom/Impact Scale **HR**: Hazard Ratio **IV**: Intravenously **ITT**: Intention to treat **M.A.:** Marketing Authorization **OS**: Oral administration **PFS**: Progression-Free Survival **P.O.**: Positive Opinion **PRO**: Patient reported outcome **PS**: Performance Status **Pts**: Patients **RECIST:** Response Evaluation Criteria in Solid Tumours **SAE**: Serious adverse events **TKI**: Tyrosine kinase inhibitor **TRAE**: Treatment related AEs **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **DeFi (NCT03785964)** was an international, double-blind, randomized, placebo-controlled, phase III trial in adults with progressing DT not amenable to surgery. Pts aged ≥18 years, with histologically confirmed diagnosis of progressing DT per RECIST v1.1 not amenable to surgery, were enrolled. Pts. were eligible if the tumour had progressed within 12 months before screening. Pts. either had not received previous treatment for progressing DT or had refractory or recurrent DT after ≥1 line of therapy. Pts. (n= 142) were randomly assigned in a 1:1 ratio to receive oral 150 mg nirogacestat (n=70) or placebo (n=72) BID in 28-day cycles. Randomisation was stratified according to the site of the target tumour. The primary endpoint was PFS as assessed by BICR in the ITT population. The change from baseline at cycle 10 in the following PROs was an additional efficacy outcome measure: BPI-SF average worst pain intensity Score, GODDESS DTSS total symptom score, GODDESS DTIS physical functioning domain score and scores on EORTC QLQ-C30 scales for global health status–quality of life, physical functioning, and role functioning. After a median follow-up of 15.9 months, 12 events occurred in the nirogacestat group vs 37 in the placebo group. The risk of disease progression or death was 71% lower in the nirogacestat group than in the placebo group (HR, 0.29; 95% CI, 0.15 to 0.55; P<0.001). At cycle 10, PROs showed higher results for nirogacestat over placebo in the following measures: BPI-SF average worst pain intensity score (P<0.001), GODDESS DTSS total symptom score (P<0.001), GODDESS DTIS physical functioning domain score (P<0.001), EORTC QLQ-C30 physical functioning score (P<0.001), role functioning score (P<0.001), and global health status–quality of life score (P≤0.01). Most differences emerged by cycle 2 and were sustained throughout the study [3]. **Summary of clinical SAFETY:** A total of 141 pts. received at ≥1 dose of nirogacestat or placebo and were included in the safety assessment. The majority of the first onset of AEs occurred during the first cycle; 95% were of grade 1 or 2. One SAE occurred in more than one pt. in the nirogacestat group (premature menopause in three pts.). The most frequent AEs resulting in discontinuation of nirogacestat included diarrhea (in 4 pts.), ovarian dysfunction (in 4), and an increased level of alanine aminotransferase (in 3). Death occurred in one pt. in the placebo group; no death occurred in the nirogacestat group [3]. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/EPAR/ogsiveo [2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217677Orig1s000_Corrected_lbl.pdf [3] https://www.nejm.org/doi/full/10.1056/NEJMoa2210140 [4] https://www.desmoidfoundation.org/en/desmoid-tumor/ [5] https://www.orpha.net/en/disease/detail/873 [6] https://www.ejcancer.com/article/S0959-8049(19)30832-9/fulltext	**Cost of therapy:** The price is not available yet. **Epidemiology:** DT is a rare tumour: its annual incidence is 2-4 cases/1 million people and represents 0.03% of all neoplasms. In most cases, DT has a sporadic origin, but 5-10% of pts. with DT have FAP or Gardner's Syndrome. Pts. affected by this syndrome usually discover that they have DT during routine screening tests. Somatic mutations in the CTNNB1 gene (3q21) encoding beta-catenin have been found in about 85% of sporadic cases. In cases with FAP, DT have been associated with mutations in the tumour suppressor gene APC (5q21-q22) encoding the adenomatous polyposis coli protein [4,5]. --- **POSSIBLE PLACE IN THERAPY**: For pts with DT, an initial approach of active surveillance is recommended as the first step following diagnosis in most cases. Surgery represents the first-line therapy. When surgery is not feasible, moderate-dose definitive radiotherapy can provide adequate local control for the majority of pts. with progressive disease. Active treatments, such as antihormonal therapies, tyrosine kinase inhibitors, or chemotherapy, should be reserved for cases of persistent progression. For intraabdominal/ retroperitoneal/ pelvic DT, systemic therapy should be considered as the first treatment option [6]. The addition of Nirogacestat to these regimens could represent a new opportunity for these pts. **OTHER INDICATIONS IN DEVELOPMENT:** Ovarian Granulosa Cell Tumours (NCT05348356) **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Sorafenib (NCT02066181); AL102 (NCT04871282); Sirolimus (NCT01265030); *Service reorganization: No *Possible off label use: Yes