NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Nirogacestat for treating desmoid tumours

Company/Developer	SpringWorks Therapeutics Ireland Limited

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27127	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Nirogacestat is in clinical development for the treatment of desmoid tumours (DT). DT is a rare condition called an intermediate tumour, which sit somewhere between non-cancerous and cancerous tumours. These types of tumours have the capacity to come back at or near the original tumour, but they do not spread. The main symptom of DT is a lump, commonly found on the arms, legs or abdomen. It can also develop in the head and neck area. There is currently no standard of care for DT, however existing treatment options include active surveillance, surgery, off-label systemic therapy and locoregional therapy. Current treatments have a risk of recurrence depending on patient age, tumour location, size and morbidity associated with the tumour. Off-label systemic therapies used in DT management either have not been studied specifically in DT or have not directly demonstrated significant improvement in patient symptom burden, functioning or overall quality of life (QoL). Thus there is a high unmet need for effective treatments that specifically target DT and improve QoL.

Nirogacestat is an inhibitor of an enzyme which breaks the bonds of proteins that are believed to play a role in activating pathways that contribute to the growth of DT. This inhibition results in blocked signalling and cell growth. Nirogacestat has shown antitumour activity in patients with DT. Nirogacestat is administered as an oral tablet, twice daily. If licensed, nirogacestat will be the first approved treatment option for patients with DT.

Proposed Indication

Nirogacestat for the treatment of adult patients with desmoid tumours (DT).[1]

Technology

Description

Nirogacestat (OGSIVEO, PF-03084014) is a selective gamma secretase (γ-secretase) inhibitor.[1,2] γ-secretase cleaves multiple transmembrane proteins, including Notch, that are believed to play a role in activating pathways that contribute to growth of desmoid tumours.[2] Inhibiting the proteolytic activity of γ-secretase prevents the release of the Notch intracellular domain (NICD) and its translocation to the nucleus—the key step for activation of all downstream effects— leading to decreased expression of several Notch target genes, including those in the hairy/enhancer of split (HES) family.[3] Nirogacestat has been shown to inhibit the Notch pathway in DTs by inhibiting NICD and HES1 expression, with this Notch pathway blockade contributing to the inhibition of DT cell growth.[4] In this way, nirogacestat has antitumour activity against DTs.[5]

Nirogacestat is in clinical development for the treatment of DT. In the phase III clinical trial (DeFi, NCT03785964), nirogacestat was administered orally at 150 mg or 100 mg twice daily until disease progression or development of toxicities.[1]

Key Innovation

There are limited treatment options for DT. Treatment options include active surveillance, surgery, off-label systemic therapy, and locoregional therapy.[6,7] However, the risk of recurrence after surgery may be high in certain patients, and systematic therapies have not demonstrated a significant improvement in patient symptom burden, functioning, or overall quality of life. There is therefore a high unmet need for treatments that specifically target DT and improve quality of life.[6]

In a phase II clinical trial (NCT01981551), nirogacestat was well tolerated and demonstrated promising clinical benefit in patients with refractory, progressive DT who receive long-term treatment. Participants who demonstrated partial response also experienced clinically meaningful and statistically significant improvements in symptom burden. Additionally, in a phase I trial of nirogacestat in patients with advanced solid tumours, five or seven evaluable patients with DT experienced partial responses, whereas two patients had some evidence of tumour shrinkage with prolonged disease stabilisation.[8] If licensed in the EU/UK, nirogacestat will provide an additional treatment option for patients with DT of which there is currently no standard of care.[9]

Regulatory & Development Status

Nirogacestat does not currently have marketing authorisation in the EU/UK for any indication.

Nirogacestat is also in phase II clinical development for ovarian cancer.[10]

Nirogacestat has the following regulatory designations/awards:

- An orphan drug in the EU in 2019 for the treatment of soft tissue sarcoma.[11]
- A Breakthrough Therapy by the US FDA for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumours or deep fibromatosis in August 2019.[12]

Patient Group

Disease Area and Clinical Need

Desmoid tumours (DT), also known as aggressive fibromatosis, is a rare type of soft tissue tumour. DT has been categorised as an intermediate (locally aggressive) fibroblastic tumour, that sit between non-cancerous and cancerous tumours. They have the capacity to come back at or near the original tumour, but they do not spread (metastasise) to other parts of the body.[13-15] Most people are diagnosed between 20-44 years of age, but can occur in other age groups as well.[16] DT can commonly occur in women after childbirth. The female to male gender ratio is 2:1 in adults.[17] The main symptom of DT is a lump, commonly found on the arms, legs or abdomen. It can also develop in the head and neck area. Patients can experience compromised quality of life due to diagnostic challenges and the high clinical burden on DT, including severe pain, impaired physical function and ability, and high recurrence rates. This can limit their everyday activities and lead to deterioration in physical, social and emotional functioning.[6]

DT constitutes 0.03% of all tumours. The estimated incidence in the general (European) population is 3-5 per million people per year.[16,18,19] In England, 2022-23, there were 5,395 finished consultant episodes (FCE) for patients with a primary diagnosis of neoplasm of uncertain or unknown behaviour of other and unspecified sites (ICD-10 D48, which includes D48.1 desmoid tumour), resulting in 3,792 day cases and 6,957 FCE bed days.[20,21] Due to variable clinical presentation and low incidence delayed or inaccurate diagnoses are common for patients with DT, it is difficult to estimate the population likely to be eligible to receive nirogacestat.[6]

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) specifically for DT.

Treatment approaches for DT can incorporate periods of no treatment and active surveillance, as well as interventions including surgery, off-label cytotoxic chemotherapy (anthracyclines, low dose methotrexate plus vinblastine or vinorelbine), tyrosine kinase inhibitors (pazopanib, imamtinib, sorafenib), local ablation, or radiation therapy.[7,22-24]

Clinical Trial Information

Trial	**DeFi;** NCT03785964; EudraCT 2018-001991-39; A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients With Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF) **Phase III** – Active, not recruiting **Location(s):** Four EU countries, UK, USA and Canada **Double-blind primary completion date:** April 2022 **Open-label extension study completion date:** December 2023
Trial Design	Randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor)
Population	N=142; aged 18 years and older; histologically confirmed DT/AF that has progressed by ≥20% as measured by RECIST v1.1 within 12 months of the screening visit scan.
Intervention(s)	Nirogacestat (oral tablet) 150mg twice daily

Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Number of progression free survival events [Time Frame: randomisation up to approximately 2 years] See trial record for full list of other outcomes
Results (efficacy)	Nirogacestat had a significant progression-free survival benefit over placebo (hazard ratio for disease or death, 0.29; 95% confidence interval, 0.15 to 0.55; P<0.01); the likelihood of being event-free at 2 years was 76% with nirogacestat and 44% with placebo. Significant between-group differences in secondary patient-reported outcomes, including pain, symptom burden, physical or role functioning, and health-related quality of life, were observed.[22]
Results (safety)	Frequent adverse events with nirogacestat including diarrhoea (in 84% of the patients), nausea (in 54%), fatigue (in 51%), hypophosphatemia (in 42%), and maculopapular rash (in 32%); 95% of adverse events were of grade 1 or 2. Among women of childbearing potential receiving nirogacestat, 27 of 36 (75%) had adverse events consistent with ovarian dysfunction, which resolved in 20 women (74%).[22]
Clinical Trial Information	
Trial	NCT05879146; Evaluation of the Response and Non-response of Nirogacestat in Desmoid Tumors- Clinical Study **Phase II** – Not yet recruiting **Location(s):** USA **Primary completion date:** January 2027
Trial Design	Single group assignment, open label
Population	N=40 (estimated); aged 18 years and older; histologically documented DT with evidence of radiographic tumour progression (≥10% or absolute increase in dimensions of ≥10mm in maximal diameter) in unidimensional measurement with the previous 18 months.
Intervention(s)	150 mg or 100 mg nirogacestat (oral tablet) twice daily for 28 days
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measure:** Incidence of adverse events [Time Frame: through study completion; an average of 1 year]
Results (efficacy)	-
Results (safety)	-

Estimated Cost
The cost of nirogacestat is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Desmoid Tumour Working Group. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. 2020.[23]
- Kasper B, Baumgarten C, Garcia J, Bonvalot S, Haas R, Haller F, et al. An update on the management of sporadic desmoid-type fibromatosis: a European Consensus Initiative between Sarcoma Patients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG). 2017.[25]

Additional Information

SpringWorks did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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