

Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453] Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nirogacestat for treating desmoid tumours [ID6453]

Contents:

The following documents are made available to stakeholders:

Access the [final scope and final stakeholder list](#) on the NICE website.

1. [Company submission from SpringWorks Therapeutics:](#)
 - a. [Full submission](#)
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2. [Clarification questions and company responses](#)
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 - a. [Professor Susan Clark – clinical expert, nominated by Association of Coloproctology of Great Britain and Ireland](#)
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nirogacestat for treatment of desmoid tumors [ID6453]

Company evidence submission

September 2025

File name	Version	Contains confidential information	Date
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1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. A summary of the decision problem that the submission addresses is provided in **Table 1.1**.

Table 1.1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults (aged 18 years and over) with DT	Adult patients (aged 18 years and over) with progressing DT who require systemic treatment	Align to population in market authorisation application
Intervention	Nirogacestat monotherapy	Per final scope	N/A
Comparator(s)	- Established clinical management using medical therapies. This may include chemotherapy or TKIs. - Best supportive care	Best supportive care	TKIs and chemotherapy were not included as relevant comparators in this submission as they do not reflect the current SoC in UK clinical practice (further details are provided in Section 1.3.7). TKIs are not licensed or reimbursed for DT (only available via compassionate use programmes) nor are they routinely used in UK clinical practice for the treatment of DT, as they are difficult to access based on feedback from UK advisers (SpringWorks Therapeutics 2025a) and are associated with considerable treatment discontinuation due to toxicity and disease progression (Garg et al. 2023, Noujaim et al. 2024, Penel et al. 2011, Toulmonde et al. 2019). Chemotherapy treatment is used more frequently than TKIs and is included in the current clinical practice guidelines as an option for patients (largely due to lack of alternative options approved for use in DT) (Kasper et al. 2024a); however, it is not considered the SoC and is associated with significant toxicity issues (Toulmonde et al. 2019), which can affect patients' QoL, adherence/persistence, and treatment preference. Furthermore, there is no robust high-quality evidence generated from randomised clinical trials on which to assess efficacy and/or compare chemotherapy to nirogacestat, with outcomes data in adults limited to retrospective studies and a single-arm trial (Bektas et al. 2023, Gennatas et al. 2020, Husson et al. 2019, Mir et al. 2020, Toulmonde et al. 2019). <i>Thus, best supportive care is the only appropriate comparator for nirogacestat as it most accurately reflects UK SoC in the treatment of DT.</i>

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Response rates (for example: partial or complete response) • Duration of response • Improvement in symptoms, including pain • Adverse effects of treatment • HRQoL • PFS • Mortality	• Response rates • Duration of response • Improvement in symptoms, including pain • Adverse effects of treatment • HRQoL • Mortality	While data for all of these outcomes (including PFS) are available from the DeFi clinical trial and included within the current submission package Section 2 , from a cost-effectiveness perspective, PFS is not included within the model because it does not allow for differentiation between disease states. Instead, level of tumour response that a patient with progressing DT will experience (e.g., stable disease, partial response, complete response, progression), as defined by the RECIST, version 1.1), is an outcome that can demonstrate the disease-modifying effect of treatment for these patients and was therefore selected for the model. PFS has been used to validate the model.
Subgroups to be considered	• People who have not had previous treatment and people whose DT is relapsed or refractory to treatment • Subgroups based on tumour site such as people with intra-abdominal or extra-abdominal DT • People with FAP	Per NICE final scope	N/A

Abbreviations: DT, desmoid tumours; FAP, familial adenomatous polyposis; HRQoL, health-related quality of life; N/A, not applicable; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SoC, standard of care; TKI, tyrosine kinase inhibitor.

1.2 Description of the technology being evaluated

Nirogacestat is a prescription medication that contains the active ingredient nirogacestat dihydrobromide, a reversible and non-competitive inhibitor of gamma secretase that blocks proteolytic activation of the Notch receptor, which mitigates the growth and progression of desmoid tumours (DT) (Kummar et al. 2025, SpringWorks Therapeutics 2025c, f). A summary of the description of technology is provided in **Table 1.2**.

Table 1.2 Technology being evaluated

UK approved name and brand name	Nirogacestat (OGSIVEO®)
Mechanism of action	Nirogacestat is a prescription medication that contains the active ingredient nirogacestat dihydrobromide, a reversible and non-competitive inhibitor of gamma secretase that blocks proteolytic activation of the Notch receptor, which mitigates the growth and progression of these tumours (Kummar et al. 2025, SpringWorks Therapeutics 2025c, f).
Marketing authorisation/CE mark status	UK Marketing Authorisation Application was submitted to the Medicines and Healthcare Regulatory Agency on July 11, 2025, with anticipated approval expected Q1 2026. Regulatory process will follow the international recognition procedure with the European Medicines Agency as the reference regulator. European Commission granted market authorisation on 18 August 2025 (SpringWorks Therapeutics 2025c, f).
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	Nirogacestat as monotherapy is indicated for the treatment of adult patients with progressing DT who require systemic treatment.
Method of administration and dosage	Oral administration of 100 mg and 150 mg film-coated tablets are being sought for registration (SpringWorks Therapeutics 2025f). The recommended dose of 150 mg twice daily, administered as one dose in the morning and one dose in the evening, with or without food (with the exception of grapefruit and grapefruit juice, which should be avoided). This dose should not be exceeded. If a dose of nirogacestat is missed, patients should not take an additional dose. Patients should take the next prescribed dose. The tablet should be taken in its complete form and should not be broken, crushed or chewed. Nirogacestat 150 mg twice daily can be continued until disease progression or unacceptable toxicity.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	Anticipated UK list price: £198,000.00, per year; £15,189.04 per pack of 56 tablets (150 mg/tablet); nirogacestat should be continued until disease progression or unacceptable toxicity.
Patient access scheme (if applicable)	N/A

Abbreviations: DT, desmoid tumours; N/A, not applicable.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

Desmoid tumour, or aggressive fibromatosis, is a rare, aggressive, non-metastasising, and locally invasive neoplasm with an annual incidence of 0.3 per 100,000 in Europe (Orphanet Report Series 2024). Currently, there are no direct estimates of incidence rates and no published prevalence rates for DT in the UK.

Arising in deep soft tissue, DT are a subgroup of soft tissue sarcoma (STS), and these monoclonal proliferations of myofibroblasts present as firm, irregular, grey-white soft-tissue masses with tentacle-like elongations that grow in the direction of, and infiltrate, muscle fibres across the body (Federman 2022, Figueredo and Schiano 2023, Garcia-Ortega et al. 2020, Kasper et al. 2017). Most (85%-90%) cases of DT are sporadic and associated with mutations in the catenin beta 1 (CTNNB1) gene, which encodes β -catenin, while the remaining cases (up to 10%) are associated with familial adenomatous polyposis (FAP), a hereditary disease caused by germline mutations in the adenomatous polyposis coli (APC) gene (Bektas et al. 2023, Garcia-Ortega et al. 2020, Husson et al. 2019).

Patients with DT are typically diagnosed between 20 and 44 years of age, with FAP-associated DT diagnosis occurring at a significantly younger age than sporadic DT (mean age 36 vs. 42 years; $p=0.031$) (Bektas et al. 2023, Nieuwenhuis et al. 2011). Desmoid tumours are 2 to 4 times more prevalent in females (Bektas et al. 2023).

Patients with DT experience substantial pain, symptom burden, and functional limitations that are influenced by tumour location and size (Bektas et al. 2023, Bell et al. 2022, Constantinidou et al. 2012). Desmoid tumours have an unpredictable clinical course marked by periods of rapid progression, spontaneous resolution, and stability, which can influence symptom burden and contribute to impaired health-related quality of life (HRQoL) (Bektas et al. 2023, Bell et al. 2022). Approximately 75% of patients experience intermediate-to-high symptom burden, including pain (Schut et al. 2023).

Patients also often experience disfigurement or altered appearance and decreased range of motion (Federman 2022, Garcia-Ortega et al. 2020, Gounder et al. 2020). Such symptoms and functional limitations result in impaired HRQoL, including negatively affected physical, social, cognitive, and emotional domains (Bell et al. 2022, Husson et al. 2019, Ingley et al. 2020, Schut et al. 2023, Timbergen et al. 2018).

Primary treatment goals for DT focus on inhibiting disease progression, reducing tumour growth, and improving symptoms, function, and quality of life (QoL) (Kasper et al. 2024a). Patients with progressing, symptomatic DT may receive systemic medical therapies such as tyrosine kinase inhibitors (TKIs) or chemotherapy (Kasper et al. 2024a). While systemic therapies such as TKIs and chemotherapy are used off-label to treat DT in the UK, TKI use is limited through compassionate use schemes, chemotherapy is used in the absence of other options, and both are associated with frequent adverse effects and neither have been associated with significant improvements in patient-reported outcomes (PROs) (Bartholomew et al. 2024, Garg et al. 2023, Gounder et al. 2018b, NICE 2025a, b, Penel et al. 2011, Toulmonde et al. 2019). In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapies, which have historically been used in the management of DT, are not recommended, due to lack of evidence establishing their efficacy and activity in patients with DT (Kasper et al. 2024a).

In specific situations, surgery, local ablative therapies, or radiotherapy may be used for treatment. Due to the high recurrence rates (up to 90%) associated with surgery (Fernandez et al. 2023), it is now only recommended as one of the first-line treatment options for DT in the mesentery to treat complications or when expected morbidity is low; to treat complications in patients with tumours in the retroperitoneum, or pelvis or FAP-associated DT in the mesentery; or for abdominal wall DT, based on the latest Desmoid Tumor Working Group (DTWG) from 2024 (Kasper et al. 2024a). Local ablative therapies such as cryoablation is currently indicated for growing DT after 2 or more lines of systemic therapy, especially some smaller DTs with functional symptoms or pain, depending on tumour location, as increasing tumour size was associated with higher rates of treatment failure (Kasper et al. 2024a). In addition, cryotherapy is limited

in availability as it is not offered in all treatment centres and relies on expertise (Kasper et al. 2024a). Radiotherapy is a second-line treatment for some DT depending on tumour location and has been associated with an increased local control rate; however, it is associated with high toxicity and should be carefully considered due to risk of secondary malignant neoplasms, especially in adults 18 to 29 years old (Kasper et al. 2024a).

Therefore, in the absence of an approved, recommended systemic therapy for the treatment of DT in the UK (National Institute for Health and Care Research 2024), a substantial unmet need remains for a clinically effective treatment option with a manageable safety profile and convenient mode of administration, that significantly improves pain, symptom burden, functioning, and HRQoL.

1.3.2 Aetiology and pathophysiology

The exact aetiology of DT is unknown, but several factors are implicated (Anneberg et al. 2022a, Bektas et al. 2023). Namely, somatic mutations in the CTNNB1 gene and germline mutations in the APC gene have been associated with the emergence of DT (Bektas et al. 2023, Garcia-Ortega et al. 2020, Husson et al. 2019, Master et al. 2025). Additionally, DT onset has been associated with trauma, surgery, and hormonal changes in oestrogen or during pregnancy (Constantinidou et al. 2012, Federman 2022, Garcia-Ortega et al. 2020).

The pathophysiology of DT is primarily a result of dysregulation of the Wnt signalling pathway, which regulates β -catenin (Federman 2022, Master et al. 2025). Two molecular pathways have been linked to the oncogenesis of DT: 1) the canonical Wnt signalling pathway, and 2) the Notch pathway (Garcia-Ortega et al. 2020). Dysregulation of these evolutionarily conserved pathways promotes transcription of pro-tumour factors involved in DT (Zheng et al. 2024).

1.3.3 Disease presentation

The clinical presentation of DT varies, ranging from asymptomatic to aggressive. Symptomatic DT can be due to local destruction, compression of nearby structures, and

other complications such as bowel obstruction, bowel perforation, haemorrhage, and sepsis (Federman 2022, Figueredo and Schiano 2023, Garcia-Ortega et al. 2020, Master et al. 2025).

Desmoid tumours typically emerge in sites across the body extra-abdominally, intra-abdominally, and in the abdominal wall (Constantinidou et al. 2012). The most common extra-abdominal DT are located in the shoulder and upper extremity (33%), followed by the gluteal region and lower extremity (30%), chest wall or back (17%), and head and neck (10%) (Rosa et al. 2020). Although less frequent, head and neck DT typically affect younger patients, with data suggesting DT in this region comprise 12% of extra-abdominal cases and the mean age of patients is approximately 17 years (Constantinidou et al. 2012). Head and neck DT are considered more aggressive than other DT locations (Constantinidou et al. 2012).

The most frequently reported symptoms across tumour locations were disfigurement (81%), nerve pain (71%), decreased range of motion (68%), and muscle pain (65%) (Gounder et al. 2020). In some cases, patients experience more severe symptoms such as bowel obstruction and perforation, organ dysfunction, and sepsis. Symptoms vary by DT location and size. For example, patients with intra-abdominal DT often do not experience symptoms until the tumour is compressing adjacent structures, leading to symptoms such as weight loss, wasting syndrome, malaise, ureter and small intestine compression and obstruction, renal failure, perforations, or bleeding (Constantinidou et al. 2012, Garcia-Ortega et al. 2020). In contrast, patients with extra-abdominal DT are typically symptomatic, with substantial pain. DT in the extremities can result in paraesthesia and polyneuropathies, while DT in the chest wall can result in dyspnoea, asphyxiation, and dysphagia (Constantinidou et al. 2012, Garcia-Ortega et al. 2020). Moreover, the larger the tumour, the greater the symptom burden and pain (Penel et al. 2023).

1.3.4 Prognostic factors

The prognosis for DT is highly variable and is influenced by patient age, primary tumour size, and primary tumour location (Bektas et al. 2023, Figueredo and Schiano 2023,

Riedel and Agulnik 2022). Specifically, shorter progression-free survival (PFS) has been associated with factors such as age (<37 years old), tumour size (>7 cm), and tumour location (extra-abdominal) (Riedel and Agulnik 2022). Additionally, primary tumour sizes larger than 10 cm have been associated with lower rates of 5-year recurrence-free survival and poorer local control (Bishop et al. 2020, Crago et al. 2013). Other factors influencing prognosis include presence of S45F or T41A CTNNB1 mutation and presence of pain at baseline (Colombo et al. 2013, Cuomo et al. 2021, Lazar et al. 2008, Penel et al. 2023, Timbergen et al. 2021).

1.3.5 Epidemiology and mortality

1.3.5.1 Risk factors

Risk factors associated with DT development include APC gene mutations; trauma such as abdominal surgery, laparoscopic port sites, and total hip replacements; female sex; pregnancy; and high estrogenic states (i.e., oral contraceptive use, childbearing age) (Anneberg et al. 2022a, Constantinidou et al. 2012, Garcia-Ortega et al. 2020).

1.3.5.2 Incidence and prevalence

Desmoid tumour was granted orphan designation by the US Food and Drug Administration (FDA) in 2018 (FDA 2018). Nirogacestat received orphan drug designation for the treatment of soft tissue sarcoma from the European Commission (EC) on 17 October 2019 (EU/3/19/2214) (EMA 2025). On 20 June 2025, the Committee for Orphan Medicinal Product issued a positive opinion for the maintenance of nirogacestat orphan designation (EMA 2025). Japan's Ministry of Health, Labor, and Welfare (MHLW) also granted orphan drug designation to nirogacestat for desmoid tumours (Pacific Bridge Medical 2025). Studies evaluating the epidemiology of DT are very limited, and the direct incidence of DT in adult patients in the UK currently are not available. The annual incidence, based on European evidence from published literature and rare disease databases, ranges from 2 to 5 cases per million per year (Anneberg et al. 2022a, Bektas et al. 2023, Orphanet Report Series 2024).

Estimates for prevalence for all DT were not found. However, DT are a subgroup of STS, and DT account for fewer than 3% of all STS (Orphanet Report Series 2019,

2024). Soft tissue sarcoma prevalence estimates from registries, published literature, rare disease databases, and for some products under development for STS recently designated as orphan products by the European Commission range from 1.52 to 4.69 per 10,000, average prevalence calculated from various sources is 14.2:50,000 (SpringWorks Therapeutics 2019). Applying the 3% for all DT, we estimate the average prevalence of all DT to be 0.43:50,000.

An estimated 40% of patients have progressing DT and require systemic treatment (Constantinidou et al. 2012, Desmoid Tumor Working Group 2020, Gounder et al. 2018b, Kasper et al. 2017, Skubitz 2017). Therefore, the prevalent population is estimated to be less than 0.17 per 50,000.

1.3.5.3 Mortality

Data on mortality in DT in the UK are limited. A recent Danish epidemiological study reported a 5-year mortality of 7 per 1,000 compared with 5 per 1,000 in a healthy matched (general population) cohort, and the adjusted hazard ratio (HR) of dying was 1.3 (95% confidence interval [CI] 0.6, 3.2) for patients with DT compared with the general population (Anneberg et al. 2022a). This data suggests that DT may affect the life expectancy of a patient.

1.3.6 Disease burden

Desmoid tumours cause significant pain, functional limitation, and disability due to the infiltrative nature of the disease, which compress structures throughout the body, affecting muscles, nerves, vessels, and joints (Bektas et al. 2023, Garcia-Ortega et al. 2020). For example, tumours affecting extremities may restrict joint movement and cause limping or difficulty in moving arms or legs (Kasper et al. 2024b, National Library of Medicine 2020). As DT is a progressive disease, patients who are initially asymptomatic may experience a greater disease-specific symptom burden over time.

1.3.6.1 Patient burden

Patients with DT commonly experience pain, disfigurement or altered appearance, decreased range of motion, fatigue, and insomnia (Kasper et al. 2024b). Evidence

suggests that pain is the most debilitating symptom of DT and affects nearly two-thirds (63%) of patients (Gounder et al. 2020, Husson et al. 2019, Rigaux et al. 2015). Three-quarters of patients with DT have intermediate to high symptom burden, including pain, and the high clinical and functional burden of DT has been associated with impaired HRQoL (Schut et al. 2023). For example, pain has been significantly associated with lower performance status ($p=0.024$, assessed by the Eastern Cooperative Oncology Group [ECOG] Performance Status scale), functional impairment ($p=0.001$), and poor event-free survival (HR 1.82; 95% CI 1.23, 2.68; $p=0.003$) (Penel et al. 2023).

In a prospective cross-sectional study evaluating the HRQoL and mental health in DT ($n=204$), patients with DT had significantly lower global health status than healthy controls (65.58 [standard deviation; SD] 22.64] vs. 81.43 [SD 17.83], $p<0.0001$), as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (Garg et al. 2022). In addition, patients with DT had poorer scores than healthy controls on all functional scales except for cognitive functioning ($p<0.0001$ for all comparisons). In a focus group of patients with DT in the UK ($n=27$), scores of HRQoL according to the EORTC QLQ-C30 reflected other studies in this population: global QoL and all functioning scale scores were low (global QoL: 56.9; physical functioning: 74.4; role functioning: 55.8; social functioning: 52.8; cognitive functioning: 70.1; and emotional functioning: 56.9) (Husson et al. 2019). To date, no studies have evaluated the HRQoL of caregivers in DT (SpringWorks Therapeutics 2025g).

Consequently, patients with DT experience negative effects on daily activities, relationships, and workplace productivity (Husson et al. 2019, Mercier et al. 2024, Rigaux et al. 2015, Timbergen et al. 2018). Patients in the UK reported that living with the DT affected daily activities (e.g., bathing, dressing, etc.) and participation in hobbies (e.g., rock-climbing) (Husson et al. 2019). Further, patients with DT experienced relationship problems between family, romantic partners, and children, including coping alone so as not to be a burden to loved ones, loss of libido, and difficulties with parental roles such as breastfeeding or playing games with their children. Employment was also commonly affected, as patients with DT were unable to work or were forced to take sick

leave, which resulted in loss of job progression and/or employment and subsequent financial difficulty that was further complicated by additional hospital expenses such as travel. In addition to the physical and role limitations of DT, patients often experienced challenged social functioning and emotional functioning resulting from a lack of understanding by others, social isolation, mood changes, negative body image, and the psychological challenges of living with a chronic disease with an uncertain disease course. Pain has specifically been linked to altered daily activity (21%) and leisure activity (18%) and socio-familial and economic impairments, including sleep disruptions (73%), mental health effects such as irritability (46%) and anxiety (15%), and caused patients to stop working (26%), only work part time due to pain (10%), or change jobs (3%) (Rigaux et al. 2015).

1.3.6.2 Economic burden

Management of DT is complex and involves various approaches and can include pharmacological therapies, pain medication, surgical interventions, and hospital visits to treat the disease and associated complications, as well as mental health and supportive care resources to navigate impaired HRQoL. Symptom burden contributes to substantial healthcare resource use (HCRU), which increases as symptoms worsen (Anneberg et al. 2022a, Schut et al. 2023). In a study of patients with DT from the UK and the Netherlands, patients with high symptom burden had significantly more general and DT-related visits to the GP and a significantly higher odds of having at least 2 general visits to their GP and at least 1 DT-related visit in the past year than those with low or intermediate symptom burden (odds ratio [OR] 2.71; 95% CI 1.08, 6.76 and OR 10.35; 95% CI 2.32, 46.16, respectively). Patients treated with active treatments and patients with recurrent DT had a significantly higher odds of at least 1 DT-related visit to a DT specialist in the past year than those who received active surveillance and those who did not have recurrent DT, respectively ($p < 0.05$ for both comparisons). Patients with DT in Denmark reported a higher average number of inpatient visits (1.0), outpatient visits (7.1), and hospitalizations (7.5 days) compared with birth year-, sex-, and region of residence-matched controls from the general population (0.8 inpatient visit, 0.1 outpatient visit, and 0.8 days) (**Table 1.3**) (Anneberg et al. 2022a).

Table 1.3 HCRU of patients with DT and a comparison-matched cohort

	Before first contact ^a		After first contact ^a	
	DT patient	Comparison cohort	DT patient	Comparison cohort
	Mean/median (IQR)			
Inpatient visit				
Within 1 year	0.1/0.0	0.0/0.0	0.7/0.0 (0.0-1.0)	0.1/0.0
Within 3 years	0.3/0.0	0.1/0.0	1.0/1.0 (0.0-1.0)	0.1/0.0
Outpatient visit				
Within 1 year	1.1/0.0 (0.0-1.0)	0.4/0.0	4.1/3.0 (1.0-6.0)	0.4/0.0
Within 3 years	2.2/0.0 (0.0-2.0)	1.2/0.0	7.1/4.0 (1.0-11.0)	0.8/0.0
Days hospitalised				
Within 1 year	0.5/0.0	0.2/0.0	4.6/0.0 (0.0-6.0)	0.3/0.0
Within 3 years	1.2/0.0	0.5/0.0	7.5/1.0 (0.0-6.0)	0.8/0.0

Note: Where median was 0.0, IQR was 0.0; assume 0.0 unless reported otherwise.

^a The first DT contact date in the Danish Sarcoma Database.

Abbreviations: DT, desmoid tumour; HCRU, healthcare resource use; IQR, interquartile range.

Source: Anneberg et al. (2022a).

Data on the economic burden of DT, such as direct and indirect costs, is lacking, particularly in the UK (Bektas et al. 2023). European studies on the economic burden largely reflect the treatment costs associated with surgery and other therapies. For example, a cost-analysis model of patients with DT in Spain found that yearly per-patient costs of percutaneous cryoablation were €5,774 and €6,780 with conventional surgery (Narvaez et al. 2024). This represents a 1-year cost among the whole patient cohort (n=80) of €459,149 for cryoablation versus €539,151 for surgery.

1.3.7 Treatment pathway

There is no standard approach for the management of DT in the UK. The 2024 joint global consensus-based guideline provided by the DTWG is the main DT management guideline used in the UK, and additional guidance is provided by the ESMO-EUROCAN-GENTURIS Guideline (2021) and SPAEN/EORTC Guidelines (2017) (Gronchi et al. 2021, Kasper et al. 2024a, Kasper et al. 2017). Generally, these guidelines align on the approach to DT management and reflect the shift away from surgery. Briefly, the 2024 DTWG management recommends (Kasper et al. 2024a):

1. Active surveillance as the initial strategy in the absence of persistent tumour growth or as long as the tumour does not threaten life, function, or QoL.
2. Upon persistent tumour growth or threat to life, function, or QoL, patients should receive active therapy integrating a clinical scenario-centric approach that considers the expected effectiveness and morbidity associated with the treatment. Primary treatment options depend on tumour location and/or whether the patient has FAP, and includes surgery, local ablative techniques, and medical therapy. The former two options are limited in their application. Briefly:
 - Surgery is only recommended as the first-line option for treatment when morbidity and risk of recurrence are low, in particular for abdominal wall DT, mesenteric (non-FAP) DT, and to treat complications for mesenteric DT in patients with FAP, and retroperitoneal and pelvic DT.
 - No recommendation on the use of cryoablation in DT was noted in the guidelines, but it is indicated for growing DT after 2 or more lines of systemic therapy or with functional symptoms or pain. Other local ablative therapies (i.e., high-intensity focused ultrasonography treatment, thermal ablative techniques such as radiofrequency and microwave, and chemical ablative techniques) are not recommended outside of randomised controlled study settings.
 - Medical therapy (including TKIs and chemotherapy) is recommended as one of the first-line treatment options for patients who require treatment for a DT in the abdominal wall, mesentery, retroperitoneum, pelvis, extremities, girdles, or chest wall, and is the only recommended first-line treatment for DT in the head, neck, or intrathoracic region. Medical therapies should be selected considering the safety profiles of the available agents in the context of the specific patient (Kasper et al. 2024a).
 - According to payer and clinical expert interviews, current standard of care for DT is variable in the UK and may depend on tumour site and the centre's clinical practice (NICE 2025a).
3. Patients who progress after first-line have limited treatment options and often receive the same treatment again, other first-line treatments, riskier treatments

such as surgery or radiotherapy, or best supportive care to help manage symptoms and pain. Treatment depends on availability of options.

In adult patients with progressing DT, treatment with nirogacestat can provide benefits in inhibiting disease progression, reducing tumour growth, and improving symptoms, including pain, functioning, and QoL (**Section 1.3.6**).

1.3.7.1 Systemic therapy

In the UK, TKIs may be prescribed off-label for the management of DT to a very limited population through compassionate use programs in the UK (NICE 2025a, b). Tyrosine kinase inhibitors have not undergone NICE technology appraisal for the treatment of DT, therefore, are neither widely funded nor commonly prescribed in clinical practice. Consequently, TKIs are difficult to access (e.g., frequency estimates were once a year to once in 5 years, according to anecdotal feedback from 2 advisors). One (1) UK advisor remarked that the turnaround time to complete the compassionate use application and start treatment ranges from 4 to 8 weeks, which is too long for some patients who need treatment as soon as possible. There is also uncertainty related to continued TKI (e.g., sorafenib) access because there is no formal commitment from the manufacturer that they will provide the drug free of charge forever (SpringWorks Therapeutics 2025a). Furthermore, off-label TKIs are associated with considerable treatment discontinuation due to toxicity and disease progression (Garg et al. 2023, Noujaim et al. 2024, Penel et al. 2011, Toulmonde et al. 2019).

Chemotherapy is also used off-label and is considered a treatment option largely due to the lack of alternative options available for patients in clinical practice and treatment guideline recommendations (NICE 2025a, b). Data for chemotherapy in DT are limited to retrospective studies or single arm trials (see **Section 1.3.3**) (Bektas et al. 2023, Gennatas et al. 2020, Husson et al. 2019, Mir et al. 2020, Toulmonde et al. 2019). The lack of high-quality evidence from randomised clinical trials and comparative studies has resulted in a lack of consensus on the standard of care for the treatment of DT, which inhibits the ability to properly assess their efficacy in this population and impedes clinicians' decision making on the choice of the most appropriate agent(s) for the

treatment of patients with progressing DT (Bektas et al. 2023, Kasper et al. 2024a, Smith 2024). In addition, high-quality data on PROs are lacking, despite the importance of these outcomes in treatment goals for DT. Furthermore, off-label chemotherapies are also associated with substantial toxicity and disease progression (Toulmonde et al. 2019), which can affect treatment adherence or persistence, treatment preference, and QoL. Patients who refuse treatment are limited to BSC, which does not modify or address the clinical course of DT. Chemotherapy is neither currently licensed for DT nor has it undergone NICE health technology appraisal in DT.

1.3.8 Unmet need

Primary goals of treatment are to inhibit disease progression, reduce tumour growth, and improve symptoms, function, and QoL (Kasper et al. 2024a). Currently, there are no approved systemic therapies for the treatment of DT in the UK, and only off-label conventional systemic therapies such as TKIs and chemotherapies can be used due to the lack of alternative options available in clinical practice (Bektas et al. 2023, National Institute for Health and Care Research 2024, NICE 2025a, Smith 2024). TKIs have not undergone NICE health technology appraisal for the treatment of DT, and their use is limited through compassionate use programs. Further, evidence supporting their use is limited; randomised trials demonstrate limited response to treatment with TKIs, and this was corroborated by recent real-world evidence (Garg et al. 2023, Gounder et al. 2018b, Noujaim et al. 2024, Toulmonde et al. 2019). Tyrosine kinase inhibitors are also associated with significant adverse effects, including hand-foot syndrome (35.4%-89.4%), fatigue (14.1%-81.3%), diarrhoea (15%-79.2%), and nausea (15%-54%) (Costa et al. 2025, Garg et al. 2023, Gounder et al. 2018b, Jo et al. 2014, Kwon et al. 2022, Toulmonde et al. 2019). Chemotherapy is not currently licensed for DT and has not undergone NICE health technology appraisal, with outcomes data in adults limited to retrospective studies and a single-arm trial (Toulmonde et al. 2019). Additionally, chemotherapy is associated with Grade 3 or higher adverse events (AEs) in approximately three-quarters of patients and frequent AEs such as neuropathy, pneumonitis, anaemia, nausea, mild alopecia, vomiting, and hepatitis (Toulmonde et al. 2019). Chemotherapy has been associated with treatment discontinuation in nearly 75%

of patients, with approximately one-third due to toxicity and more than one-third due to disease progression (Toulmonde et al. 2019). Furthermore, neither TKIs and chemotherapy have demonstrated significant improvements in DT symptoms, functional limitations, and HRQoL (Bektas et al. 2023, Husson et al. 2019). As such, there is a need for a DT-specific systemic treatment that adequately addresses patient needs related to controlling tumour size, preserving function, managing pain and DT symptoms, and improving QoL.

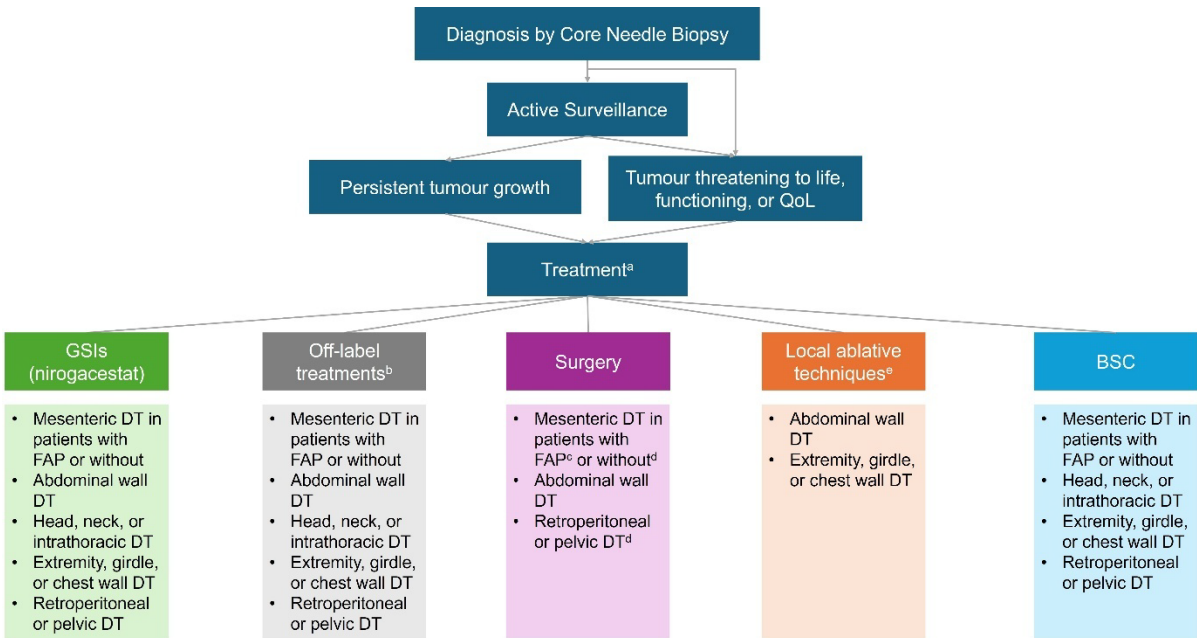
Nirogacestat (PF-03084014) is a potent, oral, small-molecule, selective, reversible, noncompetitive inhibitor of the γ -secretase enzyme that was initially developed for investigation in Notch-driven tumours (Gounder et al. 2023b, Kummar et al. 2025, Messersmith et al. 2015, Villalobos et al. 2018). Gamma secretase inhibitors (GSIs) have been shown to decrease expression of many Notch target genes and associated DT development and growth (Federman 2022, Kummar et al. 2025). In the DeFi clinical trial, the largest and most rigorous Phase 3 trial of DT to date, nirogacestat demonstrated significant improvements in PFS, objective response rate (ORR), and pre-specified PROs (i.e., pain, disease-specific symptom severity, physical functioning and role functioning, and overall QoL) (Gounder et al. 2023b, SpringWorks Therapeutics 2023c). It is an orally administered drug, which may offer a convenient treatment option for patients and providers (Eek et al. 2016, SpringWorks Therapeutics 2025f). As a clinically effective treatment option with a manageable safety profile and a convenient mode of administration, nirogacestat addresses the high unmet need among patients with progressing DT and could become the first and only monotherapy indicated for adult patients with progressing DT who require systemic treatment (SpringWorks Therapeutics 2025f).

1.3.9 Anticipated position of nirogacestat

Nirogacestat will be administered within the current DT diagnosis and treatment pathway of the NHS. **Figure 1.1** outlines the general clinical pathway of care for patients with DT. The proposed location of nirogacestat in the pathway is for the treatment of patients with progressing DT who require systemic treatment and is expected to shift current clinical practice away from off-label treatments and best

supportive care. Nirogacestat is positioned to become the new standard of care as the first and only approved treatment for DT.

Figure 1.1 Proposed Clinical Pathway of Care with Nirogacestat



^a Experimental treatments in the context of clinical trials are an option at any line of therapy.

^b In the presence of an effective approved therapy, use of an off-label therapy that is associated with considerable treatment burden may no longer be considered a first-line treatment option.

^c Surgery is only considered a first-line treatment option for these patients when the expected morbidity is low or when treating complications for mesenteric DT in patients with FAP.

^d Surgery is considered a treatment option for these patients only when treating complications.

^e Use of local ablative techniques is limited to small or moderately sized tumors without involvement of vital structures.

Abbreviations: BSC, best supportive care; DT, desmoid tumours; FAP, familial adenomatous polyposis; GSI, gamma secretase inhibitor; QoL, quality of life.

Source: Modified from the DTWG management algorithms for treatment of DT, Kasper et al. (2024a).

1.4 Equality considerations

The sponsor does not anticipate any evidence to support special considerations including issues related to equity or equality relating to the use of nirogacestat in the treatment of adult patients with progressing DT.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) of clinical evidence was performed to identify and qualitatively synthesise efficacy and safety data from clinical trials and observational studies of pharmacological therapies in adult patients with desmoid tumours (DT). The SLR was designed to identify studies that align with the intended use of nirogacestat in patients with DT. Literature searches were conducted December 2022, July 2024, and May 2025. The full details on the methods and results are presented in **Appendix B**.

2.2 List of relevant clinical effectiveness evidence

The SLR identified 44 unique studies. Of these, 1 unique randomised controlled trial provided evidence on the efficacy and safety of nirogacestat. The DeFi clinical trial (NCT03785964) was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled, parallel arm study designed to assess the efficacy, safety, and tolerability of nirogacestat in adult patients with unresectable, recurrent, or relapsed progressing DT (Gounder et al. 2023a). This study is summarised in **Table 2.1** and will be the focus of this section.

Table 2.1 Clinical effectiveness evidence

Study	DeFi (NCT03785964)
Study design	Multi-centre, randomised, double-blind, placebo-controlled, parallel arm, Phase 3 study
Population	Adults with histologically confirmed unresectable, recurrent, or relapsed progressing DT (defined as $\geq 20\%$ progression according to RECIST version 1.1 within 12 months of the screening scan)
Intervention(s)	Oral administration of 50 mg tablets (3 tablets; 150 mg) of nirogacestat twice daily, continuously for 28 days
Comparator(s)	Oral administration of 50 mg tablets (3 tablets; 150 mg) of placebo twice daily, continuously for 28 days
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem^a	• Progression-free survival • Response rates • Improvement in symptoms, including pain • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Duration of response

^a Bolded items represent outcomes used in the model.

Abbreviations: DT, desmoid tumours; N/A, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours.

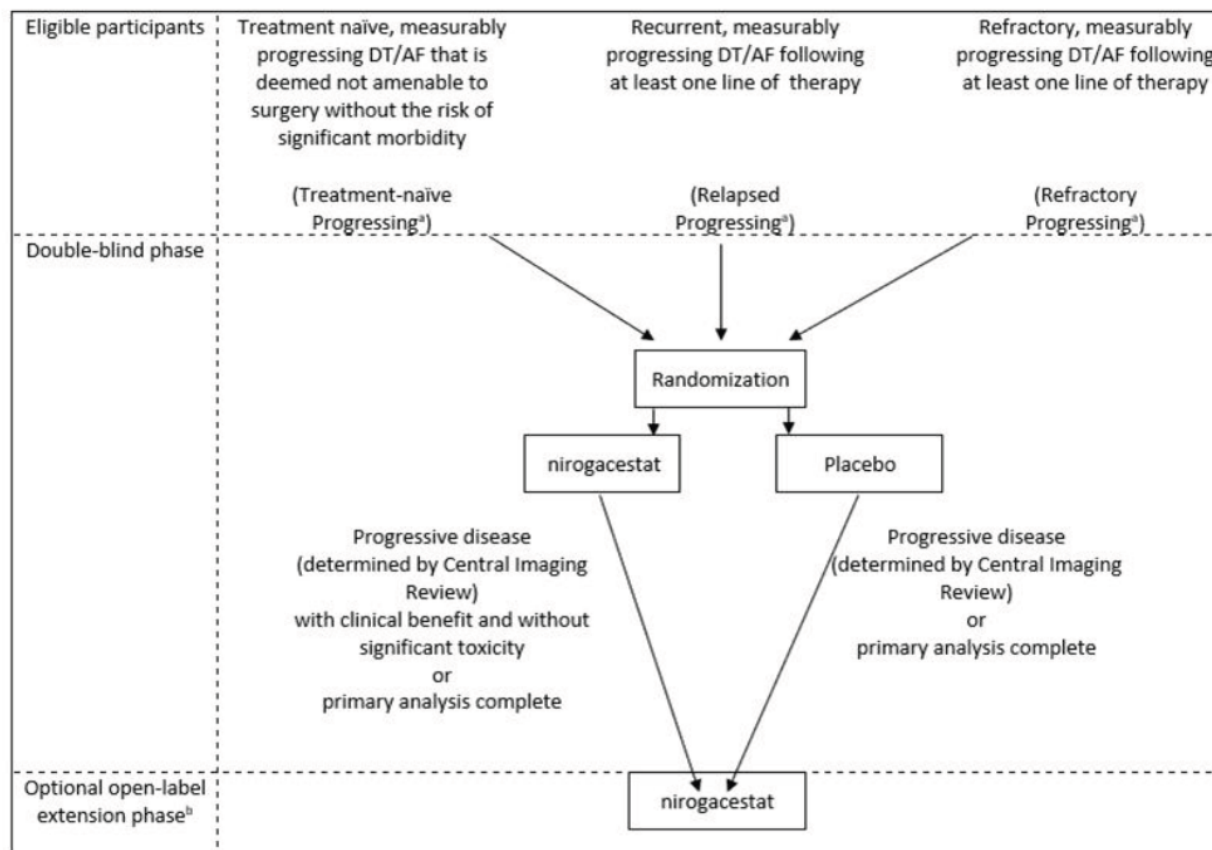
The DeFi trial was used as a primary resource for developing the cost-effectiveness model and supported the application for marketing authorisation.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 DeFi trial design

The DeFi trial was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled, parallel arm study of nirogacestat in adult patients with DT. This study was conducted at 52 sites in Canada, the US, and Europe, with 37 sites randomising at least 1 participant (SpringWorks Therapeutics 2023b). At the completion of the double-blind phase, the remaining participants had their study treatment assignment unblinded and if eligible, had the opportunity to enrol in the optional open-label extension (OLE) phase (SpringWorks Therapeutics 2023b). A schematic of the study design is presented in **Figure 2.1**. A summary of the key trial methodology is presented in **Table 2.2**.

Figure 2.1 DeFi study schema



^a All eligible participants must have histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by $\geq 20\%$ as measured by Response Evaluation Criteria in Solid Tumors version 1.1 within 12 months of the screening visit.

^b Participants discontinuing study treatment due to clinical progression were not eligible for participation in the open label extension.

Abbreviations: DT/AF, desmoid tumour/aggressive fibromatosis.

Source: SpringWorks Therapeutics (2023b).

Table 2.2 Summary of DeFi trial methodology

Trial design	Multi-centre, randomised, double-blind, placebo-controlled, parallel arm, Phase 3 study
Eligibility criteria for participants	Key Inclusion Criteria: • Participant was at least 18 years of age at the time of signing the informed consent. • Participant had histologically confirmed DT (by local pathologist prior to informed consent) that had progressed by $\geq 20\%$ as measured by RECIST v1.1 within 12 months of the screening visit scan. • Participant had any of the following: – Treatment naïve, measurably progressing DT that was deemed not amenable to surgery without the risk of significant morbidity. – Recurrent, measurably progressing DT following at least 1 line of therapy. – Refractory, measurably progressing DT following at least 1 line of therapy. • Participant had a DT tumour where continued progressive disease did not result in immediate significant risk to the participant. • Participant agreed to provide archival or new tumour tissue for re-confirmation of disease.

	• Participant completed any therapy for the treatment of DT at least 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study treatment. All toxicities from prior therapy must be resolved to $\leq$ grade 1 or clinical baseline. • Participants who received chronic NSAIDs as treatment for conditions other than DT were receiving them prior to the documented DT progressive disease and on a stable dose for at least 28 days prior to the first dose of study treatment. • Participant had an ECOG performance status ≤ 2 at screening. • Participant had adequate organ and bone marrow function at screening. • Participant could swallow tablets and had not gastrointestinal conditions affecting absorption. Key Exclusion Criteria: • Participant had known malabsorption syndrome or pre-existing gastrointestinal conditions that may have impaired absorption of nirogacestat (e.g., gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of nirogacestat via nasogastric tube or gastrostomy tube was not allowed. • Participant experienced any of the following within 6 months of signing informed consent: – Clinically significant cardiac disease (New York Heart Association Class III or IV) – Myocardial infarction – Severe/unstable angina – Coronary/peripheral artery bypass graft – Symptomatic congestive heart failure – Cerebrovascular accident – Transient ischemic attack – Symptomatic pulmonary embolism • Participant had abnormal QT interval corrected by Fridericia's formula (QTcF; >450 msec for male participants, >470 msec for female participants, or >480 msec for participants with bundle branch block) after electrolytes have been corrected (triplicate ECG readings, done approximately 2 to 3 minutes apart and averaged) at screening. • Participant was using concomitant medications that were known to prolong the uncorrected QT (QT)/QTcF interval. Non-antiarrhythmic medications which may prolong the QT/QTcF interval were allowed provided the participant did not have additional risk factors for Torsades de Pointes. • Participant has had lymphoma, leukemia, or any malignancy within the past 5 years except for any locally recurring cancer that has been treated curatively with no evidence of metastatic disease for 3 years at the time of informed consent. • Participant had current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones). • Participant previously received or was receiving therapy with GS inhibitors or anti-Notch antibody therapy. • Participant was using any treatment for DT or any investigational treatment 28 days (or 5 half-lives, whichever was longer) prior to the first dose of study treatment. Or participant started treatment for DT following documented DT progression. • Participant was using or anticipated using food or drugs that were known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3A4 inducers within 14 days prior to the first dose of study treatment. • Participant had either a positive human immunodeficiency virus antibody test, presence of Hepatitis B surface antigen at screening, or positive Hepatitis C antibody or Hepatitis C RNA test at screening or within 3 months prior to starting study treatment.
Settings and locations where the data were collected	Conducted in 52 study sites in 7 countries: Belgium (n=11), Canada (n=7), Germany (n=10), Italy (n=10), Netherlands (n=8), the UK (n=6), and the US (n=90). A total of 37 sites randomised at least one participant.

Trial drugs	Participants were stratified according to the location of the target tumour (i.e., intra-abdominal [including the mesentery and pelvis] or extra-abdominal [including the head or neck, paraspinal regions, arms or legs, abdominal wall, and chest wall]). Participants with multiple target tumours that were located both in the intra- and extra-abdominal location, the tumour was classified as intra-abdominal. Participants were randomly assigned in a 1:1 ratio to receive: • Nirogacestat (150 mg) twice daily, orally continuously in 28-day cycles (n=70) or • Placebo twice daily, orally continuously in 28-day cycles (n=72)
Permitted and disallowed concomitant medication	Permitted: Any medication or vaccine (such as prescription medication, vitamins, herbal supplements) that the patient received prior to and while on study treatment was recorded, indicating the reason of use, the dates of administration, and the dosage and frequency. Phosphate supplements and palliative care for the standard management of symptoms or supportive care for the management of the effects of study treatment were permitted at the investigator's discretion unless they were excluded per protocol. Disallowed: • Other antineoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy, TKIs, or other antibodies • Chronic daily use of NSAIDs for treatment of DT • Potentially curative radiotherapy • Surgical resection of DT tumours • Any other investigational therapy • Strong/moderate CYP3A4 inhibitors and strong CYP3A4 inducers • CYP3A substrates with a narrow therapeutic index • Gastric acid reducing agents such as proton pump inhibitors • Gastric bypass, lap band, or other gastric procedures that would alter absorption • Antiarrhythmic medications that are known to prolong the QT/QTcF interval
Pre-specified primary outcome	• PFS
Secondary outcome	• ORR – DOR^a • Change in PRO measures from baseline to Cycle 10 (BPI-SF, GODDESS DTIS, GODDESS DTSS, EORTC QLQ-C30)
Key Exploratory outcomes	• To compare tumour volume changes measured by MRI in participants with progressing DT^b • To evaluate DT symptoms and impacts using PROs
Pre-planned subgroups	Subgroup analyses were performed for the primary endpoint: • Sex • Target-tumour location • Focality • Treatment status • Previous treatments (surgery, chemotherapy, and TKI, separately) • Genetic mutation status (APC and CTNNB1, separately) • Family history of FAP

^a DOR (in months) is a supportive descriptive analysis of ORR.

^b Change in tumour volume from baseline as assessed by volumetric MRI was initially planned as a secondary endpoint but was moved to an exploratory endpoint based on feedback from the Food and Drug Administration given volumetric MRI is not a widely accepted endpoint for registration.

Abbreviations: APC, adenomatous polyposis coli; BPI-SF, Brief Pain Inventory-Short Form; CTNNB1, catenin beta 1; DT, desmoid tumour; DTIS, Desmoid Tumour Impact Scale; DTSS, Desmoid Tumor Symptom Scale; DOR, duration of response; ECG, electrocardiogram; 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 Tumor Research Foundation DESmoid Symptom/Impact Scale; GS, gamma secretase; NSAID, nonsteroidal anti-inflammatory drug; ORR, objective response rate; PFS, progression-free survival; PRO, patient reported outcome; QT, uncorrected QT interval; QTcF, corrected QT interval by Fridericia; RECIST, Response Evaluation Criteria in Solid Tumours; RNA, ribonucleic acid; TKI, tyrosine kinase inhibitor; v, version.

Source: Gounder et al. (2023a); SpringWorks Therapeutics (2023b); SpringWorks Therapeutics (2021).

2.3.2 Trial endpoints

Key trial endpoints and definitions are summarised in **Table 2.3**.

Table 2.3 Summary of primary and secondary objectives and endpoint definitions in the DeFi trial

Objectives	Endpoints
Primary	
To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT	• PFS, defined as the time from randomisation until the date of assessment of progression or death by any cause. Progression was determined radiographically using RECIST v1.1 criteria or clinically as assessed by the investigator and qualified via blinded independent central review. Clinical progression was defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (eg, radiotherapy, surgery, or systemic therapy including chemotherapy or TKIs) for DT.
Secondary	
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT as measured by the incidence of TEAEs	• Safety endpoints included incidence of TEAEs, changes in laboratory parameters, vital signs, physical examination findings, and ECGs. • Tolerability was assessed according to toxicities graded by NCI CTCAE v5.0.
To determine the objective response rate (CR + PR) of nirogacestat in participants with progressing DT	Objective response rate, defined as the proportion of participants with CR + PR assessed via central reader using RECIST v1.1 criteria
To determine the duration of response ^a	Duration of response for participants whose best response was CR or PR
To evaluate DT symptoms and impacts using PROs	Symptoms and impacts were assessed by evaluating change from baseline on the following PROs: • GODDESS • BPI-SF • EORTC QLQ-C30
Key Exploratory	
To compare tumour volume changes measured by MRI in participants with progressing DT ^b	Change in tumour volume from baseline as assessed by volumetric MRI
To evaluate DT symptoms and impacts using PROs	• PROMIS PF short form 10a plus 3 additional items from PROMIS item banks^c

^a DOR (in months) is a supportive descriptive analysis of ORR.

^b Change in tumour volume from baseline as assessed by volumetric MRI was initially planned was a secondary endpoint but was moved to an exploratory endpoint based on feedback from the Food and Drug Administration given volumetric MRI is not a widely accepted endpoint for registration.

^c Additional item 1: "Are you able to bend or twist your back", Additional item 2: "Are you able to reach into a high cupboard", Additional item 3: "I have trouble doing my regular daily work around the house".

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; DT, desmoid tumour; ECG, electrocardiogram; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GODDESS, GOUnder/DTRF DEsmoid Symptom/Impact Scale; MRI, magnetic resonance imaging; NCI, National Cancer Institute; ORR, objective response rate; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; PROMIS PF, Patient-Reported Outcomes Measurement Information System Physical Function; RECIST, Response Evaluation Criteria in Solid Tumours; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; v, version.

Source: SpringWorks Therapeutics (2023b); SpringWorks Therapeutics (2022a).

2.3.3 Participant demographics and baseline characteristics

The demographics and baseline characteristics of participants in the intent-to-treat (ITT) population of the DeFi trial are outlined in **Table 2.4**.

Overall, baseline characteristics were similar between treatment groups. A notable difference in demographics and disease characteristics between treatment groups was observed in race and ethnicity, and body mass index (BMI), with more participants in the nirogacestat arm identifying as White and Not Hispanic/Latino and enrolling in Europe, and having a normal BMI as compared to placebo. The breakdown by age quartile also varied slightly between treatment groups (SpringWorks Therapeutics 2023b).

Table 2.4 Participant demographics (ITT population)

Characteristic	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)
Age (year), median (range)	33.5 (18-73)	34.5 (18-76)	34.0 (18-76)
Age (year), mean (SD)	37.5 (14.43)	37.0 (12.89)	37.2 (13.62)
Age group, n (%)			
Aged <27 years	20 (29)	14 (19)	34 (24)
Aged 27 to <34 years	15 (21)	18 (25)	33 (23)
Aged 34 to <46 years	13 (19)	25 (35)	38 (27)
Aged ≥46 years	22 (31)	15 (21)	37 (26)
Sex, n (%)			
Female	45 (64)	47 (65)	92 (65)
Women of childbearing potential ^a	37 (82)	37 (79)	74 (80)
Male	25 (36)	25 (35)	50 (35)
Infertility history, n (%)			
Yes	0 (0)	3 (4)	3 (2)
No	67 (96)	66 (92)	133 (94)
Unknown	3 (4)	3 (4)	6 (4)
Infertility history – males ^a , n (%)			
Yes	0 (0)	1 (4)	1 (2)
No	25 (100)	23 (92)	48 (96)
Unknown	0 (0)	1 (4)	1 (2)
Infertility history – females ^a , n (%)			
Yes	0 (0)	2 (4)	2 (2)
No	42 (93)	43 (91)	85 (92)
Unknown	3 (7)	2 (4)	5 (5)
Menstrual history ^b			
History of amenorrhea, n (%)			
Yes	6 (16)	10 (27)	16 (22)
No	28 (76)	26 (70)	54 (73)
Missing	3 (18)	1 (3)	4 (5)

Characteristic	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)
History of menstrual irregularities			
Yes	11 (30)	10 (27)	16 (22)
No	23 (62)	26 (70)	54 (73)
Missing	3 (8)	1 (3)	4 (5)
Race, n (%)			
White	64 (91)	54 (75)	118 (83)
Black or African American	4 (6)	5 (7)	9 (6%)
Asian	1 (1)	3 (4)	4 (3%)
Other	1 (1)	10 (14)	11 (8%)
Ethnicity, n (%)			
Non-Hispanic or Latino	67 (96)	55 (76)	122 (86)
Hispanic or Latino	1 (1)	9 (13)	10 (7)
Unknown	0 (0)	3 (4)	3 (2)
NR	2 (3)	5 (7)	7 (5)
Baseline BMI ^{c,d} (kg/m ²)			
n	69	71	140
Mean (SD)	26.275 (6.9440)	27.103 (6.1171)	26.695 (6.5273)
Median (min, max)	23.846 (17.72, 52.34)	25.693 (17.53, 44.83)	25.135 (17.53, 52.34)
BMI group, n (%)			
<18.5 kg/m ²	3 (4)	2 (3)	5 (4)
18.5 to <25 kg/m ²	36 (51)	28 (39)	64 (45)
25 to <30 kg/m ²	15 (21)	23 (32)	38 (27)
≥30 kg/m ²	15 (21)	18 (25)	33 (23)
Geographic region, n (%)			
US or Canada	44 (63)	53 (74)	97 (68)
Europe	26 (37)	19 (26)	45 (32)
Country, n (%)			
Belgium	6 (9)	5 (7)	11 (8)
Canada	4 (6)	3 (4)	7 (5)
Germany	7 (10)	3 (4)	10 (7)
United Kingdom	4 (6)	2 (3)	6 (4)
Italy	5 (7)	5 (7)	10 (7)
Netherlands	4 (6)	4 (6)	8 (6)
US	40 (57)	50 (69)	90 (63)

^a Percentages were based on the number of the sex summarised.

^b Percentages were based on the number of female participants of childbearing potential.

^c Baseline was defined as the most recent measurement prior to the first administration of study treatment.

^d Baseline BMI was calculated as: baseline weight in kg/(baseline height in m)².

Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; NR, not reported; SD, standard deviation.

Source: SpringWorks Therapeutics (2023b).

A summary of disease characteristics in the ITT population is provided in **Table 2.5**. Baseline disease characteristics were generally similar across trial groups and representative of the population of participants with DT (Gounder et al. 2023a). It is important to note that participants included in the DeFi trial were eligible if they had a histologically confirmed diagnosis of progressing desmoid tumours (defined as ≥20%

progression according to the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) within 12 months before screening (Gounder et al. 2023a, SpringWorks Therapeutics 2023b). Although other published DT studies assessed tumour response using RECIST criteria, the DeFi trial differed in that it had a higher minimum progression threshold compared to other studies (e.g., the sorafenib study used a lower threshold of 10% to measure disease progression (Gounder et al. 2018a)).

Table 2.5 Participant baseline disease characteristics (ITT population)

	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)
Time since diagnosis to randomisation (months) ^a			
n	70	72	142
Mean (SD)	59.25 (72.903)	61.70 (76.974)	60.49 (74.739)
Median (min, max)	30.19 (0.7, 307.2)	31.15 (3.4, 343.1)	30.97 (0.7, 343.1)
Focal category, n (%)			
Single	43 (61)	41 (57)	84 (59)
Multifocal	27 (39)	31 (43)	58 (41)
Desmoid tumour treatment status, n (%)			
Treatment naive	18 (26)	14 (19)	32 (23)
Refractory	43 (61)	55 (76)	98 (69)
Recurrent	9 (13)	3 (4)	12 (8)
Number of target tumours, n (%)			
n	69	72	141
1	50 (71)	45 (63)	95 (67)
2	15 (21)	18 (25)	33 (23)
3	3 (4)	4 (6)	7 (5)
4	1 (1)	4 (6)	5 (4)
5	0	1 (1)	1 (<1)
Number of target tumours			
n	69	72	141
Mean (SD)	1.3 (0.64)	1.6 (0.93)	1.5 (0.81)
Median (min, max)	1.0 (1, 4)	1.0 (1, 5)	1.0 (1, 5)
Target tumour location(s), n (%) ^b			
Abdominal wall	12 (17)	19 (26)	31 (22)
Chest wall	9 (13)	9 (13)	18 (13)
Neck and head	8 (11)	6 (8)	14 (10)
Lower extremities	14 (20)	11 (15)	25 (18)
Mesentery and pelvis	16 (23)	16 (22)	32 (23)
Paraspinal	6 (9)	8 (11)	14 (10)
Upper extremities	10 (14)	13 (18)	23 (16)
Other	4 (6)	8 (11)	12 (8)
Baseline target tumour size per RECIST (mm) ^c			
n	69	72	141
Mean (SD)	111.19 (70.563)	121.16 (66.373)	116.28 (68.393)
Median	91.60	115.70	100.35
Q1, Q3	64.7, 134.1	73.5, 161.7	68.9, 155.4
Min, max	22.3, 356.2	19.9, 400.9	19.9, 400.9
Baseline target tumour size group (mm), n (%) ^c			
Baseline target tumour size <68.90	19 (27)	16 (22)	35 (25)
Baseline target tumour size 68.90 to <100.35	21 (30)	14 (19)	35 (25)

	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)
Baseline target tumour size 100.35 to <155.35	15 (21)	20 (28)	35 (25)
Baseline target tumour size ≥155.35	14 (20)	22 (31)	36 (25)
Number of non-target tumours, n (%)			
0	47 (67)	37 (51)	84 (59)
1	11 (16)	19 (26)	30 (21)
2	8 (11)	4 (6)	12 (8)
3	3 (4)	7 (10)	10 (7)
4	1 (1)	2 (3)	3 (2)
5	0	1 (1)	1 (<1)
6	0	0	0
7	0	2 (3)	2 (1)
Number of non-target tumours			
n	70	72	142
Mean (SD)	0.6 (0.96)	1.0 (1.57)	0.8 (1.32)
Median (min, max)	0 (0, 4)	0 (0, 7)	0 (0, 7)
Number of non-target tumours where tumour present			
n	23	35	58
Mean (SD)	1.7 (0.86)	2.1 (1.65)	2.0 (1.40)
Median (min, max)	2.0 (1, 4)	1.0 (1, 7)	1.0 (1, 7)
Non-target tumour location(s), n (%) ^b			
Abdominal wall	0	4 (6)	4 (3)
Chest wall	1 (1)	4 (6)	5 (4)
Neck and head	0	0	0
Lower extremities	8 (11)	6 (8)	14 (10)
Mesentery and pelvis	2 (3)	3 (4)	5 (4)
Paraspinal	0	0	0
Upper extremities	3 (4)	3 (4)	6 (4)
Other	5 (7)	5 (7)	10 (7)
Family history of FAP, n (%)			
Yes	11 (16)	13 (18)	24 (17)
No	59 (84)	59 (82)	118 (83)
Any Somatic Mutation, n (%)			
Yes	52 (74)	53 (74)	105 (74)
No	0	1 (1)	1 (<1)
Unknown	18 (26)	18 (25)	36 (25)
Any APC Somatic Gene Mutation, n (%)			
Yes	11 (16)	11 (15)	22 (15)
No	41 (59)	43 (60)	84 (59)
Unknown	18 (26)	18 (25)	36 (25)
Any CTNNB1 Somatic Gene Mutation, n (%)			
Yes	43 (61)	42 (58)	85 (60)
No	9 (13)	12 (17)	21 (15)
Unknown	18 (26)	18 (25)	36 (25)
Concomitant medications ^d , n (%)	69/69 (100)	70/72 (97)	139/141 (99)
ECOG performance-status score, n (%)			
0	51 (73)	52 (72)	103 (73)
1	18 (26)	20 (28)	38 (27)
2	1 (1)	0	1 (<1)
Uncontrolled pain ^e , n (%)	27 (39)	31 (43)	58 (41)

^a The time since diagnosis to randomisation was calculated as: (date of randomisation – date of diagnosis + 1)/30.4375.

^b It was not possible for population counts to be summed across locations due to the possibility of patients having a tumour in more than one location.

^c Baseline target tumour size was determined as the sum of the longest diameter for each tumour and reviewer and presented as the average sum across reviewers.

^d Reported for the Safety Population (N=141; n=69 in nirogacestat group and n=71 in placebo group).

^e Uncontrolled pain was defined as a Brief Pain Inventory–Short Form average worst pain intensity score of more than 4 (range 0-10 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.
Abbreviations: APC, adenomatous polyposis coli; CTNNB1, catenin beta 1; ECOG, Eastern Cooperative Oncology Group; FAP, familial adenomatous polyposis; ITT, intent-to-treat; max, maximum; min, minimum; Q, quantile; RECIST, Response Evaluation Criteria for Solid Tumours; SD, standard deviation.
Source: Gounder et al. (2023a); SpringWorks Therapeutics (2023b).

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis populations in the DeFi trial are presented in **Table 2.6** and included the ITT population, the per-protocol population, and the safety population. The ITT population was the analysis population used for all efficacy analyses and the safety population was used for all safety analyses (SpringWorks Therapeutics 2023b).

Table 2.6 Analysis populations in the DeFi trial

Analysis Population	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)	Definition
ITT Population, n (%)	70 (100)	72 (100)	142 (100)	Consisted of all participants who were enrolled and randomised to receive treatment in the study (nirogacestat or placebo). Participants were analysed according to the treatment they were randomised to and the strata to which they were assigned. Participants who were randomised but did not subsequently go on to receive study treatment were included in the ITT Population.
Per-protocol Population, n (%) ^a	62 (89)	67 (93)	129 (91)	Consisted of participants who received study treatment and had no major protocol deviations. Additionally, participants who did not have a confirmed DT diagnosis or were found not to have DT per central confirmatory review, permanently discontinued due to non-compliance with study treatment, received <60% of the planned dose of study treatment during the treatment phase, or were mis-randomised were also excluded from this analysis population. Participants were analysed according to the study treatment actually received.

Analysis Population	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)	Definition
Safety Population, n (%) ^a	69 (99)	72 (100)	141 (>99)	Consisted of all participants randomly assigned to study treatment and who took at least 1 dose of study treatment. Participants were analysed according to the treatment they actually received.

^a Percentage of the ITT population.

Abbreviations: DT, desmoid tumour; ITT, intent-to-treat.

Source: SpringWorks Therapeutics (2023b).

Statistical methods used in the DeFi trial are outlined in **Table 2.7**.

Table 2.7 Summary of statistical analyses in the DeFi trial

Hypothesis Objective	• The null hypothesis for testing the primary efficacy outcome was that the PFS for nirogacestat and placebo were equal. • The alternative hypothesis for testing the primary efficacy outcome was that the PFS for nirogacestat was longer than that for placebo.
Statistical Analysis	The primary and secondary efficacy endpoints were tested in a hierarchical stepdown procedure to control for multiplicity in the following order: PFS, ORR, pain, disease symptoms, disease impact, and HRQoL evaluations of GHS/QoL, physical functioning, and role functioning, by PRO. If the null hypothesis was rejected at the 1-sided significance level of 0.025 the testing could proceed to the next endpoint, but if the null hypothesis was not rejected, all subsequent results were considered descriptive only. <u>Primary Endpoint: PFS</u> • A 1-sided stratified log-rank test was performed to compare the distributions between nirogacestat and placebo at alpha level of 0.025. • Kaplan-Meier methods were used to summarise PFS data. • A Cox proportional hazards model was used to estimate HR and the 2-sided 95% CIs controlling for the stratification factor to which the participant was assigned at randomisation (target tumour(s) location – intra-abdominal vs. extra-abdominal). • For each PFS subgroup, the HR and associated CIs were calculated from a stratified Cox proportional hazards model and presented in a forest plot. <u>Secondary Endpoint: ORR</u> • ORR was calculated for each treatment arm and the proportions were compared using the Cochran-Mantel-Haenszel test stratified by randomisation factor. Summaries of ORR and the 2-sided 95% exact CI were presented. • Response used for the definition of ORR was defined as having a confirmed BOR of CR or PR by RECIST v1.1 during the blinded portion of the study. – Confirmed BOR (as reported from central imaging review) was defined as the best response obtained across all time points during the DB phase of the study, given that: PR or CR was confirmed by a subsequent scan at least 4 weeks after the initial PR or CR was observed, to be assigned to stable disease as BOR a participant was required to have at least 1 non-PD/non-evaluable time point response at least 8 weeks after baseline and not meet the requirements for BOR of PR or CR, and when one or more NE time points are interleaved between CR or PR time points, these NE time points will not impact response confirmation. • Duration of objective response was analysed using the Kaplan-Meier method based on participants with a documented response (CR or PR) only. Duration of response was defined as the duration in months from the time measurement criteria were met for CR or PR (whichever came first) until the date of progression or death (whichever came first). • Duration of stable disease was analysed using the Kaplan-Meier method based on participants with CR, PR, or stable disease only. Duration of stable disease was defined as the duration in months from the start of treatment until the date of progression or death (whichever came first). • Since the number of the participants available for analysis is random, no formal testing between the two treatment arms was conducted for both duration of objective response and duration of stable disease. <u>Secondary Endpoint: PRO Assessment</u>

	• Secondary efficacy endpoints related to the PRO, and their testing order, are as follows: – Mean change from baseline at Cycle 10 in BPI-SF API score, – Mean change from baseline at Cycle 10 in DTSS Total Symptom Score, – Mean change from baseline at Cycle 10 in DTIS Physical Functioning Domain Score, – Mean change from baseline at Cycle 10 in EORTC QLQ-C30 GHS/QoL, – Mean change from baseline at Cycle 10 during the double-blind phase period in EORTC QLQ-C30 Physical Functioning – Mean change from baseline at Cycle 10 during the double-blind phase period in EORTC QLQ-C30 Role Functioning • The PROMIS questionnaire was not formally tested in the endpoint hierarchy. • Change from baseline during the double-blind phase in PRO scores was analysed using a REML based repeated measures approach (Mixed Model Repeated Measures) in a primary analysis and a Pattern Mixture Model in a sensitivity analysis. • Other than the pre-specified hierarchical testing of efficacy outcomes, no additional adjustments for multiplicity were made. <u>Secondary Endpoint: Safety</u> • Safety analyses were conducted using the Safety Population. • Analyses of AEs were performed for those events that are considered TEAEs, where treatment-emergent was defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. • Severity of AEs were classified according to NCI CTCAE v5.0. <u>Exploratory Endpoint: Change in Tumour Volume Assessed by MRI</u> • Percent change in tumour volume assessed by MRI was analysed using a repeated measures model adjusting for baseline tumour volume and randomisation strata. • The analysis used a MMRM, and the model included treatment, baseline volume, visit, and randomisation strata as covariates. • Treatment by visit interaction was included in the model and if significant, treatment differences were assessed by timepoint. • The covariance structure was assumed to be unstructured, although if the matrix failed to converge, alternative structures were used in the following order until convergence was reached: TOEPH, ARH, TOEP, and AR. • The assessment timepoints were analysed as categorical. • The model used a Kenward-Rogers approximation for the degrees of freedom. Adjusted mean estimates per treatment arm and 95% CIs along with an estimate of treatment difference, 95% CI, and p-value were presented. In addition, unadjusted summary statistics for tumour volume were presented by visit and treatment arm. <u>Exploratory Endpoint: PRO Assessment of PROMIS PF10a</u> • A total sum score was computed using all 10 items. A T-score and standard error of the T-score associated with the total score was assigned based on the short form conversion table accompanying the scale. • T-score was summarised over scheduled visit by treatment arms.
Sample Size, Power Calculation	• The study sample size was based on the primary PFS endpoint. • A total of 51 events was estimated to provide 90% power and a 1-sided type 1 error rate of 0.025 (1-sided hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat arm was 20 months and 8 months in the placebo arm (corresponding to a HR of 0.4 relative to placebo). • Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants would be needed to be randomised in a 1:1 ratio to observe the estimated number of events.

Data Management, Patient Withdrawals	Missing Data: • In general, there were no substitutions made to accommodate missing data points. • In case of missing PRO items, the scale and total scores were calculated as indicated in the scoring manual for the PRO instrument for the existing instruments. – For GODDESS, all items for a given total or domain score should be present in order to create the total or domain score. – Weekly scores (GODDESS and BPI-SF) were calculated only if there were 4 or more days of assessments with non-missing data within the respective week. – Missing PRO data was assumed to be missing at random in general and was analysed using the MMRM analysis when appropriate. To address the possibility that missing data was not missing at random, sensitivity analysis with pattern mixture model will be conducted. Discontinuations: • Participants who are withdrawn or discontinue from the study were not replaced. • In situations where study participants were discontinued early from the study by investigators for clinical progression but could not be verified as qualified events, they were considered as dropouts and were censored for the primary analysis. Similarly, participants who did not progress or die were censored at the date of the last valid CT/MRI assessment.

Abbreviations: AE, adverse event; API, average pain intensity; AR, autoregressive; ARH, autoregressive with heterogeneity; BOR, best overall response; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DB, double-blind; DT, desmoid tumours; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; GODDESS, Gounder–Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; HR, hazard ratio; HRQoL, health-related quality of life; MMRM, mixed model with repeated measures; NCI, National Cancer Institute; NE, non-evaluable; ORR, objective response rate; PD, progressed disease; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; PROMIS, Patient Reported Outcomes Measurement Information System; PROMIS PF10a, Patient Reported Outcomes Measurement Information System Physical Functioning Short-Form 10a; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; REML, restricted maximum likelihood; SD, standard deviation; TEAE, treatment-emergent adverse event; TOEP, Toeplitz; TOEPH, Toeplitz with heterogeneity; v, version.

Source: SpringWorks Therapeutics (2023b); SpringWorks Therapeutics (2022b); SpringWorks Therapeutics (2022a).

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment of the DeFi trial is provided in **Appendix B**.

2.6 Clinical effectiveness results of the relevant studies

A summary of the results for the primary and secondary efficacy outcomes is presented in **Table 2.8**. The primary analysis had a data cut-off date of 7 April 2022. Compared to the placebo group, treatment with nirogacestat was associated with significant improvements in all primary and secondary efficacy endpoints, which included progression-free survival (PFS), objective response rate (ORR), and patient-reported outcomes (PROs; i.e., pain, disease-specific symptom severity, physical functioning and role functioning, and overall quality of life [QoL]) (Gounder et al. 2023a). Consistent results were observed for PFS and ORR, providing further support for favourable treatment with nirogacestat. Patient-reported outcomes had significant and clinically meaningful improvement at the pre-specified Cycle 10, with differences between groups for most PROs emerging as early as Cycle 2 and sustaining through Cycle 24 (Gounder et al. 2023a).

Table 2.8 Summary of results for primary and secondary endpoints in the DeFi trial

Endpoints	Results	
	Nirogacestat (n=70)	Placebo (n=72)
Primary: PFS		
Number of participants with progression or death, n (%)	12 (17%)	37 (51%)
██		
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████████████████	████████████████	████████████████
Kaplan-Meier estimate of median PFS, months (95% CI)	NE (NE, NE)	15.1 (8.4, NE)
PFS hazard ratio (95% CI)	0.29 (0.15, 0.55)	
One-sided p-value	<0.001	
Secondary: Response		
Best overall response - Confirmed, n (%)		
Complete response	5 (7%)	0

Endpoints	Results	
	Nirogacestat (n=70)	Placebo (n=72)
Partial response	24 (34%)	6 (8%)
██████████	██████████	██████████
██████████	██████████	██████████
██████████	██████████	██████████
ORR (complete response + partial response), n (%)	29 (41%)	6 (8%)
95% CI	29.8, 53.8	3.1, 17.3
Two-sided p-value	<0.001	
██	██████████	██████████
██		
██		
████████████████████	██████████	██████████
Secondary: PROs		
BPI-SF average worst pain intensity score		
██	██████████	██████████
Difference to placebo at Cycle 10, LS mean (SE)	-1.34 ██████████	
One-sided p-value	<0.001	
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^a Kaplan-Meier median duration of response could not be estimated for either treatment arm due to small number of progressions for those who responded.

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; LS, least-squares; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; QoL, quality of life; SD, standard deviation; SE, standard error.

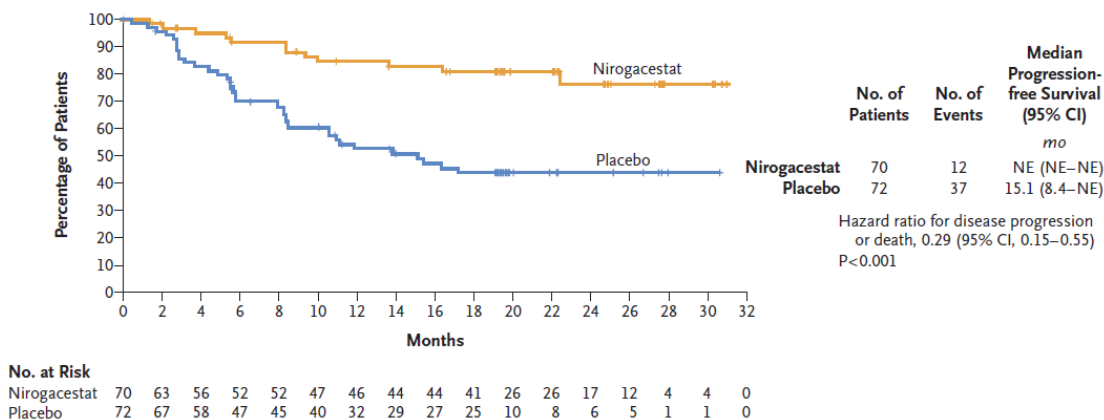
Source: SpringWorks Therapeutics (2023b).

2.6.1 Primary endpoint: PFS

For the primary endpoint of PFS, the overall median follow-up was [REDACTED] in the nirogacestat arm and [REDACTED] in the placebo arm (SpringWorks Therapeutics 2023b). Nirogacestat was associated with a statistically significantly improved PFS, with a 71% reduction in the risk of disease progression or death compared with placebo (hazard ratio [HR] 0.29; 95% confidence interval [CI] 0.15, 0.55; p<0.001) (Table 2.8; Figure 2.2).

The Kaplan-Meier estimate of median PFS could not be estimated in the nirogacestat group due to a low number of events; Kaplan-Meier estimate of median PFS was 15.1 months (95% CI 8.4, not estimable) in the placebo group (SpringWorks Therapeutics 2023b).

Figure 2.2 PFS Kaplan Meier curve in the DeFi trial



Abbreviation: CI, confidence interval; mo, month; NE, not estimable; PFS, progression-free survival.
Source: Gounder et al. (2023a).

2.6.2 Secondary endpoint: ORR

The ORR was calculated based on the confirmed best overall response per central review 41% (95% CI 29.8, 53.8) in the nirogacestat group compared with 8% in the placebo group (95% CI 3.1, 17.3; p<0.001) (Table 2.8) (SpringWorks Therapeutics 2023b). Among participants treated with nirogacestat, 7% were in complete response (CR) and 34% were in partial response (PR) compared with no participants in CR and

8% in PR among those in the placebo group (SpringWorks Therapeutics 2023b) (Figure 2.3 A and B).

2.6.3 Pre-specified supportive and exploratory ORR endpoints

2.6.3.1 Duration of objective response

[REDACTED]
[REDACTED]

[REDACTED] The probability of remaining in response after 1 year was [REDACTED] with nirogacestat and [REDACTED] with [REDACTED] (SpringWorks Therapeutics 2023b).

2.6.3.2 Best percent change in tumour size

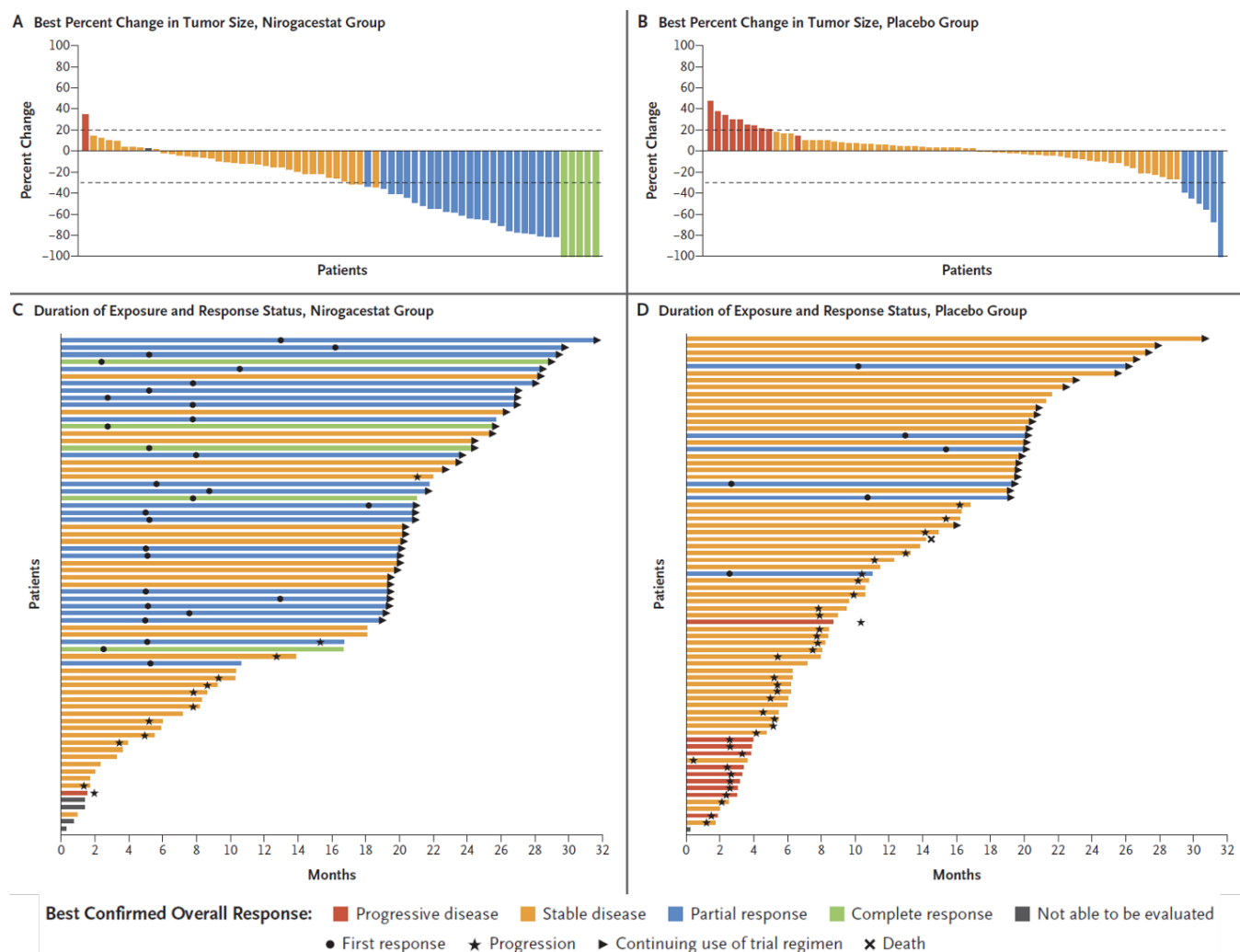
The best percent change in tumour size was a supportive analysis for ORR. In measuring change in tumour size, a reduction in size (negative value) indicated an improvement. The median best percent change in tumour size was -27.1% (range -100-37) in the nirogacestat group compared with 2.3% (range -100-47) in the placebo group (Figure 2.3 A and B) (Gounder et al. 2023a).

2.6.3.3 Time to response

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] At the time of the analysis, 28 of 29 participants (97%) who had a response in the nirogacestat group and 5 of 6 participants (83%) who had had a response in the placebo group were still having a response (Figure 2.3 C and D) (Gounder et al. 2023a).

Figure 2.3 Best percent change in tumour size^a in nirogacestat (A) and placebo (B) and duration of exposure and response status^b in nirogacestat (C) and placebo (D), DeFi trial



^a Best percent change at any time point from baseline in target-tumour size per patient according to RECIST version 1.1. Values for best percent change were averaged between the two independent reviewers unless a reader was selected for adjudication, in which case only the adjudicated value is presented.

^b Best overall response according to RECIST version 1.1.

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumours.

Source: Gounder et al. (2023a).

2.6.4 Exploratory efficacy endpoints

2.6.4.1 Change in tumour volume assessed by MRI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.6.5 Secondary endpoint: PROs

Nirogacestat had statistically significant and clinically meaningful between-group improvements compared with placebo in the PROs of pain, disease-specific symptom severity, physical functioning and role functioning, and overall QoL, by the pre-specified Cycle 10. Differences between treatment groups emerged as early as Cycle 2 (the first post-treatment time point evaluated) and were sustained through Cycle 24 (Gounder et al. 2023a).

2.6.5.1 BPI-SF

The BPI-SF is a tool that evaluates the severity of pain and degree to which it interferes with feeling and function on a scale from 0 to 10, with a 24-hour recall period; higher scores indicating worse pain (SpringWorks Therapeutics 2023a). A between-group threshold of 1.0 represents an approximately 30% to 35% change from baseline, which was considered clinically meaningful (Mease et al. 2011). For the BPI-SF average worst pain intensity score, the LS mean difference at Cycle 10 was -1.34 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



A proportion of participants in each group experienced statistically significant and clinically meaningful improvements from baseline to Cycle 10 on both GODDESS DTSS and DTIS. A greater proportion of participants who received nirogacestat experienced clinically meaningful improvement in DTSS. (Table 2.9) (SpringWorks Therapeutics 2023a).

Table 2.9 Percent of participants with clinically meaningful improvement in GODDESS DTSS total symptom score and DTIS physical functioning from baseline at Cycle 10

Measure	Eligible Participants (n)		Responder %		OR (95% CI)	p-value
	Nirogacestat	Placebo	Nirogacestat	Placebo		
DTSS Total Symptom Score ^a	■	■	■	■	■	■
DTIS Physical Function ^b	■	■	■	■	■	■

Note: The analysis was limited to participants with baseline values that could improve by at least the meaningful change thresholds for each measure. Missing values were imputed using multiple imputation. A total of 50 datasets were produced.

^a Meaningful within-person change threshold for DTSS total symptom score was ≤-1.4.

^b Meaningful within-person change threshold for DTIS physical functioning was ≤-0.8.

Abbreviations: CI, confidence interval; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; GODDESS, Gounder–Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; OR, odds ratio. Source: SpringWorks Therapeutics (2023a).

2.6.5.3 EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) instrument (version 3.0) with a 7-day recall period is a health-related quality of life (HRQoL) instrument used in international clinical trials of cancer patients. This scale was used in the DeFi trial and incorporated the global health status (GHS)/QoL scale, 5 functional scales, and 3 symptom scales (SpringWorks Therapeutics 2023a). Scores range from 0 to 100, with higher scores on functional scales and Global Health/QoL representing better functioning or QoL and high scores on a symptom scale representing greater symptomology (SpringWorks Therapeutics 2023a). A change of at least 5 to 10 in the EORTC QLQ-C30 score between groups was considered a clinically meaningful difference (Osoba et al. 1998).

In the EORTC QLQ-C30, clinically meaningful between-group differences were observed in change from baseline at Cycle 10 and were [REDACTED] for physical functioning, [REDACTED] for role functioning, and [REDACTED] for GHS/QoL, demonstrating favourable results with nirogacestat treatment compared with placebo (**Figure 2.9 A-C**) (SpringWorks Therapeutics 2023b).

[REDACTED]

[REDACTED]

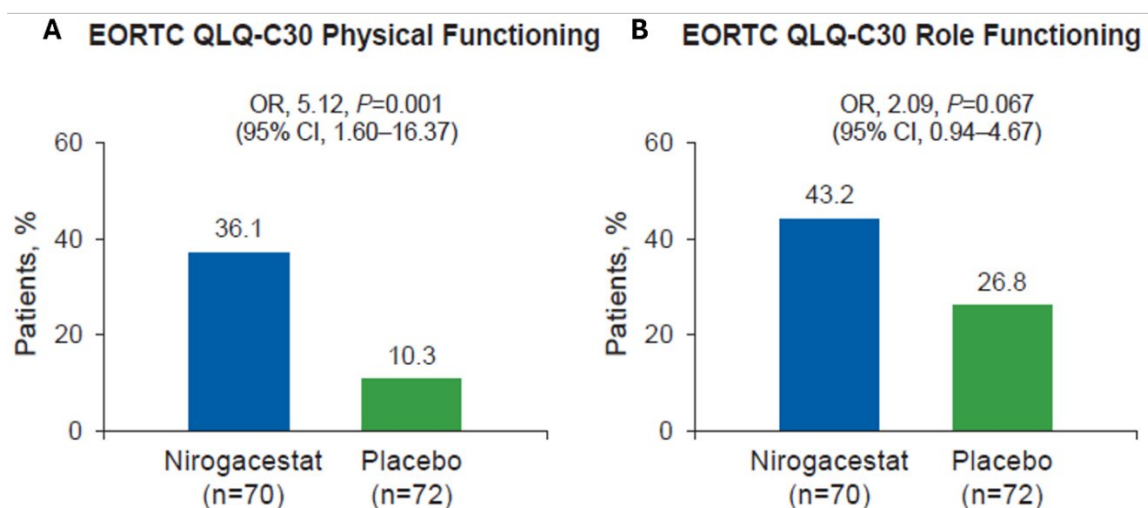
[REDACTED]

[REDACTED]

[REDACTED]

(Table 2.10) (SpringWorks Therapeutics
2023d).

Figure 2.10 Percent of participants with clinically meaningful improvement in EORTC QLQ-C30 physical functioning (A) and EORTC QLQ-C30 role functioning (B) from baseline at Cycle 10



Note: The analysis was limited to participants with baseline values that could improve by at least the meaningful change thresholds for each measure. Missing values were imputed using multiple imputation. A total of 50 datasets were produced.

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; OR, odds ratio.

Source: Kasper et al. (2023).

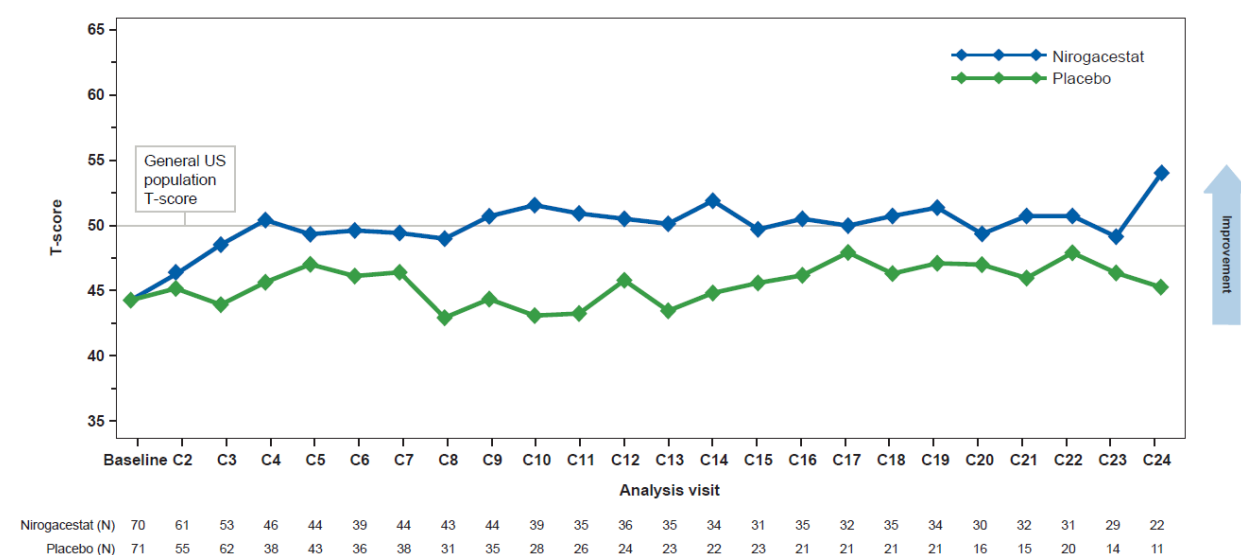
2.6.6 Exploratory PRO endpoint

2.6.6.1 PROMIS PF10a

The Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) is an instrument with a 7-day recall period used to assess self-reported capability of physical activities, including dexterity, walking or mobility, functioning of neck and back, and instrumental activities of daily living (SpringWorks Therapeutics 2023a). Higher scores indicate better physical function (T-score of 60 is one standard deviation better than the average general US population [T-score of 50]; a participant with a T-score of 40 is one standard deviation worse than the average) (SpringWorks Therapeutics 2023a).

Participants treated with nirogacestat reached the average PROMIS PF Short Form 10a (PROMIS PF10a) score observed in the general US population by Cycle 4, while the placebo group did not (**Figure 2.11**) (Kasper et al. 2023). Improvements with nirogacestat were demonstrated at the prespecified Cycle 10 and were maintained through Cycle 24, indicating favourable results with nirogacestat treatment compared with placebo (Kasper et al. 2023).

Figure 2.11 Mean PROMIS PF10a T-score through Cycle 24



Abbreviations: PROMIS PF10a, Patient-Reported Outcomes Measurement Information System Physical Function Short Form 10a.

Source: Kasper et al. (2023).

2.6.6.2 Long-term efficacy (OLE)

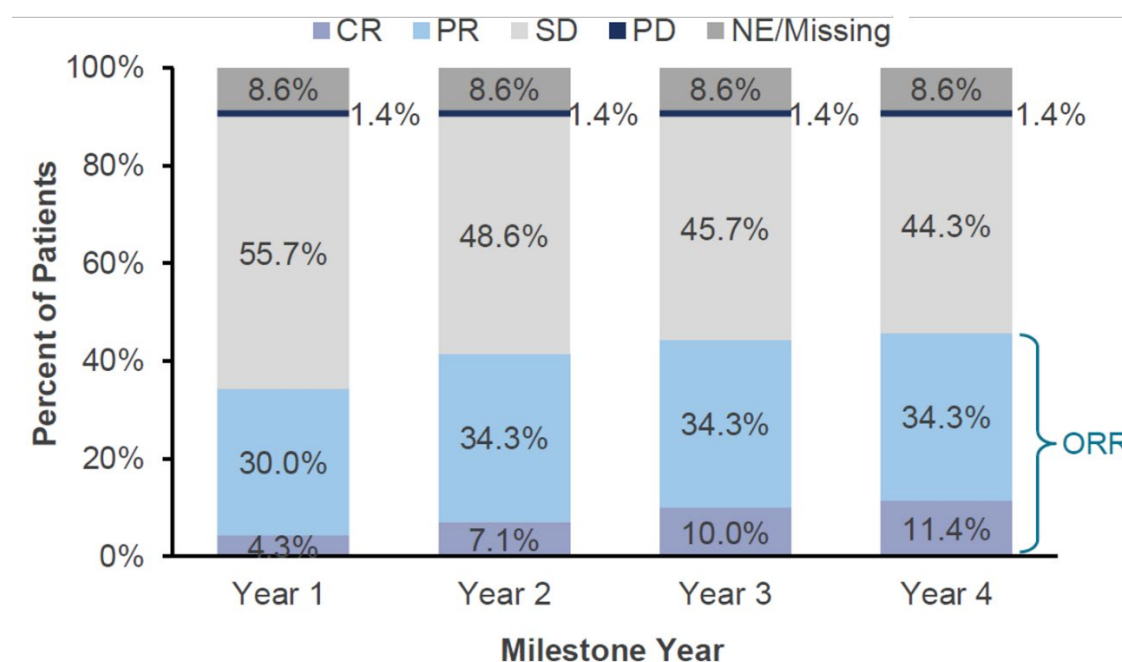
Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

The OLE phase of the study for participants who were on nirogacestat in the double-blind phase and continued to receive nirogacestat at annual landmark milestones of 1, 2, 3, and 4 years had a database lock date of 19 December 2024 (Kasper et al. 2025).

2.6.6.3 Tumour Response and Durability

The ORR increased from 34.3% at Year 1 to 45.7% at Year 4 for participants who continued receiving nirogacestat (**Figure 2.12**) (Kasper et al. 2025). A total of 8 (11.4%) participants had CR at Year 4. In the third and fourth years, 3 new incidents of CR (PR to CR) and 3 new incidents of PR were reported with nirogacestat. Longer-term treatment with nirogacestat was also associated with durable reductions in tumour size, with annual improvements in the median best percent change from baseline tumour size (**Figure 2.13**). Participants who continued to receive nirogacestat showed a median best percent reduction in tumour size of 32.3% at Year 1 (n=46), 42.5% at Year 2 (n=40), 51.3% at Year 3 (n=33), and 75.8% at Year 4 (n=15) (Kasper et al. 2025).

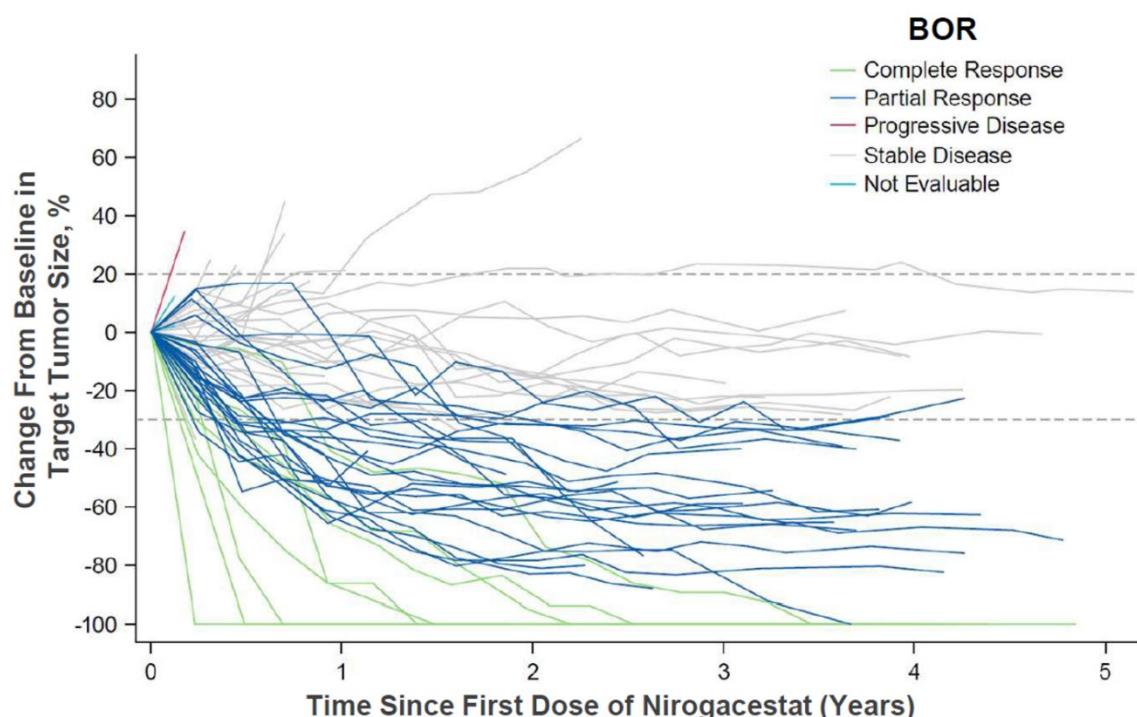
Figure 2.12 Best overall response^a in long-term analysis (19 Dec. 2024, database lock date, DeFi trial)



^a Best overall response was defined as the best response obtained across all assessments per independent central review. PR and CR required confirmation by subsequent scans. At each year, NE was 7.1% and Missing was 1.4%.

Abbreviations: CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressed disease; PR, partial response; SD, stable disease.
Source: Kasper et al. (2025).

Figure 2.13 Percent change of target tumour size from baseline through Year 4 of follow-up, DeFi trial^a



^a Results available for 66 participants; 1 patient had no tumour size assessments, and 3 participants had missing post-baseline tumour size measurements. BOR was defined as the best response obtained across all assessments per independent central review. Partial response and complete response required confirmation by subsequent scans.

Abbreviations: BOR, best overall response.

Source: Kasper et al. (2025).

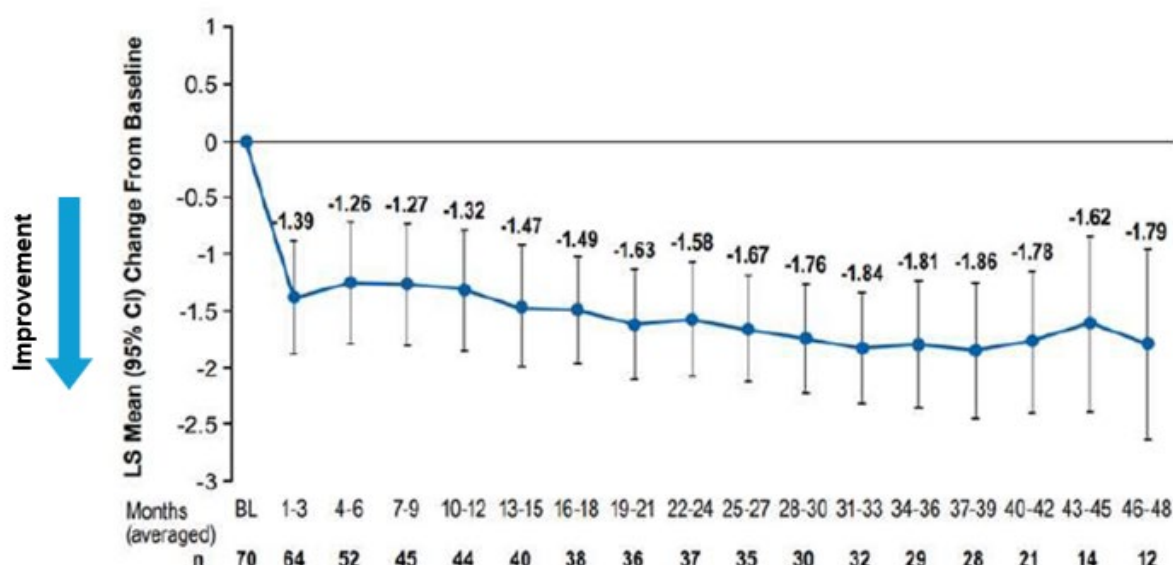
2.6.6.4 Patient-reported Outcomes

Participants who continued nirogacestat treatment had sustained overall improvement in PROs at up to 48 months of follow-up (Kasper et al. 2025). The LS mean change from baseline to 48 months in BPI-SF average worst pain intensity improved, with scores ranging from -1.26 to -1.86. The rapid decrease from baseline in BPI-SF average worst pain intensity score¹ observed at Months 1 to 3 (LS mean

² Scores range from 0-10, with higher scores indicating worse pain.

change -1.39) was sustained through to Months 46 to 48 (LS mean change -1.79), with the most substantial change occurring at months 37 to 39 (LS mean change -1.86; **Figure 2.14**).

Figure 2.14 BPI-SF Average worst pain intensity score^a up to 48 months follow-up, DeFi trial



^a Average worst pain intensity was up to a 7-day average of worst pain in the last 24 hours on a scale of 0-10. Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; LS, least-squares. Source: Kasper et al. (2025).

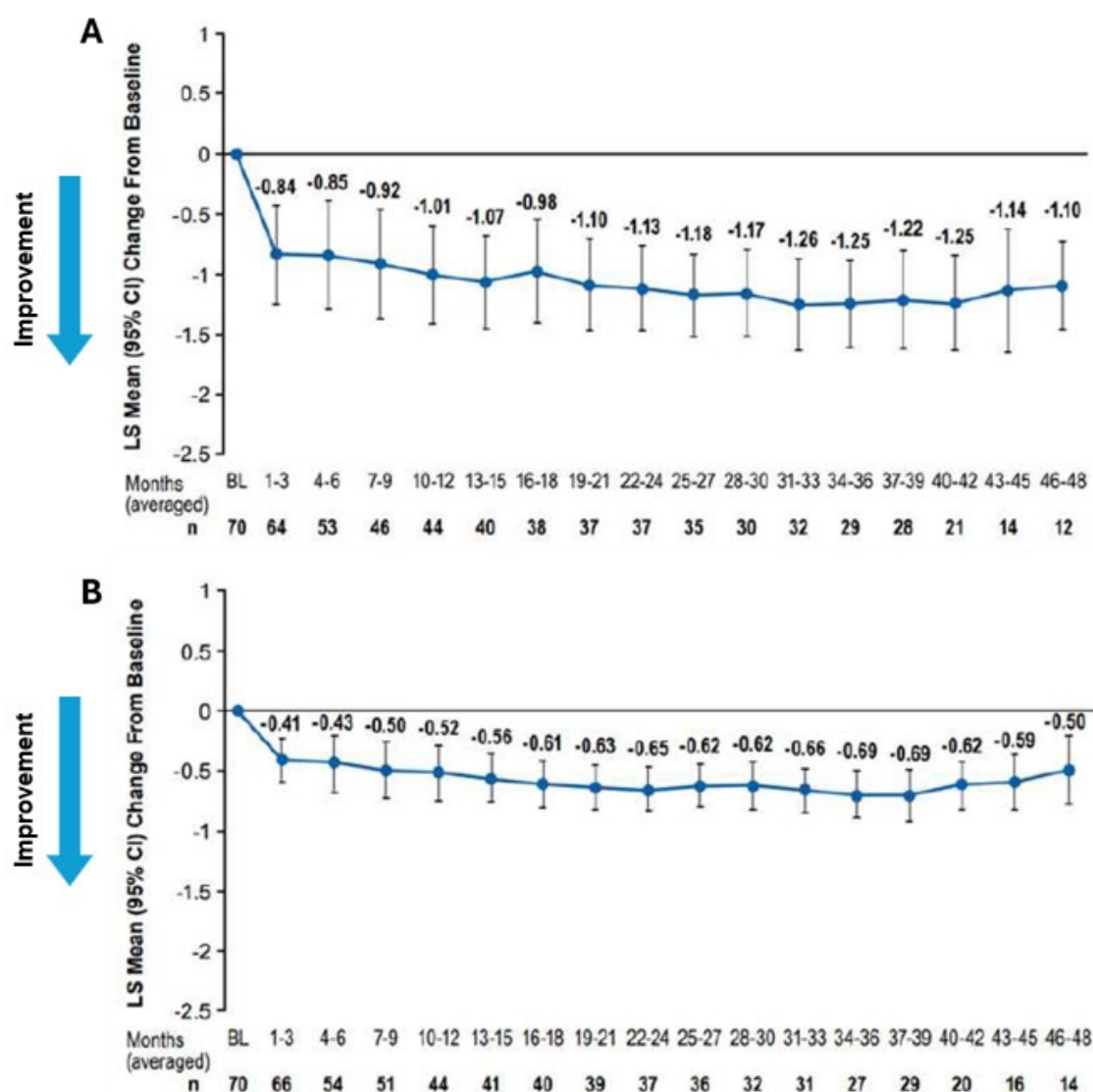
For the DTSS total symptom score,² the LS mean change from baseline to 48 months improved, with scores ranging between -0.84 to -1.26 (**Figure 2.15 A**) (Kasper et al. 2025). The decrease from baseline in DTSS total symptom score observed at Months 1-3 (LS mean change -0.84) was sustained through to Months 46 to 48 (LS mean change -1.10), with the most substantial change occurring at Months 31 to 33 (LS mean change -1.26). Additionally, the LS mean change from baseline to 48 months in DTIS physical functioning improved³ with scores ranging between -0.41 to -0.69 (**Figure 2.15 B**). The decrease from baseline in DTIS physical functioning observed at Months 1-2 (LS mean change -0.41) was sustained at Months 46 to 48 (LS mean change -0.50), with the most substantial change

² Scores range from 0-10, with higher scores indicating more severe symptom burden.

³ Assessed on a 5-point Likert scale ranging from "none of the time" to "all of the time" for frequency.

occurring at Months 34 to 36 and Months 37 to 39 (LS mean change -0.69 for both) (Kasper et al. 2025).

Figure 2.15 GODDESS DTSS Total symptom score^a (A) and DTIS Physical functioning^b (B) up to 48 months follow-up, DeFi trial



^a Total symptom score based on 7-day average of 24-hour recall scores on a scale of 0-10.

^b Physical functioning domain score was 7-day recall of a 5-point Likert scale for frequency.

Abbreviations: CI, confidence interval; DTSS, Desmoid Tumor Symptom Scale; DTIS, Desmoid Tumor Impact Scale; GODDESS, Gounder–Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; LS, least-squares.

Source: Kasper et al. (2025).

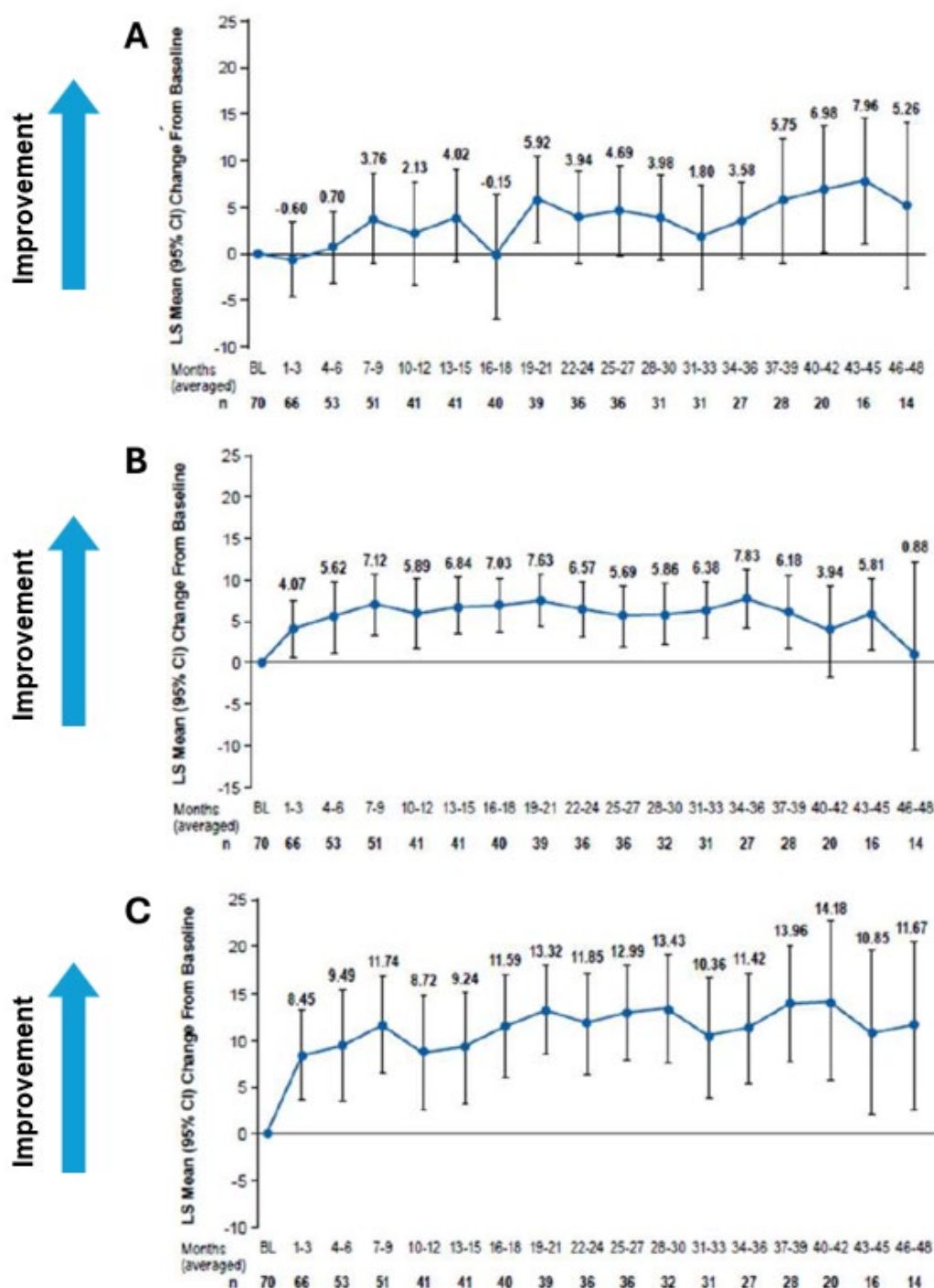
For the EORTC QLQ-C30 GHS/QoL scale,⁴ the LS mean change from baseline to 48 months improved, with scores ranging from -0.60 to 7.96 (Kasper et al. 2025). The score initially decreased at Months 1 to 3 (LS mean change -0.60) before demonstrating a sustained trend of improvement up to Months 46 to 48 (LS mean change 5.26), with the most substantial change occurring at Months 43 to 45 (LS mean change 7.96) (**Figure 2.16 A**). In addition, the EORTC QLQ-C30 physical functioning scale⁵ demonstrated an improved LS mean change from baseline ranging from 0.88 to 7.83. The rapid increase from baseline observed at Months 1 to 3 (LS mean change 4.07) was sustained throughout the study, though improvement was smallest at Months 46 to 48 (LS mean change 0.88). The most substantial change occurred at Months 34 to 36 (LS mean change 7.83) (**Figure 2.16 B**). The EORTC QLQ-C30 role functioning scale⁶ demonstrated an improved LS mean change from baseline ranging from 8.45 to 14.18. The rapid increase from baseline observed at Months 1 to 3 (LS mean change 8.45) was sustained through to Months 46 to 48 (LS mean change 11.67), with the most substantial change occurring at Months 40 to 42 (LS mean change 14.18) (**Figure 2.16 C**) (Kasper et al. 2025).

⁴ Assessed on a 7-point Likert scale, where 1=very poor and 7=excellent; scores linearly transformed to 0-100 scale.

⁵ Assessed on a 4-point Likert scale, where 1=not at all and 4=very much; scores linearly transformed to 0-100 scale.

⁶ Assessed on a 4-point Likert scale, where 1=not at all and 4=very much; scores linearly transformed to 0-100 scale.

Figure 2.16 EORTC QLQ-C30 GHS/ QoL^a (A), physical functioning (B), and role functioning^b (C) up to 48 months follow-up, DeFi trial



^a EORTC QLQ-C30 Global health status/QoL based on Likert scale ranging from 1 to 7, where high scores denote better QoL; scores linearly transformed to 0-100 scale.

^b EORTC QLQ-C30 physical functioning and role functioning based on Likert scale ranging from 1 to 4, where higher scores denote improved physical and role functioning; scores linearly transformed to 0-100 scale. Abbreviations: BL, baseline; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer-Core 30; GHS, global health status; LS, least-squares; QoL, quality of life.

Source: Kasper et al. (2025).

2.7 Subsequent treatments used in the relevant studies

Please note that this section is not applicable to the DeFi trial, as no subsequent treatments were used.

2.8 Subgroup analysis

Prespecified subgroup analyses were conducted to determine whether PFS and ORR findings in the entire ITT population were consistent across participant demographic and disease-related subgroups. Subgroups were defined according to sex, target-tumour location, focality, treatment status, previous treatments (surgery, chemotherapy, tyrosine kinase inhibitors [TKIs]; separately), genetic mutation status (adenomatous polyposis coli [APC], catenin beta 1 [CTNNB1]; separately), and family history of familial adenomatous polyposis (FAP) (Gounder et al. 2023a).

Prespecified regional subgroup analyses were also conducted to understand consistency and generalisability of PFS and ORR results in Europe relative to the ITT population.

Please refer to **Appendix C** for the results of subgroup analyses.

2.9 Meta-analysis

Efficacy data supporting the use of nirogacestat for the treatment of DT are provided by a single Phase 3 study (DeFi Trial). Therefore, a meta-analysis was not conducted. For further details on the identification, selection, and synthesis of clinical evidence, please refer to **Appendix B**.

2.10 Indirect and mixed treatment comparisons

Please note that an indirect treatment comparison (ITC) was not necessary for this submission given the most relevant comparator was best supportive care (BSC) which was informed by the placebo arm of the DeFi trial.

2.11 Adverse reactions

2.11.1 Extent of exposure

A summary of the treatment exposure and relative dose intensity is presented in **Table 2.11**.

The safety assessment comprised 141 participants who received at least one dose of nirogacestat or placebo (Gounder et al. 2023a). The median duration of exposure was [REDACTED] in the nirogacestat arm and [REDACTED] in the placebo arm. [REDACTED]

The median relative dose intensity [REDACTED] for nirogacestat and [REDACTED] for placebo (Gounder et al. 2023a, SpringWorks Therapeutics 2023b).

Table 2.11 Study treatment exposure, DeFi trial (safety population, double-blind phase)

	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Duration of study drug exposure (months) ^a			
Mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]
Min, max	[REDACTED]	[REDACTED]	[REDACTED]
Participants who received study treatment for at least:			
1 cycle, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
2 cycles, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
3 cycles, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
4 cycles, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
5 cycles, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
6 cycles to <13 cycles, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
13 cycles or longer, n (%)	[REDACTED]	[REDACTED]	[REDACTED]
Actual dose intensity (mg/day) ^b			
Mean (SD)	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]
Min, max	[REDACTED]	[REDACTED]	[REDACTED]

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	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Relative dose intensity (%) ^c			
Mean (SD)	██████████	██████████	██████████
Median	██████	██████	██████
Min, max	██████████	██████████	██████████

Table 2.12 Summary of treatment-emergent adverse events, DeFi trial (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Adverse events (any grade) ^a			
TEAEs			
Maximum grade			
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			
TRAEs			
Maximum grade			
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			
Treatment-emergent SAEs			
Maximum grade			
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			
Treatment-related SAEs			
Maximum grade			
Grade 1			
Grade 2			
Grade 3			
Grade 4			
Grade 5			
Grade ≥3 TEAEs			
Grade ≥3 TRAEs			
TEAEs leading to death			
TEAEs leading to study treatment discontinuation			

^a Irrespective of relation to study product (includes TEAEs, TRAEs, and TEAEs not related to study treatment). Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Source: SpringWorks Therapeutics (2023b).

2.11.3 Treatment-emergent adverse events

TEAEs of any grade that were reported in at least 15% of participants in either treatment arm are presented in **Table 2.13**.

The TEAEs of diarrhoea, hypophosphatemia, hypokalaemia, and skin events were frequently managed by dose modifications, dose interruptions, and medications, including anti-diarrhoeal agents, supplementation, topical glucocorticoids, and antibiotics (Gounder et al. 2023a).

Table 2.13 Any-grade TEAEs occurring in ≥15% of participants in either treatment arm (safety population)

TEAE Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
TEAE (any grade)			
Diarrhoea	58 (84)	25 (35)	83 (59)
Nausea			
Fatigue			
Hypophosphatemia			
Maculopapular rash	22 (32)	4 (6)	26 (18)
Stomatitis			
Headache			
Dermatitis acneiform			
Vomiting			
Ovarian failure ^a			
Rash			
Hot flush			
Alopecia			
ALA increased		6 (8)	
COVID-19			
Weight gain			
Cough			
Abdominal pain			
ASA level increased		8 (11)	
Dyspnoea			
Premature menopause ^a			
Decreased appetite			
Dry skin			
Tumour pain			

^a The frequency of female-specific TEAEs are based on the total number of participants in the Safety Population. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Source: SpringWorks Therapeutics (2023b).

A summary of grade 3 or higher TEAEs that occurred in at least 2 participants is presented in **Table 2.14**. Grade 3 or higher TEAEs were reported in participants in the nirogacestat arm and participants in the placebo arm.

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The most frequently reported (>5% of participants) grade 3 or higher TEAEs in the nirogacestat arm were [REDACTED] Grade 3 or higher events reported by at least 2 participants in the placebo arm at a higher frequency than the nirogacestat arm included [REDACTED]

Table 2.14 Grade ≥3 TEAEs occurring in ≥2 participants (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Any TEAE with CTCAE ≥3	[REDACTED]	[REDACTED]	[REDACTED]
Diarrhoea	11 (16)	1 (1)	12 (9)
Folliculitis	[REDACTED]	[REDACTED]	[REDACTED]
Rash maculopapular	[REDACTED]	[REDACTED]	[REDACTED]
Stomatitis	[REDACTED]	[REDACTED]	[REDACTED]
Hypophosphatemia	2 (3)	0 (0)	2 (1)
Weight increased	[REDACTED]	[REDACTED]	[REDACTED]
ALA increased	2 (3)	1 (1)	3 (2)
ASA increased	2 (3)	1 (1)	3 (2)
Anaemia	[REDACTED]	[REDACTED]	[REDACTED]
Hypertension	[REDACTED]	[REDACTED]	[REDACTED]
Fatigue	[REDACTED]	[REDACTED]	[REDACTED]
Tumour pain	[REDACTED]	[REDACTED]	[REDACTED]
COVID-19	[REDACTED]	[REDACTED]	[REDACTED]
Sepsis	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
Source: SpringWorks Therapeutics (2023b).

2.11.4 Serious adverse events

A summary of serious adverse events (SAEs) is presented in **Table 2.15** [REDACTED]

[REDACTED] The only SAE reported in greater than 1 participant in the nirogacestat arm was [REDACTED]

SAEs reported by greater than 1 participant in the placebo arm included [REDACTED]

Table 2.15 Summary of treatment-emergent SAEs (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Any treatment-emergent SAE	██████	██████	██████
Premature menopause	3 (4)	███	███
Tumour haemorrhage	███	███	███
Tumour pain	███	███	███
Abdominal abscess	███	███	███
Abdominal infection	███	███	███
Abdominal pain	███	███	███
Appendicitis	███	███	███
Atrial fibrillation	███	███	███
Cholecystitis	███	███	███
Groin abscess	███	███	███
Haematuria	███	███	███
Infected cyst	███	███	███
Ovarian failure	███	███	███
Rash maculopapular	███	███	███
Small intestinal obstruction	███	███	███
Spindle cell sarcoma	███	███	███
Stomatitis	███	███	███
Sepsis	███	███	███
COVID-19	███	███	███
Diarrhoea	███	███	███
Drug-induced liver injury	███	███	███
Duodenal perforation	███	███	███
Gastrointestinal fistula	███	███	███
Infection	███	███	███
Pulmonary embolism	███	███	███

Abbreviations: SAE, serious adverse event.
Source: SpringWorks Therapeutics (2023b).

study treatment are presented in **Table 2.16**. Serious AEs related to
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 tumours (DT) [ID6453]

Table 2.16 SAEs related to study treatment (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Any serious TEAE related to study treatment			
Premature menopause	3 (4)		
Atrial fibrillation			
Cholecystitis			
Groin abscess			
Infected cyst			
Ovarian failure			
Rash maculopapular			
Stomatitis			

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Source: (SpringWorks Therapeutics 2023b).

2.11.5 Treatment-related adverse events

A summary of treatment-related adverse events (TRAEs) occurring in greater than 3 participants in the nirogacestat arm is presented in **Table 2.17**. TRAEs related to study treatment were reported in [REDACTED] in the nirogacestat arm and [REDACTED]. The most frequently reported (>25% of participants) TRAEs related to study treatment in the nirogacestat arm were [REDACTED].

Table 2.17 TRAEs occurring in >3 participants in the nirogacestat arm (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Any TEAE related to study treatment			
Diarrhoea			
Nausea			
Fatigue			
Hypophosphatemia			
Rash maculopapular			
Stomatitis			
Hot flush			

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Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Alopecia			
Ovarian failure			
Vomiting			
Rash			
ALA increased			
Dermatitis acneiform			
Premature menopause			
Dry skin			
Headache			
ASA increased			
Folliculitis			
Pruritus			
Dry mouth			
Blood follicle stimulating hormone increased			
Decreased appetite			
Epistaxis			
Abdominal pain			
Constipation			
Menstruation irregular			
Gastro-oesophageal reflux disease			
Heavy menstrual bleeding			
Hidradenitis			
Hypokalemia			
Weight decreased			
Cough			
Nasal congestion			

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
Source: SpringWorks Therapeutics (2023b).

A summary of TRAEs with Common Technology Criteria for Adverse Events

(CTCAE) grade 3 or higher occurring in 2 or more participants is presented in **Table**

2.18. A total of [REDACTED] in the nirogacestat arm experienced grade 3 TRAEs and [REDACTED] in the placebo arm reported maximum grade 3 TRAEs (SpringWorks Therapeutics 2023b). [REDACTED]

[REDACTED] The grade 3 or higher TRAEs reported by greater than 2 participants in the nirogacestat arm were [REDACTED]

[REDACTED] (SpringWorks Therapeutics 2023b).

Table 2.18 Grade ≥3 TRAEs occurring in ≥2 participants in the nirogacestat arm

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Any TEAE with CTCAE ≥ 3 related to study treatment	██████	██████	██████
Diarrhoea	██████	██████	██████
Folliculitis	██████	██████	██████
Rash maculopapular	██████	██████	██████
Stomatitis	██████	██████	██████
ALA increased	2 (3)	0 (0)	2 (1)
ASA increased	2 (3)	0 (0)	2 (1)
Fatigue	██████	██████	██████
Hypophosphataemia	2 (3)	0 (0)	2 (1)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Source: SpringWorks Therapeutics (2023b).

2.11.5.1 Diarrhoea

In the double-blind phase of the DeFi study, diarrhoea was reported in 84% of participants receiving nirogacestat compared to 35% in participants receiving placebo. Grade 3 events occurred in 16% and 1% of participants, respectively (SpringWorks Therapeutics 2025f). Grade 2 or lower diarrhoea resolved in 74% of participants who continued on nirogacestat treatment. The median time to first onset of diarrhoea in participants receiving nirogacestat was 9 days (range 2-234 days). Diarrhoea led to dose reduction in 10% of participants and treatment discontinuation in 7% receiving nirogacestat (SpringWorks Therapeutics 2025f).

2.11.5.2 Skin and subcutaneous tissue disorders

In the double-blind phase of the DeFi study, dermatologic reactions were reported at a higher incidence in participants receiving nirogacestat than in those receiving placebo; they included maculopapular rash (32% vs. 6%), hidradenitis (9% vs. 0%), and folliculitis (13% vs. 0%) (SpringWorks Therapeutics 2025f). The median time to rash events was 22 days (range 2-603 days). Skin and subcutaneous disorders led to dose reduction in 9% of participants receiving nirogacestat, including maculopapular rash in 4% and hidradenitis in 3%. Maculopapular rash led to treatment discontinuation in 1% (SpringWorks Therapeutics 2025f).

2.11.5.3 Ovarian dysfunction

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Ovarian dysfunction (OD; defined by the Medical Dictionary for Regulatory Activities [MedDRA] preferred terms of amenorrhea, premature menopause, menopause, and ovarian failure) was reported in 75% (27/36) of women of reproductive potential who received nirogacestat and no participants (0/37) who received placebo as of the primary analysis (Gounder et al. 2023a). There were 3 serious adverse reactions of OD, all premature menopause, representing 11% of all participants reporting OD (SpringWorks Therapeutics 2025f). The median time to first onset of OD was 8.9 weeks (range 1 day-54 weeks), and the overall median duration was 18.9 weeks (range 11 days-215 weeks). Ovarian dysfunction has been reported to resolve in 79% of women of childbearing potential during treatment (SpringWorks Therapeutics 2025f).

2.11.5.4 Electrolyte abnormalities

Electrolyte abnormalities were reported in participants receiving nirogacestat in the double-blind phase of the DeFi study, including hypophosphataemia (43%) and hypokalaemia (12%), compared to 7% and 1%, respectively, in participants receiving placebo (SpringWorks Therapeutics 2025f). Median time to first onset of hypophosphataemia and hypokalaemia was 15 days (range 1-833 days) and 15 days (range 1-57 days), respectively. Grade 3 events of hypophosphataemia and hypokalaemia occurred in 3% of participants receiving nirogacestat compared to no participants receiving placebo. Hypophosphataemia and hypokalaemia led to dose reduction in 4% and 1% of participants receiving nirogacestat, respectively. Hypophosphataemia led to dose discontinuation in 1% of participants receiving nirogacestat (SpringWorks Therapeutics 2025f).

2.11.5.5 Hepatic abnormalities

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were reported in 19% and 17%, respectively, of participants receiving nirogacestat in the double-blind phase of the DeFi study compared to 8% and 11%, respectively, in participants receiving placebo (SpringWorks Therapeutics 2025f). Median time to first onset of ALT and AST elevations was 22 days (ALT range 8-924 days; AST range 1-1023 days). Grade 3 ALT and AST elevations (>5 x upper limit of normal [ULN]) occurred in 3% of participants treated with nirogacestat compared to 1% in

the placebo arm. Alanine aminotransferase and AST elevations each led to dose reduction in 1% of participants receiving nirogacestat. Alanine aminotransferase and AST elevations led to dose discontinuation in 4% and 3% of participants receiving nirogacestat, respectively (SpringWorks Therapeutics 2025f).

2.11.5.6 Non-melanoma skin cancers

Non-melanoma skin cancers were reported at a higher incidence in participants receiving nirogacestat than in those receiving placebo in the double-blind phase of the DeFi study, including squamous cell carcinoma (3% vs. 0%) and basal cell carcinoma (1% vs. 0%), with one patient reporting both types of non-melanoma skin cancer. An additional 2 cases of non-melanoma skin cancer were reported outside of the double-blind phase of the DeFi study (SpringWorks Therapeutics 2025f).

2.11.5.7 Proximal renal tubule effect

Glycosuria and proteinuria were observed in 52% and 46%, respectively, of participants receiving nirogacestat in the double-blind phase of the DeFi study, compared with 1% and 39%, respectively, in participants receiving placebo (SpringWorks Therapeutics 2025f). Median time to onset of glycosuria and proteinuria was 85 days (range 55-600 days) and 72 days (range 38-937 days), respectively. There was 1 patient in the DeFi study that reported renal tubular disorder with increased urinary excretion of uric acid, glucose and phosphate, but no excess excretion of low molecular weight proteins (beta2-microglobulin) or any change in renal function. The event was managed with dose reduction (SpringWorks Therapeutics 2025f).

2.11.5.8 Bone fracture

In the double-blind phase of the DeFi study, bone fractures were reported in 6% of participants receiving nirogacestat compared with no participants receiving placebo. All reports of bone fracture were non-serious and grade 1 or 2 (SpringWorks Therapeutics 2025f). [REDACTED]

[REDACTED] The median time to first onset of bone fracture events in participants receiving nirogacestat was 125 days (range 1-739 days). Bone fracture events did not lead to dose reduction or

treatment discontinuation in any participants receiving nirogacestat (SpringWorks Therapeutics 2025f).

2.11.6 TEAEs leading to dose reduction, dose interruption, and treatment discontinuation

Dose modifications, including dose interruptions and/or reductions, were experienced by [REDACTED] in the nirogacestat arm and [REDACTED] in the placebo arm, [REDACTED] (SpringWorks Therapeutics 2023b).

The TEAEs that most frequently ($\geq 5\%$) led to any dose modification (interruption or reduction) in the nirogacestat arm were [REDACTED]

[REDACTED] Of the most frequent TEAEs leading to dose modification in the nirogacestat arm, those that were grade 3 severities included [REDACTED]

The TEAEs that most frequently ($\geq 5\%$) led to dose interruption in the nirogacestat arm were diarrhoea [REDACTED] and rash maculopapular (7 participants [10%]). Of these most frequent TEAEs leading to dose interruption, those that were grade 3 severity included [REDACTED] (SpringWorks Therapeutics 2023b).

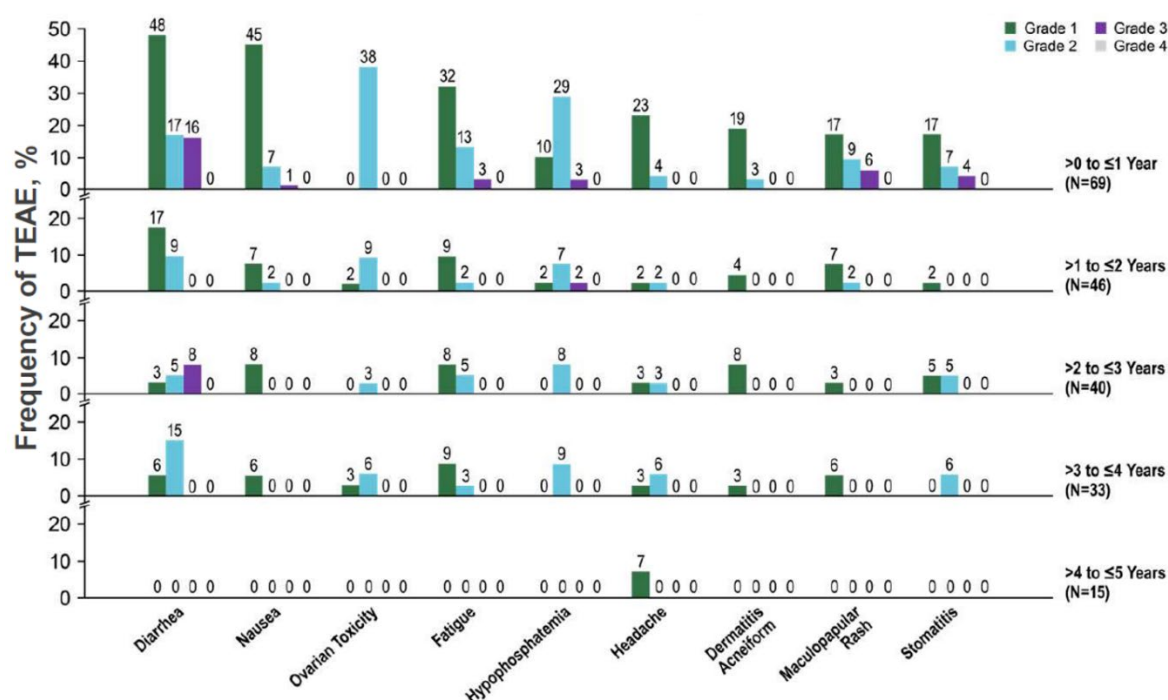
Discontinuation of the study treatment due to TEAEs occurred in [REDACTED] participants in the nirogacestat group and [REDACTED] participants in the placebo group (SpringWorks Therapeutics 2023b). [REDACTED]

[REDACTED] The TEAEs that led to the discontinuation of study treatment by more than 1 participant in the nirogacestat arm were [REDACTED] (SpringWorks Therapeutics 2023b).

2.11.7 Long-term safety (OLE)

The 4-year safety follow-up for participants who received nirogacestat in the double-blind phase and continued to receive nirogacestat in the OLE phase (n=69), were consistent with the primary analysis (Kasper et al. 2025). Most events were grade 1 or 2, and first onset occurred in the first year of the treatment course (**Figure 2.17**). Frequently reported all-grade TEAEs were diarrhoea, nausea, OD, fatigue, hypophosphatemia, and headache. Incidence and severity of frequently reported TEAEs decreased in Years 2 to 4 (Kasper et al. 2025). There were 3 participants who previously reported an OD event reported an additional event. Dose reductions due to TEAEs occurred in 5 participants between Years 2 and 3, but none occurred after Year 3 (Kasper et al. 2025).

Figure 2.17 New onset of TEAEs by greatest severity^a per year through 4-year follow-up, DeFi trial



^a New-onset TEAEs reported by ≥15% of participants are listed in order of frequency. TEAEs were defined as events occurring or worsening after the initiation of nirogacestat through 30 days after the last dose or the date of the patient's last dose before starting another treatment. Abbreviations: TEAE, treatment-emergent adverse event. Source: Kasper et al. (2025).

2.12 Ongoing studies

There are no further data-cuts for the DeFi trial that will provide additional evidence in the next 12 months for the indication being appraised.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Overall efficacy conclusions

The DeFi trial was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled study that demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, PFS, compared to placebo (SpringWorks Therapeutics 2023b). The nirogacestat arm demonstrated a 71% reduction in the risk of disease progression (HR 0.29; 95% CI 0.15, 0.55; $p < 0.001$)

[REDACTED]

[REDACTED]

[REDACTED]

Key secondary endpoints also exhibited statistically significant improvements in the nirogacestat arm compared to the placebo arm. The ORR in the nirogacestat arm demonstrated a statistically significant improvement over placebo in (41% vs. 8%; $p < 0.001$). Among participants treated with nirogacestat, 7% were in CR and 34% were in PR compared with no participants in CR and 8% in PR among those in the placebo group (see **Section 2.6.2**) (SpringWorks Therapeutics 2023b). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Statistically and clinically significant improvements occurred as early as Cycle 2 and were generally sustained throughout the double-blind phase (Gounder et al. 2023c, Mease et al. 2011, Osoba et al. 1998). These findings highlight the rapid and durable impact of nirogacestat on physical functioning and symptom burden, which is of key importance due to the chronic pain, impaired mobility, and psychosocial stress associated with DT. The significant and consistent PRO benefits demonstrate that nirogacestat offers improvement in participants QoL. Overall, the durability of the PFS and response benefit over a time scale of up to 2 years, combined with the statistically significant findings observed for all PROs at Cycle 10, support a clinically meaningful benefit conferred by nirogacestat.

2.13.1.1 Long-term efficacy assessment

The OLE phase of the study demonstrated clinically meaningful improvements in efficacy in participants who remained on nirogacestat from the double-blind phase. Consistent with the double-blind phase, long-term treatment with nirogacestat was associated with improved ORR, further reduction in tumour size, and sustained PRO gains (few progressions were observed and the probability of being event-free remained high at Months 12, 24, 36, and 48, supporting sustained clinical benefit over time for participants who continued to receive treatment with nirogacestat). Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

including pain, DT symptom burden, physical functioning, role functioning, and HRQoL) (Kasper et al. 2025).

2.13.1.2 Disease modifying impact of nirogacestat

Overall, nirogacestat represents an efficacious treatment option for patients with progressing DT, offering significant benefits in tumour control, symptom relief, and QoL. Importantly, nirogacestat is a proven disease-modifying therapy, with clinical evidence demonstrating its durable disease-modifying effect. Imaging data from its Phase 2 study showed measurable drug-induced regressions of tumour volume in 10 out of 11 evaluated participants who had volumetric responses by MRI (Kummar et al. 2017, O'Sullivan Coyne et al. 2022). These results were corroborated in the Phase 3 DeFi trial, where nirogacestat was associated with significant reductions in MRI-assessed tumour volume (median best percent change of largest target tumour: -58.9% for nirogacestat vs. +13.8% for placebo, $p < 0.001$) (Alcindor et al. 2023). Furthermore, there were no additional radiographic progressions after the first year of treatment in the nirogacestat arm, even up to a 4-year treatment landmark milestone (Kasper et al. 2025).

Imaging data from the DeFi trial also show significant reduction in tumour activity with nirogacestat as evidenced by T2 signal intensity (best percent change in T2 hyperintensity signal ratio: -55.1% for nirogacestat vs. -21.4% for placebo, $p < 0.001$), suggesting decreased disease activity at the cellular level (Alcindor et al. 2023, Cassidy et al. 2020, Zanchetta et al. 2021). Changes at the cellular level were also observed in a retrospective analysis of 7 patients with DT who received 9 (21-day) cycles of treatment with nirogacestat in an open-label, Phase 1 study. A biopsy performed on a patient who stopped treatment after 42 months in the absence of progression showed decreased tumoral cellularity and more densely collagenous background compared with the pre-treatment biopsy. The study reported that this patient remained off therapy with no evidence of clinical or radiographic progression for over 15.9 months. In total, 4 participants from the study stopped treatment and continued to be progression-free between 11 and 53 or more months, leading the study authors to suggest that there could be prolonged disease control even after therapy discontinuation (Villalobos et al. 2018). This is in line with discussions with clinical advisors, where it was understood that after a disease-modifying treatment Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

like nirogacestat, the tumour becomes inactive and remains as scar tissue, which does not have the structure to grow. These clinical results collectively establish nirogacestat as a disease-modifying therapy that can reduce tumour burden/volume and halt disease progression, even allowing patients to be progression-free while off treatment.

2.13.2 Overall safety conclusions

Nirogacestat was found to have a manageable safety profile and was tolerated by the majority of participants (SpringWorks Therapeutics 2023b). There were few grade 3 or higher AEs observed in the study, with 95% of all AEs being reported as grade 1 or 2 (Gounder et al. 2023a). Treatment with nirogacestat in women of childbearing potential was observed to result in AEs consistent with OD in 75% of participants in the DeFi trial (Gounder et al. 2023a, SpringWorks Therapeutics 2025f). This finding may be attributable to nirogacestat disrupting the Notch signalling that is required for ovarian follicular cycling, as a result, symptoms including irregular menses, amenorrhea, and vasomotor symptoms may arise (Gounder et al. 2023a, Vanorny and Mayo 2017). Given that the DeFi trial included a large number of women who were of childbearing potential, amenorrhea was a safety signal identified in the trial. This finding may be a by-product of the patient population in the trial and may not be observed to the same degree among a trial population that includes older patients. However, symptoms of OD were observed to resolve in 79% of participants who continued on nirogacestat treatment in the DeFi trial and discontinuation of treatment with nirogacestat resolved OD symptoms in all participants (SpringWorks Therapeutics 2025f).

2.13.2.1 Long-term safety assessment

The safety profile of participants who were on nirogacestat and continued to receive nirogacestat in the OLE phase was consistent with the primary analysis, with primarily grade 1 or 2 events reported that occurred early after commencing treatment (within the first year) (Kasper et al. 2025). These findings provide further support for the manageable safety profile of nirogacestat. Overall, fewer TEAEs led to dose reductions in OLE phase (Kasper et al. 2025).

2.13.3 Strengths and limitations of the clinical evidence base

Overall, the DeFi trial provides an appropriate evidence base for assessment of the clinical and cost-effectiveness of nirogacestat.

The strengths of the clinical evidence base are as follows:

- The DeFi trial is a robust, high-quality study that was used in the marketing authorisation submission.
- The study population is consistent with the population in the NICE scope.
- The DeFi trial is a Phase 3, randomised, multi-centre, double-blind, placebo-controlled study. This study design minimises the risk of bias and confounding variables, thereby enhancing the internal validity of the study.
 - The participants and investigators were blinded to the treatments administered, which mitigates the placebo effect and observer bias.
 - The trial was conducted across multiple sites in 7 countries, which enhances the external validity by supporting the generalisability of the findings across different clinical settings.
- The data are sufficiently mature to demonstrate the effects of nirogacestat on PFS, ORR, and change in PRO outcomes and provide sufficient certainty around the clinical benefits of nirogacestat compared to placebo.
- Subgroup analyses of PFS demonstrated consistent effects across subgroups defined by sex, tumour location, focality, treatment status, previous treatments, genetic mutation status, and history of FAP.

The limitations of the clinical evidence base are as follows:

- As discussed in **Section 2.3.3**, the DeFi trial applied a stricter minimum progression threshold compared to other studies [e.g., the sorafenib study used a lower threshold of 10% to measure disease progression (Gounder et al. 2018a)] and thus represents a more difficult to treat population compared to other published studies.
- The DeFi trial did not collect EQ-5D data and due to the rarity of DT, no published literature was available to inform health state utility values. Therefore, values informing the cost-effectiveness model were sourced from soft tissue sarcoma (STS) studies. Soft tissue sarcoma was deemed to be a

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reasonable disease analogue as DT is a type of soft tissue tumour and STS was identified as a disease analogue by NICE given their similarities in origins, clinical presentation, symptoms, diagnostic and treatment pathway, and management by oncologists/STS specialists (Desmoid Tumor Working Group 2020, Huss et al. 2013, Kasper et al. 2011, Mercier et al. 2020, Penel et al. 2016).

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was performed in December 2022 and updated in July 2024 and May 2025 to identify cost-utility analyses (CUAs), cost-effectiveness analyses (CEAs), and measurement and valuation studies (i.e., costs) for pharmacological therapies in patients with desmoid tumours (DT). The search strategy was developed, and study eligibility was assessed according to pre-specified population, intervention, comparator, outcomes, and study design (PICOS) criteria. The detailed SLR methodology and results can be found in **Appendix E**.

Briefly, the initial database search on 29 December 2022 identified 1,489 records. After removing 860 duplicates, 629 records were screened at the title and abstract stage, with 536 excluded. The remaining 93 full-text reports were assessed for eligibility. An additional 106 records were identified through grey literature searches, of which 77 were excluded at the title and abstract stage. The remaining 29 reports were assessed for eligibility. Overall, 120 reports were excluded at the full-text stage, resulting in 2 reports representing 2 unique studies included as of the December 2022 search. The search update conducted on 11 July 2024 identified 50 additional deduplicated records. Of these, 44 were excluded during title and abstract screening, and 6 full-text reports were assessed for eligibility. Two (2) reports were excluded with reasons during full-text screening. An additional 80 records were identified through grey literature searches, of which 44 were excluded at the title and abstract stage. The remaining 36 reports were assessed for eligibility, with 35 excluded for various reasons. In total, the original and updated searches identified 7 records reporting on 7 unique studies as of July 2024. The final search update conducted on Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

13 May 2025 identified 25 additional deduplicated records, of which 17 were excluded during title and abstract screening. Eight (8) full-text reports were excluded with reasons during full-text screening. An additional 53 records were identified through grey literature searches; 20 were excluded at the title and abstract stage. The remaining 33 reports were sought for retrieval, 1 of which was not retrievable. Of the 32 records assessed for eligibility, 31 were excluded for various reasons. In total, 1 report, representing 1 unique study, was identified from this SLR update, resulting in a combined 8 reports, representing 8 unique studies, included in the DT SLR.

Of the 8 unique studies identified in the SLR, no economic evaluations or studies describing pharmacoeconomic models for any treatment for patients with DT were identified.

3.2 Economic analysis

No economic evaluations were identified in the SLR that focused on treatment for patients with DT, and a literature search of previous health technology assessment (HTA) submissions (e.g., NICE, Canada's Drug Agency [CDA], Program Budget Advisory Committee [PBAC], etc.) did not identify any completed or accepted submissions for DT; therefore, a de novo model was required to assess the cost-effectiveness of nirogacestat compared with relevant comparators.

3.2.1 Participant population

The participant population included in this economic evaluation aligns with the decision problem outlined in **Section 1**. This is in line with the marketing authorisation for nirogacestat and the final NICE scope.

The target population in the DeFi trial was adult patients with progressing DT. According to clinical experts in DT, compared to patients enrolled in observational studies that were placed on active surveillance as a first-line treatment approach, the participants in the DeFi trial represent a subset of the DT population with the most active and severe disease that cannot be sufficiently managed with a 'watch and wait' approach (e.g., spontaneous regression is unlikely to happen and thus an active/systemic treatment is recommended to manage the disease, progression is likely to be faster without a "plateau," etc.) (Colombo et al. 2025). An estimated 40%

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of patients with DT experience progression, including 30% of patients with DT who cycle through periods of progression and resolution and 10% of patients who progress rapidly (Bektas et al. 2023). Therefore, up to 40% of all patients with DT would fall into the target population for nirogacestat. In alignment with the expected indication and reimbursement request for nirogacestat in the UK, the baseline characteristics of the intent-to-treat (ITT) population of the DeFi trial were used to inform the patient characteristics for the reference case. The baseline characteristics of ITT participants in the DeFi trial are expected to reflect those of adult patients seen in UK real-world clinical practice for progressing DT, as confirmed by UK clinical advisers. Of note, the trial included study sites in the UK (Gounder et al. 2023a). **Table 3.1** summarises patient characteristics used in the analysis, such as age, body surface area (BSA), and proportion of females.

Table 3.1 Patient characteristics in the DeFi trial and used in the model (reference case)

Patient Characteristic	DeFi Trial (ITT population; N=142)
Mean age, years (SE)	37.20 (1.14)
Mean BSA, m ² (SE)	1.90 ^a (0.02)
Female (%)	64.8%

^a Mean BSA was calculated based on individual patient-level data; each patient's BSA was calculated using the following formula: square root of [(baseline weight [kg] × baseline height [cm])/3600].

Abbreviations: BSA, body surface area; ITT, intent-to-treat; SE, standard error.

Source: SpringWorks Therapeutics (2023b).

3.2.2 Model structure

There have been no previous economic studies or accepted or completed HTA submissions for any treatment for patients with DT. Therefore, a de novo Markov cohort model (or more specifically, a semi-Markov model because the per-cycle probability of death changes over time) was developed to capture all costs and outcomes associated with nirogacestat and best supportive care (BSC) or placebo for patients with progressing DT. Considering the variability in patient experiences and unpredictability of the disease, a simple 3-state model (e.g., pre-progression, post-progression, and death) was not appropriate to sufficiently capture the natural history of DT and the benefits and quality of life (QoL) gains associated with treatment. Within the pre-progression state, patients can experience different outcomes (e.g., varying degrees of improvements in pain and symptom burden

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which would translate to differences in healthcare costs and health-related QoL/utilities) related to tumour size changes. The model, therefore, was developed to reflect the different levels of tumour response (as defined by the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1); that patients with progressing DT will experience from start of systemic treatment until death (Eisenhauer et al. 2009). This would enable the pre-progression state to incorporate stable disease, partial response (PR), and complete response (CR) and thereby reflect the different treatment outcomes within the pre-progression state.

The model includes 5 health states across 2 different treatment phases (**Figure 3.1, Table 3.2**). The 5 health states are: stable disease, PR, CR, progressed disease (PD), and death. All patients begin in the stable disease health state. Patients in the stable disease, PR, or CR health states may transition from the on-treatment (“During treatment period”) stage to the off-treatment (“After treatment period”) stage, depending on the assumed treatment duration. During the treatment period, patients in the stable disease state can transition to PR, CR, or PD states, or remain in stable disease. Although tumour size changes are inherently continuous and all CR patients could have been considered “PR” at one point, transition between model health states from stable disease to PR or CR were informed by ‘best confirmed response’ (as reported from the DeFi study) and, therefore, the model assumes that patients can transition directly from stable disease to CR.

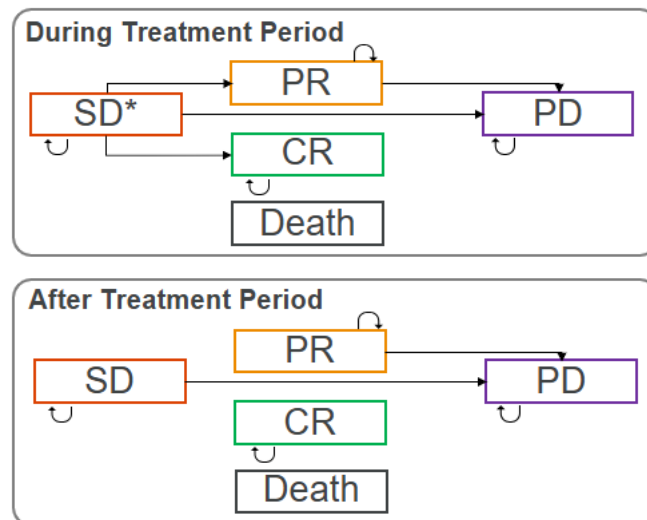
Of note, the median time to any response was 5.6 months with nirogacestat and 11.1 months with placebo, and all participants who achieved CR with nirogacestat in the DeFi trial did so within the first year of treatment (Gounder et al. 2023a). After the treatment period, patients in stable disease can progress (i.e., transition to PD) or remain stable (i.e., stay in stable disease), but they cannot improve (i.e., transition to PR or CR), as it is assumed that these health states represented the “best” and final response achieved during treatment as per the DeFi study. During and after the treatment period, patients who transitioned to the PR state from stable disease as their “best” response cannot further improve (i.e., transition to CR), though they can progress (i.e., transition to PD). The model structure includes flexibility to allow progression from PR to PD to be modified by treatment.

According to the clinical experts, spontaneous regression can happen, but it is a phenomenon of the disease observed with patients on active surveillance (i.e., patients with DT without disease progression, symptoms, or QoL loss) rather than a treatment effect (Colombo et al. 2025). The indicated and modelled population represents adult patients with progressing DT (i.e., those with the most active and severe disease), rather than stable patients, with tumours that require systemic treatment and are not commonly expected to spontaneously regress. Transitions for spontaneous regression (e.g., transition from stable disease off treatment [tx] to PR/CR, from PR to CR after confirmed best response, or from PD to stable disease/PR/CR) was, therefore, not included to avoid complicating the model design with respect to the decision problem and because existing literature to inform the model would have overestimated the spontaneous regression rate (i.e., no other DT studies had populations as severe as DeFi).

It is assumed that those in CR (i.e., those patients who experience full disappearance of all target lesions) cannot transition to PR, stable disease, or PD, and would therefore remain in their current health state (regardless of treatment status) on the basis of feedback from clinical advisers that tumours in their CR patients have yet to return and observed evidence of duration of exposure and response data from the DeFi trial that showed no progression events among the participants achieving CR (Gounder et al. 2023a).

Patients face a risk of death in every health state.

Figure 3.1 Model structure



Note: “during treatment period” and “after treatment period” correspond to the “on tx” and “off tx” health states in the model, respectively. The treatment period will be either up to 1 year or 2 years. Patients can transition to “death” from any health state. Progression to PD ‘after tx’ can be modified by treatment and it is assumed in the reference case that there is no progression from PR to PD for patients treated with nirogacestat. Responses were measured by CT or MRI and were evaluated by Central Imaging Review for all participants using RECIST v1.1.

*All patients start here.

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; tx, treatment; v, version.

Source: Gounder et al. (2023a).

Table 3.2 Model health states

Health State	Treatment Period	Description
Stable disease	On tx	• All patients start in the model in this health state. • Patients can either stay in stable disease, transition to PR or CR on tx health states, progress to PD, or die.
	Off tx	• Patients can transition to this health state from the stable disease on tx state. • Patients can either stay in stable disease, progress to PD, or die.
Partial response	On tx	• Patients can transition to this health state from the stable disease on tx state. • Patients can either stay in PR, progress to PD, or die.
	Off tx	• Patients can transition to this health state from the PR on tx state. • Patients can either stay in PR, progress to PD, or die.
Complete response	On tx	• Patients can transition to this health state from the stable disease on tx state. • Patients can either stay in CR or die.
	Off tx	• Patients can transition to this health state from the CR on tx state. • Patients can either stay in CR or die.
Progressed disease	-	• Patients can transition to progressed disease from either stable disease on tx, stable disease off tx, PR on tx, or PR off tx health states. • Patients can either stay in PD or die.
Death	-	• Patients can transition to death from any health state. • Terminal state.

Note: “on tx” and “off tx” health states in the model correspond to “during treatment period” and “after treatment period”, respectively.

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; tx, treatment.

The features of the economic analysis are presented in **Table 3.3**. The analysis was constructed to be from the perspective of the NHS and the Personal Social Services as per the NICE guidelines (National Institute for Health and Care Excellence 2013). A discount rate of 3.5% was used in the global reference case analysis for both costs and effects, as per NICE guidelines (National Institute for Health and Care Excellence 2025). As recommended in the NICE guidelines, an alternative discount rate of 1.5% was tested in a scenario analysis. A lifetime horizon (i.e., 62.8 years) was selected because treatment with nirogacestat can have an impact on costs and outcomes over a patient’s lifetime. The cycle length in the model was 28 days to align with treatment cycles and to adequately capture events. There is a user-selection drop-down option in the model to apply (or not) a half-cycle correction. If applied, as in the reference case analysis, a half-cycle correction is applied to the calculation of costs and health effects accrued throughout each cycle to account for the transition of patients from 1 health state to another happening in a continuous

process. With the correction, transitions occur halfway through a cycle (i.e., not at the beginning or end of a cycle) to represent timing of an average transition.

Table 3.3 Features of the economic analysis

Factor	Current evaluation, chosen values	Current evaluation, justification
Time horizon	62.8 years (=lifetime)	According to the NICE scope, the model time horizon should be sufficiently long to reflect all important differences in costs or outcomes between technologies being compared. A lifetime horizon (i.e., 62.8 years, calculated as 100-years minus the baseline age from the DeFi trial), resulting in <1% of patients being alive by the end of this time horizon, was selected because treatment with nirogacestat can have an impact on costs and outcomes over a patient's lifetime.
Model structure	Semi-Markov model	A semi-Markov model was used to capture all costs and outcomes associated with nirogacestat and comparator treatments for patients with progressing DT. Considering the variability in patient experiences and unpredictability of the disease, a simple 3-state or partitioned survival model (e.g., pre-progression, post-progression, and death) was not appropriate to sufficiently capture the natural history of DT and the QoL gains associated with treatment. Within the pre-progression state, patients can experience different outcomes (e.g., varying degrees of improvements in pain and symptom burden which would translate to differences in healthcare costs and health-related QoL/utilities) related to tumour size changes. The model, therefore, was developed to reflect the different levels of tumour response that patients with progressing DT will experience from start of systemic treatment until death.
Health states	5 health states across 2 treatment phases (on or off treatment): • Stable disease • PR • CR • PD • Death	Health states are reflective of the DT disease pathway (i.e., the different levels of tumour response that patients with progressing DT will experience from start of systemic treatment until death) and validated by UK clinicians.
Cycle length	28 days	Corresponds to the treatment cycle length needed to adequately capture events
Half-cycle correction	Yes	As per NICE reference case
Measurement of health effects	QALYs	As per NICE reference case
Discount (costs/effects)	3.5%	As per NICE reference case
Perspective	UK NHS	As per NICE reference case
Treatment waning effect	No	There is a lack of evidence suggesting that there is a treatment waning effect. Treatment benefits on duration of response were assumed to be maintained over the model time horizon after treatment stops given the disease modifying effect that is expected to change the tumour structure/biology. This assumption was supported by UK clinical expert opinion (SpringWorks Therapeutics 2025a).
Source of utilities	• Shingler et al. (2013) for PR, stable disease, and PD health states.	• The DeFi trial did not collect EQ-5D. Since no utility values specific to DT were identified in the SLR of published literature, a review of utility values in STS was then undertaken to address this gap. STS

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Factor	Current evaluation, chosen values	Current evaluation, justification
	As CR patients are absent of tumour, the utility value for the CR health state was assumed to be equal to that of the UK population norm.	represents the most suitable surrogate data for patients with progressed disease in the DeFi trial and the indicated population, as DT and STS share similarities in terms of origins, clinical presentation, symptoms, diagnostic and treatment pathway, and management by oncologists/STS specialists (Desmoid Tumor Working Group 2020, Huss et al. 2013, Kasper et al. 2011, Mercier et al. 2020, Penel et al. 2016). - Utility mapping of BPI-SF and the GODDESS instruments was not possible because no direct mapping algorithm was available to map a utility value. - Mapping the EORTC QLQ-C30, a non-preference-based cancer-specific PRO measure, to EQ-5D-3L using published algorithms presents several methodological limitations. The mapping algorithm is not specific to DT as it was developed using oncology patient samples. Methodological limitations with associating a utility to PD should also be noted, given that PRO visits and assessment of disease progression did not always happen concurrently. EORTC QLQ-C30 and the PROs were assessed monthly, whereas RECIST was assessed quarterly (every 3 months). Even when mapping to 2 health states based on progression status (i.e., pre-progression and post-progression), few observations were categorized as “Yes” for clinical progression status, which led to large standard error for this variable and high variance for the predicted utility values. Additionally, the small sample size of the DeFi trial, combined with the even smaller sample sizes resulting from these instruments required distribution of participants into respective health states, was found to be a major limitation to the proposed mapping method, as there were few observations in the DeFi dataset for the response (CR and PR) and progression (PD) health states; reduced sample size can lead to large standard errors and a high variance in predicted utility values. Overall, it is strongly suggested that mapping EORTC QLQ-C30 to EQ-5D-3L cannot be practically implemented to the model design since the mapping is likely to unreliably produce CR, PR, stable disease, and PD state utility values.
Source of costs	National Schedule of NHS Costs 2023/2024	Costs are reflective of the UK setting.

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CR, complete response; DT, desmoid tumours; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GODDESS, Gounder–Desmoid Tumour Research Foundation; HTA, health technology assessment; PD, progressed disease; PR, partial response; PRO, patient reported outcome; QALY, quality-adjusted life year; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SLR, systematic literature review; STS, soft tissue sarcoma.

3.2.3 Intervention technology and comparators

The pathway and full justification of comparators are presented in **Section 1**.

3.2.3.1 Intervention

The intervention is nirogacestat, a potent, small molecule, selective, reversible, noncompetitive inhibitor of gamma-secretase that blocks proteolytic activation of the Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

Notch receptor (Gounder et al. 2023a). Gamma-secretase is an enzyme involved in the Notch signalling pathway, which plays a role in tumour growth and progression, including in DT. Nirogacestat is available as 50 mg, 100 mg, or 150 mg film-coated tablets, with a recommended dose of 150 mg orally twice daily, once in the morning and once in the evening. Nirogacestat is a promising therapeutic option for patients with progressing DT as a targeted gamma-secretase inhibitor, especially in cases where other treatments are ineffective or if the tumour is resistant to traditional therapies (Gounder et al. 2023a).

3.2.3.2 Comparator – Best Supportive Care

Based on clinical expert interviews, it was noted that current standard of care (SoC) for DT is variable and may depend on tumour site and the centre's clinical practice. No definitive recommendation for a first-line treatment approach is provided by international and European guidelines, and there are no pharmacological treatments approved for use in DT and no defined global SoC.

Best supportive care (assumed to be similar to placebo from the DeFi trial) was chosen as the most relevant comparator for the base case analysis. As per clinical expert feedback, BSC consists of symptom management, rehabilitation/physical therapy, and overall holistic care. This represents SoC in current clinical practice because there are currently no therapies approved for use in the treatment of DT in the UK, as noted in clinical expert interviews and evidenced by the lack of previous NICE health technology assessments in the same disease area (further details are provided in **Section 1.3.7**).

Tyrosine kinase inhibitor (TKIs) and chemotherapy were not included as relevant comparators in this submission as they do not reflect the current SoC in UK clinical practice.

Tyrosine kinase inhibitors are not licensed or reimbursed for DT and are difficult to access because they are only available via compassionate use programmes (e.g., frequency estimates were once a year to once in 5 years, according to anecdotal feedback from 2 advisers) (SpringWorks Therapeutics 2025a). One (1) UK advisor remarked that the turnaround time to complete the compassionate use application

and start treatment ranges from 4 to 8 weeks, which is too long for some patients who need treatment as soon as possible (SpringWorks Therapeutics 2025a). Furthermore, there is uncertainty related to continued TKI (e.g., sorafenib) access because there is no formal commitment from the manufacturer that they will provide the drug free of charge forever (SpringWorks Therapeutics 2025a). Furthermore, TKIs are not routinely used in UK clinical practice for the treatment of DT, as they are associated with considerable treatment discontinuation due to toxicity and disease progression (Garg et al. 2023, Noujaim et al. 2024, Penel et al. 2011, Toulmonde et al. 2019).

Chemotherapy treatment is used more frequently than TKIs and is included in the current clinical practice guidelines (Kasper et al. 2024a) as an option for patients (largely due to lack of alternative options approved for use in DT); however, it is not considered the SoC and is associated with significant toxicity issues (Toulmonde et al. 2019), which can affect patients' QoL, adherence/persistence, and treatment preference. Furthermore, there is no robust high-quality evidence generated from randomised clinical trials on which to assess efficacy and/or compare chemotherapy to nirogacestat, with outcomes data in adults limited to retrospective studies and a single-arm trial (Bektas et al. 2023, Gennatas et al. 2020, Husson et al. 2019, Mir et al. 2020, Toulmonde et al. 2019).

3.3 Clinical parameters and variables

The Phase 3 DeFi trial was used to inform efficacy of nirogacestat in the model (Gounder et al. 2023a, SpringWorks Therapeutics 2023b). **Table 3.4** provides a summary of the trial design for DeFi for nirogacestat that was used to inform the economic evaluation.

The analyses presented in this section used data from the 7 April 2022, data cut-off date, which represents the most recent data for the primary analysis of the DeFi trial.

Table 3.4 Overview of Phase 3 clinical trials

	DeFi
Patient population	Patients aged 18 years or older with progressing DT
Intervention	Nirogacestat
Comparator(s)	Placebo
Study design	Multicentre double-blind, randomised, placebo-controlled
Countries	Germany, the United States, Canada, Belgium, the Netherlands, Italy, and the United Kingdom
Primary efficacy endpoint(s)	Progression-free survival: the time from randomisation until date of assessment of progression or death by any cause
Key secondary efficacy endpoint(s)	Objective response rate: the percentage of patients who had a confirmed response to treatment, as assessed by RECIST v1.1. Duration of response (in months) as supportive and descriptive analyses of ORR. Patient-reported outcomes: changes in patient-reported outcomes, such as pain, DT-specific symptom burden, physical and role functioning, and overall quality of life.

Abbreviations: DT, desmoid tumours; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; v, version.

3.3.1 Treatment duration

While DT is a lifelong condition, patients are not necessarily on chronic treatment, as close monitoring and a ‘watch and wait’ strategy can be an effective option once a tumour is stabilised/under control (Colombo et al. 2025, Kasper et al. 2024a). It is important to note that an optimal duration of treatment with systemic treatments in DT remains to be determined. A 2-year maximum treatment duration was selected for the reference case analysis to most closely reflect the median treatment duration of nirogacestat in the DeFi trial of 20.6 months. In addition, clinical advisers experienced in the treatment of DT in the UK stated that although the DeFi trial had no stopping rules, the full disease-modifying effect should have occurred, and a best and final confirmed response is reasonably expected to be achieved by 2 years for most patients. Clinical advisers in other regions (e.g., Germany, Italy) have also noted that treatment duration is not expected to exceed 2 years. A 1-year maximum treatment duration can be selected to reflect that the benefits of treatment and a best and final confirmed response could be achieved within the first year of treatment, as the median time to response for nirogacestat in the DeFi study of 5.6 months (and the median time to response for the placebo arm was also within a year at 11.1 months).

3.3.2 Best overall response

Best overall response data for nirogacestat and BSC/placebo in the model were sourced from post-hoc analyses of the DeFi trial (SpringWorks Therapeutics 2025b). Best overall response was defined as the best response obtained across all assessments per independent central review (Eisenhauer et al. 2009). All patients start in the model by initiating treatment in the stable disease health state. The observed proportions of best overall responses of PR and CR among participants with up to either 1-year or 2-years of treatment from the DeFi trial were converted to 28-day cycle transition probabilities of transitioning from stable disease to PR and from stable disease to CR health states while on treatment for use within the model (**Table 3.5** for the ITT population used in the reference case analysis). Patients who did not achieve PR or CR, and did not progress, were assumed to have stable disease as their best response (and thus, would stay in the stable disease health state).

Table 3.5 Best overall response by treatment among patients with up to 1- or 2-years of treatment (ITT population; reference case)

Best Confirmed Response	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
CR	████	7.1%	████	0.0%
PR	████	34.3%	████	8.3%

Note: For incorporation into the model, the proportion of best overall response of CR or PR was converted to 28-day model cycle rate by the formula: $r = \frac{-\ln(1-p)}{t}$, then converted to transition probability by formula: $p = 1 - \exp(-rt)$, where p=probability, r=rate, t=time.
Abbreviations: BSC, best supportive care; CR, complete response; ITT, intent-to-treat; PR, partial response.
Source: SpringWorks Therapeutics (2025b).

3.3.3 Rate of progression

Rates of progression from PR or stable disease to PD for nirogacestat and BSC/placebo were based on rates of duration of response from the DeFi data (where loss of response, and thus rate of progression to PD, would be equal to 1 minus the probability of remaining in response). Different rates of progression can be specified based on the selected treatment duration (i.e., 1 vs. 2 years) and according to treatment status (i.e., during the treatment period [**Section 3.3.3.1**] or after the treatment period [**Section 3.3.3.2** the treatment period]).

3.3.3.1 Rate of progression ‘during treatment period’ (“on tx” health states)

3.3.3.1.1. Uncalibrated rate progression ‘during treatment period’ (“on tx” health states)

The probability of remaining in PR at month 12 (reported as per the DeFi statistical analysis plan) among participants with up to either 1-year or 2-years of treatment from the DeFi trial was used to inform the annual rate of patients in the PR health state who would experience a progression event, whereby the annual rate of progression from PR to PD was calculated by subtracting the rate of duration of PR at 12-months from 1. Subsequently, in order to apply these rates in the model, the annual rate of progression from PR to PD was converted to 28-day cycle transition probabilities. For the ITT population (reference case), the rate of duration of PR from DeFi and the calculated annual rate of progression from PR to PD are shown in **Table 3.6** and **Table 3.7**, respectively.

Table 3.6 Rate of duration of PR from DeFi trial among patients with up to 1- or 2-years of treatment (ITT population; reference case)

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Rate of duration of response at month 12	██████	██████	██████	██████

^a The rate of duration among patients in PR with up to 1 year of treatment at month 12 could not be calculated as there was no data reported at month 12 (i.e., patients were either censored or had an event before month 12); therefore, it was assumed that these patients would have the same duration of response as patients with up to 2 years of treatment. A 100% duration of response was not appropriate, as there was one progression event by month 12.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PR, partial response.

Source: SpringWorks Therapeutics (2025b).

Table 3.7 Annual rate of progression from PR to PD among patients with up to 1- or 2-years of treatment (ITT population; reference case)

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
On tx	██████	██████	██████	██████

Note: The annual rate of progression from PR to PD was determined by subtracting the rate of duration of PR at 12-months (see **Table 3.5**) from 1. Subsequently, for incorporation into the model, the annual rate of progression from PR to PD shown in this table was converted to a 28-day rate and then a model cycle transition probability by the formula: $p = 1 - \exp(-rt)$, where p=probability, r=rate, t=time.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

Similar calculations were done using the rate of duration of stable disease response at 12 months from the DeFi trial to inform the rate of progression from stable disease to PD in the model. For the ITT population (reference case), the rate of duration of Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

stable disease from the DeFi trial and the calculated annual rate of progression from stable disease to PD are shown in **Table 3.8** and **Table 3.9**, respectively.

Table 3.8 Rate of duration of stable disease from DeFi trial among patients with up to 1- or 2-years of treatment (ITT population) – uncalibrated

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Rate of duration of response at month 12	████	████	████	████

Abbreviations: BSC, best supportive care; ITT, intent-to-treat.

Source: SpringWorks Therapeutics (2025b).

Table 3.9 Annual rate of progression from stable disease to PD among patients with up to 1- or 2-years of treatment (ITT population) – uncalibrated

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
On tx	████	████	████	████

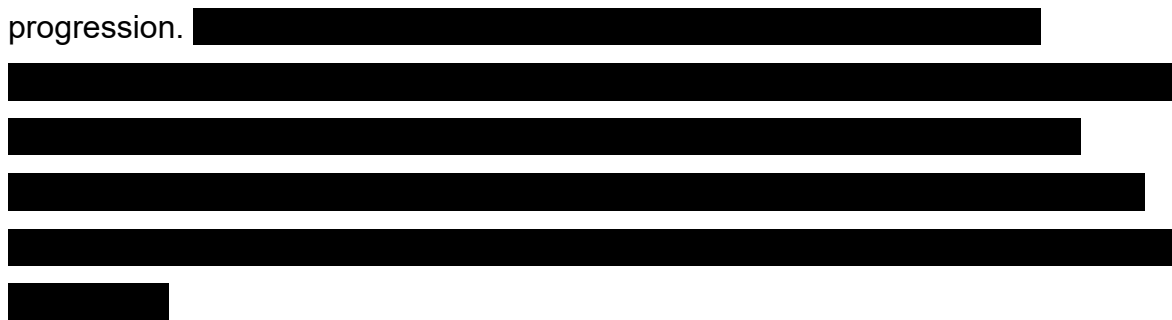
Note: The annual rate of progression from stable disease to PD was determined by subtracting the rate of duration of stable disease at 12 months (see **Table 3.7**) from 1. Subsequently, for incorporation into the model, the annual rate of progression from stable disease to PD shown in this table was converted to a 28-day rate and then a model cycle transition probability by the formula: $p = 1 - \exp(-rt)$, where p=probability, r=rate, t=time. Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; tx, treatment.

As described previously in **Section 3.2.2**, the model structure does not allow for transition from the CR health state to PD. Anecdotal reports/clinical opinion and data from the DeFi trial for duration of treatment exposure and response showed that during the trial period, no participants progressed to PD from CR (i.e., the probability of remaining in CR response is 100%).

Based on the annual rates of progression in the tables above, the model projects out the number of patients on each treatment who would progress to PD health state over time. The extrapolated values were compared with the DeFi trial, which reported 12 out of 70 (17%) events of disease progression within the first 2 years of treatment with nirogacestat. These progression events were based on RECIST (imaging-based) and clinical progression events. For BSC/placebo, the progression-free survival (PFS) data from DeFi was also considered. While median PFS (mPFS) was not reached for nirogacestat, the mPFS for placebo was 15.1 months; therefore, it was expected that the proportion of BSC/placebo participants in PD by 15 months should be approximately 50%. Data was available for the BSC participants at 24

months, which showed that 50% of participants (36/72) had progressed. However, this data was considered to be less reliable than the earlier measurements as it was based on fewer patients (1 patient at risk). The UK clinical advisers also did not expect the progression rate in the untreated population to rapidly change (i.e., slow down) given that the DeFi population represents participants with progressing DT (i.e., a subset of the general DT population with more severe disease). Related to this, no external natural history data source was identified that reflected a comparable population to the DeFi population. Rates of progression from existing publications, such as the observational data from Colombo et al. (2025) were deemed during discussions with the UK clinical advisers to be too optimistic for participants enrolled in DeFi who would be on BSC/placebo only (Colombo et al. 2025).

Visual inspection of the model-predicted proportions of the cohort in the PD health state over time (generated from the unadjusted duration of response data from the DeFi study) for the BSC/placebo (**Figure 3.2**) and nirogacestat (**Figure 3.3**) treatment arms revealed that some calibration/adjustment would be needed to better fit the DeFi trial data, based on an assessment of the internal validity with the DeFi publication and discussions with the UK advisers on their expectations for progression.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.3.3.1.2. Calibrated rate progression ‘during treatment period’ (“on tx” health states)

Using the observed data points for percentage of progressed patients up to mPFS or 24 months (to align with the 2 year treatment duration) and the clinician feedback, the annual rate of progression from stable disease to PD during treatment shown in **Table 3.10** for BSC/placebo was gradually increased until [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Of note, there were 2 model parameters that could have been adjusted to achieve the target progression estimate: the annual rate of progression from stable disease to PD (on treatment) and the annual rate of progression from PR to PD (on treatment). Only stable disease to PD rates (on treatment) were changed during calibration to minimise introducing bias, with PR to PD (on treatment) rates kept the same [REDACTED]

[REDACTED] based on the reported duration of response data from the post-hoc analysis since the UK clinical advisers agreed that PR is predictable but stable disease is a more heterogeneous health state.

Table 3.10 Annual rate of progression from stable disease to PD among patients with up to 2-years of treatment (ITT population; reference case) – calibrated

	Nirogacestat	BSC/placebo
	2 years	2 years
On tx	11.0%	55.0%

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; tx, treatment.
Source: Assumption/calibrated.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.3.3.2 Rate of progression ‘after treatment period’ (“off tx” health states)

The model has flexibility to separately adjust the rate of progression after the treatment period.

For BSC/placebo, the annual rates of progression from PR to PD and from stable disease to PD ‘after treatment’ were assumed to be the same as the annual rate ‘during treatment,’ given no disease-modifying effect with this comparator.

In contrast, nirogacestat is a proven disease-modifying therapy, with clinical evidence demonstrating its durable disease-modifying effect. Imaging data from its Phase 2 study showed measurable drug-induced regressions of tumour volume in 10 out of 11 evaluated participants who had volumetric responses by MRI (Kummar et al. 2017, O'Sullivan Coyne et al. 2022). These results were corroborated in the Phase 3 DeFi trial, where nirogacestat was associated with significant reductions in MRI-assessed tumour volume (median best percent change of largest target tumour: -58.9% for nirogacestat vs. +13.8% for placebo, $p < 0.001$) (Alcindor et al. 2023). Furthermore, there were no additional radiographic progressions after the first year of treatment in the nirogacestat arm, even up to a 4-year treatment landmark milestone (Kasper et al. 2025).

Imaging data from the DeFi trial also show significant reduction in tumour activity with nirogacestat as evidenced by T2 signal intensity (best percent change in T2 hyperintensity signal ratio: -55.1% for nirogacestat vs. -21.4% for placebo, $p < 0.001$), suggesting decreased disease activity at the cellular level (Alcindor et al. 2023, Cassidy et al. 2020, Zanchetta et al. 2021). Changes at the cellular level were also observed in a retrospective analysis of 7 patients with DT who received 9 (21-day) cycles of treatment with nirogacestat in an open-label, Phase 1 study. A biopsy performed on a patient who stopped treatment after 42 months in the absence of progression showed decreased tumoral cellularity and more densely collagenous background compared with the pre-treatment biopsy. The study reported that this patient remained off therapy with no evidence of clinical or radiographic progression for over 15.9 months. In total, 4 participants from the study stopped treatment and continued to be progression-free between 11 and 53 or more months, leading the study authors to suggest that there could be prolonged disease control even after

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therapy discontinuation (Villalobos et al. 2018). This is in line with discussions with clinical advisers, where it was understood that after a disease-modifying treatment like nirogacestat, the tumour becomes inactive and remains as scar tissue, which does not have the structure to grow. These clinical results collectively establish nirogacestat as a disease-modifying therapy that can reduce tumour burden/volume and halt disease progression, even allowing patients to be progression-free while off treatment.

In other words, once a treatment gets a tumour into a state of response (i.e., CR and PR), there is no evidence that it will progress again. Therefore, a disease-modifying treatment could be stopped without increasing the risk of progression because the tumour would have been altered during treatment.

Feedback from UK clinicians indicated that successful disease control (minimised symptoms due to tumour stabilisation or dimensional regression) is very durable (i.e., decades of being progression-free, based on anecdotal feedback) and that it is clinically valid to assume a lifelong benefit of treatment (SpringWorks Therapeutics 2025a). The clinical advisers were aligned with the assumption that patients who achieve at least PR would not progress after treatment due to the disease-modifying effects of active treatment on the tumour(s). According to the UK clinicians, unlike PR/CR, the stable disease health state is more variable in terms of tumour behaviour. Therefore, the model assumed the rates of progression from the stable disease health state would be the same for during the treatment period (“on tx”) and after the treatment period (“off tx”) for nirogacestat and BSC/placebo in the reference case analysis. That is, there is no increased risk of progression after active treatment is stopped.

The annual rates of progression from PR to PD and from stable disease to PD after 1 or 2 years of treatment are presented in **Table 3.11** and **Table 3.12**, respectively, for the ITT population (reference case analysis). These rates were then converted to 28-day transition probabilities, shown in **Section 3.3.4**.

Table 3.11 Annual rate of progression from PR to PD after 1- or 2-years of treatment (ITT population; reference case)

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Off tx	████	████	████	████

Note: All rates were assumed to be the same as 'on tx' rates of progression in the absence of data.
Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

Table 3.12 Annual rate of progression from stable disease to PD after 1- or 2-years of treatment (ITT population; reference case)

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Off tx	████	████	████	████

Note: All rates were assumed to be the same as 'on tx' rates of progression in the absence of data.
Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; tx, treatment.

3.3.3.2.1. Treatment waning

The duration of treatment effect is a source of uncertainty in the model, as there is currently no data to inform how long the effect of nirogacestat will last (i.e., no duration of response data for participants who discontinued nirogacestat treatment in DeFi). In the model, there is a drop-down menu with an option for no waning or an option to apply gradual/linear treatment waning over user-specified time interval (Stargardter et al. 2022, Trigg et al. 2024). In the reference case, treatment waning is excluded and treatment benefits on duration of response were assumed to be maintained over the model time horizon after treatment stops given the disease modifying effect that is expected to change the tumour structure/biology. Once tumours stabilise or decrease in size, they will remain inactive due to the disease modification from active treatment (Colombo et al. 2025). This was demonstrated with imaging and biopsy data for nirogacestat showing measurable reductions in tumour size and volume as well as decreased tumoral cellularity (Anneberg et al. 2022b, Gounder et al. 2023a, Kummar et al. 2017).

3.3.4 Model cycle transition probabilities (reference case)

An overview of the resulting 28-day model cycle transition probabilities for the reference case analysis are shown below for nirogacestat and BSC/placebo (**Table 3.13** and **Table 3.14**, respectively). Transition probabilities to the 'Death' health state Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

were informed by per-cycle mortality probabilities (**Section 3.3.5**), which changed over time, and are therefore not shown in the treatment-specific transition probability tables below.

Health state			To (during treatment period)							To (after treatment period)						
			Stable disease		PR		CR		PD	Stable disease		PR		CR		PD
			on tx	off tx	on tx	off tx	on tx	off tx		on tx	off tx	on tx	off tx	on tx	off tx	
From	Stable disease	on tx														
		off tx														
	PR	on tx														
		off tx														
	CR	on tx														
		off tx														
	PD															

Note: Light grey cells indicate transitions between health states that are not possible.
Abbreviations: CR, complete response; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

Health state			To (during treatment period)							To (after treatment period)						
			Stable disease		PR		CR		PD	Stable disease		PR		CR		PD
			on tx	off tx	on tx	off tx	on tx	off tx		on tx	off tx	on tx	off tx	on tx	off tx	
From	Stable disease	on tx														
		off tx														
	PR	on tx														
		off tx														
	CR	on tx														
		off tx														
	PD															

Note: Light grey cells indicate transitions between health states that are not possible.
Abbreviations: BSC, best supportive care; CR, complete response; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

3.3.5 Mortality

3.3.5.1 Disease-specific mortality

Mortality rates for patients with DT were searched for as part of the SLR. One (1) publication reporting mortality was found: Anneberg et al. (2022b) estimated the 5-year mortality rate among Danish DT patients as 7 per 1,000 (95% confidence interval [CI] 3, 16) compared with 5 per 1,000 (95% CI 4, 7) in the general population (Anneberg et al. 2022b). They calculated the adjusted hazard ratio (HR) of dying was 1.3 (95% CI 0.6, 3.2) for patients with DT compared with the general population.

The model includes health state-specific mortality risks relative to general population mortality. In the reference case analysis, it was assumed that patients with DT that were stabilised and/or under control (stable disease, PR, and CR) were assumed to have a risk of death equal to general population mortality (HR=1.0), whereas the mortality risk for patients with DT from Anneberg et al. (2022b) was applicable to PD patients only (HR=1.3) (Anneberg et al. 2022b). The assumed HRs for all health states are shown in **Table 3.15**.

Table 3.15 Hazard ratios used to calculate transition probabilities to death

Transition	Assumptions
CR to death	Assume general population mortality (age and sex adjusted life tables) HR=1.0
PR to death	Assume HR of dying vs. general population is 1.0
Stable disease to death	Assume HR of dying vs. general population is 1.0
PD to death	Assume HR of dying vs. general population is 1.3

Abbreviations: CR, complete response; HR, hazard ratio; PD, progressed disease; PR, partial response; vs, versus.

3.3.5.2 General population mortality

Patients from all health states have a probability of death. The annual probabilities of death by sex and age from the general population life tables were converted to rates of death and weighted for the percentage of males and then converted to per cycle probabilities of death by age. The model used the sex-weighted per cycle probability of death based on the mean patient age each cycle.

General population mortality was obtained from the most recent life tables available from the Office for National Statistics (ONS; National Life Tables, England and

Wales, period expectation of life, based on data for the years 2021-2023) (Office for National Statistics 2024b).

3.3.6 **Adverse Events**

The criteria for identifying one-off adverse events (AEs) for inclusion in the model was defined as grade 3 or higher AEs occurring in greater than or equal to 5% of participants in the DeFi trial. The proportion of patients experiencing one-off AEs is presented in **Table 3.16**.

Table 3.16 Percentage of patients experiencing grade ≥3 one-off AEs

One-off AE	Nirogacestat	BSC/placebo
Diarrhoea	15.9%	1.4%
Folliculitis	5.8%	0.0%
Any rash or skin disorders	8.7%	0.0%

Abbreviations: AE, adverse event; BSC, best supportive care.
Source: SpringWorks Therapeutics (2023b).

3.4 **Measurement and valuation of health effects**

3.4.1 **Health-related quality-of-life data from clinical trials**

The DeFi trial did not collect EQ-5D, and therefore the trial was not used to inform utility values for health states in the model. In lieu of this data being available from the clinical trial, based on the hierarchy of preferred health related quality of life (HRQoL) methods laid out in NICE guidelines (National Institute for Health and Care Excellence 2013), the other options for the reference case were to either source utilities from literature using a systematic search or estimate from another measure in the clinical trial using statistical mapping.

3.4.2 **Feasibility of Utility Mapping**

There were no EQ-5D estimates derived from patients with DT (or caregivers of patients with DT) identified in the SLR as discussed in **Section 3.4.3**. Therefore, a feasibility assessment of mapping of an outcome from the DeFi clinical trial was explored. The DeFi study collected patient-reported outcomes (PROs) using the Brief Pain Inventory Short Form (BPI-SF) (for pain), the Gounder–Desmoid Tumour Research Foundation Desmoid Symptom/Impact Scale (GODDESS DTSS) (for

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disease-specific symptom severity), the GODDESS Desmoid Tumour Impact Scale (GODDESS DTIS) (for disease-specific physical functioning), and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) (for overall HRQoL) (SpringWorks Therapeutics 2023b). It was evaluated whether mapping these outcomes onto a generic QoL outcome measure was feasible. Mapping could not be undertaken for BPI-SF and the GODDESS instruments because no direct mapping algorithm was available to map a utility value. A response mapping algorithm is described in Young et al. 2015 for EORTC QLQ-C30 (Young et al. 2015). However, several key limitations precluded its practical implementation for mapping of available EORTC QLQ-C30 data from the DeFi trial.

Of the 142 total participants in the DeFi trial, 134 participants had a complete baseline EORTC QLQ-C30 measurement and at least 1 follow-up EORTC QLQ-C30 measurement during the double-blind phase. The small sample size of the DeFi trial, combined with the even smaller sample sizes resulting from required distribution of participants into respective health states, was found to be a major limitation to the proposed mapping method, as there were few observations in the DeFi dataset for the response (CR and PR) and progression (PD) health states; reduced sample size can lead to large standard errors and a high variance in predicted utility values. Methodological limitations with associating a utility to PD should also be noted, given that PRO visits and assessment of disease progression did not always happen concurrently. EORTC QLQ-C30 and the PROs were assessed monthly, whereas RECIST was assessed quarterly (every 3 months). Even when mapping to 2 health states based on progression status (i.e., pre-progression and post-progression), few observations were categorised as “Yes” for clinical progression status⁷, which led to large standard error for this variable and high variance for the predicted utility values.

An additional consideration that would make predicted utilities from this mapping study potentially unreliable is that oncology patient samples were used to develop the mapping algorithms, whereas the DeFi trial consisted of patients with DT. For instance, the published mapping algorithm was based on 572 patients with multiple

⁷ Radiological progression events were excluded from the progression observations because these events are unlikely to have impact on the HRQoL of patients with DT.

myeloma (VISTA study; ClinicalTrials.gov registry NCT00111319), and 100 patients with breast cancer and 99 patients with lung cancer having consultations at a Canadian cancer clinic (Vancouver Cancer Clinic data). Participants had a mean age of 68 years and 44% were men, whereas the patient population in DeFi was younger (mean age of 37 years) and had a lower proportion of men (35% male). Since it is recommended that mapping should be based on empirical data and direct statistical association through the use of a regression model obtained from the mapping literature, and samples used in the current study should be similar to the samples in the published mapping algorithms (Longworth and Rowen 2011), the mapping function was determined to be non-generalisable to the DeFi population, as important differences in the patient populations could affect health state utility values and limit the suitability of the mapping algorithm.

Overall, it is strongly suggested that mapping EORTC QLQ-C30 to EQ-5D-3L cannot be practically implemented to the model design since the mapping is likely to unreliably produce CR, PR, stable disease, and PD state utility values.

3.4.3 Health-related quality-of-life studies

No utility values specific to a DT population were identified in an SLR of the published literature (see **Appendix F**). A review of utility values in a similar disease was then undertaken to address this gap. An economic SLR of soft tissue sarcoma (STS) was conducted, as STS represents the most suitable surrogate data for participants with progressed disease in DeFi and the indicated population, as DT and STS share similarities in terms of origins, clinical presentation, symptoms, diagnostic and treatment pathway, and management by oncologists/STS specialists (Desmoid Tumor Working Group 2020, Huss et al. 2013, Kasper et al. 2011, Mercier et al. 2020, Penel et al. 2016). These similarities suggest that STS is an appropriate disease analogue (as confirmed through discussion with NICE [Decision Problem Meeting on 24 June 2025]) and information relating to STS may help to address the identified gaps in the literature relating to the humanistic burden of DT. One identified cost-effectiveness study in the STS SLR used Shingler et al. (2013) as a data source to inform health state utilities (Shingler et al. 2013). This study sampled 100 members of the UK general public who participated in a valuation exercise to elicit utility values using the time trade-off (TTO) procedure. Health state vignettes were Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

developed using a review of published literature, exploratory interviews with clinical experts, and interviews with advanced STS patients (Shingler et al. 2013). The utility values reported by Shingler et al. (2013) were selected for use in the base case (see **Table 3.18**) as the best available data source because it reported EQ-5D utilities for disease states that could be applied to the model health states and was directly elicited from a UK population.

3.4.4 Adverse reactions

Utility decrements were used in the model to capture the HRQoL impact of AEs, with the flexibility to exclude disutilities if required. An overview of AEs included in the model is provided in **Table 3.16**. The literature-derived utility decrements used in the model are shown in **Table 3.17**. These decrements, including any assumptions where data were unavailable, were validated with the UK clinical advisers.

The disutility of one-off treatment-emergent adverse events (TEAEs) was applied in the first cycle of the model. The duration of each AE was assumed to be 7 days, reflecting that it could take approximately a week to make dose modifications to manage AEs in accordance with clinical feedback, and was used to calculate the total utility decrement applied. More specifically, the quality-adjusted life year (QALY) decrement related to AEs (i.e., the utility impact adjusted for the duration) was applied in each model cycle based on the percentage of patients experiencing each AE. The disutility of recurring AEs was applied for the full █████ in each cycle of the model that patients remain on treatment.

Table 3.17 Adverse event utility decrements

Adverse Event	Utility Decrement	Source/Notes	Duration of AE	Source/Notes
One-off TEAEs (grade ≥3; occurring in ≥5% of patients in any of the included treatment arms [in their respective trials])				
Diarrhoea	-0.3270	Shingler 2013 (Shingler et al. 2013)	7.0	Assumption
Folliculitis	-0.0325	Assumed to be equal to rash/skin	7.0	Assumption
Any rash or skin disorders	-0.0325	Nafees 2008 (Nafees et al. 2008)	7.0	Assumption
Recurring adverse event (grade 1-2)				
OD	-0.095	Assumption (utility at diagnosis minus after chemotherapy, Stein 2023) (van Stein et al. 2023)	████	Assumption

Abbreviations: AE, adverse event; OD, dysfunction; TEAE, treatment-emergent adverse event.

3.4.5 Utility decrements for caregiver burden

The model includes the flexibility to include or exclude caregiver disutility for an analysis from the societal perspective. A utility decrement of -0.07 was sourced from a previous NICE submission in symptomatic and inoperable plexiform neurofibromas associated with type 1 NF (HST20 for selumetinib) (National Institute for Health and Care Excellence 2022). This estimate was deemed appropriate by UK clinical advisers, given the lack of alternative data for DT. The caregiver utility impact was added to the patient utility value assigned to the PD health state to sum to a new net utility value for that health state.

3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

Given the data challenges with mapping PROs from the trial to EQ-5D described above, health state utilities for PR, stable disease, and PD were sourced from the literature for the reference case analysis. In line with the understanding that CR patients are absent of tumour, the utility value for the CR health state was assumed to be equal to that of the UK population norm (Kind et al. 1999). The health state utilities used in the reference case are shown in **Table 3.18**. The model also includes the flexibility to specify different utilities by health states “on” or “off” treatment; however, for the reference case it was assumed that the utilities would be independent of treatment status. The reference case utilities were also adjusted based on patient age using an age-adjustment factor (Ara and Brazier 2010) (Hernández Alava et al. 2022). Sex-specific utility values for each age were used to calculate a utility decrement for each age in the model, versus the baseline age. This utility decrement was then applied for each model cycle, based on mean patient age during the given cycle.

Table 3.18 Health state utility values

Health State	Utility Value ^a	Data Source/Notes
Stable disease (on or off treatment)	0.7360	Shingler, 2013 (mean utility value for 'SD') (Shingler et al. 2013)
PR (on or off treatment)	0.7920	Shingler, 2013 (mean utility value for 'treatment response') (Shingler et al. 2013)
CR (on or off treatment)	0.8600	UK population norms for EQ-5D (Kind et al. 1999)
PD	0.2630	Shingler, 2013 (mean utility value for 'PD') (Shingler et al. 2013)

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^a Utilities are then adjusted to reflect aging / decreasing utility over time, using an age-adjustment factor per cycle. Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease.

A scenario analysis was conducted assuming that patients in the CR health state would have a slightly worse utility than the general population due to having DT. In this scenario, the CR health state had the same utility value as the PR health state.

Neurofibromatosis (NF) was a disease analogue suggested by the UK advisers. There was only one NICE submission for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 NF in children aged 3 and over (for selumetinib); however, the utility values used in the 3-state NF model submitted to NICE were not reported (National Institute for Health and Care Excellence 2022). The health state utilities from the NF economic evaluation submitted to CDA were, on the other hand, publicly available, reporting that the “progression-free” state was associated with a utility value of 0.74 while the “progressed” state was associated with a utility value of 0.51 based on direct elicitation of population preferences in a TTO study commissioned by the sponsor involving 100 adult participants from the UK (Canada's Drug Agency 2023). Based on these estimates, two additional scenario analyses were conducted: one where the 0.51 was used for the utility for PD only and another scenario where the 0.74 was used as the utility for the pre-progression states (CR/PR/stable disease) and the 0.51 was used as the post-progression utility for the PD state.

3.5 Cost and healthcare resource use identification, measurement and valuation

Healthcare resource use (HCRU) and cost data relevant to the UK were identified through relevant databases, as described further in **Sections 3.5.1 to 3.5.5**. An SLR was conducted to identify healthcare resource use and cost data relevant to the decision problem and NICE reference case. Details regarding the SLR methodology and results are presented in **Appendix E** and **Appendix G**. In addition, UK clinical experts validated the costs and resources used in the model.

The model considered several cost categories that can be included or excluded in the analysis. Direct medical costs include:

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- Drug acquisition costs
- Treatment administration costs
- AE management costs
- Subsequent therapy costs
- Disease management (HCRU) costs
- End-of-life costs.

Indirect productivity loss costs can be included, but in the reference case analysis, all costs except productivity loss costs were included.

Costs from the Unit Costs of Health and Social Care 2023 Manual and the National Schedule of NHS Costs 2023/24 were based on the latest cost in 2023/24 Great British Pound (GBP; £) and were not inflated (Personal Social Services Research Unit 2025). All costs are applied on a per-cycle basis (unless otherwise specified).

3.5.1 Intervention and comparators' costs and resource use

All patients initiate treatment in the first model cycle. Drug acquisition costs were applied in each cycle for patients who were alive until treatment discontinuation (based on the 2-year maximum treatment duration), progression, or death.

The general dosing schedule for each therapy, according to their Summary of Product Characteristics (SPCs), are summarized in **Table 3.19**.

Table 3.19 Drug dosing schedules

Treatment	Dosing Schedule	Source
Nirogacestat	150 mg twice daily (orally)	SpringWorks data on file (UK SPC) (SpringWorks Therapeutics 2025f)
BSC/placebo	N/A	N/A

Abbreviations: BSC, best supportive care; N/A, not applicable; SPC, Summary of Product Characteristics.

Drug acquisition costs were calculated based on treatment dose, the unit price, and mean relative dose intensity (RDI). **Table 3.20** provides the drug formulations and

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unit costs for nirogacestat and BSC/placebo, along with the calculated costs per dose and per cycle as used in the reference case, which was provided by SpringWorks (SpringWorks Therapeutics 2025e). Given that the patient access scheme has not been formally agreed with NHS England at the time of submission to NICE, scenario analyses were performed over a plausible range of prices (as noted in **Section 3.11.10** of the NICE user guide) to evaluate the impact of various discount ranges on the prices for nirogacestat (National Institute for Health and Care Excellence 2024). For further price details, please refer to **Appendix I**.

Table 3.20 Drug acquisition costs

Treatment	Unit ^a strength	Cost per unit ^a	Cost per pack ^b	Dose per admin	Cost per admin	Cost per 28-day cycle	Annual cost ^c	Cost per 28-day cycle (with RDI) ^d	Annual cost (with RDI) ^d
Nirogacestat	150 mg	£271.23	£15,189.04	150 mg	£271.23	£15,189.04	£198,135.60	████████	████████
BSC/ placebo	N/A				£0.00		£0.00	████	████

^a A unit refers to a tablet or capsule.

^b Each pack contains 56 tablets.

^c Calculated assuming 365.25 days in a year.

Abbreviations: admin, administration; BSC, best supportive care; N/A, not applicable; RDI, relative dose intensity.
Source: SpringWorks Therapeutics (2025e); SpringWorks Therapeutics (2023b).

The model can apply a cost per treatment administration for intravenous (IV) or oral treatments. A drug administration cost of £152.00 was assumed for IV treatments, which was based on the National Schedule of NHS Costs (2023/2024) (National Health Service England 2024); no drug administration cost was assumed for oral treatments. Because nirogacestat is administered orally and no administration is associated with BSC/placebo, no drug administration cost is associated with any first-line treatments in the reference case analysis.

3.5.2 Health-state unit costs and resource use

No specific sequence of agents and no specific duration of treatment is recommended in the Desmoid Tumor Working Group (DTWG) guidelines (Kasper et al. 2024a). Given this variability, a mixed basket treatment approach was considered to be most appropriate for costing subsequent therapy in the model (**Table 3.21**).

Subsequent therapy costs are applied only to the PD health state, as a cost per cycle to reflect ongoing management of the disease. The basket of subsequent therapies is assumed to affect costs only (i.e., not efficacy). For the reference case analysis, clinical advisers recommended that the distribution of subsequent therapies be the same across treatment arms given the absence of a standard treatment sequence (**Table 3.22**). According to the UK clinical advisers, subsequent treatments typically include cytotoxic chemotherapy (even for patients who initially received chemotherapy), and a small proportion of patients might receive radiation or participate in clinical trials as an option (however, no numbers were provided). For simplicity, it was assumed that only chemotherapy would be used in subsequent lines as a ‘last resort’ treatment option.

Table 3.21 Subsequent therapy regimens

Subsequent treatment	Dosing description	Source(s)/Notes
Cytotoxic chemotherapy (doxorubicin)	The recommended dose is 60-75 mg/m ² body surface IV as a single dose with 21 day's intervals.	Doxorubicin SmPC (2025) (Electronic Medicines Compendium 2025); Drugs and pharmaceutical eMIT (2024) (Department of Health and Social Care 2024)
Radiation	A dose of 56 grays in 28 fractions, 2 grays per fraction, 5 fractions per week.	Keus et al. (2013); Royal College of Radiologists (2024)
Clinical trial	N/A	Clinical expert opinion

Abbreviations: eMIT, electronic market information tool; IV, intravenous; N/A, not applicable; SmPC, Summary of Product Characteristics.

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Table 3.22 Subsequent therapy cost per 28-day cycle

Subsequent treatment	% of patients	Unit ^a strength	Cost per unit ^a	Dose per admin	Admin cost	Cost per 28-day cycle
Cytotoxic chemotherapy (doxorubicin)	100%	10 mg	£4.2011	130 mg	£152.00 ^b	£258.27
Weighted average cost (per 28-day cycle)						£258.27

^a A unit refers to a tablet, capsule, or vial.

^b A drug administration cost of £152.00 per IV administration was assumed.

Abbreviations: admin, administration; IV, intravenous.

3.5.3 Disease Management Costs

The economic evaluation included medical costs based on HCRU associated with routine patient monitoring, including physician visits and laboratory tests, and hospitalisation. Medical resource use was not evaluated in the DeFi trial; therefore, disease management costs were informed by published literature. One (1) publication identified through the SLR reported HCRU by physical symptom burden clusters from the observational QUALIFIED study, which enrolled patients with DT from the UK and the Netherlands (Schut et al. 2023). It was assumed (and validated with UK clinical experts) that HCRU associated with the high symptom burden cluster could inform the PD health state, the intermediate symptoms cluster could inform the stable disease health state (with intermediate symptoms-low pain cluster for nirogacestat and intermediate symptoms-high pain cluster for BSC/placebo), and the low symptom burden cluster could inform the PR health state. As this study focused only on care services such as general practitioner (GP) and specialist visits, an additional publication was sourced to inform utilisation of monitoring tests and hospitalisations. Data for pre- and post-progression HCRU were available from a CEA in STS (Verboom et al. 2019). Despite the different patient population, given the lack of alternative data sources, clinical advisers validated that the frequencies of laboratory tests, MRI and CT scans, and the distribution of hospitalisations were reasonable.

Table 3.23 provides a summary of resource use by health state. Given the absence of tumour in patients achieving CR, it was assumed that there would be no HCRU for this health state. Notably, HCRU can be specified by treatment for the stable disease health state, based on data from the DeFi trial that showed that, among participants with stable disease response, nirogacestat was associated with significantly and

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clinically meaningful differences in PROs (i.e., pain, DT-specific symptom burden, physical functioning, role functioning, and overall QoL) compared with placebo (Stacchiotti et al. 2024). Clinical advisers agreed that this was compelling data to support that nirogacestat patients in stable disease are different than placebo patients in stable disease and would, thus, have different HCRU assumptions. As such, the HCRU in the stable disease health state for nirogacestat was based on the frequency of GP and specialist visits for the ‘intermediate symptoms – low pain’ cluster. (Schut et al. 2023) reported numerically but not statistically significantly higher mean GP visits for the ‘intermediate symptoms – low pain’ cluster used for nirogacestat versus the ‘intermediate symptoms – high pain’ cluster used for BSC/placebo; therefore, using these granular costs could be considered a conservative approach. There were no other publications of HCRU identified in a DT population to serve as an alternative data source.

Table 3.23 Annual frequency of resource use for disease management by health state

Resource	Stable disease for nirogacestat	Stable disease for comparators	PR	CR	PD
GP (per visit) ^a	2.55	1.61	1.18	0.00	3.68
GP DT (per visit) ^a	0.40	0.21	0.18	0.00	1.02
Specialist (per visit) ^a	1.96	2.24	1.14	0.00	2.38
Full lab test (per test)	12.24	12.24	12.24	0.00	14.88
MRI (per test)	0.12	0.12	0.12	0.00	0.00
CT scan (per test)	3.72	3.72	3.72	0.00	4.44
Hospitalisation (per visit)	2.52	2.52	2.52	0.00	5.76

^a Data were digitised from Figure 3 from the Schut et al. 2023 publication for healthcare resource use by physical symptom burden clusters. The assumption that high symptom burden could inform PD, intermediate symptoms could inform stable disease (low pain for nirogacestat, high pain for BSC/placebo), and low symptom burden could inform PR was validated with clinical experts.

Abbreviations: BSC, best supportive care; CR, complete response; DT, desmoid tumour; GP, general practitioner; PD, progressed disease; PR, partial response.

Source: Schut et al. (2023); Verboom et al. (2019).

The unit costs for physician visits were obtained from the Unit Costs of Health and Social Care 2023 Manual and the National Schedule of NHS Costs 2023/24 (National Health Service England 2024). All unit costs are summarised in **Table 3.24**.

Table 3.24 Disease management unit costs

Resource	Unit Cost	Source(s)/Notes
GP (per visit)	£45.00	Unit Costs of Health and Social Care 2023 Manual, Unit costs for a GP, per surgery consultation lasting 9.22 minutes, with direct care staff costs and qualifications (Personal Social Services Research Unit 2023)
GP DT (per visit)	£162.00	Weighted average of National Schedule of NHS Costs 2023/24, Clinical Oncology Service, Non Consultant led, WF01A-WF02D (Outpatient Care) (National Health Service England 2024)
Specialist (per visit)	£159.00	Weighted average of National Schedule of NHS Costs 2023/24, Clinical Oncology Service, Consultant led, WF01A-WF02D (Outpatient Care) (National Health Service England 2024)
Full lab test (per test)	£5.00	Weighted average of National Schedule of NHS Costs 2023/24, PATH04 - Clinical biochemistry, PATH05 - Haematology (Other currency) (National Health Service England 2024)
MRI (per test)	£171.00	Weighted average of National Schedule of NHS Costs 2023/24, RD01A-RD07Z (Diagnostic Imaging) (National Health Service England 2024)
CT scan (per test)	£119.00	Weighted average of National Schedule of NHS Costs 2023/24, RD20A-RD27Z (Diagnostic Imaging) (National Health Service England 2024)
Hospitalisation (per visit)	£2,597.00	Weighted average of National Schedule of NHS Costs 2023/24, Weighted mean cost for non-elective inpatient long stay and short stay (Admitted patient care) (National Health Service England 2024)

Abbreviations: DT, desmoid tumour; GP, general practitioner.

The frequencies of use for each resource (**Table 3.23**) were multiplied by the unit costs (**Table 3.24**) to determine the total weighted average disease management cost per cycle associated with each health state (**Table 3.25**).

Table 3.25 Disease management costs per cycle by health state

Resource	Stable disease for nirogacestat	Stable disease for BSC/placebo	PR	CR	PD
Total Disease Management Cost (per cycle)	£579.60	£577.39	£562.09	£0	£1,247.25

Abbreviations: BSC, best supportive care; CR, complete response; PD, progressed disease; PR, partial response.

Patients who transition to the death health state incur a one-time cost for end-of-life care. The terminal care cost is £1,117.42 based on the Unit Costs of Health and Social Care 2024 Manual, which is applied in full to all patients who die in each model cycle (Personal Social Services Research Unit 2025).

3.5.4 Adverse reaction unit costs and resource use

To reflect the safety profile of treatments in the model, TEAE data from the DeFi trial was used, where AEs were modelled as either severe/serious (i.e., grade ≥ 3) one-off events or mild-to-moderate (i.e., grade 1 or 2) recurring events. One-off AEs were applied as a one-time cost in the first model cycle because these AEs are most likely to occur with treatment initiation and lead to treatment discontinuation, while costs for recurring AEs were applied in each cycle during the treatment period.

3.5.4.1 One-off adverse event costs

The criteria for identifying one-off AEs for inclusion in the model was defined as grade 3 or higher AEs occurring in greater than or equal to 5% of participants in the DeFi trial (SpringWorks Therapeutics 2023b). The proportion of patients experiencing one-off AEs is presented in **Table 3.16**.

Costs for managing each AE episode were obtained from the National Schedule of NHS Costs 2023/24 (National Health Service England 2024) (**Table 3.26**). Clinical experts from the UK were consulted to validate the costs for these AEs and the associated resources used.

Table 3.26 One-off grade ≥ 3 AE unit costs

Adverse Event	Unit Cost	Source(s)/Notes
Diarrhoea	£595.00	Weighted average of National Schedule of NHS Costs 2023/24, FD01-FD01J (non-elective short stay) (National Health Service England 2024)
Folliculitis	£512.00	Assumed to be equal to rash/skin
Any rash or skin disorders	£512.00	Weighted average of National Schedule of NHS Costs 2023/24, JD07A–JD07K (non-elective short stay) (National Health Service England 2024)

Abbreviation: AE, adverse event.

The first-cycle AE cost was calculated by multiplying the percentage of patients experiencing each AE (**Table 3.16**) by the cost per event (**Table 3.26**) and summing all one-off AEs per treatment arm (**Table 3.27**).

Table 3.27 One-off AE costs at the first cycle

	Nirogacestat	BSC/placebo
Total one-off AE cost (applied in the first model cycle)	£552.15	£26.00

Abbreviations: AE, adverse event; BSC, best supportive care.

3.5.4.2 Recurring adverse event costs

The recurring AE considered in the model was ovarian dysfunction (OD), as this was raised by clinical experts to be of particular clinical importance. This recurring AE was grade 1-2 (mild to moderate) and would not require treatment discontinuation; therefore, it was assumed that patients would experience this AE throughout their treatment duration. The percentage of participants experiencing OD were sourced from the DeFi trial for nirogacestat and BSC/placebo. **Table 3.28** summarises the percentage of patients experiencing this recurring AE for each treatment and then standardised to a proportion per 28-day model cycle (**Table 3.29**).

Table 3.28 Percentage of patients experiencing recurring grade 1-2 AEs

Recurring AE	Nirogacestat	BSC/placebo
OD	██████	████
Mean follow-up time (months)	████	████

Abbreviations: AE, adverse event; BSC, best supportive care; OD, ovarian dysfunction.
Source: SpringWorks Therapeutics (2023b).

Table 3.29 Percentage of patients experiencing recurring grade 1-2 AEs per 28-day model cycle

Recurring AE	Nirogacestat	BSC/placebo
OD	████	████

Abbreviations: AE, adverse event; BSC, best supportive care; OD, ovarian dysfunction.

The cost for managing each recurring AE episode was obtained from the National Schedule of NHS Costs 2023/24 (National Health Service England 2024) (**Table 3.30**). Clinical experts from the UK were consulted to validate this cost and the associated resources used.

Table 3.30 Recurring adverse event unit costs

Recurring Adverse Event	Unit Cost	Source(s)/Notes
OD	£486.00	Calculation including National Schedule of NHS Costs 2023/24 costs: first visit, follow-up, and diagnostic ultrasound. WF01A, WF01B, RD40Z

Abbreviations: OD, ovarian dysfunction.

Because the number of alive patients in each cycle during the treatment period is reduced over time, there is no fixed cost of recurring AEs per cycle.

3.5.5 Miscellaneous unit costs and resource use

Patient and caregiver indirect costs could be included to capture lost productivity due to missed work (i.e., absenteeism). In the reference case analysis, indirect costs associated with productivity loss costs were excluded. In a scenario analysis from a societal perspective, productivity loss costs were calculated by multiplying the number of working hours lost per week by health state by the hourly wage and employment rate in the UK. The hourly wage was £18.64 sourced from the ONS 2024 (Office for National Statistics 2024a). The total productivity loss cost considers the proportion of patients employed because unemployed patients do not contribute to lost work productivity. Furthermore, productivity loss costs were only applied up to retirement age (66 years old in the UK).

Data on work loss due to DT is very limited. A Dutch publication reporting experiences from a focus group found that some participants with DT had to stop working temporarily after treatment, ranging from a couple of weeks to two years or not being able to work at all (Timbergen et al. 2018). No other work loss data for patients with DT were identified in the literature. A systematic review of neuropathic pain literature identified a study reporting number of workdays lost for Spanish older adults with post-herpes zoster pain and their caregivers (Diez-Domingo et al. 2021). While pain is a common and burdensome symptom of DT, the clinical experts stated that, because DT can also be associated with mobility issues, this study could be considered an underestimate of the number of work-days lost for a patient with DT.

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Therefore, the indirect costs in the scenario analysis from the societal perspective should be taken as a conservative assumption.

It was assumed that productivity loss for employed patients would only occur in the PD health state, since it is the most “severe” state (i.e., stable disease, PR, and CR do not have productivity loss). Patients in the PD health state were assumed to lose 6.16 working hours per week, based on the study by Díez-Domingo 2021 that reported a mean of 9.9 workdays was lost over a period of 90 days (Diez-Domingo et al. 2021). This amounts to a total productivity loss cost per cycle of £399.12 for patients in the PD health state, based on an assumption that each workday consists of 8 hours.

To account for productivity losses for caregivers (by health state), an informal caregiver cost was included based on an hourly wage of £18.64 (Office for National Statistics 2024a). It was assumed that 0.81 hours of informal caregiver time per week was needed for patients in the PD health state based on the study by Díez-Domingo 2021 that reported caregivers lost an average of 1.3 paid workdays over a period of 90 days (Diez-Domingo et al. 2021). It was assumed that stable disease, PR, and CR patients do not require caregiver time. The total caregiver cost per cycle was £60.31 for patients in the PD health state.

3.6 Severity

The criteria for a severity weight may be met by DT. The QALY shortfall was calculated using pre-programmed software built in R (Schneider et al. 2021). Data informing the QALY shortfall calculation for the reference case were based on:

- Life tables: England, 2017-2019 (pooled) (Office for National Statistics 2024b);
- Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study (MVH Group 1995);
- Health state profiles: EQ-5D-3L from the Health Survey for England 2014 (University College London 2014), Model: ALDMMM by Hernández Alava et al. (2022).

Currently, no previous economic evaluations and QALY shortfall analyses exist for DT.

Table 3.31 outlines the health state benefits and utility values that were used for the QALY shortfall analysis. The estimated QALYs for the BSC/placebo are [REDACTED] QALYs, based on a lifetime model horizon, with outcomes discounted at 3.5% and age-adjusted utilities applied. The results of QALY shortfall calculation are shown in **Table 3.32**.

Table 3.31 Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years ^a
Stable disease on tx	0.7360 (0.0213)	1.255
Stable disease off tx	0.7360 (0.0213)	0.541
PR on tx	0.7920 (0.0169)	0.051
PR off tx	0.7920 (0.0169)	0.106
CR on tx	0.8600 (0.0860)	0.000
CR off tx	0.8600 (0.0860)	0.000
PD	0.2630 (0.0231)	41.149

^a Note that undiscounted life years are not used in the QALY shortfall analysis reported in **Table 3.32** below, as the base-case model applies age-adjustment to the utilities and a 3.5% discount rate to outcomes over the time horizon.

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; QALY, quality-adjusted life year; tx, treatment.

Table 3.32 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
19.39	BSC/placebo: [REDACTED]	Absolute shortfall: 13.05 Proportional shortfall: 67.30% QALY weight: x1.2

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

3.7 Uncertainty

There were gaps in the literature needed to inform some model inputs (e.g., utilities and long-term progression data for the target population) due to the rarity of DT and the available data from the DeFi trial (e.g., no follow-up data after participants progress or discontinue nirogacestat, low number of progression events, small

starting sample sizes for some subgroups, etc.), which required assumptions or the use of inputs from other disease analogues.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

A summary of the variables that were used in the economic model are presented in **Table 3.33**.

Table 3.33 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)		Reference to section in submission
		Standard error ^a	Distribution	
Model characteristics				
Perspective	Healthcare payer (NHS and PSS)	Not varied	Not varied	3.2.2
Time horizon	62.8 years	6.28	Normal	3.2.2
Discount rates for costs and effects ^b	3.50%	0.004	Beta	3.2.2
Patient characteristics				
Mean baseline age, years (SE)	37.20	1.14	Normal	3.2.1
Female (%)	64.8%	0.06	Beta	3.2.1
Efficacy data				
Maximum treatment duration	2 years	Not varied	Not varied	3.3.1
CR at 2 years (Best overall response - Nirogacestat)	7.1%	████	Beta	3.3.2
CR at 2 years (Best overall response - BSC/placebo)	0.0%	████	Beta	3.3.2
PR at 2 years (Best overall response - Nirogacestat)	34.3%	████	Beta	3.3.2
PR at 2 years (Best overall response - BSC/placebo)	8.3%	████	Beta	3.3.2
Annual rate of progression from PR to PD during 2-year treatment period (Nirogacestat)	████	████	Beta	3.3.3.1
Annual rate of progression from PR to PD after 2-year treatment period (Nirogacestat)	████	████	Beta	3.3.3.2
Annual rate of progression from PR to PD during 2-	████	████	Beta	3.3.3.1

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)		Reference to section in submission
		Standard error ^a	Distribution	
year treatment period (BSC/placebo)				
Annual rate of progression from PR to PD <u>after</u> 2-year treatment period (BSC/placebo)	████	████	Beta	3.3.3.2
Annual rate of progression from stable disease to PD <u>during</u> 2-year treatment period (Nirogacestat)	████	████	Beta	3.3.3.1
Annual rate of progression from stable disease to PD <u>after</u> 2-year treatment period (Nirogacestat)	████	████	Beta	3.3.3.2
Annual rate of progression from stable disease to PD <u>during</u> 2-year treatment period (BSC/placebo)	████	████	Beta	3.3.3.1
Annual rate of progression from stable disease to PD <u>after</u> 2-year treatment period (BSC/placebo)	████	████	Beta	3.3.3.2
Mortality data				
HR of death in patients with stable disease vs. general population	1.00	0.100	Lognormal	3.3.5.1
HR of death in patients with PR vs. general population	1.00	0.100	Lognormal	3.3.5.1
HR of death in patients with CR vs. general population	1.00	0.100	Lognormal	3.3.5.1
HR of death in patients with PD vs. general population	1.30	0.427	Lognormal	3.3.5.1
Safety data (One-off grade 3-4 TEAEs; occurring in ≥5% of patients in any of the included treatment arms)				
Diarrhoea (Nirogacestat)	15.9%	0.016	Beta	3.3.6
Folliculitis (Nirogacestat)	5.8%	0.006	Beta	3.3.6
Any rash or skin disorders (Nirogacestat)	8.7%	0.009	Beta	3.3.6
Diarrhoea (BSC/placebo)	1.4%	0.001	Beta	3.3.6
Folliculitis (BSC/placebo)	0.0%	0.000	Beta	3.3.6
Any rash or skin disorders (BSC/placebo)	0.0%	0.000	Beta	3.3.6
Safety data (Recurring grade 1-2 AEs)				
OD (Nirogacestat)	████	████	Beta	3.5.4.2
OD (BSC/placebo)	████	████	Beta	3.5.4.2
Costs data				
Drug acquisition cost per cycle with RDI (Nirogacestat)	████████	████████	Gamma	3.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)		Reference to section in submission
		Standard error ^a	Distribution	
Relative dose intensity (Nirogacestat)	████	████	Beta	3.5.1
Oral administration cost	£0.00	£0.000	Gamma	3.5.1
IV administration cost	£152.00	£15.200	Gamma	3.5.1
AE costs				
Diarrhoea (Unit costs)	£595.00	£59.500	Gamma	3.5.4.1
Folliculitis (Unit costs)	£512.00	£51.200	Gamma	3.5.4.1
Any rash or skin disorders (Unit costs)	£512.00	£51.200	Gamma	3.5.4.1
OD (Unit costs)	£486.00	£48.600	Gamma	3.5.4.2
Subsequent therapy costs				
Nirogacestat	£256.45	£25.645	Gamma	3.5.2
BSC/placebo	£256.45	£25.645	Gamma	3.5.2
HCRU (disease management) costs				
GP (per visit) (Unit costs)	£45.00	£4.500	Gamma	3.5.3
GP DT (per visit) (Unit costs)	£162.00	£16.200	Gamma	3.5.3
Specialist (per visit) (Unit costs)	£159.00	£15.900	Gamma	3.5.3
Full lab test (per test) (Unit costs)	£5.00	£0.500	Gamma	3.5.3
MRI (each) (Unit costs)	£171.00	£17.100	Gamma	3.5.3
CT scan (each) (Unit costs)	£119.00	£11.900	Gamma	3.5.3
Hospitalization (per visit) (Unit costs)	£2,597.00	£259.700	Gamma	3.5.3
GP visit (Frequency per year – stable disease for nirogacestat)	2.55	0.255	Gamma	3.5.3
GP DT visit (Frequency per year – stable disease for nirogacestat)	0.40	0.040	Gamma	3.5.3
Specialist visit (Frequency per year – stable disease for nirogacestat)	1.96	0.196	Gamma	3.5.3
Full lab test (Frequency per year – stable disease for nirogacestat)	12.24	1.224	Gamma	3.5.3
MRI (Frequency per year – stable disease for nirogacestat)	0.12	0.012	Gamma	3.5.3
CT scan (Frequency per year – stable disease for nirogacestat)	3.72	0.372	Gamma	3.5.3
Hospitalization visit (Frequency per year – stable disease for nirogacestat)	2.52	0.252	Gamma	3.5.3
GP visit (Frequency per year – stable disease for BSC/placebo)	1.61	0.161	Gamma	3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)		Reference to section in submission
		Standard error ^a	Distribution	
GP DT visit (Frequency per year – stable disease for BSC/placebo)	0.21	0.021	Gamma	3.5.3
Specialist visit (Frequency per year – stable disease for BSC/placebo)	2.24	0.224	Gamma	3.5.3
Full lab test (Frequency per year – stable disease for BSC/placebo)	12.24	1.224	Gamma	3.5.3
MRI (Frequency per year – stable disease for BSC/placebo)	0.12	0.012	Gamma	3.5.3
CT scan (Frequency per year – stable disease for BSC/placebo)	3.72	0.372	Gamma	3.5.3
Hospitalization visit (Frequency per year – stable disease for BSC/placebo)	2.52	0.252	Gamma	3.5.3
GP visit (Frequency per year - PR)	1.18	0.118	Gamma	3.5.3
GP DT visit (Frequency per year - PR)	0.18	0.018	Gamma	3.5.3
Specialist visit (Frequency per year - PR)	1.14	0.114	Gamma	3.5.3
Full lab test (Frequency per year - PR)	12.24	1.224	Gamma	3.5.3
MRI (Frequency per year - PR)	0.12	0.012	Gamma	3.5.3
CT scan (Frequency per year - PR)	3.72	0.372	Gamma	3.5.3
Hospitalization visit (Frequency per year - PR)	2.52	0.252	Gamma	3.5.3
GP visit (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
GP DT visit (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
Specialist visit (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
Full lab test (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
MRI (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
CT scan (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
Hospitalization visit (Frequency per year - CR)	0.00	0.000	Gamma	3.5.3
GP visit (Frequency per year - PD)	3.68	0.368	Gamma	3.5.3
GP DT visit (Frequency per year - PD)	1.02	0.102	Gamma	3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)		Reference to section in submission
		Standard error ^a	Distribution	
Specialist visit (Frequency per year - PD)	2.38	0.238	Gamma	3.5.3
Full lab test (Frequency per year - PD)	14.88	1.488	Gamma	3.5.3
MRI (Frequency per year - PD)	0.00	0.000	Gamma	3.5.3
CT scan (Frequency per year - PD)	4.44	0.444	Gamma	3.5.3
Hospitalization visit (Frequency per year - PD)	5.76	0.576	Gamma	3.5.3
End-of-life care cost (one-off)	£1,117.42	£111.742	Gamma	3.5.3
Utilities				
Health state utilities (at baseline)				
Stable disease	0.7360	0.021	Beta	3.4.6
PR	0.7920	0.017	Beta	3.4.6
CR	0.8600	0.086	Beta	3.4.6
PD (Health state utility)	0.2630	0.023	Beta	3.4.6
Utility decrements for AEs				
Diarrhoea (Mean one-off AE disutilities)	-0.3270	0.025	Beta	3.4.4
Folliculitis (Mean one-off AE disutilities)	-0.0325	0.012	Beta	3.4.4
Any rash or skin disorders (Mean one-off AE disutilities)	-0.0325	0.012	Beta	3.4.4
OD (Mean one-off AE disutilities)	-0.0950	0.010	Beta	3.4.4
Diarrhoea (Mean one-off AE duration [Days])	7	0.700	Gamma	3.4.4
Folliculitis (Mean one-off AE duration [Days])	7	0.700	Gamma	3.4.4
Any rash or skin disorders (Mean one-off AE duration [Days])	7	0.700	Gamma	3.4.4
██████████	█	████	████	████
Utility decrements for caregiver burden				
Caregiver disutility – Stable Disease	0.0000	0.000	Beta	3.4.5
Caregiver disutility - PR	0.0000	0.000	Beta	3.4.5
Caregiver disutility - CR	0.0000	0.000	Beta	3.4.5
Caregiver disutility - PD	-0.0700	0.007	Beta	3.4.5

Note: For deterministic one-way sensitivity analysis, inputs are varied 20% around the base case values except where estimates could not exceed 100% to create low and high values for testing.

^a Standard error was based on the sources that informed the point estimates (when reported/available); if a CI was available, that was used to calculate the SE for the parameter (SEs informed by sources are presented with their respective references). For parameters that lacked uncertainty data, the SE was assumed to be 10% of the point estimate. This was assumed to represent a reasonable degree of uncertainty and provided realistic values.

^b Not included in PSA but included in DSA.

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; CR, complete response; DSA, deterministic sensitivity analysis; DT, Desmoid tumour; GP, general practitioner; HCRU, healthcare resource use; HR, hazard ratio; IV, intravenous; OD, ovarian dysfunction; PD, progressed disease; PR, partial response; PSA, probabilistic sensitivity analysis; SE, standard error; SRA, scenario risk analysis; T, total; UK, United Kingdom; V, value; W, weight; Y, year.

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response; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; SE, standard error; TEAE, treatment-emergent adverse event.

3.8.2 Assumptions

Table 3.34 provides an overview of assumptions that were applied in the model, which should be taken into consideration when assessing the results provided in **Section 3.9**.

Table 3.34 Model assumptions

Assumption	Rationale/Support
A lifetime horizon for the modelled population is ~63 years.	As per NICE reference case. Additionally, this is the time horizon at which <1% of modelled patients are alive. A long time horizon was necessary to capture the lifespan of the model cohort and the lifetime treatment benefits. Further details are provided in Section 3.2.2 .
The maximum treatment duration in the model is up to 2 years, and rates of best overall response achieved among participants with up to 2 years of treatment in DeFi are used to predict the QALY gains for nirgacestat.	An optimal duration of treatment with systemic treatments in DT has not been reported in treatment guidelines (Kasper et al. 2024a). Treatment up to 2 years is in line with the median duration of treatment for nirgacestat (20.6 months) from the DeFi study (Gounder et al. 2023a), and confirmed with UK clinical advisers that a best response should be achieved within 2-years. This is further supported by the nirgacestat median time to response of 5.6 months, which is well within this treatment duration. Further details are provided in Section 3.3.1 .
After the treatment duration (i.e., after treatment discontinuation), a patient's response status cannot improve further.	UK clinical advisers agreed that a best and final response should be achieved within the treatment duration for most patients. Although spontaneous regression is a characteristic of the natural history of DT and is commonly observed in patients whose disease can be stabilised on active surveillance alone, it is not likely to occur within the DeFi population because the participants had progressing tumours. Clinical expert opinion supports the assumption that further improvement in tumor response status without treatment is not expected in this group. Further details are provided in Section 3.2.2 .
Patients in CR do not progress (transition to PD), according to the model design.	UK clinical advisers validated the model design and provided clinical expert opinion / anecdotal feedback that tumours did not return among patients who achieved CR. Duration of exposure and response data from the DeFi study, moreover, showed no progression events among the participants achieving CR (Gounder et al. 2023a). Further details are provided in Section 3.2.2 .
Patients who achieve PR during treatment with nirgacestat were assumed to experience no tumour progression after treatment stops (i.e., annual rate of off-treatment progression from PR to PD is 0%).	Clinical adviser feedback that disease-modifying treatments would effectively change the tumour structure and cellularity, and achieving a PR would indicate that a tumour has been modified and would be expected to stabilise (or potentially continue to shrink). Further details are provided in Section 3.3.3.2 .
Treatment benefit in stable disease is assumed to persist after stopping treatment (i.e., the annual rates	Once tumours stabilise or decrease in size, they will remain inactive due to the disease modification from active treatment (Colombo et al. 2025). This was

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Assumption	Rationale/Support
of progression from stable disease to PD are the same during and after the treatment period).	demonstrated with imaging and biopsy data for nirogacestat showing measurable reductions in tumour size and volume as well as decreased tumoral cellularity (Anneberg et al. 2022b, Gounder et al. 2023a, Kummar et al. 2017). The lifelong durability of response was also validated with clinical expert opinion. Further details are provided in Section 3.3.3.2.
Patients who are alive in PD will stay in PD for the rest of the model time horizon, accruing the PD utility value and HCRU.	Time in a health state is not tracked in the model, which is a common limitation and property of Markov models. The model design, which was validated with 3 clinical experts, does not allow patients to transition out of PD except for death; therefore, patients will remain in PD until death. As a rare disease, there is limited information to inform long-term outcomes or the impact of subsequent treatment on post-progression survival. Further details are provided in Section 3.2.2.
Patients who achieve stabilised or reduced tumour burden (i.e., stable disease, PR, or CR) are assumed to have the same mortality risk as general population. The hazard ratio for mortality risk for patients with PD (i.e., advancing disease) was assumed to be 1.3 times higher than that of general population mortality. Risk of mortality of patients with DT in the model cannot be lower than the risk of mortality of the general population.	Mortality data from Anneberg et al. 2022 suggest that patients with DT have a numerically (HR=1.3) higher risk of mortality than matched cohort (general Danish population) (Anneberg et al. 2022b). Therefore, excess mortality was applied to the most severe disease health state (i.e., PD). General population mortality was used in the model to ensure mortality estimates remained clinically plausible (i.e., patients do not live longer than life expectancy). Further details are provided in Section 3.3.5.1.
Resource use differs by health state rather than by treatment received (except HCRU in the stable disease health state differs between nirogacestat and BSC/placebo). The CR health state is assumed to have no HCRU, whereas the PD health state is assumed to have the highest frequency of resource utilization.	The HCRU estimates were validated by clinical experts from the UK. They also confirmed that stable disease patients treated with nirogacestat would have different resource use (and QoL), based on data from the DeFi study showing nirogacestat benefits on pain/PRO among patients achieving a best response of stable disease compared with placebo (Stacchiotti et al. 2024). Further details are provided in Section 3.5.3.
RDI was accounted for in drug acquisition costs and reflects the average dose received.	It is important to accurately calculate the true (real-world) treatment cost for an average patient, as it reflects the average dose across all patients in the ITT population, including patients who discontinued or had dose modifications. Further details are provided in Section 3.5.1.
Subsequent therapy costs are applied as a mixed treatment basket and recurring cost (without impact to efficacy).	As confirmed by the clinical expert advisers, there is no defined treatment sequence and therapies used in subsequent lines are variable (e.g., depends on what is available to the physician). It was agreed that a mixed basket approach applied to PD patients was an appropriate reflection of clinical management in later lines. Further details are provided in Section 3.5.2.
Health state utilities (except for CR) are based on EQ-5D utility values elicited for STS. CR utility was assumed to reflect the population norm for UK.	Since there was no utility data in a DT population, utility options were discussed with clinical experts. Deriving mapped utilities from the DeFi study was associated with methodological challenges (e.g., PRO assessment time points did not fully overlap, no data for participants after they progress, and small sample size in the DeFi trial). Therefore, mapping utilities from the DeFi trial could not reliably produce valid health state utilities and, as such, literature-based utility values were considered the best available data source for informing the model. DT is a type of soft tissue tumour, with STS being identified as a disease analogue by NICE given their similarities in origins, clinical presentation, symptoms, diagnostic

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Assumption	Rationale/Support
	and treatment pathway, and management by oncologists/STS specialists (Desmoid Tumor Working Group 2020, Huss et al. 2013, Kasper et al. 2011, Mercier et al. 2020, Penel et al. 2016). Additionally, given that CR patients are defined by the absence of tumour, it was reasonable to assign a utility value that reflects general population. Further details are provided in Section 3.4.3 and 3.4.6 .
AE management costs/disutilities reflect grades 3 and 4 events and are applied as a one-time upfront cost/disutility in the first cycle. However, grade 1-2 recurrent AEs of special interest were also included and costed on a per-cycle basis.	Grade 3-4 AEs were assumed to be costly/severe events that would require hospitalization and utility decrements. Because AEs were assumed to be treatment-emergent, AE management costs and disutilities were applied in the first cycle such that they would apply to all patients that received treatment. For the recurring AEs, since they were grade 1-2, they were assumed to be mild enough that they would persist during treatment without requiring treatment discontinuation. Further details are provided in Section 3.4.4 .

Abbreviations: AE, adverse event; CR, complete response; DT, desmoid tumours; HCRU, healthcare resource use; HR, hazard ratio; ITT, intent-to-treat; PD, progressed disease; PR, partial response; PRO, patient-reported outcome; QALY, quality-adjusted life year; QoL, quality of life; RDI, relative dose intensity; STS, soft-tissue sarcoma.

3.9 Base-case results

The economic model results are presented below. The comparison between the clinical trial results and the model results are presented in **Appendix H** with the disaggregated base case results.

3.9.1 Base-case incremental cost-effectiveness analysis results

The discounted pairwise reference case results for nirogacestat versus BSC/placebo are summarised below. The total costs life years (LYs), quality-adjusted life years (QALYs), incremental costs, incremental LYs, and incremental QALYs, are shown in **Table 3.35**. Compared with BSC/placebo, nirogacestat was more effective (■■■■■ QALYs) and associated with higher costs (£198,419) over a lifetime time horizon, resulting in an incremental cost utility ratio (ICUR) of ■■■■■ per QALY gained.

Table 3.35 Base-case results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICUR (£/QALY)
BSC/ Placebo	£413,285	22.204	■■■■■	-	-	-	-
Nirogacestat	£611,704	22.436	■■■■■	£198,419	0.232	■■■■■	■■■■■

Abbreviations: BSC, best supportive care; ICUR, incremental cost-utility ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The net health benefit of nirogacestat and BSC/ placebo is presented in **Table 3.36**.

Table 3.36 Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
BSC/ Placebo	£413,285		-	-	-	-
Nirogacestat	£611,704		£198,419			

Abbreviations: BSC, best supportive care; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

3.10 Exploring uncertainty

The robustness of the cost-effectiveness results was assessed by addressing uncertainty through several methods. Probabilistic sensitivity analysis (PSA) was used to quantify the impact of parameter uncertainty on cost-effectiveness estimates by varying all model inputs simultaneously according to their respective probability distributions. One-way sensitivity analyses (OWSAs) of key input parameters were used to identify parameters to which the model ICUR results are most sensitive (i.e., model drivers) by adjusting the default value by 20% (except where estimates could not exceed 100%) to create a low and high value. Lastly, deterministic scenario analyses were used to explore the model's robustness to alternative assumptions, particularly to parameters that were identified as being key model drivers.

The PSA showed minimal impact related to uncertainty in the sampling distribution of included parameters, supporting the reliability of the mean variables used in the deterministic base case analysis. The uncertainty associated with different model structure assumptions had a noticeable impact on cost-effectiveness estimates, as shown by the scenario analysis results.

3.10.1 Probabilistic sensitivity analysis

The PSA was conducted in order to account for the joint uncertainty of the underlying parameter estimates (National Institute for Health and Care Excellence 2025).

Common distributions used in probabilistic analyses are beta (e.g., for utilities), gamma (e.g., for costs), log-normal (e.g., for hazard ratios), and normal (e.g., for baseline characteristics), and the choice of distribution was selected based on recommendations in Briggs et al. (2006). Correlation between select inputs were

considered in the PSA (e.g., health state utility values should show highest utility for CR and lowest utility for PD, best overall response for nirogacestat would be higher than for BSC/placebo, and progression rates for nirogacestat would be lower than BSC/placebo) by using the same random numbers for each “set” of inputs. The list of PSA inputs was presented in **Table 3.33**. The PSA was conducted using 1,000 iterations, which showed convergence in the probabilistic results.

The results of the PSA based on 1,000 iterations are presented in **Table 3.37**. The probabilistic sensitivity results were similar to the base-case deterministic results.

Table 3.37 Mean (95% CI) discounted probabilistic sensitivity results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICUR (£/QALY)
BSC/placebo	£413,161 (£327,196, £516,109)	22.186 (19.963, 23.985)					
Nirogacestat	£611,982 (£512,020, £689,541)	22.451 (21.051, 23.616)		£198,821	0.265		

Abbreviations: BSC, best supportive care; CI, confidence interval; ICUR, incremental cost-utility ratio; LYG, life years gained; QALYs, quality-adjusted life years.

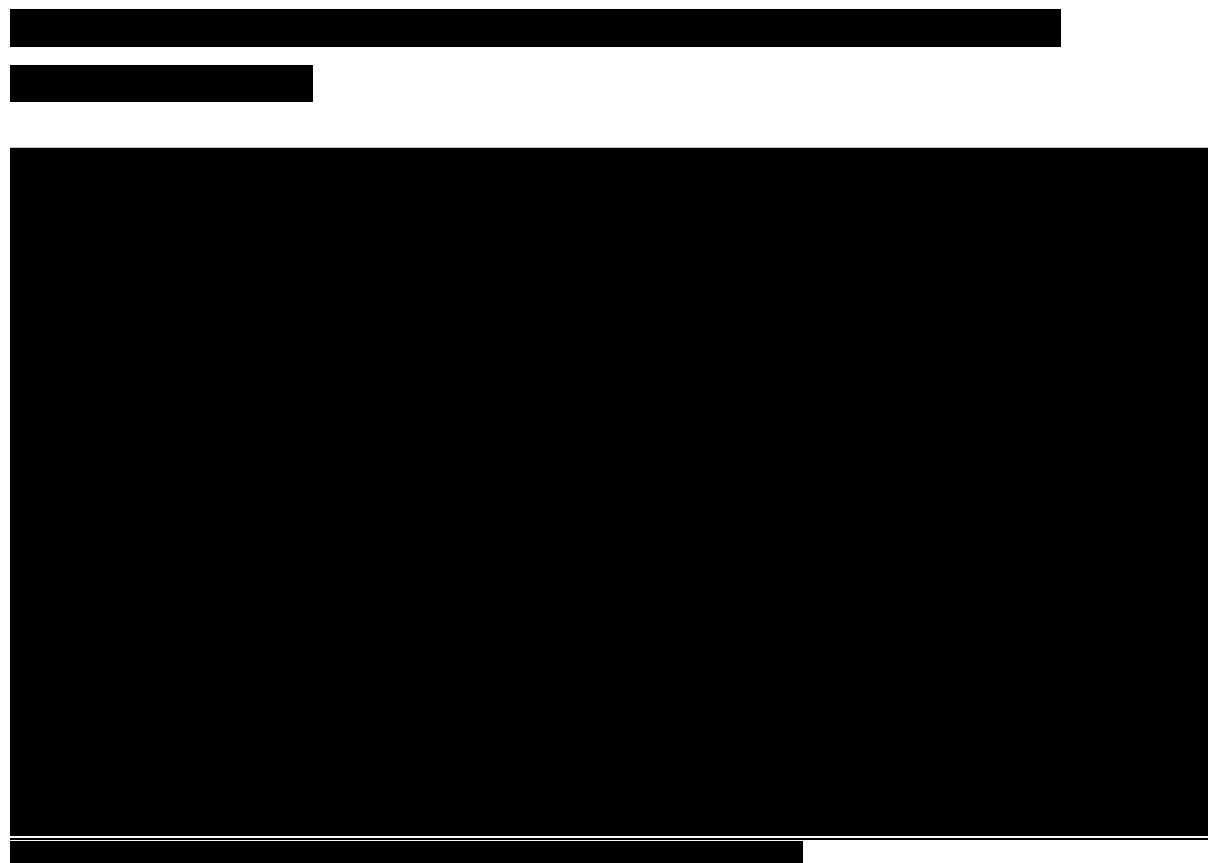
The scatter plot of incremental costs versus incremental QALYs for nirogacestat versus BSC/placebo is presented in **Figure 3.6**.



The cost-effectiveness acceptability curve, which was constructed using net monetary benefit, showing the probability of being the most cost-effective therapy at

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different willingness-to-pay thresholds is presented in **Figure 3.7**. At willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, nirogacestat was cost-effective in [REDACTED] and [REDACTED] of iterations, respectively. Further, when the QALY shortfall weight (severity modifier) was applied, the ICUR was [REDACTED] per QALY gained and nirogacestat was cost-effective in [REDACTED] and [REDACTED] of iterations at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively.



3.10.2 Deterministic sensitivity analysis

The OWSA of all input parameters was used to identify parameters to which the model ICUR results were most sensitive (i.e., model drivers) by adjusting the default value by 20% (except where estimates could not exceed 100%) to create a low and high value. During this analysis, all model parameters except the one that is being changed, remained at their reference case values (i.e., one-way). Distributions that needed to sum to 100% were not incorporated into the OWSAs, as a single outcome

cannot be varied without also varying the other dependent outcomes. The list of inputs included in the OWSA were presented above in **Table 3.33**.

The tornado diagram (**Figure 3.8**) presents the 10 variables having the greatest impact on the base-case ICUR. Drug acquisition cost, relative dose intensity, health state utility of PR, HCRU (namely hospitalisation) in the PD health state, and achievement of PR as best overall response for nirogacestat were among the most impactful parameters on the ICUR.



3.10.3 Scenario analysis

In order to test the impact of uncertainty in key model inputs and assumptions, several deterministic scenario analyses were conducted. Model analyses were re-run after changing selected inputs to reflect alternative assumptions/scenarios. The results of scenario analyses are summarised in **Table 3.38**. Incremental results and the ICUR reported as costs per QALY gained are summarised by treatment arm. The deterministic ICURs of nirogacestat versus BSC/placebo ranged from [REDACTED] per QALY gained to [REDACTED] per QALY gained (-62% to 85% relative change in the base-case ICUR). The probabilistic scenario analysis results (**Table 3.39**) were consistent with the deterministic scenario analysis results.

Table 3.38 Summary of cost-effective results of deterministic scenario analyses

Scenario	Base case value	Alternative value	Nirogacestat versus BSC/placebo		
			Incremental costs	Incremental QALYs	ICUR (£/QALY)
Deterministic base case	N/A		£198,419	████	████
Alternative discount rates for costs and effects	3.5%	1.5%	£155,018	████	████
Assume no progression from stable disease to PD after treatment (for nirogacestat)	Annual rate of progression from stable disease to PD 'off tx': █████	Annual rate of progression from stable disease to PD 'off tx': ███	████	████	████
Hospitalisation annual frequency	PR and stable disease=2.52 PD=5.76	PR, stable disease, and PD=0	£287,673	████	████
Lower utility value for CR health state (assume equal to PR health state utility)	CR = 0.860	CR = 0.792	£198,419	████	████
Alternative utility value for PD health state from selumetinib CDA submission in NF	PD: 0.263	PD: 0.51	£198,419	████	████
Societal perspective	NHS and PSS perspective (i.e., indirect costs and caregiver disutility excluded)	Indirect costs and caregiver disutility included	£146,701	████	████
Discount range on nirogacestat list price	Discount = 0%	████	████	████	████
		████	████	████	████
		████	████	████	████

Abbreviations: AE, adverse event; BSC, best supportive care; CDA, Canadian Drug Agency; CR, complete response; ICUR, incremental cost-utility ratio; N/A, not available; NF, neurofibromatosis; PD, progressed disease; PR, partial response; PSS, Personal Social Services; QALY, quality-adjusted life year; tx, treatment.

Table 3.39 Summary of cost-effective results of probabilistic scenario analyses

Scenario	Base case value	Alternative value	Nirogacestat versus BSC/placebo		
			Incremental costs	Incremental QALYs	ICUR (£/QALY)
Probabilistic base case	N/A		£198,821	■	■
Alternative discount rates for costs and effects	3.5%	1.5%	£155,073	■	■
Assume no progression from stable disease to PD after treatment (for nirogacestat)	Annual rate of progression from stable disease to PD 'off tx': ■	Annual rate of progression from stable disease to PD 'off tx': ■	■	■	■
Hospitalisation annual frequency	PR and stable disease=2.52 PD=5.76	PR, stable disease, and PD=0	£288,067	■	■
Lower utility value for CR health state (assume equal to PR health state utility)	CR = 0.860	CR = 0.792	£198,821	■	■
Alternative utility value for PD health state from selumetinib CDA submission in NF	PD: 0.263	PD: 0.51	£198,821	■	■
Societal perspective	NHS and PSS perspective (i.e., indirect costs and caregiver disutility excluded)	Indirect costs and caregiver disutility included	£147,776	■	■
Discount range on nirogacestat list price	Discount = 0%	■	■	■	■
		■	■	■	■
		■	■	■	■

Abbreviations: AE, adverse event; BSC, best supportive care; CDA, Canadian Drug Agency; CR, complete response; ICUR, incremental cost-utility ratio; N/A, not available; NF, neurofibromatosis; PD, progressed disease; PR, partial response; PSS, Personal Social Services; QALY, quality-adjusted life year; tx, treatment.

3.11 Subgroup analysis

Subgroup analyses were conducted for the following narrower populations: patients with prior treatment/treatment-exposed (i.e., these patients had refractory or recurrent disease after previous treatment), treatment-naïve patients, patients with intra-abdominal tumours, patients with extra-abdominal tumours, and patients with history of familial adenomatous polyposis (FAP). These subgroups were identified

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from the final scope and decision problem specified by NICE for the NICE technology evaluation (see **Section 1**). The baseline demographics for these subgroups were similar to the total ITT population (**Table 3.40**).

Table 3.40 Patient characteristics of subgroups

Subgroups from DeFi Trial	Patient Characteristic		
	Mean age, years (SE)	Mean BSA ^a , m ² (SE)	Female (%)
Treatment naïve subgroup (n=32)	41.62 (2.99)	1.86 (0.04)	56.25
Previously treated subgroup (n=110)	35.95 (12.30)	1.92 (0.27)	67.27
Intra-abdominal tumour subgroup (n=33)	39.06 (2.65)	1.99 (0.05)	42.42
Extra-abdominal tumour subgroup (n=109)	36.67 (1.26)	1.88 (0.03)	71.56
FAP subgroup (n=24)	30.08 (1.45)	1.92 (0.07)	54.17

^a Mean BSA was calculated based on individual patient-level data; each patient's BSA was calculated using the following formula: square root of [(baseline weight [kg] × baseline height [cm])/3600].

Abbreviations: BSA, body surface area; FAP, familial adenomatous polyposis; SE, standard error.

Source: SpringWorks Therapeutics (2025b).

The deterministic ICURs of nirogacestat versus BSC/placebo ranged from [REDACTED] per QALY gained in the intra-abdominal tumour location subgroup to [REDACTED] per QALY gained in the treatment-naïve subgroup, and support the conclusions drawn from the base-case analysis that nirogacestat is associated with greater QALY gains and higher costs across all patient populations (**Table 3.41**). The probabilistic subgroup analysis results (**Table 3.42**) were consistent with the deterministic subgroup analysis results.

Table 3.41 Deterministic cost-effective results of subgroups

Scenario	Analysis population	Subgroup	Nirogacestat versus BSC/placebo		
			Incremental costs	Incremental QALYs	ICUR (£/QALY)
Deterministic base case	N/A		£198,419	[REDACTED]	[REDACTED]
Subgroup analysis	ITT population	Treatment-naïve subgroup	£226,834	[REDACTED]	[REDACTED]
		Previously treated subgroup	£199,519	[REDACTED]	[REDACTED]
		Intra-abdominal tumour location subgroup	£177,545	[REDACTED]	[REDACTED]
		Extra-abdominal tumour location subgroup	£213,729	[REDACTED]	[REDACTED]
		Patients with FAP	£212,898	[REDACTED]	[REDACTED]

Abbreviations: BSC, best supportive care; FAP, familial adenomatous polyposis; ICUR, incremental cost-utility ratio; ITT, intent-to-treat; N/A, not available; QALY, quality-adjusted life year.

Table 3.42 Probabilistic cost-effective results of subgroups

Scenario	Analysis population	Nirogacestat versus BSC/placebo		
		Incremental costs	Incremental QALYs	ICUR (£/QALY)
Probabilistic base case	ITT population	£198,821	■■■■	■■■■
Subgroup analysis	Treatment-naïve subgroup	£227,931	■■■■	■■■■
	Previously treated subgroup	£200,600	■■■■	■■■■
	Intra-abdominal tumour location subgroup	£177,441	■■■■	■■■■
	Extra-abdominal tumour location subgroup	£214,533	■■■■	■■■■
	Patients with FAP	£213,048	■■■■	■■■■

Abbreviations: BSC, best supportive care; FAP, familial adenomatous polyposis; ICUR, incremental cost-utility ratio; ITT, intent-to-treat; QALY, quality-adjusted life year.

3.12 Benefits not captured in the QALY calculation

The model captures the impact of response health state, AE, and caregiver burden in the QALY calculations. Nirogacestat may offer some benefit to QALYs through increasing the capacity for patients and caregivers to work and allowing patients to have a long-term positive outlook on life; however, it was not possible to capture this in the model design and economic analysis because there were no published data available.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

The model underwent an extensive technical validation/verification, with a thorough review of all mathematical formulas, sequences of calculations, and Visual Basic Application programming code by a second programmer not involved in the original development of the model. A standard operating procedure was followed, with detailed checklists, to ensure validation was thorough and appropriately documented. The technical validation process also included logic checking and applying extreme values to verify that the model behaves as expected. A quality check of the data inputs was also performed by an independent reviewer. Following the validation, any identified errors were subsequently corrected before the model was finalised.

In addition, the model face validity was reviewed with 3 UK clinical experts in 3 virtual advisory boards in terms of appropriateness of the model structure and disease dynamics (ensuring the model appropriately reflected the disease course), data sources, key clinical and input assumptions, and results (SpringWorks Therapeutics 2025a). Assumptions that are supported by clinical expert validation have been noted, where applicable. The clinical experts sought for consultation were all medical oncologists with a combined total of more than 25 years of experience in bone and soft tissue sarcomas and in managing patients with DT.

Internal validation was conducted to ensure consistency with the DeFi trial (e.g., that the proportion of nirogacestat and BSC/placebo participants in the PD health state lined up with the observed progression or PFS from the trial in terms of the cumulative incidence of RECIST and clinical progression events by 12-months and/or mPFS). Using a post-hoc reanalysis of duration of response data from the trial to estimate fixed rates of progression led to a model that underpredicted progression for BSC/placebo over time while progression was slightly overestimated for nirogacestat. To address this, the BSC/placebo and nirogacestat progression rates from stable disease to PD during treatment were calibrated/refined to produce progression curves that better fit the trial data and line up with clinical expert expectations.

External validation comparing progression rates predicted by the model to other publications in DT populations could not be conducted because of differences in patient populations, namely that the population enrolled in DeFi had more severe disease than any population described in available studies on the natural history of DT (e.g., real-world data from Colombo et al. (2025)). There is, consequently, no study with a comparable population to validate the untreated population in the model. No publications were identified to validate long-term progression projections for nirogacestat.

Cross-validation and predictive validation also could not be performed due to the absence of other economic analyses in this indication.

3.14 Interpretation and conclusions of economic evidence

This economic evaluation is the first to consider the cost effectiveness of nirogacestat compared with BSC/placebo in the treatment of progressing DT in the UK. In the reference case analysis, nirogacestat was more effective (██████ QALYs) and associated with higher costs (£198,419) than BSC/placebo, resulting in an ICUR of ██████ per QALY gained. The cost-effectiveness of nirogacestat was also shown in all groups of patients who could potentially use the technology, as identified in the decision problem. The results were generally stable across a variety of scenario analyses. The scenario analyses that resulted in the lowest and highest ICURs were the ones that assumed no progression from stable disease to PD after treatment for nirogacestat and used health state utility values from an alternative STS publication, respectively.

This economic evaluation has a number of methodological strengths. The model was informed by robust efficacy and safety data for nirogacestat from DeFi, a Phase 3 randomised clinical trial. The model underwent extensive internal validation to ensure consistency with the DeFi trial findings (e.g., that the proportion of nirogacestat and BSC/placebo participants in the PD health state aligned with the observed progression or PFS from the trial) and progression rates from stable disease to PD during treatment were calibrated to ensure alignment with the trial data and clinical expert opinion, as uncalibrated rates underpredicted progression for BSC/placebo over time while progression was slightly overestimated for nirogacestat. A comprehensive SLR was also used to support model design and parameterisation, and model structure, inputs, and key assumptions were validated by an advisory board of external clinical experts from England to ensure accuracy, completeness, and alignment with the disease course and UK clinical practice. The model is flexible in terms of comparators and cost categories that can be included or excluded in the analyses. The model's flexibility also allows for a broad range of scenario analyses to be conducted. Several scenarios were conducted to understand model drivers and test model sensitivity to assumptions and data gaps.

As with all economic models, this analysis is not without limitations. The key limitations of this analysis include those inherent to all economic modelling studies

(availability, accuracy and robustness of data and assumptions). There were gaps in the literature available to inform some model inputs, due to the rarity of DT and the available data from the DeFi trial (e.g., no follow-up data after patients progress or discontinue nirogacestat, low number of progression events, small starting sample sizes for some subgroups, etc.), which required assumptions or the use of inputs from other disease analogues. For example, since the DeFi trial did not collect EQ-5D and no published literature was identified to inform health state utility values collected from patients with DT, data for STS was used. The model design simplistically assumed constant transition probabilities for response and progression, that subsequent treatments would have no efficacy impact, and that patients remain in PD until death, which were all due to the limited availability of long-term data for the target population.

Overall, this economic evaluation suggests that nirogacestat is associated with greater costs and QALYs compared with BSC in the treatment of adults with progressing DT. As there is a significant unmet need for an effective and accessible treatment option that can provide comprehensive disease control for patients with progressing DT, and given the favourable clinical data for nirogacestat, SpringWorks requests that nirogacestat be considered for reimbursement for adult patients with progressing DT, in alignment with the reimbursement request.

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Company evidence submission template for nirogacestat for the treatment of desmoid tumours (DT) [ID6453]

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5 Appendices

Appendix A: Summary of product characteristics (SPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality-of-life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nirogacestat for treatment of desmoid tumours [ID6453]

Summary of Information for Patients (SIP)

September 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6453_OGSIVEO_summary-of-information-for-patients.docx	1.0	No	September 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Nirogacestat
Brand name: OGSIVEO®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult patients (aged 18 years and over) with progressing desmoid tumours who require a prescription medication by mouth or injection that works throughout the entire body (i.e., systemic therapy).

Signs of desmoid tumour progression may include:(1)

- Changes in imaging tests: The tumour may appear bigger on a CT scan or MRI
- New or changing symptoms: You may have new symptoms, or your existing symptoms such as pain may worsen

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Market authorisation for OGSIVEO® as a systemic monotherapy (single medicine) for progressing desmoid tumours is pending. UK Marketing Authorisation Application was submitted to the Medicines and Healthcare Regulatory Agency on July 11, 2025, with anticipated approval expected Q1 2026 (see Section 1.2 in the company submission).

On 18 August 2025, the European Commission granted approval for nirogacestat to treat desmoid tumours in patients with progressing desmoid tumours.(2)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

SpringWorks has existing collaborative relationships with Sarcoma UK, Desmoid Aid UK, and Desmoid Fibromatosis Facebook group, including financial support.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main condition that the medicine plans to treat: Desmoid tumours may develop in soft tissues such as muscle, fat, tendons, ligaments, lymph and blood vessels, or nerves that connect, support, and surround other structures in the body (connective tissue).(3) Because these tissues are found throughout the body, desmoid tumours can occur in almost any area.(4)

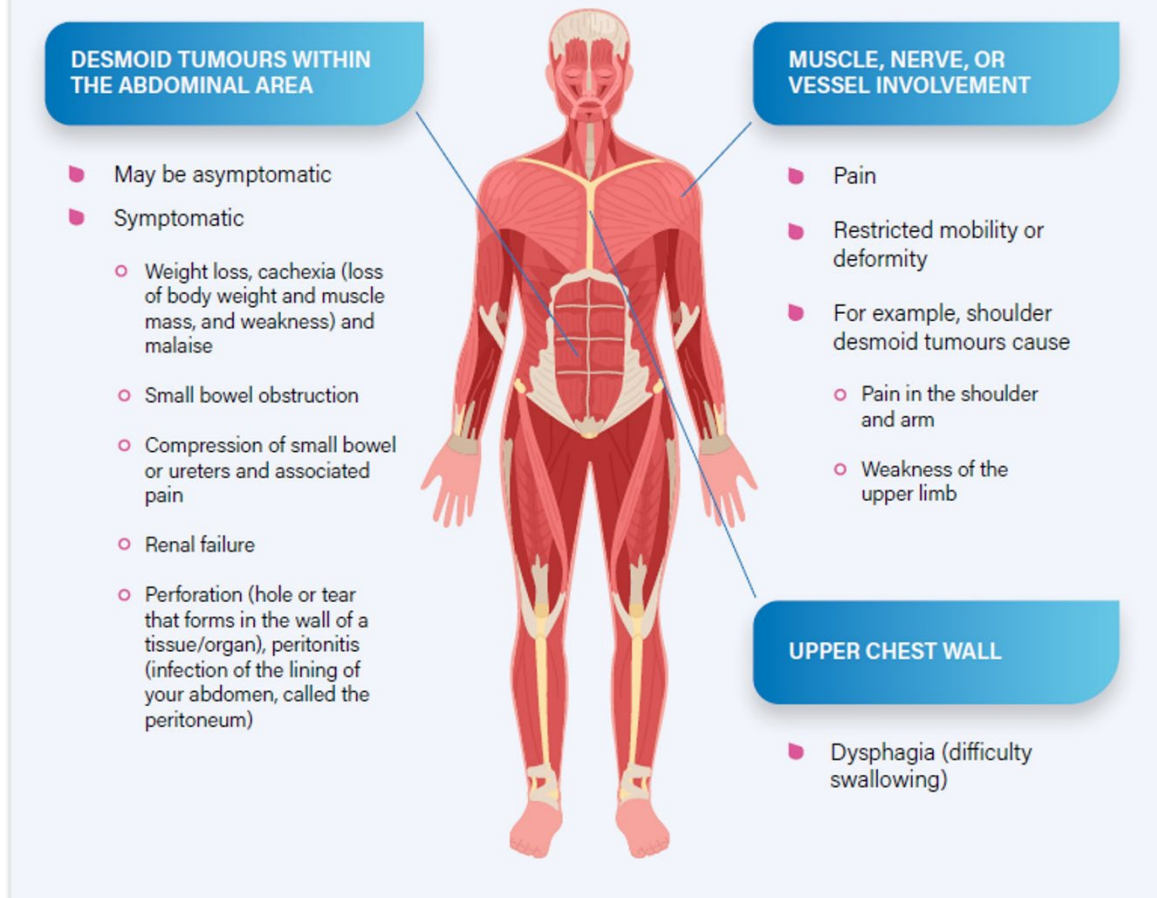
Desmoid tumours do not spread to other parts of the body (metastasise), but they can grow aggressively and affect and damage nearby tissues and organs, and can cause serious health problems as they grow.(3, 5)

Although desmoid tumours are not malignant, pain associated with tumours pressing on nerves and blood vessels can significantly impact your quality of life(QoL), including social interactions, ability to work, and personal relationships.(3, 6, 7)

It is important to know that desmoid tumours can also be referred to as the following medical terms: aggressive fibromatosis, desmoid-type fibromatosis, and deep fibromatosis.(8)

Main symptoms of the disease: The symptoms that you may experience with desmoid tumours depend on their location.(9, 10) For example, a tumour inside the abdomen may cause digestive system blockages, pain, a general feeling of discomfort, illness or lack of well-being, abdominal swelling, weight loss, or muscle loss.(10-12) Tumours in the arms or legs may cause limited movement, deformity, pain, or muscle problems.(10, 13, 14)

POSSIBLE SYMPTOMS ACCORDING TO THE LOCATION OF DESMOID TUMOURS MAY INCLUDE



How many people have the disease: In the UK, approximately 1 person out of every 150,000 develop desmoid tumours each year.(15, 16) Most desmoid tumour cases appear in adults aged 20–44 years.(17) Additionally, desmoid tumours are more common in women.(17)

Impact on QoL: People with desmoid tumours often deal with serious symptoms that affect their daily lives. The most common and difficult symptom is pain, which affects about 63% of patients.(18-20) Other problems include changes in appearance, limited movement, feeling tired, and trouble sleeping.(21)

Most people with desmoid tumours experience a moderate to high level of symptoms, which can make it hard to function normally and can lower a person's QoL.(22) People with desmoid tumours tend to have low overall health scores and more trouble with physical activity, emotional health, and social life.(19, 23)

Desmoid tumours also impact daily routines, relationships, and work.(18, 19, 24, 25) People have trouble with basic tasks like bathing and dressing, and do not enjoy hobbies.(19) Relationships with family, partners, and children often become strained, and some people deal with their illness alone so they do not burden others. Others struggle with parenting, like breastfeeding or playing with their kids.(18)

Work and finances are also affected. Many people have to stop working, take sick leave, or change jobs, which leads to financial problems.(18) Hospital visits and travel add to the financial stress. On top of that, people often feel isolated, anxious, or depressed. They struggle with how they look and with the uncertainty of living with a long-term illness.(18)

Pain, specifically, has been linked to lower QoL, including worse physical performance, difficulty doing everyday tasks, and shorter periods without health problems.(26) Pain made it harder for patients with desmoid tumours to sleep well and keep a job.(18) It also affected mental health, causing mood swings, irritability, and anxiety. Some people had to quit working, reduce their hours, or switch careers because of the pain.(18)

Burden of the disease: Desmoid tumours can affect each person differently depending on where the tumour is in the body, how fast it grows, and other factors. Seventy-five percent (75%) of people with desmoid tumours experience a moderate-to-high level of pain and other serious symptoms that affect daily living and QoL. Because of this, patients with desmoid tumours require a lot of medical care using a mix of treatments, which can be very costly to the healthcare system.(22, 27) For instance, patients with desmoid tumours whose symptoms substantially interfere with daily living are much more likely to visit their medical doctor for general and desmoid-tumour specific complaints.(22, 27) Patients with desmoid tumours are also much more likely to be hospitalised, and the chance of being hospitalised grows the longer the patient has lived with desmoid tumours.(27)

Treatments for desmoid tumours, including surgery and medicines, can be very expensive. Costs can exceed over €500,000 for 1 year of treatment in Europe.(28)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How desmoid tumours are diagnosed: Diagnosis of desmoid tumours can be tricky because it shares symptoms and often looks like several other soft-tissue tumours.(17, 29, 30)

Typically, diagnosis involves a combination of medical history, physical examination, symptomatology, imaging, and biopsy.(17, 29, 31, 32) At presentation, patients usually have a lump or mass that can be felt by touch (also known as palpable).(8) A needle biopsy performed by a pathologist with expertise in soft-tissue tumours is needed for definitive diagnosis,(6) and imaging (i.e., ultrasonography, computerized tomography [CT], and magnetic resonance imaging [MRI]) can support DT diagnosis and provide insight into the tumour location, size, and affected structures.(17, 31, 33) Genetic testing may be needed to identify the presence of mutations in 2 genes associated with desmoid tumours, namely the *CTNNB1* and *APC* genes.(7, 17) Of note, these mutations are mutually exclusive; indication of one of these mutations precludes the presence of the other.(8) Given the complexity of diagnosis and treatment, referral to a sarcoma specialist is encouraged.(6, 31) No new diagnostic tests are needed with nirogacestat.

Because desmoid tumours are very rare and there is low awareness of the disease, 30%-40% of desmoid tumours cases are misdiagnosed for other soft-tissue tumours, and patients often experience delays in getting diagnosed.(17, 31, 34)

Why speed of diagnosis matters: Quick diagnosis of desmoid tumours is important for patients to help control damage to surrounding tissues and organs, effectively manage symptom severity, and improve QoL.(17) Forty-six percent (46%) of patients with desmoid tumours are diagnosed in

the first year of developing symptoms.(8) People who experience delays in diagnosis experience distress and fear that desmoid tumour is a form of cancer, chronic and severe symptoms, uncertainty of disease course, fear of recurrence or relapse, and lack of efficient treatment.(32, 35)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The challenge: There is no standard treatment for desmoid tumours in the UK and desmoid tumours either cannot be removed directly or can be removed but are highly likely to grow back, with as many as 77% of patients experiencing recurrence after surgical procedures for desmoid tumours.(36, 37)

Goals of treatment: The main goals for treating desmoid tumours are to stop or slow down disease progression, shrink tumours, and improve symptoms, function, and QoL.(6)

What treatments are currently used: Current treatments can shrink desmoid tumours and this can help improve patients' symptoms and ability to function. Currently, doctors use medical treatments approved for other diseases to treat desmoid tumours. This is known as "off-label" use because the treatments are not licensed to treat desmoid tumours.(38) These treatments have been tested in clinical studies, but the manufacturers have not sought regulatory approval for licensed use in patients with desmoid tumours. There is concern that current medical treatments do not treat desmoid tumours as well as they could and that there are significant side effects.(6, 17, 19, 39-46)

Guidelines for treating desmoid tumours recommend watching the tumour first before treating it right away.(6) Once the tumour starts growing quickly or causes serious problems like pain, trouble with body functions, or lowers the person's QoL, treatment would begin. The type of treatment depends on where the tumour is located. Medicines are recommended as treatment in many body areas, including the belly, pelvis, arms, legs, and chest. For tumours in the head, neck, or inside the chest, medicine is the only recommended first treatment. Doctors choose the medicine based on how safe it is and how well it might work for that specific patient. If a patient decides not to get treatment, doctors focus on helping the patient feel better and managing pain (known as best supportive care). While it does not stop the tumour from growing, it helps the person feel more comfortable.

Current medicines that may be used off-label include tyrosine kinase inhibitors (TKIs) and chemotherapies. TKIs are a type of targeted therapy that have been specifically designed to stop some tumour cells from growing out of control. In the UK, TKIs are available to a very limited number of people with desmoid tumours through compassionate use programs, so it can be very difficult to access. (47, 48) While TKIs may shrink some tumours, many people stop treatment

early because either their tumours eventually grow (disease progression) or they experience significant side effects.(39, 43-46)

Chemotherapy is also used to treat desmoid tumours and is used off-label. Doctors may choose it when another good option is not available.(47, 48) There is limited research showing how well chemotherapy works for desmoid tumours, which makes it harder for doctors to decide which medicine is best for each patient.(6, 17, 19, 39-42) Research does show that chemotherapy can cause serious side effects. (39) These side effects can make it hard for patients to stick with treatment and can affect how they feel day-to-day.

It is important to note that there is a lack of high-quality data on how TKIs and chemotherapy improve symptoms, ability to function, and QoL.(19, 49) This highlights a need for a desmoid tumour-specific systemic treatment that effectively addresses patient needs related to controlling tumour size, preserving function, managing pain and desmoid tumour symptoms, and improving QoL.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients' perspective on desmoid tumours: Desmoid tumours and its treatments can place a heavy physical and emotional burden on patients. Disease symptoms significantly affect patients' QoL.

Feedback from patient focus groups: People in the UK who have desmoid tumours said the disease made everyday life harder. Things like getting dressed, taking a bath, and doing fun activities like horse riding and rock climbing became difficult.(35)

The disease also caused problems in relationships. Some people in the UK and Netherlands felt they had to deal with things alone so they would not worry their loved ones. Others could not start or grow their families because of the disease or its treatments. It also affected their romantic lives and made it hard to play with or care for their kids.(24, 35) Some even lost friendships because they did not get enough support.(24)

Work was another big challenge. Many people had to stop working or take time off, which hurt their careers and caused money problems. Traveling to hospitals added to the costs.(24, 35)

Besides physical problems, people felt lonely and sad. They said others did not understand what they were going through. They felt bad about how they looked and struggled with the stress of having a disease that is hard to predict (risk of recurrence, treatment decisions).(35, 50) They also felt psychologically burdened by inadequate psycho-oncological support and anxiety disorders among relatives.(50)

Getting diagnosed was also difficult and very stressful. Diagnosis took a long time and tumours were often discovered by chance or misdiagnosed for a long time.(50) People felt anxious while

waiting to find out what was wrong. Some were relieved when they learned it was not cancer, but others were frustrated because their symptoms were ignored until things got worse.(24, 35)

In the UK, patients said it was hard to make treatment decisions because doctors did not always have clear answers or clear evidence. They worried about the tumour coming back and had to deal with strong side effects from treatments.(35)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

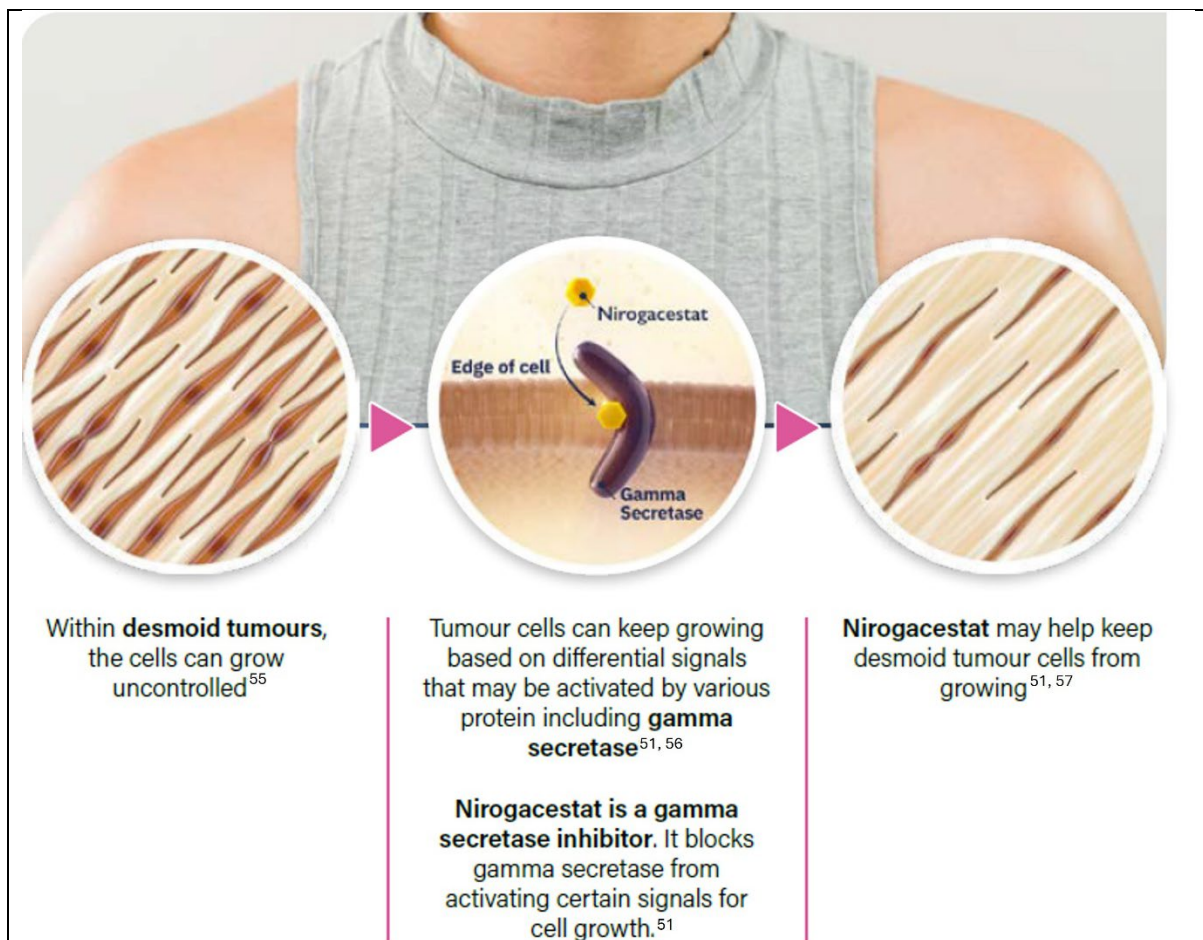
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is nirogacestat and how does it work?

Nirogacestat works throughout the entire body, making it a systemic therapy, unlike surgery and radiation, which are local therapies typically targeting a single area.(51-53)

Nirogacestat is a prescription medicine that works by interfering with gamma secretase, an enzyme that may influence the growth of certain cell types, including desmoid tumour cells.(51, 54)

How nirogacestat is thought to work is shown in the figure below, but the precise mechanism of action is unknown.(55) This example is of a desmoid tumour on a person's upper arm.(4)



Innovation in patient care: Nirogacestat works by blocking gamma secretase from activating certain cell signals for cell growth, including desmoid tumour cells.(51, 56) Although the precise mechanism of action is not yet fully known, nirogacestat may help stop the growth of desmoid tumour cells.(51, 56)

Nirogacestat is the first and only therapy approved in the European Union (EU) to treat desmoid tumours in adult patients with progressing desmoid tumours.(2) Patients with desmoid tumours are treated with a range of options in the UK, many of which are limited by poor efficacy and considerable safety concerns.(6, 17, 19, 39-47)

Without a standard treatment, patients with desmoid tumours live with significant pain and functional limitations, and poor QoL.(18-21, 24, 25, 35, 50) The benefits to patients of getting an innovative treatment like nirogacestat is that is the first disease-modifying treatment that would provide significant clinical benefits that uniquely targets desmoid tumours effectively.(2, 57)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of

life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, this medicine is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Nirogacestat is available as a tablet and is convenient to take at home. The recommended starting dose is 150 mg to be taken 2 times a day. Nirogacestat tablets should be swallowed whole, and are not meant to be broken or chewed.(51)

Nirogacestat tablets can be taken with or without food. Consuming grapefruit and grapefruit juice should be avoided when taking nirogacestat, as this may increase the likelihood and or severity of side effects.(51)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The following table shows you eight clinical trials to date about nirogacestat in desmoid tumours. Five are ongoing and three have been completed. This information was taken from Clinicaltrials.gov website (www.clinicaltrials.gov) on 17 September 2025.

Study Name/Title, NCT Number	Phase	Location	Patient group	Patient group size (N)	Treatments studied	Key eligibility criteria	Expected completion date
DeFi trial NCT03785964 (57-60)	3	Belgium, Canada, Germany, Italy, Netherlands, United States, United Kingdom	Progressive DT that is cannot be removed by surgery	142	• Nirogacestat • Placebo	• Adults (≥18 years) • Histologically confirmed progressive DT • No previous treatment and DT is not amenable to surgery OR have recurring or refractory DT after at least one line of therapy	Completed
Phase II Trial of the Gamma-Secretase Inhibitor PF-03084014 in Adults With Desmoid Tumors/Aggressive Fibromatosis NCT01981551 (61, 62)	2	United States	Progressive DT that that cannot be removed by surgery or treated with radiation	17	• Nirogacestat	• Adults (≥18 years) • Histologically confirmed progressive DT • DT is not amenable to surgery or radiation that has progressed after at least one line of therapy	Completed

A Phase I Trial of PF-03084014 in Patients with Advanced Solid Tumor Malignancy and T-cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma NCT00878189 (63-65)	1	Italy, United States	Advanced solid tumours, including DT, resistant to standard therapy or for which no therapy was available	72	• Nirogacestat	• Patients with advanced cancer that is resistant to standard therapy or for which no standard therapy is available • Patients with acute T cell leukemia/lymphoblastic lymphoma that is resistant to standard therapy or for which no standard therapy is available • Men and women >16 years old	Completed
Evaluation of the Response and Non-response of Nirogacestat in Desmoid Tumours-Clinical Study NCT05879146 (66)	2	United States	Progressive DT	40	• Nirogacestat	• Adults (≥18 years) • Histologically confirmed progressive DT • Treatment naïve or progression on or after any prior therapy for DT • No history of familial adenomatous polyposis (FAP)	31/1/2028
Study of Cryoablation and Nirogacestat for Desmoid Tumour NCT05949099 (67)	2	United States	Progressive or symptomatic DT and is 50% to <75% cryoablatable	28	• Nirogacestat + cryoablation	• Adults (≥18 years) • Histologically confirmed progressive or symptomatic DT • DT is 50% to <75% cryoablatable	1/2/2028
A Single-Arm, Open-Label Phase 4 Study of Nirogacestat in Adult Premenopausal Females With Desmoid Tumors/Aggressive Fibromatosis (DT/AF) NCT07176689 (68)	4	Belgium, Germany, Italy, Netherlands, United Kingdom	Adult premenopausal females with DT	50	• Nirogacestat	• Postpubertal, premenopausal females aged ≥18 and ≤40 years old • Uses 1 highly effective non-hormonal contraceptive method • Negative pregnancy test • Not breastfeeding • Agrees to not harvest or donate eggs during study • Histologically confirmed DT/AF with symptomatic or progressive disease requiring systemic treatment	30/3/2031
A Study of Nirogacestat in Japanese Adults With Desmoid Tumors/Aggressive Fibromatosis (DT/AF) NCT07170644 (69)	2	Japan	Japanese adults with progressing desmoid tumours/aggressive fibromatosis	18	• Nirogacestat	• Adults (≥18 years) • Histologically confirmed progressive DT • DT is not amenable to surgery after at least one line of therapy	31/12/2030

A Safety, Pharmacokinetic and Efficacy Study of a γ-Secretase Inhibitor, Nirogacestat (PF-03084014), in Children and Adolescents With Progressive, Surgically Unresectable Desmoid Tumors NCT04195399 (70)	2	Australia, Canada, New Zealand, Puerto Rico, United States	Children and adolescents with desmoid tumours that has grown after at least one form of treatment that cannot be removed by surgery	35	• Nirogacestat	• Children and adolescents (12 months and <18 years) with a body surface area of >0.3 m² • Histologically confirmed progressive DT • DT is not amenable to surgery after at least one line of systemic therapy	30/9/2025

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

On 14 August 2025, the European Commission granted market authorisation approval for nirogacestat in patients with progressing desmoid tumours.(2) This decision is based on the results from a phase 3 clinical trial (DeFi trial). This trial tested the benefits and safety of how well nirogacestat worked in patients with progressing desmoid tumours.(57) This study is the largest completed desmoid tumour trial.(6) In total, 142 patients with progressive desmoid tumours received either nirogacestat (70 patients) or placebo (72 patients).(57)

In the DeFi trial, how well nirogacestat worked was measured by how well it improved the following items:

1. Patients' progression-free survival: a measure of disease progression that tracks whether desmoid tumour(s) grew bigger by 20% or more or the person felt new or worsening symptoms that caused them to stop treatment and leave the trial, and possibly start a different type of treatment for desmoid tumour(s).(57)
2. Patients' objective response: a measure of whether the size of desmoid tumours are effectively responding to treatment by measuring whether a tumour shrinks by 30% or more or disappears completely.(57)

Nirogacestat provided effective desmoid tumour control.(57)

In the clinical trial, 17% of patients treated with nirogacestat experienced disease progression compared to 51% in the placebo group.(51, 57) Treatment with nirogacestat reduced the chance of a participant's disease getting worse during the study by 71% compared with a placebo (known as progression-free survival).

Results with nirogacestat were generally consistent across different participant characteristics (importantly, the study was not designed to specifically compare these characteristics and detect differences):(57)

- Gender
- Whether a person had prior treatment for desmoid tumours or not
- Type of prior treatment

- Changes in tumour DNA
- Number and location of tumours
- Family history of familial adenomatous polyposis (FAP)

Nirogacestat helped shrink desmoid tumours or caused them to completely disappear in some people, as confirmed by MRI or CT scans.(57)

Forty-one percent (41%) people on nirogacestat had an objective response. Of these, 5 people (7%) had their tumours completely disappear (known as complete response) vs. 0 people on placebo, and 24 people (34%) had their tumours reduced in size by 30% or more (known as partial response) vs. 6 people (8%) on placebo.(51, 57) Nirogacestat did not work in all patients, as one (1) patient's desmoid tumour grew by 20% while on treatment with nirogacestat compared to 10 patients (14%) treated with placebo.(51, 57)

In patients who responded to nirogacestat, tumours began to shrink between 2.6 and 19.4 months after starting therapy. The **median (middle) amount of time it took for tumours to begin shrinking was 5.6 months**, compared to 11.1 months (2.8 to 16.4 months) for patients taking placebo.(57)

Limitations: The time to when tumours began to shrink was an *exploratory analysis*, meaning it was not specifically designed to find differences between nirogacestat and placebo and results should be interpreted carefully.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The DeFi trial found that nirogacestat provided effective disease control and shrank tumours or helped them completely disappear compared with those who received placebo. Reducing the size or presence of tumours slowed down the growth of the disease and the degree to which surrounding tissues and organs are impacted, which improves pain, symptoms, and QoL.

Patients reported reduced pain—one of the most common symptoms of desmoid tumours—with nirogacestat.(57)

Patients reported that nirogacestat reduced pain:(57)

- More than 50% of patients entering the clinical trial had pain. Over the course of the trial, people continued to report any pain they may have experienced
- People taking nirogacestat reported reductions in worst pain compared with those taking placebo

Treatment with nirogacestat quickly improved symptoms, physical functioning, and QoL that was long-lasting.(57)

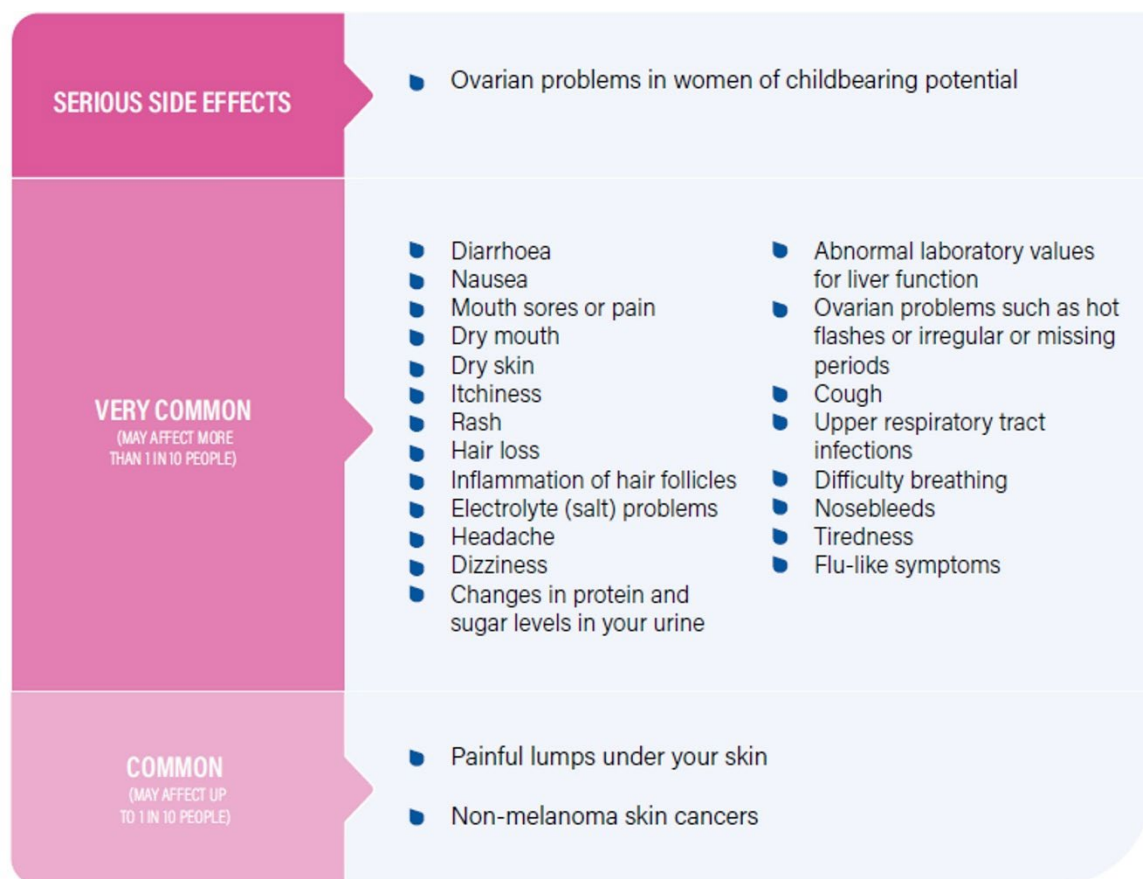
Patients reported that nirogacestat improved symptoms, physical functioning, and QoL quickly (about 2 months) after starting treatment and that improvements were long lasting (to end of the study, at 2 years).(57)

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

It is common for side effects to occur when taking medicines, the severity of these effects are dependent on the type and dose of the medicine. In the DeFi trial side, effects have been reported in patients who received nirogacestat are listed below, and 95% of side effects were mild or moderate in intensity and occurred within 1 month of starting treatment.(51, 57)



Managing key side effects

Most common side effects of nirogacestat, including diarrhoea, rash, electrolyte problems, and abnormal lab values for liver function, can be managed by medications such as anti-diarrhoeal medication, topical medication like steroid cream, or supplements to correct any electrolyte (salt) problems.(51, 71) Other measures include running blood tests, monitoring for skin reactions, and adjusting the dose of nirogacestat.(51, 71)

Women of childbearing potential may experience symptoms such as hot flashes and menstrual cycle changes, including irregular periods or no periods.(51, 71) These symptoms were resolved in the majority of women while they were still on treatment and in all women who stopped taking nirogacestat.(51, 71)

Certain types of skin cancer, called basal cell carcinoma and squamous cell carcinoma, have been reported in patients receiving nirogacestat.(51, 71) In case of occurrence, non-melanoma skin cancer should be managed in accordance with clinical practices.(71)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Nirogacestat is a novel, effective, treatment with a manageable safety profile that can meets patients' treatment goals by achieving higher desmoid tumour control and improving symptoms, pain, function, and QoL.(57)

Key benefits of nirogacestat for patients with desmoid tumours include:(57)

- Providing highly effective control of desmoid tumours in many patients by preventing the disease from getting worse and shrinking the tumours or causing them to completely disappear, which helps to protect surrounding tissues and organs from damage
- Providing quick and long-lasting improvements in patients' symptoms, pain, and functioning, so patients' can have a better QoL
- Permitting self-administration at home as an orally administered therapy, which may be a more convenient treatment option for patients and providers
- A limited impact on healthcare budget spending, as desmoid tumours are an orphan indication.(72) Delayed disease progression with nirogacestat may help to offset costs by reducing healthcare resource use and second-line treatment costs.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Key disadvantages of nirogacestat for patients with desmoid tumours include:(51, 71)

- High chance of side effects in the first year of treatment, including diarrhoea, rash, electrolyte problems, abnormal lab values for liver function, and non-melanoma skin cancer. Importantly, most side effects are not serious and are manageable with appropriate care.
- Risk of ovarian dysfunction in women of childbearing potential. Most cases (79%) of ovarian dysfunction were not permanent and resolved during treatment with dose modification or after treatment was stopped. The effect of nirogacestat on female fertility is unknown. Women of childbearing potential should be advised about the risk of ovarian

dysfunction before starting treatment with nirogacestat and should be monitored for changes in menstrual cycle regularity or with development of symptoms of oestrogen deficiency, including hot flashes, night sweats, and vaginal dryness.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Model design:

- An economic model was developed to track changes in the health, costs, and QoL of patients with progressing desmoid tumours from the start of treatment with either nirogacestat or best supportive care (BSC)/placebo until death.
- Since patients on treatment can experience different outcomes related to tumour size changes (e.g., varying degrees of improvements in pain and symptom burden, which would translate to differences in healthcare costs and health-related QoL), the model was developed to reflect the different levels of tumour response before disease progression.(73)
- The model included five health states that patients with desmoid tumours could experience, as follows: stable disease (SD; where the disease is not getting better or worse), partial response (PR; where there is a decrease in the size of a tumour in response to treatment), complete response (CR; where there is disappearance of all signs of tumours in response to treatment), progressed disease (PD; where the tumour that is growing, spreading, or getting worse), and death (the person passes away). Patients move through these health states in the model and incur costs and quality of life implications which vary by health state.

Modelling how much a treatment extends life:

- Mortality (the risk of death) was modelled as an increased risk compared to the risk of dying in the general population, depending on the health state that a patient was in. It was assumed that patients in the SD, PR, and CR health states had a risk of death equal to the general population, and that there was a slightly higher risk of dying for patients in the PD health state (1.3 times greater risk).(27)
- Nirogacestat could impact mortality by delaying disease progression due to its disease-modifying effects on the tumour(s). Anecdotal feedback from UK clinicians was that treatment can lead to decades of being free from disease progression, indicating that successful disease control, where the presence of symptoms is reduced because the

tumour has stabilised or shrunk in size, among patients who achieve at least PR is very durable.(74)

Use of trial data in the model:

- In the model, data for the best overall response patients experienced for up to 2 years of treatment with niraparic acid and BSC/placebo were from the DeFi trial (75) and were used to determine the likelihood of moving from one state to another.
- The likelihood of moving between health states were based on rates of duration of response for niraparic acid and BSC/placebo from the DeFi data.

Modelling how much a treatment improves quality of life:

- Niraparic acid improves a person's QoL by delaying disease progression and keeping patients in better (less severe) states of health, thereby improving symptoms due to the disease-modifying effects on the tumour(s). Given the disease-modifying effect of niraparic acid, it is expected that the positive impacts on a person's QoL would continue even after treatment has been stopped.
- A person's QoL is included in the model in the form a utility value, a number that represents the strength of an individual's preferences for certain health conditions. Numbers range from 0 to 1, where 1 means perfect health and 0 means a health state as bad as death. The QoL measure known as the EQ-5D (EuroQoL-5 Dimensions) was used to estimate a person's QoL over time and on treatments in the model.
- Niraparic acid may offer some additional QoL benefit through increasing the capacity for patients and caregivers to work and allowing patients to have a long-term positive outlook on life; however, it was not possible to capture this in the model because there were no published data available.

Modelling how the costs of treatment differ with the new treatment:

- Niraparic acid is anticipated to lead to higher drug costs (for a limited treatment duration), with partial offset in costs resulting from lower healthcare resource utilisation and delaying subsequent treatment.
- Niraparic acid will be administered as an oral treatment within the current desmoid tumour diagnosis and treatment pathways in the NHS healthcare system. The ease and convenience of niraparic acid administration will benefit the patient experience and reduce costs because a healthcare worker is not needed to give the treatment.

Uncertainty:

- Because of a lack of data, the model includes key assumptions about niraparic acid's benefit. Specifically, these assumptions are about how long niraparic acid's benefit would last after stopping treatment. Some clinicians believe there is no evidence that a tumour will grow once it has effectively responded to a disease-modifying treatment like niraparic acid. So, the model assumes that for patients who responded to niraparic acid treatment (a PR or CR) and for patients who had SD with niraparic acid, their disease would not worsen (patients would not move to a PD health state in the model).
- The assumptions that had the largest impact on the model results were a longer duration of niraparic acid benefit and the QoL patients experienced when in the PD health state (when disease worsened).

Additional factors:

- A quality adjusted life year (QALYs) is a way to measure how long someone may live for and how good the quality of their life is for those remaining years. People with desmoid tumours who are not getting treatment have poor QoL, so a patient with desmoid

tumours who does not receive treatment will gain only about half as much in QALYs compared to someone without desmoid tumours.

- Due to data limitations, additional benefits of nirogacestat that could not be captured in the economic model include improvement on physical functioning and role functioning, increasing the capacity for patients and caregivers to work, and improvements in overall QoL (particularly in patients with a best overall response of stable disease), allowing patients to have a long-term positive outlook on life.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Patients with desmoid tumours are treated with a range of options in the UK, many of which are limited by poor efficacy and considerable safety concerns.(6, 17, 19, 39-47) Without a standard treatment, patients with desmoid tumours live with significant pain and functional limitations, and poor QoL.(18-21, 24, 25, 35, 50) Nirogacestat is the first disease-modifying treatment approved by the European Commission that would provide significant clinical benefits in terms of desmoid tumour control, including tumour shrinking or completely disappearing, with reduced pain and symptoms, improved QoL, and mild-to-moderate side effects.(2, 57)

On top of the health benefits of desmoid tumour control, including shrinking or complete disappearance of tumours, and mild-to-moderate side effects, nirogacestat may also offer some benefits that are not captured as a QALY benefit in the economic model and should be considered. These include improvements in physical functioning and role functioning, increasing the capacity for patients and caregivers to work, and improvements in overall QoL in (particularly in patients whose disease remained stable in the DeFi trial), which allows patients to have a long-term positive outlook on life.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are no potential equality issues relating to the use of nirogacestat in the treatment of adult patients with progressing DT.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be

useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Additional resources on desmoid tumours:

- Desmoid Aid UK: www.desmoidaiduk.com
- Sarcoma UK: www.sarcoma.org.uk
- Desmoid Tumour Research Foundation: www.dtrf.org
- The Desmoid Project: www.thedesmoidproject.org
- European SARcoma (EuSARC): www.eusarc.net
- Sarcoma Patient Advocacy Global Network (SPAGN): www.sarcoma-patients.org

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Abdomen (intra-abdominal): The area inside the body that includes the stomach, the small and large intestines, liver, spleen, gallbladder, and pancreas, the uterus, fallopian tubes, and ovaries, the kidneys, ureters, bladder, and blood vessels.

Best supportive care (BSC): Care given to improve the QoL of people who have an illness or disease by preventing or treating, as early as possible, the symptoms of the disease and the side effects caused by treatment of the disease. There are many types of BSC. Examples include pain management, nutritional support, counseling, exercise, music therapy, meditation, and palliative care. BSC may be given with other treatments from the time of diagnosis until the end of life. Also known as supportive care.

Chemotherapy: Treatment that uses drugs to stop the growth of tumour cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery, radiation therapy, or biologic therapy.

Complete response (CR): The disappearance of all signs of tumours in response to treatment. This does not always mean the tumour has been cured. Also called complete remission.

Connective tissue: Tissue that supports, protects, and gives structure to other tissues and organs in the body. Bone, cartilage, fat, blood, and lymphatic tissue are all types of connective tissue.

CT: A CT (or computerized tomography) scan is a procedure that may help diagnose a medical condition, plan treatment, or find out how well treatment is working. A computer is linked to an x-ray machine to record detailed pictures of different areas inside the body.

Disease-modifying treatment: Medications used to treat chronic conditions by altering their underlying disease process and slowing down its progression.

Electrolytes: Minerals with an electrical charge (also known as ions) like sodium, potassium, and phosphate. The body needs electrolytes to help keep the muscles, nerves, heart, and brain working. High or low levels of electrolytes can disrupt normal bodily function.

Exploratory analysis: Research that was not specifically designed to find an answer, but rather to uncover trends and patterns within data. For example, in the clinical trial, the amount of time it took for tumours to shrink in people taking OGSIVEO versus in people taking placebo was an exploratory analysis.(51, 57, 71)

Familial adenomatous polyposis (FAP): FAP is caused by a gene mutation that runs in families. In this inherited condition, abnormal growths called polyps form on the inner walls of the colon and rectum. Polyps may become cancer if they are not removed. People with FAP are at higher risk of developing desmoid tumours, often in the abdominal area.

Health state: A specific health condition or status of an individual, such as being in a state of perfect health, a specific stage of a disease like progressive or stable disease, or being deceased.

Malignant: Cells are described as malignant when their growth is uncontrolled, with the potential to spread to other parts of the body (metastasise).

Metastasise: To spread from one area of the body to another, as when cancer cells form other tumours elsewhere in the body. For example, when cancer starts in the breast but spreads to the bones.

MRI: An MRI (magnetic resonance imaging) is a type of scan that takes a series of detailed images of areas inside the body. MRI uses radio waves, a powerful magnet, and a computer to record the images that can help in diagnosing a medical condition or in planning treatment or seeing how well a treatment may be working.

Objective response: When a person's tumours shrink by at least 30% or disappear completely at some point during the trial. Confirmed objective response in the trial only includes participants who had a response to treatment for at least 4 weeks.

Partial response (PR): A decrease in the size of a tumour, or in the extent of tumour in the body, in response to treatment. Also called partial remission.

Physical functioning: An individual's ability to be mobile, and perform daily activities and self care.

Placebo: An inactive substance that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or other intervention are compared to the effects of the placebo.

Progressed disease (PD): Tumour that is growing, spreading, or getting worse.

Progression: When a desmoid tumour is getting larger in size.

Progression-free survival: How long a person lives without: 1) their tumour progressing (growth) on imaging, 2) their disease symptoms or health status getting worse, or 3) dying from any cause.

Quality of life (QoL): The overall enjoyment of life. Many clinical trials measure aspects of an individual's sense of well-being and ability to carry out activities of daily living and they are impacted by the effects of disease and its treatment.

Quality adjusted life year (QALY): A number that takes into account both the quantity and quality of life generated by a treatment. It considers life expectancy and the quality of the remaining life-years.

Role functioning: An individual's ability to perform their occupational and societal roles. This can include work or school duties, hobbies, and engaging with family and friends.

Soft-tissue tumours: Tumours that form in areas such as muscle, fat, tendons, ligaments, lymph and blood vessels, nerves, or other connective tissues in the body.

Stable disease: Tumour that is neither decreasing nor increasing in extent or severity.

Systemic therapy: Treatment with medicine that travels through the bloodstream to affect cells all over the body.

Transition probability: The chance of moving from one health state or event to another during a specified period of time in a health economic model.

Treatment duration: The length of time a treatment is administered to a patient.

Tyrosine kinase inhibitor (TKI): A substance that blocks the action of enzymes called tyrosine kinases. Tyrosine kinases are a part of many cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of tumour cells, and blocking them may help keep tumour cells from growing. Some tyrosine kinase inhibitors are used to treat tumours and cancers. They are a type of targeted therapy.

Utility value: Numbers that represents the strength of an individual's preferences for certain health conditions. Numbers range from 0 to 1, where 1 means perfect health and 0 means a health state as bad as death.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Clarification questions

October 2025

File name	Version	Contains confidential information	Date
ID6453 Nirogacestat Clarification letter [CON]	1	Yes	17.10.2025
ID6453 Nirogacestat Clarification letter [CON]	1.1	Yes	31.10.2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Priority A1. Do you understand there to be a population of people with desmoid tumours (DTs) who would be eligible for nirogacestat but not for chemotherapy/tyrosine kinase Inhibitors (TKIs)?

Response: Off-label chemotherapy and TKIs are used in the UK due to the lack of any approved treatment options in DT. There are no criteria that define patients as eligible for nirogacestat but not for chemotherapy/TKIs.

A2. The draft SmPC criteria considered the indication of nirogacestat to be adults with progressing desmoid tumours who require systemic treatment.

- a) How would you expect these criteria to be implemented i.e. what would be the definition of progressing disease and what population requires systemic treatment?

Response: The established guidelines (i.e., Desmoid Tumor Working Group [DTWG], etc)(Kasper et al. 2024) do not specify a universal definition for progressing disease and the population that require systemic treatment, but instead leaves this to the clinician's discretion to assess the extent of progression and whether clinical intervention with systemic therapy will be the most effective option.

- b) Please can you provide the files embedded in appendix A (SPC, UK public assessment report).

Response: Please note that the SPC and CHMP Public Assessment Report have been attached. The UK public assessment report is not available, yet.

A3. How were refractory and recurrent defined in De-Fi?

Response: Participants with no prior therapy were classified as treatment naïve. Participants with a prior line of therapy and a best overall response of complete response (CR) or partial response (PR) prior to randomisation were classified as having recurrent disease. Otherwise, participants with a prior line of therapy were classified as having refractory disease.

A4. The power calculation assumed a 20% spontaneous regression rate. What was actually observed in De-Fi?

Response: The spontaneous regression rate observed in DeFi, based on the objective response rate observed in the placebo arm, was 8% (Gounder et al. 2023, SpringWorks Therapeutics 2025).

A5. The De-Fi trial used a 20% criteria for progression when 10% was used in the sorafenib RCT.

- a) What was the reason for this change?

Response: The criteria for progression used in DeFi (20%) follows the RECIST v1.1 definition of progressive disease (Eisenhauer et al. 2009). This approach was endorsed by the US FDA and the EMA.

- b) How many people were excluded from the trial for not meeting the 20% criteria who would have met the 10% criteria?

Response: This information was not collected in the DeFi clinical trial database.

- c) Did you assess how different the results of the trial would be if a 10% criteria was used for progression?

Response: No, this was not performed as the trial was designed to follow RECIST v1.1 guidelines. The inclusion criterion for disease characteristics in DeFi trial was

that participants had histological confirmed DT that has progressed by $\geq 20\%$ as measured by RECIST 1.1 with 12 months of the screening visit.

A6. The following questions relate to ovarian dysfunction:

- a) Is there a mechanism by which niraparic acid could trigger premature menopause?

Response: The ovarian toxicity (OT) observed with niraparic acid appears to be due to a disruption of the follicular cycling of the ovary, along with impaired activation of primordial follicles, with 2 leading possibilities for the mechanism for the disruption of follicular cycling:

1. Interference with angiogenesis needed to support luteal development
2. Interference with cell-to-cell signalling needed to control luteal development

In adults, the ovary is one of the few organs that maintains normal physiology by angiogenesis. Abnormal angiogenesis is involved in the pathogenesis of ovarian diseases (Xie et al. 2017). Primordial and primary follicles have no established blood vessels of their own, and growing follicles recruit blood vessels from the ovarian stroma. The development and growth of the corpus luteum is reliant on angiogenesis from pre-existing vessels of the follicular theca layer (Woad and Robinson 2016). Inhibition of angiogenesis leads to the attenuation of follicular growth, disruption of ovulation and drastic effects on development of the corpus luteum (Robinson et al. 2009). The Notch and vascular endothelial growth factor (VEGF) signalling pathways, of which gamma-secretase (GS) is an integral part, are critically involved in angiogenesis in the ovary (Xie et al. 2017). Hayashi et al. (2007) have observed that GS may be involved in a regulatory loop with VEGF with regard to angiogenesis, and that GS inhibition attenuated postnatal angiogenesis through inhibition of endothelial cell growth and expression of angiogenic growth factors. In addition, inhibitors targeting the PI3K/AKT/mTOR pathway have been shown to decrease VEGF secretion and angiogenesis (Karar and Maity 2011). Hales et al. (2014) showed that Notch1, signalling through the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), can activate AKT; hence inhibition of Notch1 via GS inhibition would be expected to decrease AKT activity and interfere with

angiogenesis. Thus, there are 2 possible mechanisms by which GS inhibition can disrupt angiogenesis in the developing ovary.

The Notch pathway promotes the growth and maturation of ovarian follicles through interactions between juxtaposed follicular cells. Cellular interactions between other populations of cell types within the developing ovary also facilitate productive Notch signalling that is critical for ovarian processes including luteinization and vascular development (Vanorny and Mayo 2017). Li et al. (2021) have recently reviewed the signalling pathways involved in ovarian follicle development and noted that in addition to its role in angiogenesis, the Notch pathway has other roles in follicular development. Notch2 is expressed in theca cells to a greater extent in medium and big follicle stages compared to the small follicle stages, and Notch2 protein could not be detected in the preantral follicles, suggesting that Notch2 likely mediates the growth of theca cells at the later stages of follicular development (Jing et al. 2017). In contrast, Notch2 is expressed in granulosa cells to a greater extent as the follicle grows (Jing et al. 2017). Treatment with a gamma-secretase inhibitor (GSI) led to a decrease in the number of granulosa cells and decreased estradiol levels in vitro (Jing et al. 2017). Lunatic fringe null female mice, who lack an important regulator of Notch signalling that is expressed in the granulosa cells of developing follicles, are infertile; their ovaries demonstrate aberrant folliculogenesis, and their oocytes do not complete meiosis (Hahn et al. 2005). Treatment of cultured primary follicles with Notch signalling inhibitors resulted in the complete termination of follicle development, granulosa cell detachment, and oocyte degeneration with cytoplasm condensation (Zhang et al. 2011).

Activation of PI3K/AKT results in FOXO3 phosphorylation and nuclear export, thereby triggering primordial follicle activation (John et al. 2008). As described above, Notch1 can activate AKT, and as such, GS inhibition has the potential to interfere with activation and further development of the primordial follicle (Hales et al. 2014), mechanisms that are distinct from its effect on angiogenesis and cell-to-cell signalling in thecal cells. Since gamma-secretase inhibition has the potential to block the activation and further development of the primordial follicle, treatment with nirogacestat may not affect the oocyte reserve.

- b) Please confirm the number of people who experienced ovarian dysfunction and premature menopause in each arm of De-Fi.

Response: In the nirogacestat arm, 27 (75%) women of childbearing potential experienced ovarian dysfunction, out of whom 11 experienced premature menopause. No patients experienced ovarian dysfunction in placebo arm.

- c) How many people in each arm experienced a Grade 3+ adverse event related to ovarian dysfunction?

Response: No patients experienced a Grade 3+ adverse event related to ovarian dysfunction.

- d) Please make a comparison of the safety of nirogacestat in relation to Grade 3+ ovarian dysfunction with the safety of chemotherapy in relation to Grade 3+ ovarian dysfunction based on data from the studies found in the clinical SLR.

Response: A comparison of Grade 3+ ovarian dysfunction between nirogacestat and chemotherapy is not possible because neither nirogacestat nor any of the chemotherapy studies identified in the clinical SLR reported this outcome.

A7. Please present a fuller definition of BSC as performed during De-Fi.

Response: Best supportive care (BSC) was left to investigator discretion/institutional guidelines, with the following instructions provided in the protocol on what could constitute BSC:

Phosphate supplements: Nirogacestat has been associated with hypophosphatemia which may require phosphate supplementation. The choice of phosphate replacement, as well as the duration, is at the investigator's discretion.

Palliative Care: During the double-blind and open-label extension (OLE) phase of the study, systemic therapy or local therapy to the DTs were not permitted.

Medications for the standard management of symptoms or supportive care for the management of the effects of study treatment may be administered at the investigator's discretion; unless they were excluded concomitant medications (see

table below). Palliative radiation therapy may be permitted in the OLE phase of the study after consultation with the medical monitor/sponsor. Radiation will be limited to non-target lesions only.

Thus, the following therapies are **not** permitted during the double-blind or OLE phases of the study:

- Other anti-neoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy;
- Surgical resection of DTs; and
- Any other investigational therapy.

Anti-Emetic and Anti-Diarrheal Therapy: The choice of anti-emetic drug(s) and anti-diarrheal drug(s), as well as the duration of treatment, was up to the investigator assuming there was no known or expected drug-drug interaction (DDI). If a DDI is expected, then the drug(s) must have been approved by the medical monitor/sponsor.

Cytochrome P450 Inhibitors and Inducers: Because inhibition of CYP3A4 isoenzymes may increase nirogacestat exposure leading to potential increases in toxicities, the use of known strong/moderate CYP3A4 inhibitors was not allowed throughout the double-blind and OLE study phases and must be stopped at least 14 days prior to the first dose of double-blind study treatment.

Gastric acid reducing agents: Co-administration of gastric acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, etc.) may reduce the absorption of nirogacestat. These drugs should be avoided if possible or, when necessary, administered 2 to 4 hours following the morning dose of study treatment.

Excluded/Restricted Concomitant Medications and/or Procedures

Medication/Procedure	Restriction/Exclusion Time Frame
- Chronic daily use of NSAIDs for treatment of DT;^a - Tyrosine kinase inhibitors; - Other antineoplastic therapy, including cytotoxic agents, small molecule inhibitors, targeted agents, endocrine therapy or other antibodies; and - Any investigational treatment for DT.	- Not allowed after the documented DT progressive disease or within 28 days (or 5 half-lives, whichever is longer) prior to the first dose of double-blind study treatment; and - Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
- Strong/moderate CYP3A4 inhibitors; and - Strong CYP3A4 inducers.	- Not allowed within 14 days prior to the first dose of double-blind treatment; and - Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
CYP3A4 substrates with a narrow therapeutic index.	- Should be avoided if possible; and - If co-administration is unavoidable, the participant should be monitored closely for toxicity and the investigator should consider reducing or titrating the dose of the substrate as necessary.
Gastric acid-reducing agents, such as proton pump inhibitors.	- Should be avoided if a reasonable alternative is available; and - If administration is necessary, should be administered 2 to 4 hours after the morning dose of study treatment.
- GS inhibitors; - Anti-Notch antibody therapy; and - Gastric bypass, lap band, or other gastric procedures that would alter absorption.	- No prior use, therapy, or procedure is allowed; and - Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
- Anti-arrhythmic medications that are known to prolong the QT/QTcF interval, including Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) anti-arrhythmics; - Potentially curative radiotherapy; and - Surgical resection of DT tumours.	- Not allowed at the time of informed consent; and - Not allowed throughout the duration of the treatment period during the double-blind or OLE phases.
Delivery of nirogacestat via nasogastric tube or gastrostomy tube.	Not allowed throughout the double-blind or OLE phases.
Enrollment in another clinical study with any investigational drug or device.^b	- Not allowed within 28 days prior to the first dose of study treatment; and - Not allowed throughout the duration of the double-blind or OLE phases.

Abbreviations: CYP: cytochrome P450; DT: desmoid tumour; GS: gamma secretase; NSAID: nonsteroidal anti-inflammatory drug; QTcF: QT interval corrected by Fridericia's formula.

Occasional use (defined as ≤ 3 days per week) of NSAIDs for the treatment of pain or as an anti-inflammatory in conditions such as headache, arthritis, etc, is allowed throughout the treatment period during the study.

Dose increases of NSAIDs will not be permitted during the treatment period during the study.

- ^a. Participants who are receiving chronic NSAIDs as a treatment for conditions **other than** DT must be receiving them prior to the documented DT progressive disease and must be on a stable dose for at least 28 days prior to the first dose of study treatment.
- ^b Participation in an observational study may be allowed on a case-by-case basis with prior medical monitor/sponsor approval.

A8. Our experts noted the limitations of RECIST v1.1 criteria for assessing DTs. They explained that DTs appear differently on magnetic resonance imaging (MRI) based on their fibrous and myxoid (gelatinous) content; hyperintense areas on T2-weighted images typically represent areas of higher water content, indicating increased cellularity or myxoid stroma, while "black" areas (hypointense) correspond to denser, more fibrotic regions with less water. Desmoid tumours with $\geq 90\%$ hyperintensity are more likely to progress.(Cassidy et al. 2020)

- a) How concerned are you that RECIST v1.1 criteria limitations bias the results of the trial?

Response: As a regulatory-intent Phase 3 study, the study protocol needed to establish a standard definition of response using RECIST v1.1 as this is the standard assessment tool in oncology to evaluate how a tumour responds to treatment. This approach was established in conjunction with the Medical Experts within the Study Steering Committee. Although the use of RECIST v1.1 is not standard clinical practice within DT management in the UK, in clinical practice, physicians will still use radiological scan data along with clinical outcomes to decide when response has been achieved.

In clinical practice, physicians may consider stopping treatment sooner because functional and symptom improvement can occur sooner than if this decision was purely based on RECIST v1.1. Therefore, the threshold of what constitutes a response in clinical practice is not expected to be as stringent as RECIST v1.1 criteria in the trial. Based on the above, the likelihood that the use of RECIST v1.1 criteria unfairly biases the results of the trial seems low.

- b) Does the company understand a person with a stable DT and $<90\%$ hyperintensity (unlikely to progress) to have the same quality of life as a person with a stable DT with $\geq 90\%$ hyperintensity(Cassidy et al. 2020) (more likely to progress)?

Response: Clinical experts shared that there is no difference in quality of life between a person with stable DT and <90% hyperintensity and a person with stable DT and ≥90% hyperintensity.

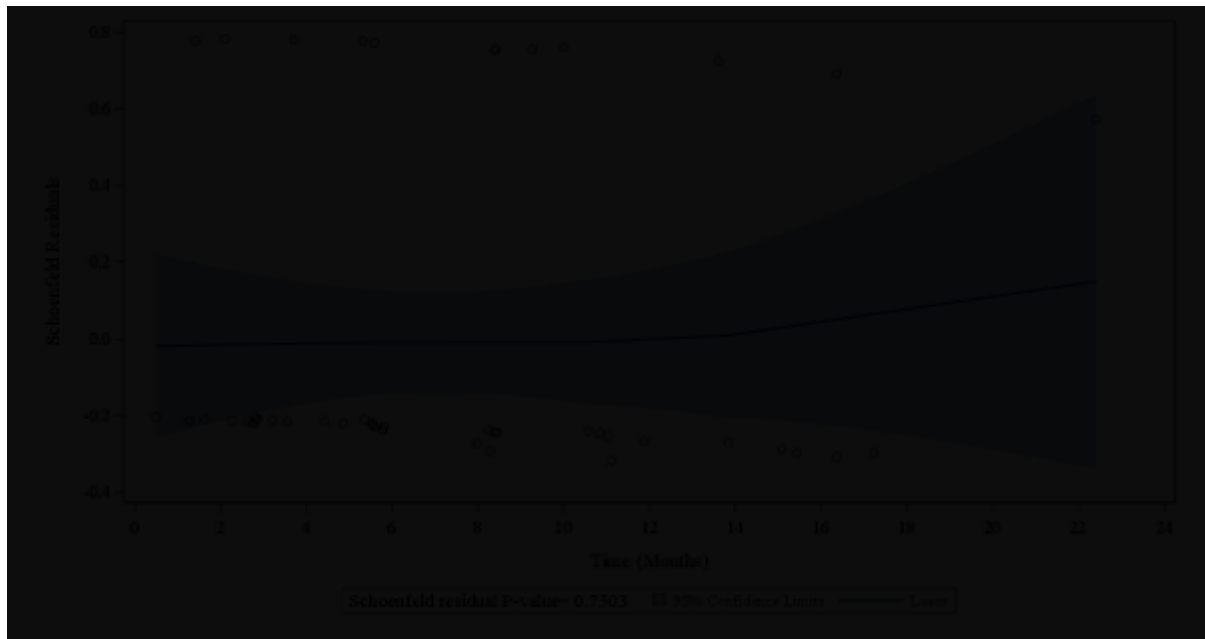
- c) We understand from Alcindor et al. (2023), (Alcindor et al. 2023) you found <90% hyperintensity (at any time) in 34% of the people in the nirogacestat arm and 15% of those in the placebo arm. Is this benefit of nirogacestat adequately reflected in the PFS and ORR results in De-Fi?

Response: Per the trial endpoints, agreed upon by FDA and EMA, progression-free survival (PFS) and objective response rate (ORR) was based on central review imaging using RECIST v1.1 criteria. Evaluation of T2 hyperintensity was an exploratory endpoint and thus was not a requirement for every patient. This is clearly reflected by the differences in sample sizes shown in Alcinor et al (nirogacestat = 53, placebo = 56) compared to the predefined primary endpoint population nirogacestat = 70, placebo = 72. There have been no additional analyses calculating ORR and PFS using T2 hyperintensity outcomes, and there are no Clinical Study Report (CSR) post-text tables nor any mention in the Marketing Authorisation Application (MAA) using hyperintensity measures to recalculate ORR and PFS or any queries received as part of the D120 or D180 questions. Also, it is not a true like-for-like comparison as RECIST uses up to 5 tumours in the assessment compared to the exploratory analyses which only used the largest tumour for the assessment.

In summary, the study was not powered to analyse ORR and PFS using hyperintensity responses and thus those formal analyses were not performed.

A9. It is unclear whether proportional hazards is appropriate for the analysis of PFS. Please present a log-log plot, Schoenfeld residual plot, and Schoenfeld residual test.

Response: Both the log-log plot and Schoenfeld residual plot indicate that the proportional hazards assumption is valid, which is further supported by the proportional hazards test [REDACTED]



[REDACTED]



[REDACTED]

A10. Please present the reasons for both events and censoring for PFS with n for each. In particular how many events related to clinical progression (rather than progression via RECIST).

Response: Among 70 intent-to-treat patients in nirogacestat arm, 12 (17%) developed PFS event including 11 patients with radiographic progression and 1 patient with qualified clinical progression. In placebo arm, 37 (51%) developed PFS events including 30 patients with radiographic progression, 6 patients with qualified clinical progression, and 1 patient with death. See the reasons for censoring in the table below.

	Nirogacestat (N = 70)	Placebo (N = 72)
Number of participants with event, n (%) Type of event:	12 (17)	37 (51)
Progression	12 (17)	36 (50)
Radiographic progression	11 (16)	30 (42)
Qualified clinical progression	1 (1)	6 (8)
Death before progression	0	1 (1)
██ ██	████████	████████
██	████	████
██	████████	████████
██ ██	████	████
██ ██	█	████

A11. In De-Fi, if people required radiotherapy, surgery, or systemic treatment (chemotherapy or TKIs) then this was classed as clinical progression.

- a) Please present the criteria for clinical progression used by investigators in De-Fi.

Response: Clinical progression was defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or TKIs) for DT.

The date of clinical progression was the earliest date of onset or worsening of symptoms resulting in a global deterioration of health status. In addition, AEs and serious adverse events (SAEs) associated with clinical progression and concomitant medications and procedures initiated for the treatment of DT/AF within 30 days of the last dose of study treatment were documented in the electronic Case Report Form (eCRF). A clinical progression narrative was to be developed by the Investigator for events of clinical progression and included a description of onset or worsening of symptoms resulting in a global deterioration of health status, the location of progressing lesions, and evidence of vital structure involvement (as reported by the Investigator), as applicable.

When disease progression was suspected (e.g., symptomatic deterioration), imaging was performed and submitted to the central imaging core laboratory for Central Imaging Review. If progressive disease is not determined radiologically via central review of RECIST v1.1, but the participant met the definition of clinical progression, the participant could be discontinued for clinical progression.

Imaging data from participants who discontinued due to clinical progression was evaluated for changes in tumour characteristics or involvement of vital organ structure at the site of progression. Events of clinical progression were adjudicated by an independent blinded central clinical review committee which qualified events of clinical progression for inclusion in the primary analysis of PFS prior to study unblinding according to a Central Clinical Review Charter.

- b) The CS stated that no subsequent treatments were received. Please provide numbers receiving subsequent radiotherapy, surgery, or systemic treatment (chemotherapy or TKIs) in both arms, or confirm that there were no clinical progression events linked to the requirement of subsequent therapy and not patients received any subsequent treatment either during the double blind or open label phases of the trial.

Response: In the De-Fi trial, if a participant had clinical progression as determined by the investigator, the participant returned to the site for an end of treatment (EOT) visit within 14 days of the date of clinical progression and was not eligible to enter the optional OLE phase. These participants were discontinued from the study after completing an EOT and follow-up visit, as specified in the study protocol. There was no further data collection upon disease progression and no patients received subsequent therapy in double blind or open label phases of the trial.

A12. You noted a higher proportion of people developing non-melanoma skin cancers while on nirogacestat.

- a) Do you know of a mechanism by which nirogacestat is linked to non-melanoma skin cancer?

Response: The Notch signalling pathway exerts a crucial role in regulating and maintaining skin homeostasis, orchestrating keratinocyte differentiation at the level of inter-follicular epidermis and hair follicles, and finally working in epithelial barrier formation (Condorelli et al. 2021). In the skin, Notch signalling functions as a molecular switch between proliferation and differentiation during epidermal homeostasis, inducing the detachment of basal cells from the basement membrane and also inducing their commitment to activate early genes in the differentiation program, thus resulting in epidermal barrier formation (Okuyama et al. 2008). In addition to the direct effects on differentiation in the skin, Notch signalling affects inflammatory processes in the skin. Loss of Notch activity leads to release of the proinflammatory cytokine thymic stromal lymphopoietin, which results in chronic inflammation, a condition related to atopic dermatitis (Siebel and Lendahl 2017).

Mouse models using genetic knockout methods to completely eliminate Notch signalling have demonstrated increased development of squamous cell carcinoma of the skin compared to control animals (Proweller et al. 2006). Notch signalling may have oncogenic and oncosuppressor functions in different skin cancers. In vitro studies of cancerous melanoma cells and Merkle cells show Notch2 and Notch1 overexpression, respectively, suggesting that gamma-secretase inhibition may have a protective effect if it reduces Notch signalling. However, in vitro studies of

The data presented above do not suggest that nirogacestat treatment is directly causing nonmelanoma skin cancer.

b) Why was this not included in the economic analysis?

Response: A total of 2 [3%] patients developed non-melanoma skin cancers while on nirogacestat in the April 2022 datacut (1 [1%] patient reported treatment-related squamous cell carcinoma of skin and basal cell carcinoma, and 1 [1%] participant reported treatment-related squamous cell carcinoma, all at Grade 2). As such, this adverse event (AE) was not identified based on the criteria for inclusion in the economic model, which was Grade 3+ AE occurring in $\geq 5\%$ of patients in any treatment arm.

Priority A13. Please present pain scores by response level by timepoint for both arms in De-Fi

Response: The mean pain scores (as assessed by BPI-SF) and mean change from baseline by overall response level by timepoint for both arms in De-Fi are reported below. Scans for tumour measurement (using RECIST v1.1) were scheduled every 3 cycles, while patient-reported outcome assessments were conducted at each cycle. The data shown correspond to overall response assessments within 7 days and 14 days of the patient-reported outcome assessment, respectively. Please note that due to small sample sizes, analyses exploring association/correlation between response level and pain were not conducted and that no conclusions regarding this can be made. Please also note that data for EQ-5D pain scores are not available from the current study, as they were not assessed (see response to **B15**).

Nirogacestat arm:

	Mean BPI-SF Score (n=Number of Patients) by Overall Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					

	Mean BPI-SF Score (n=Number of Patients) by Overall Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 15					
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Placebo arm:

	Mean BPI-SF Score (n=Number of Patients) by Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					

Clarification questions

	Mean BPI-SF Score (n=Number of Patients) by Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Nirogacestat arm:

	Mean BPI-SF Score (n=Number of Patients) by Overall Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					
Cycle 16					

	Mean BPI-SF Score (n=Number of Patients) by Overall Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 17	■	■	■	■	■
Cycle 18	■	■	■	■	■
Cycle 19	■	■	■	■	■
Cycle 21	■	■	■	■	■
Cycle 22	■	■	■	■	■
Cycle 23	■	■	■	■	■
Cycle 25	■	■	■	■	■
Cycle 27	■	■	■	■	■
Cycle 28	■	■	■	■	■
Cycle 31	■	■	■	■	■
Cycle 32	■	■	■	■	■
Cycle 34	■	■	■	■	■
Cycle 40	■	■	■	■	■
Follow-up	■	■	■	■	■

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Placebo arm:

	Mean BPI-SF Score (n=Number of Patients) by Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3	■	■	■	■	■
Cycle 4	■	■	■	■	■
Cycle 5	■	■	■	■	■
Cycle 6	■	■	■	■	■
Cycle 7	■	■	■	■	■
Cycle 8	■	■	■	■	■
Cycle 9	■	■	■	■	■
Cycle 10	■	■	■	■	■

	Mean BPI-SF Score (n=Number of Patients) by Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 21					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Nirogacestat arm:

	Mean Change from Baseline BPI-SF Score by Overall Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					

Clarification questions

	Mean Change from Baseline BPI-SF Score by Overall Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Placebo arm:

	Mean Change from Baseline BPI-SF Score by Response Level (assessed within 7 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Nirogacestat arm:

	Mean Change from Baseline in BPI-SF Score by Overall Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					
Cycle 16					
Cycle 17					
Cycle 18					
Cycle 19					
Cycle 21					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Placebo arm:

	Mean Change from Baseline in BPI-SF Score by Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 3					
Cycle 4					
Cycle 5					
Cycle 6					
Cycle 7					
Cycle 8					
Cycle 9					
Cycle 10					
Cycle 11					
Cycle 12					
Cycle 13					
Cycle 15					
Cycle 16					
Cycle 17					

	Mean Change from Baseline in BPI-SF Score by Response Level (assessed within 14 days)				
Timepoint	CR	PR	SD	PD	NE
Cycle 18					
Cycle 19					
Cycle 21					
Cycle 22					
Cycle 23					
Cycle 25					
Cycle 27					
Cycle 28					
Cycle 31					
Cycle 32					
Cycle 34					
Cycle 40					
Follow-up					

Abbreviations: BPI-SF = Brief Pain Inventory Short Form; CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Priority A14.

The company did not include any analysis comparing people treated with nirogacestat to people treated with the other systemic therapies: chemotherapy or TKIs. The EAG's clinical experts noted that both chemotherapy (primarily vinorelbine) and TKIs (primarily sorafenib) are effective therapies used in their practices. Ou et al. (2023)(Ou et al. 2024) published a systematic review and network meta-analysis of RCTs comparing nirogacestat to chemotherapy (methotrexate with vinblastine) and to TKIs (sorafenib).

Please can the company present an indirect treatment comparison (ITC) comparing chemotherapy (vinorelbine) to nirogacestat in people with DTs. They could use the RCT noted above (found in the company's SLR) and assume a similarity of effect and safety between methotrexate with vinblastine and vinorelbine.(Toulmonde et al. 2019) Alternatively, the company could conduct an ITC matching analysis using retrospective studies or single arm trials.

Please include the following endpoints where data is available:

- PFS

- **ORR**
- **CR**
- **PR**
- **Grade 3+ adverse events**
- **Time to discontinuation**
- **Quality of life**

Response: After conducting a systematic literature review (SLR) and feasibility assessment (FA), the company determined that an indirect treatment comparison (ITC) between nirogacestat and vinorelbine is not appropriate due to methodological and data-related limitations, including study design and data collection issues.

The SLR identified 1 full text publication (Palassini et al. 2017) and 2 conference abstracts (Costa et al. 2022, Wood et al. 2022) as the only available evidence for vinorelbine. However, these studies present significant limitations that make an ITC with nirogacestat not feasible.

First, the sample sizes for vinorelbine were small in all studies. In Palassini et al. (2017), only 2 patients received vinorelbine monotherapy while 43 received methotrexate plus vinorelbine; in Costa et al. (2022), just 8 received methotrexate plus vinorelbine; and in Wood et al. (2022), 37 patients received single agent oral vinorelbine. Evidence informing the treatment effect of vinorelbine alone would only be inferred by an extremely small sample that would cause the results to be less generalisable and reflective of the true effect in the context of an ITC; similar concerns also apply to methotrexate and vinorelbine.

Second, both the Palassini et al. (2017) and Costa et al. (2022) studies had significantly longer median follow-up periods than the DeFi trial, which could bias progression free survival (PFS) estimates by potentially underestimating PFS in DeFi. Moreover, the timeframe of the observational periods (1989–2014 for Palassini et al. (2017) and 2000–2021 for Costa et al. (2022)) may also reflect out-of-date care

regimens. While the Wood et al. (2022) study may have a relevant observational period (2020-2022), the median time on treatment was substantially shorter, at 7 months (range 3 – 14 months), than that in DeFi, at 20.6 months (Gounder et al. 2023).

Third, differences in patient populations also make the comparison challenging. Paediatric patients were included in Costa et al. (2022) (median age at diagnosis was 37, with a range of 5-77 years; median follow-up was 5.6 years, with a range of 0-7.9 years) and Wood et al. (2022) (median age was 33, with a range of 17-62 years) but were excluded from DeFi. Importantly, no further details were provided on the proportion of paediatric versus adult patients that were included in these studies, and results were not provided separately for paediatrics and adults. As a result, per MAIC methodology, matching (i.e., removing patients in DeFi to align with the comparator population) on age is not feasible as the comparator studies had a broader population in comparison to DeFi. In addition, Costa et al. (2022) only enrolled treatment-naïve patients, while DeFi enrolled both first-line and relapsed/refractory patients. These discrepancies introduce heterogeneity and potentially bias the analysis.

Fourth, baseline characteristics and outcomes were also insufficiently reported in the studies to conduct a robust MAIC. Baseline characteristics were not reported in Wood et al. (2022), and the Palassini et al. (2017) and Costa et al. (2022) studies reported baseline characteristics only for the overall population and not stratified by the relevant treatment arms, preventing any appropriate adjustment between nirogacestat versus vinorelbine alone and versus methotrexate and vinorelbine. In Palassini et al. (2017), PFS and median time to response (mTTR) were reported only for the overall population, with no treatment arm-specific data nor Kaplan-Meier curves. In Costa et al. (2022), response outcomes were not assessed, and PFS was reported only for the cytotoxic therapy group but not for the vinorelbine subgroup. Grade 1-2 adverse events (AEs) were also only reported for the cytotoxic group and no outcomes were available for the comparison of nirogacestat to methotrexate and vinorelbine. In Wood et al. (2022), PFS, ORR, or CR were not reported, and PR was only reported at first imaging. Additionally, only symptomatic response (categorised as improvement or progression) was assessed. Furthermore, none of the studies

assessed quality of life. Therefore, sufficient outcome data was not available to inform a comparison between nirogacestat and vinorelbine.

Finally, all 3 comparator studies were retrospective in design, which are at increased risk of confounders that would be difficult to adjust for in indirect treatment comparisons.

The combination of small sample size, differences in patient populations, outdated treatment periods, short time on treatment, lack of baseline characteristics for treatment arms data, missing outcome information, and retrospective study design undermines the validity of any ITC between nirogacestat and vinorelbine (Costa et al. 2022, Palassini et al. 2017, Wood et al. 2022).

In addition to vinorelbine, there were also studies that published data for methotrexate with vinblastine (MV). An FA was performed using the DESMOPAZ trial, an open-label RCT that evaluated the efficacy of pazopanib compared to MV (Toulmonde et al. 2019). Based on the evaluations from the FA, the company concluded that an ITC between nirogacestat and chemotherapy is not feasible due to several methodological limitations, including the lack of common comparator, different baseline characteristics between studies, small sample size and differences in study masking.

The DeFi trial, which provides the clinical evidence for nirogacestat, does not share a common comparator with the identified studies for MV (Gounder et al. 2023). As a result, only unanchored matching-adjusted indirect comparisons (MAICs) would be an option. Unanchored MAICs require adjustment for clinically relevant prognostic factors (and/or effect modifiers), an assumption that is difficult to satisfy in practice and introduces risk of residual confounding. Although a rigorous process was undertaken to identify and prioritise relevant clinical factors, several of these were not reported in the comparator studies in a format that would allow for appropriate adjustment with the DeFi dataset, including race, tumour size, familial adenomatous polyposis (FAP) status, presence of multifocal disease, relapsed/refractory disease status, and Gardner syndrome, further limiting the feasibility of unanchored comparison.

In addition, substantial differences in baseline characteristics were observed between DeFi and the comparator studies. Compared to DeFi, the DESMOPAZ trial included a lower proportion of patients with prior radiation therapy (4.1% in DESMOPAZ vs 23% in DeFi) and surgery (33.3% in DESMOPAZ vs 44% in DeFi), and higher proportion of patients with prior systemic therapy (75% in DESMOPAZ vs 61% in DeFi) (Toulmonde et al. 2019). Moreover, the DESMOPAZ trial included only 20 patients in the MV arm for the efficacy analysis (compared to the 24 patients in the intent-to-treat (ITT) population; 2 patients were removed for not starting treatment, and 2 were removed for non-eligibility for the efficacy analysis), limiting the statistical power and reliability of treatment effect estimates (Toulmonde et al. 2019). Furthermore, the use of efficacy populations rather than ITT populations in the DESMOPAZ study presents a methodological limitation for conducting ITCs. Due to the lack of reported baseline characteristics for the efficacy populations, an assumption would be needed that their distributions in the efficacy population were comparable to those of the ITT population. As such, the use of different analysis populations (i.e., efficacy population vs. ITT population) introduces bias that cannot be controlled within an ITC and, in combination with the limitations listed above, severely reduces the comparability across studies, potentially leading to overestimation of treatment effects and limiting the validity of the ITC.

Differences in study design between the DeFi trial and the comparator studies is also a key limitation. Given that the DESMOPAZ trial has an open-label design, there is an increased risk of performance and detection bias, particularly in the assessment of subjective endpoints such as symptom reporting and progression evaluation. These biases may lead to an overestimation of treatment efficacy, as both patient and investigator expectations can influence outcome reporting and assessment which cannot be controlled for in an ITC.

Given the aforementioned limitations, the company strongly believes that conducting an ITC would not yield robust or clinically meaningful results, and should not be performed.

Priority A15. Please can the company present an ITC comparing TKIs (sorafenib) to nirogacestat in people with DTs. Based on the company's SLR,

they are aware there was an RCT conducted comparing sorafenib to placebo in people with DTs.(Gounder et al. 2018)

- PFS
- ORR
- CR
- PR
- Grade 3+ adverse events
- Time to discontinuation
- Quality of life

Response: Following the FA phase, the company has determined that conducting a robust and reliable ITC between nirogacestat and sorafenib is not methodologically appropriate due to key limitations in the available evidence base. The limitations include differences in patient inclusion criteria across trials, inconsistencies in the analysis population used, different study designs, and issues related to the reporting of outcomes.

The DeFi trial enrolled patients with histologically confirmed, progressing DT, defined as $\geq 20\%$ progression per RECIST v1.1 within 12 months prior to screening. In contrast, the Gounder et al. (2018) RCT defined progression as a $\geq 10\%$ increase in tumour size within 6 months of registration. This discrepancy suggests that patients in DeFi may have had more actively progressing or aggressive disease, while Gounder et al. (2018) may have included a broader or potentially healthier population. This difference in eligibility criteria limit the comparability of the two studies and introduce potential bias in performing an ITC.

Furthermore, the use of efficacy population rather than the ITT population in Gounder et al. (2018) presents a methodological limitation for conducting ITCs. In the efficacy analysis, 49 patients were included in the sorafenib arm (compared to the 50 patients in the ITT population; 1 patient was removed for withdrawing before

initiation of trial regimen) and 35 patients were included in the placebo arm (compared to the 37 patients in the ITT population; 1 patient was removed for withdrawing before initiation of trial regimen and 1 patient was removed for non-eligibility for the efficacy analysis). Due to the lack of reported baseline characteristics for the efficacy populations, an assumption is needed that distributions of baseline characteristics in efficacy population were comparable to those of the ITT population. Using different analysis populations (i.e., efficacy population vs. ITT population) may introduce selection bias that cannot be controlled within an ITC and reduces the comparability of patient populations across studies, potentially leading to overestimation of treatment effects and limiting the validity of the ITC.

In addition to the RCT, the company identified two prospective observational studies through an SLR (Garg et al. 2023, Noujaim et al. 2024). The lack of randomisation in these studies introduces confounding and selection bias. Outcome reporting bias may also occur because patients and investigators were aware of the treatment received, which could potentially lead to overestimation of treatment benefits. Furthermore, the Garg et al. (2023) study included only patients from India, which may limit its generalisability to a UK setting.

For key outcomes such as duration of response (DOR), there were 2 events in the DeFi trial and no events reported in Gounder et al. (2018) (Gounder et al. 2023). As a result, the median DOR was not reached in either trial, making it infeasible to derive meaningful comparative estimates. Additionally, follow-up data for patient-reported outcomes (PROs), including the Brief Pain Inventory – Short Form (BPI-SF), were not available in the sorafenib studies.

Given the aforementioned limitations, the company has concluded that an ITC between nirogacestat and sorafenib would not yield robust or clinically meaningful results, and should not be performed. Instead, the company has chosen to transparently present the limitations of the available evidence and the rationale for not pursuing an ITC in this context.

Additionally, sorafenib is not widely funded by the NHS, as individual requests for its use are only available on a compassionate use basis (NICE 2025a). Comparators

Clarification questions

may include technologies that do not have regulatory approval for the population defined in scope if they are considered to be established clinical practice for the population in the NHS (NICE 2025b). Given that sorafenib is only available through individual requests under a compassionate use basis, it is not the established clinical practice for the treatment of DTs.

A16. Please present the data in Figure 2.12 Best overall response in long-term analysis in a table. It should detail what the % reduction in the year before was for the patients remaining in sample e.g. what was reduction at Year 3 for the 15 still in sample at year 4. Please include the n alongside each percentage.

Response: The requested data showing the best overall response for the nirogacestat arm in the long-term analysis are presented below.

Year 1 (N=70):

	Year 1
CR	
PR	
SD	
PD	
NE/Missing	

Abbreviations: CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressed disease.

Year 1 to 2 (N=)::

From/To ^a	CR	PR	SD	PD
CR				
PR				
SD				

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

Year 2 to 3 (N=)::

From/To ^a	CR	PR	SD	PD
CR				
PR				
SD				

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

Year 3 to 4 (N=)::

From/To ^a	CR	PR	SD	PD
CR				
PR				
SD				

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

A17. When is the next database lock (DBL) of the OLE expected?

Response: The final database lock of the OLE was on December 19, 2024.

A18. Please present the number of new progressed disease (PD) events per year in the OLE. Separate by on and off treatment.

Response: In the OLE, among patients who were on nirogacestat in the double-blind (DB) phase and continued to receive nirogacestat, [REDACTED] progressed in the DB phase but continued to receive nirogacestat in OLE and developed new PD. [REDACTED] progressed in the first year in OLE while on nirogacestat treatment and [REDACTED] progressed in the second year or later.

In the OLE, among patients who were on placebo in the DB phase and receive nirogacestat in OLE, [REDACTED] developed PD in OLE while on nirogacestat treatment ([REDACTED] had PD in DB phase), with [REDACTED] having progressed in the first year in OLE and [REDACTED] progressed in the second year of OLE.

Section B: Clarification on cost-effectiveness data

Economic analysis structure

Priority B1: The company have not included chemotherapy as a comparator. Clinical experts have advised that vinorelbine is in regular use within this patient group.

a) Please can the company include vinorelbine as a comparator in the economic analysis?

Response: As described in the response to question A14 above, there are several study quality and data limitations that preclude an indirect comparison to vinorelbine. Specifically, the only available evidence for vinorelbine comes from retrospective observational studies (Costa et al. 2022, Palassini et al. 2017, Wood et al. 2022) that have considerable limitations for data availability and comparability. Including this data in an ITC would introduce significant heterogeneity and is therefore not

recommended. On this basis, vinorelbine will not be included as a comparator in the economic analysis.

b) The company says that chemotherapy ‘is not considered the SoC’ (page 90 of the submission). If the company has data suggesting that chemotherapy is not used for people with desmoid tumours, please present this. Note comparison is still required even if such data is presented

Response: As noted on p22-23 of the submission dossier, there are no approved therapies for desmoid tumours and there are no robust clinical studies demonstrating, to a high scientific standard, the benefit of chemotherapy in this population. Chemotherapy is used by physicians due to lack of other options, and not due to robust scientific evidence or MHRA approval; therefore, chemotherapy should not be considered a SOC.

As described in the response to question A14 above, robust indirect comparisons of nirogacestat and chemotherapy are limited by several methodological challenges, including the lack of common comparator, different baseline characteristics between studies, small sample size and differences in study masking. Therefore, comparisons to chemotherapy have not been conducted.

Priority B2: The company’s model structure implies that there may be a stopping rule proposed. Clinical experts have advised us that they would be willing to take people off treatment after 2 years if their tumour hasn’t changed size/responded or if there is evidence that their tumour has plateaued i.e. stabilised after complete or partial response to treatment. They indicated that they would like the opportunity to keep people on treatment past 2 years if there is evidence their tumour was continuing to shrink/respond. They would also like the option to restart treatment for people who experience recurrence.

a) Please can the company indicate whether they are proposing a stopping rule and what that stopping rule would be? Would the stopping rule only be based on length of treatment or also level of response or whether the persons’ tumour has plateaued? If the company are not proposing a

stopping rule the assumed duration of treatment should be in line with the draft SmPC and therefore we would request the cap at 2 years should be removed (applying a maximum treatment duration based upon the median observed in the trial as stated on page 91 is not appropriate).

Response: The company confirms that we are proposing a 2-year stopping rule. Within the economic model, the 2-year treatment stopping rule is considered a conservative assumption that may overestimate the costs accrued with nirogacestat based on expected real-world clinical use. According to feedback from a clinical expert consulted by the company, in clinical practice patients are likely to stop treatment prior to 2 years, with the clinical decision to stop treatment largely influenced by symptomatic improvements (it is expected that response to treatment would be assessed initially at 1 year, where the majority of patients would be expected to discontinue, and then re-assessed every 2-3 months thereafter). Furthermore, most clinical benefits of treatment reflected in the model are observed prior to the 2-year cap (31/32 [96.9%] of nirogacestat-treated patients who achieved ORR did so by 24.4 months) (Ratan et al. 2025), further justifying the current rationale for ceasing the accumulation of treatment costs after 2 years. This timeframe for the onset of clinical benefits coincides with symptomatic improvements (as assessed by PRO data), which were observed during the DB phase (i.e., prior to the 2-year cap) and sustained throughout the OLE phase (Ratan et al. 2025).

b) Please can the company provide:

- The number and proportion of people on treatment categorised as stable at the end of each year of treatment (RCT and OLE), whose tumour size has plateaued, in each arm.**
- The number and proportion of complete responders and partial responders on treatment whose tumour size has plateaued at the end of each year of treatment (RCT and OLE), in each arm.**

Response: The requested data are provided below.

Overall Response at End of Year 1 for Those who Reached Year 1 Landmark (DB+OLE Phase for Nirogacestat and DB Phase for Placebo) and With Tumour Size Plateaued at Any Time of Year 1

	Nirogacestat (1 Year Landmark) (N=46)	Placebo (1 Year Landmark) (N=34)
CR		
PR		
SD		
PD		

Abbreviations: CR = complete response; DB = double-blind; OLE = open-label extension; PR = partial response; SD = stable disease; PD = progressed disease.

Overall Response at End of Year 2 for Those who Reached Year 2 Landmark (DB+OLE Phase for Nirogacestat and DB Phase for Placebo) and With Tumour Size Plateaued at Any Time of Year 2

	Nirogacestat (2 Year Landmark) (N=40)	Placebo (2 Year Landmark) (N=8)
CR		
PR		
SD		

Abbreviations: CR = complete response; DB = double-blind; OLE = open-label extension; PR = partial response; SD = stable disease.

Overall Response at End of Year 1 for Those who Reached Year 1 Landmark (DB+OLE Phase for Nirogacestat and DB Phase for Placebo) and With Tumour Size Plateaued at the End of Year 1

	Nirogacestat (1 Year Landmark) (N=43)	Placebo (1 Year Landmark) (N=31)
CR		
PR		
SD		

Abbreviations: CR = complete response; DB = double-blind; OLE = open-label extension; PR = partial response; SD = stable disease.

Overall Response at End of Year 2 for Those who Reached Year 2 Landmark (DB+OLE Phase for Nirogacestat and DB Phase for Placebo) and With Tumour Size Plateaued at the End of Year 2

	Nirogacestat (2 Year Landmark) (N=39)	Placebo (2 Year Landmark) (N=8)
CR		
PR		
SD		

Abbreviations: CR = complete response; DB = double-blind; OLE = open-label extension; PR = partial response; SD = stable disease.

c) Would you be willing to have the stopping rule written into the NICE recommendation if it is considered appropriate?

Response: The company is willing to have the stopping rule written into the NICE recommendation if it is considered appropriate.

Clinical parameters and variables

Please note, the company has generated a new base case ICUR, incorporating changes requested by the EAG throughout this section. The new company revised base case deterministic ICUR is [REDACTED] per QALY (with PAS discount applied). The new company revised base case probabilistic ICUR is [REDACTED] per QALY (with PAS discount applied). Please see **Appendix A** at the end of this document with a summary of all the changes incorporated into this new company revised base case analysis.

Priority B3: The company found that their model structure was a poor fit to the data and ‘calibrated’ the rate of transition from stable disease to progressed disease, so that the modelled proportion of progressed patients, matched the number of progressed patients in the trial.

- a) Please can the company provide a rationale as to why they believe their model did not fit the trial data?**

Response: The differences seen between trial data and modelled data might be due to assuming constant transition probabilities for PR and stable disease (SD) progression based on observed rates at one timepoint (month 12) to predict events over time.

- b) The company states that DeFi [REDACTED] events of disease progression within the first 2 years of treatment with nicoracetam’. The company then compares this [REDACTED] progression rate reported in Table 3.9. It appears that the reason for this discrepancy is that the company are not accounting for the [REDACTED] who discontinued the treatment prematurely and the [REDACTED] who did not start treatment (reported in the CSR). Excluding these patients gives a progression rate of [REDACTED] which is much closer**

to the figures presented in Table 3.9. Please can the company clarify if this is correct?

Response: No, the [REDACTED] represents the observed proportion of nirogacestat patients with PD in the trial and is not being compared with the annual rate of progression used by the model. The [REDACTED] was compared with the [REDACTED] of the company submission.

As noted in the response to the question above, the progression rate at month 12 was used to inform PR and SD probability of progression per cycle. Most progression events happened early on, within the first year. Therefore, this might have led to an overestimate of progression events that would happen with nirogacestat after year 1, which was confirmed when we compared the ‘uncalibrated’ patient trace (i.e., using the month 12 progression rate in the model) to the trial. The nirogacestat SD progression rate was downward adjusted until the model predicted the number of PD patients that was more in line with the observed [REDACTED] by 2 years in the trial.

c) The company states that DeFi reported that in the placebo arm at 24 months [REDACTED] had progressed’. The company then compares this [REDACTED] with the [REDACTED] and [REDACTED] presented in Table 39. In the CSR, there are 35 patients who progress in the placebo arm and 14 who prematurely discontinue treatment. This gives [REDACTED] who progress. This suggests the discrepancy is because the company may have incorrectly inputted the progression rate, failed to account for discontinuation and inadvertently switched the proportion of patients who progress with those who did not progress. Is that a correct interpretation? If this is correct, then the transition probability for progression for these patients in the model should be [REDACTED] as these patients cannot discontinue treatment.

Response: No, the [REDACTED] represents the observed proportion of BSC/placebo patients with PD at 2-years in the trial. However, when long-term progression with BSC/placebo was discussed with UK advisors, they stated that the plateau in the

PFS curve was unrealistic and might be due to the shrinking sample size in the trial over time rather than an accurate representation of long-term disease trajectory in patients with progressing DT, and thus the BSC/placebo data after median PFS should not be considered reliable evidence (i.e., the advisors would expect to see untreated patients continue to progress). We therefore anchored our calibration on mPFS instead, which showed [REDACTED] [REDACTED] in the company submission), and we upward adjusted the SD progression rate until the model aligned with the observed PFS and clinical expectations about BSC/placebo progression.

- d) If the reason for lack of consistency between trial reported outcomes and the model was due to the data being compared not being consistent, please revise the assumptions in the model accordingly e.g. remove the calibration.**

Response: No revisions to model needed, as trial reported outcomes and the model were being compared consistently.

Priority B4: The company have informed transition probabilities using 'best overall response.' Please include a scenario in which transition probabilities are informed by patients' actual response at year 1 and year 2.

Response: A deterministic scenario in which transition probabilities are informed by patients' actual responses at year 1 and year 2 has been included in the company revised model. This scenario analysis decreased the ICUR [REDACTED] per QALY in this scenario analysis within the company revised model [with PAS discount applied] compared to [REDACTED] per QALY in the base case analysis of the company revised model [with the PAS discount applied]).

Priority B5: Can the company provide charts that compare modelled state membership with state membership observed in the trial, both for the randomised period and the OLE?

- This should be for the uncalibrated version of the model**
- This should be for 'best overall response' (as currently implemented in the model) and response (i.e. status at most recent monitoring visit).**

Response: The requested charts are provided below. However, the company strongly encourages that direct comparison of the data below should be interpreted with caution given differences in timepoint definitions between the trial and the model. In the trial, EOT is a patient-specific timepoint depending on when each patient stopped treatment. Similarly, in the trial, the start of the OLE is a patient-specific timepoint depending on when a patient completed the DB phase of the trial (i.e., progression) and became eligible for enrolment in the OLE. In contrast, in the model, the company has assumed that EOT would correspond to the final cycle in Year 2 (i.e., Cycle 26), given the 2-year treatment stopping rule, and used a simplifying assumption that the OLE would begin in Cycle 27 (following EOT). These assumptions were necessary given the model structure, wherein the overall patient journey is modelled across a continuous the time horizon. Both the model and the trial employed a 28-day (4-week) cycle length.

Time point	Health State	Observed Response				Best Overall Response			
		Nirogacestat		BSC		Nirogacestat		BSC	
		Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial	Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial
Cycle 4 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 7 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 10 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 13 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 16 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 19 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 22 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 25 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 28 Day 1	CR								
	PR								
	SD								
	PD								
Cycle 31 Day 1	CR								
	PR								
	SD								
	PD								

Time point	Health State	Observed Response				Best Overall Response			
		Nirogacestat		BSC		Nirogacestat		BSC	
		Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial	Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial
Cycle 34 Day 1	CR								
	PR								
	SD								
	PD								
End of Treatment ^b	CR								
	PR								
	SD								
	PD								
Cycle 4 Day 1 OLE ^c	CR								
	PR								
	SD								
	PD								
Cycle 7 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 10 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 13 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 19 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 25 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 31 Day 1 OLE	CR								
	PR								
	SD								
	PD								
Cycle 37 Day 1 OLE	CR								
	PR								
	SD								
	PD								

Clarification questions

Time point	Health State	Observed Response				Best Overall Response			
		Nirogacestat		BSC		Nirogacestat		BSC	
		Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial	Model (uncalibrated)	Trial (DB+OLE)	Model (uncalibrated)	Trial
End of Treatment OLE ^d	CR								
	PR								
	SD								
	PD								

^a Please note that it is not possible to show best overall response for each visit, as the best overall response definition is the best response recorded during a period of time, and for best overall response of CR and PR, a confirmation assessment is required. Thus, there is only one best overall response record per patient.

^b In the model, a simplifying assumption was made that EOT would correspond to the last cycle in Year 2 (i.e. Cycle 26), given that the model assumed a 2-year treatment duration. However, in the model, not all patients will have treatment for 2 years, as patients could progress (and thus discontinue) before the maximum treatment duration. In contrast, in the DB phase of the DeFi Trial, EOT was not a fixed time event, but instead could occur at any time of the study when a participant ended that phase of the study.

^c In the model, the OLE was assumed to be in Cycle 27 (which would equate to the first cycle after the 2-year treatment period). However, in the DeFi Trial, the DB and OLE cycles are not chronologic, in that a patient does not have to complete all cycles of the DB phase (e.g., Cycle 34 Day 1) to enter OLE. For example, a patient on nirogacestat may have entered the OLE after 1 year of treatment, which would make their OLE Cycle 4 correspond to Cycle 16 in total.

^d In the model, this was assumed to correspond to Cycle 64 (which would equate to the 2-year treatment period plus 38 cycles following treatment discontinuation), in order to align most closely with the trial data of OLE Cycle 38).

Abbreviations: BSC = best supportive care; CR = complete response; DB = double blind; N/A = not applicable; OLE = open-label extension; PD = progressed disease; PR = partial response; SD = stable disease.

Priority B6: The company has implemented transition probabilities for a 1- or 2-year stopping rule by assuming that all patients continue treatment up until the stopping rule, assessing the level of response at this time point, then calculating the implied transition probability. This is not an appropriate approach and, among other things, means that patients health outcomes in the first year are dependent on whether there is a 1- or 2-year stopping rule, which doesn't make sense.

- a) **Please calculate transition probabilities in the first year based on the outcomes observed in the first year and the transition probabilities in the second year based on the outcomes observed in the second year.**

Response: The company, respectfully, does not agree with the statement above: “The company has implemented transition probabilities for a 1- or 2-year stopping rule by assuming that all patients continue treatment up until the stopping rule, assessing the level of response at this time point, then calculating the implied transition probability”. Instead, the company would like to clarify the model does not assume that all patients will continue treatment for 1 or 2 years. In the model, response is assessed at every cycle, and transition probabilities are calculated as a linear probability based on ORR (proportion of patients who achieved response by 1 or 2 years). On this basis, patients could progress (and thus discontinue treatment) before the maximum treatment duration. In other words, at each cycle, patients with SD, PR, or CR can either (1) stay where they are (and stay on treatment), (2) transition to a better health state (and stay on treatment), or (3) progress to PD (and discontinue treatment). Once the model reaches the maximum treatment duration, any patients remaining on treatment then discontinue treatment. Please note that when transition probabilities are reported within tables in the original submission using a “1 year” or “2 year” heading, these **do not** show transition probabilities that apply only during year 1 and then only during year 2; instead, the headings indicate the chosen stopping rule and the inputs reflect data derived from patients who were treated for **up to** 1 year or **up to** 2 years of treatment (and do not reflect only data at the 2-year timepoint). As such, the company respectfully feels that the data currently utilized within the model is the most appropriate to inform per-cycle transition probabilities.

The company would like to highlight that based on the current model structure, the company-submitted base case model cannot be readily adapted to incorporate transition probabilities in the first year based on the outcomes observed in the first year and the transition probabilities in the second year based on the outcomes observed in the second year.

b) Table 3.6, Table 3.7, Table 3.8, Table 3.9, Table 3.11 and Table 3.12

currently present data for patients with up to 1 year of treatment and up to 2 years of treatment. These should be amended to present:

- Outcomes during first year of treatment for all patients who received treatment at any point during the first year.**
- Outcomes during second year of treatment, for all patients who received the treatment in the second year of the trial.**
- Please report the numerator and denominator for each value, as well as the percentage.**

Response: The listed tables are amended below.

Amended Table 3.6: Rate of duration of PR during year 1 or year 2 from DeFi trial among patients who received treatment at any point during year 1 or year 2 (ITT population; reference case)

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Rate of duration of response at month 12				

N shown is number of patients with best overall response of PR.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PR, partial response.

Amended Table 3.7: Annual rate of progression from PR to PD during year 1 or year 2 among patients who received treatment at any point during year 1 or year 2 (ITT population; reference case), on tx

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
On tx				

N shown is number of patients with best overall response of PR.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

Amended Table 3.8: Rate of duration of SD during year 1 or year 2 from DeFi trial among patients who received treatment at any point during year 1 or year 2 (ITT population) – uncalibrated

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Rate of duration of response at month 12				

N shown is number of patients with best overall response of SD.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat.

Amended Table 3.9: Annual rate of progression from SD to PD during year 1 or year 2 among patients who received treatment at any point during year 1 or year 2 (ITT population) – uncalibrated, on tx

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
On tx				

N shown is number of patients with best overall response of SD.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; tx, treatment.

Amended Table 3.11: Annual rate of progression from PR to PD during year 1 or year 2 among patients who received treatment at any point during year 1 or year 2 (ITT population; reference case), off tx

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Off tx				

Note: All rates were assumed to be the same as 'on tx' rates of progression in the absence of data.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; PR, partial response; tx, treatment.

Amended Table 3.12: Annual rate of progression from SD to PD during year 1 or year 2 among patients who received treatment at any point during year 1 or year 2 (ITT population; reference case), off tx

	Nirogacestat		BSC/placebo	
	1 year	2 years	1 year	2 years
Off tx				

Note: All rates were assumed to be the same as 'on tx' rates of progression in the absence of data.

Abbreviations: BSC, best supportive care; ITT, intent-to-treat; PD, progressed disease; tx, treatment.

B7: Can the company provide mean (and variance) for age and BSA for men and women included in the trial?

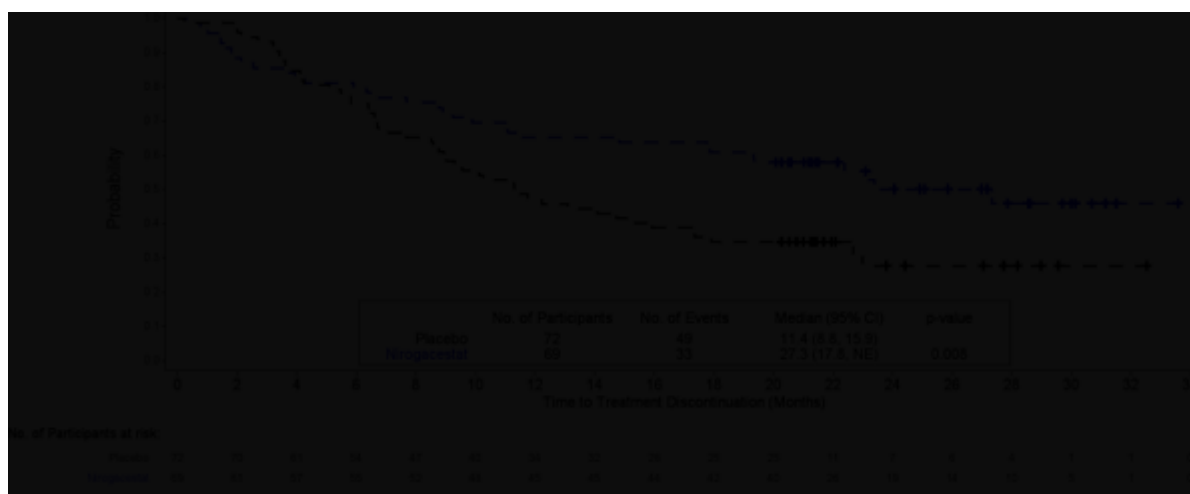
Response: The mean age was [REDACTED] for females and [REDACTED] for males. The mean body surface area (BSA) was [REDACTED] for females and [REDACTED] for males.

Priority B8:

- a) Please provide data on how many patients discontinued treatment in each arm during the DeFi trial each month. This should be presented as

a Kaplan-Meier curve with numbers at risk and tabulated data (time point, number of patients experiencing either an event or being censored).

Response:

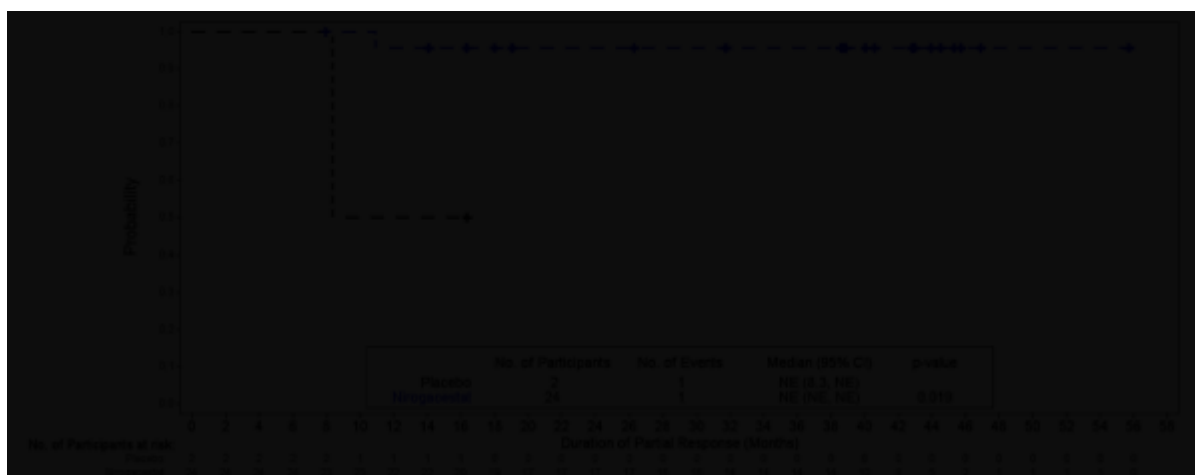


b) Please provide data on state membership for patients who discontinue for each year post treatment, divided by their level of response at the point of discontinuation.

Response: Please note that this data is not available due to the trial design, wherein scans of tumour response assessment were not collected post treatment discontinuation.

B9: The company claim that patients who achieve a partial response cannot go on to experience progression on nirogacestat, but half of patients will do in the placebo arm. Please provide evidence to support this by analysing the outcomes achieved in the long-term by patients who achieved partial response in the first year of DeFi (including OLE data for nirogacestat).

Response: [REDACTED] was observed after achieving PR in nirogacestat [REDACTED] among those participants who reached confirmed PR in the year 1 of exposure. [REDACTED]



[REDACTED]

B10: Please provide a rationale for not incorporating the OLE results in the model.

Response: We can confirm that the model included data from the double-blind and OLE phases for the nilrogacestat treatment arm and from the double-blind phase for the placebo arm.

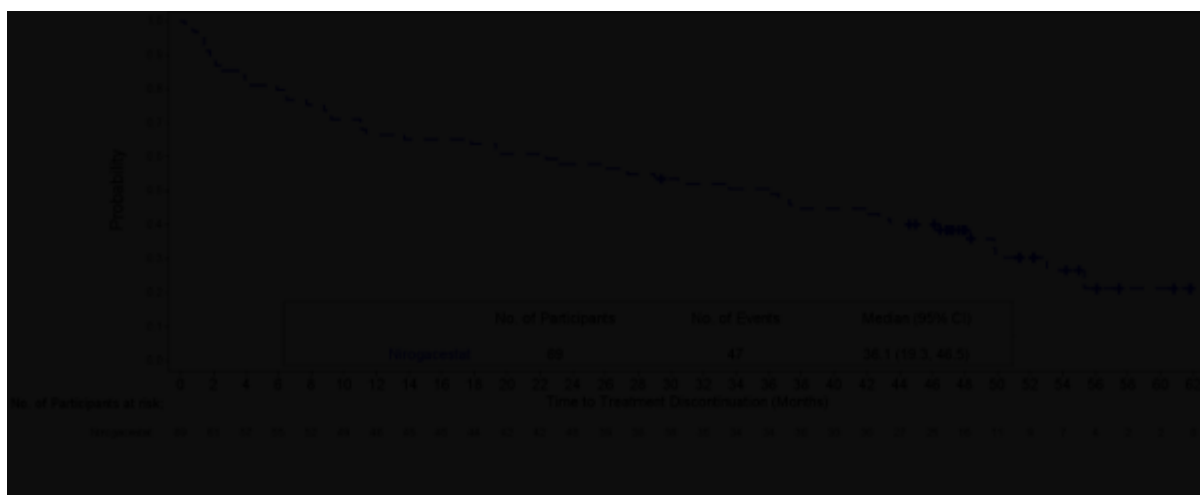
Priority B11: Please provide data from the combined randomised period and open label extension including:

a) The number and proportion of patients in each state (stable disease, progressed disease, partial response, complete response) at each point in the study.

Response: Please refer to the chart provided in response to **B5**, which includes this requested data.

b) The number of patients who discontinued at each time point (Kaplan-Meier including numbers at risk and tabulated).

Response: The number of patients who discontinued at each time (Kaplan-Meier figure including numbers at risk and tabulated) is presented below.



c) Please provide a scenario where these data are incorporated into the model.

Response: As described in response to **B4**, the company has provided a scenario in the revised model where response is based on patients' actual observed response at 1 and 2 years. The company has chosen to focus on the 1- and 2-year timepoints in accordance with the current model programming.

Priority B12: In the primary endpoint for the trial, progression is defined as imaged-based progression (using RECIST) or clinical progression. In the health economics section, this is not consistent. In some sections, progression is described as being informed by RECIST alone. Other sections state that that 'these progression events were based on RECIST (imaging-based) and clinical progression events) (On page 94). The definition of progression used should be consistent. If the definition of progression used within the model, differs from the trial, this should be justified. Please provide a rationale for the chosen response definition and ensure it is applied consistently throughout.

Response: Since the model uses trial data, any inconsistency in definitions within the text is an oversight and it should be understood that PD reflects radiographic (using RECIST) and clinical progression events in both trial and model.

B13: The submission uses mortality estimates from the Anneberg 2022 study which includes patients from 2009 to 2018. The study gives a mortality hazard ratio of 1.3

for DT patients compared with the general population. Clinical experts indicated that the study may be outdated and the increased mortality risk may be attributable to inappropriate use of surgery, which would no longer take place. They indicated that they believe the hazard ratio for mortality is lower (much closer to the general population). Please indicate how you sourced the Anneberg 2022 study and whether alternative sources are available and comment on the validity of using historical data given reduction in the use of surgery.

Response: The study was identified in the DT epidemiology SLR and was the only source of mortality data identified. Since it cannot be confirmed that the Anneberg 2022 results are fully attributable to surgery use, this publication should still be considered the best available data source to inform mortality risk for patients with DT.

Health related quality of life

Priority B14. In Appendices E and G, systematic literature reviews (SLR) of economic evidence and health related cost and resource use (HCRU) were conducted. Due to the limited availability of published data in adult patients with desmoid tumours, secondary SLRs were undertaken to review the economic evidence and HCRU related to soft tissue sarcoma (STS). In Appendix F, an SLR of health-related quality of life (HRQoL) evidence was conducted. Again, given the limited availability of published data in adult patients with desmoid tumours, a secondary SLR was undertaken; however, in this case the evidence reviewed was related to chronic neuropathic pain (CNP).

a) Could the company clarify why the secondary SLR for HRQoL evidence was conducted on CNP rather than STS?

Response: The primary SLRs were conducted in DT as it is the main population of interest. However, data gaps in the HRQoL and economic evidence were observed, so supplementary searches were designed to address these gaps.

To identify appropriate proxy conditions for these supplementary searches, clinical experts were consulted, and CNP and STS were identified as suitable proxy conditions for these supplementary searches.

CNP was considered relevant for HRQoL evidence because pain is one of the most debilitating symptoms experienced by patients with DT, significantly affecting the physical and psychological health of patients (Bektas et al. 2023, Husson et al. 2019). The chronic pain and functional impairment experienced by patients with DT share similarities with that of CNP and can be characterised by uncomfortable sensations such as burning, shooting, and stabbing (Rugnath et al. 2024). CNP disrupts physical health through sleep disturbances, fatigue, and limited mobility (Martins and Marson 2024). It also affects mental health by increasing the risk of depression, anxiety, and emotional suffering (Martins and Marson 2024). As such, a strategic decision was made to search for HRQoL evidence in CNP due to the alignment with the pain burden of DT.

b) Was the information identified from the CNP SLR incorporated into the HRQoL analysis? If not, please explain why. If it was, please explain exactly how.

Response: No. While the values identified from the SLR for CNP provide an estimate for the impact of the **pain** burden of DT on HRQoL, it was determined that the utility estimates would underestimate the full HRQoL burden of patients with DT as they may not fully consider other important considerations for an economic analysis (particularly for PD), including the impact of progression and other functional impacts relevant to DT (e.g., mobility). As a result, the company utilised a separate SLR conducted for economic evidence using STS as an analogue condition, as it shares similarities with DT in clinical presentation, diagnostic pathway, and treatment. This SLR also identified sources for utilities in STS through the identified economic evaluations, with the utility estimates identified from this SLR providing a better holistic representation of the impact of disease burden on HRQoL.

Priority B15. In Table 3.3. the company describe their attempts to map EORTC QLQ-C30 data from the DeFi trial to EQ-5D.

a) Please present the full results of this analysis including. This should include:

- EORTC QLQ-C30 values from the trial,

- **The sample size and proportion of missing data missing at each timepoint, and description of what has been done to handle missing data (if anything)**
- **An assessment of the quality and relevance of the mapping algorithm used and alternative algorithms considered**
- **The country tariff the algorithm is based on**
- **The covariates tested, rationale for their selection and fit statistics for the final fitted model (AIC / BIC, residual plots etc..) any alternative models explored**
- **The statistical code used as part of the mapping process**
- **Mapped EQ-5D values and confidence intervals**
- **An assessment of any limitations associated with the data**

Response: Due to the methodological limitations in mapping from EORTC-QLQ-C30, to EQ-5D-3L using published algorithms, the company was not able to robustly map a utility value for each model health state and considers the analysis results to lack face validity for the available health states and therefore inappropriate for presentation.

As mentioned in Table 3.3 and Section 3.4.2, one of the main limitations is the generalisability of the mapping function to the target population given that differences in the population characteristics can affect health state utility values. There is no mapping algorithm specific to DT and the closest available mapping algorithm considering populations and geographic representation (Longworth and Rowen 2011), included oncology patient samples from three different tumour types. The mapping algorithm was based on 572 patients with multiple myeloma (VISTA study; ClinicalTrials.gov registry NCT00111319), 100 patients with breast cancer and 99 patients with lung cancer having consultations at a Canadian cancer clinic (Vancouver Cancer Clinic data). Patients had a mean age of 68 years old and 44% were men, whereas the patient population in DeFi was younger (mean age of 37 years) and had a lower proportion of men (35% male). Since it is recommended that mapping is based on empirical data and direct statistical association through the use of a regression

model obtained from the mapping literature, and samples used in the current study should be similar to the samples in the published mapping algorithms (Longworth and Rowen 2011), the mapping function was determined to be non-generalisable to the DeFi population, as important differences in the patient populations could affect health state utility values and severely limit the suitability of the mapping algorithm from Young et al. (2015).

Additionally, there are methodological limitations associating a utility to the different model health states. The current model includes SD, PR and CR health states before progression, and progressive disease. The DeFi trial enrolled 142 patients, and for the analysis only patients with a baseline QLQ-C30 measurement and at least one follow-up QLQ-C30 could be included in the analysis, decreasing the sample size from 142 to 134. The effective sample size was further reduced in order to obtain a utility for each specific model health state (i.e., CR, PR, and PD), and the attempts resulted to large standard errors, showing that mapping cannot be practically implemented. Another potential methods limitation is the temporal mismatch between disease progression and EORTC-QLQ-C30 assessment, this limitation was further exacerbated for the PD health state because few observations were categorised as “Yes” for progression status (for example, [REDACTED] of placebo patients that switched to nirogacestat in the OLE phase did not have EORTC-QLQ-30 data collected at the same date as centrally-confirmed disease progression).

b) Please conduct the analysis using the RECIST criteria as well as/instead of clinical response

Response: Given the reasons above, we do not present the results by RECIST.

c) Please present the analysis described in Section 3.4.2 in which the utility values from the DeFi trial were mapped to two health states: progressed and non-progressed

Response: Given the reasons above, we do not present the results by progressed and non-progressed health states.

Priority B16. In the company submission (p.108), the company state that the Shingler et al. (2013)(Shingler et al. 2013) study was used as the utility source as it “*reported EQ-5D utilities for disease states that could be applied to the*

model health states and was directly elicited from a UK population.” The economic evaluation SLR presented in Appendix E identified two economic evaluations conducted from a UK perspective: Shingler et al. (2013),(Shingler et al. 2013) which was used in the base case, and Tikhonova et al. (2018).(Tikhonova et al. 2018)

- a) Can the company provide a justification for selecting Shingler et al. (2013) over Tikhonova et al. (2018) as the source of utilities for the base case analysis? Please provide an assessment of the quality of the available studies and how well they meet the NICE reference case as part of this answer**

Response: Shingler et al. (2013) reported utility values that could inform different levels of response/health states considered in the nirugacestat model design (i.e., PR, SD, PD), whereas Tikhonova et al. (2018) provided utilities for pre- and post-progression health states, which were sourced from Reichardt et al. (2012). Having only one health state utility for pre-progression would mask the value of achieving better tumour responses; therefore, the Shingler et al. (2013) paper was determined to be the most suitable source of utilities for the base case analysis.

As the NICE Quality Assessment Checklist for Health State Utility Values does not allow for an overall quality score, a global assessment cannot be provided for the two sources of utilities used in the identified UK economic models. The model by Amdahl et al. (2014) used utility inputs from Shingler et al. (2013), while Tikhonova et al. (2018) used utility values from Reichardt et al. (2012). Both studies had similar sample sizes and cross-sectional designs, with noted selection bias. Additional limitations of Shingler et al. (2013) include the potential for hypothetical bias and the exclusion of health states worse than death. Reichardt et al. (2012) did not impute missing data or collect information on chemotherapy regimens or adverse events. Notably, Reichardt et al. (2012) collected utilities from patients with STS and bone sarcoma using the EQ-5D, while Shingler et al. (2013) elicited utility values from the UK general public using the time trade-off (TTO) procedure based on health state vignettes.

[URID] Author, Year	[204]Amdahl et al. (2014)	[4223] (Tikhonova et al. 2018)
Study Design (Y/N/NA)	5/2/0	7/0/0

[URID] Author, Year	[204]Amdahl et al. (2014)	[4223] (Tikhonova et al. 2018)
1. Was the research question stated?	Y	Y
2. Was the economic importance of the research question stated?	N	Y
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Y	Y
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Y	Y
5. Were the alternatives being compared clearly described?	Y	Y
6. Was the form of economic evaluation stated?	Y	Y
7. Was the choice of form of economic evaluation justified in relation to the question addressed?	N	Y
Data Collection (Y/N/NA)	10/1/3	10/1/3
8. Was/were the source(s) of effectiveness estimates used stated?	Y	Y
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	Y
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of several effectiveness studies)?	Y	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Y	Y
12. Were the methods used to value health states and other benefits stated?	Y	Y
13. Were the details of the subjects from whom valuations were obtained given?	Y	Y
14. Were productivity changes (if included) reported separately?	NA	NA
15. Was the relevance of productivity changes to the study question discussed?	NA	NA
16. Were quantities of resources reported separately from their unit cost?	Y	N
17. Were the methods for the estimation of quantities and unit costs described?	Y	Y
18. Were currency and price data recorded?	Y	Y
19. Were details of price adjustments for inflation or currency conversion given?	N	Y
20. Were details of any model used given?	Y	Y
21. Was there a justification for the choice of model used and key parameters on which it was based?	Y	Y
Analysis and interpretation of results (Y/N/NA)	13/1/1	11/3/1
22. Was time horizon of cost and benefits stated?	Y	Y
23. Was the discount rate stated?	Y	Y
24. Was the choice of rate justified?	Y	Y
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Y	Y
27. Was the approach to sensitivity analysis described?	Y	Y
28. Was the choice of variables for sensitivity analysis justified?	N	N
29. Were the ranges over which the parameters were varied stated?	Y	N
30. Were relevant alternatives compared? (ie, Were appropriate comparisons made when conducting the incremental analysis?)	Y	Y
31. Was an incremental analysis reported?	Y	Y
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Y	N
33. Was the answer to the study question given?	Y	Y
34. Did conclusions follow from the data reported?	Y	Y
35. Were conclusions accompanied by the appropriate caveats?	Y	Y
36. Were generalisability issues addressed?	Y	Y

[URID] Author, Year	[204]Amdahl et al. (2014)	[4223] (Tikhonova et al. 2018)
Overall (Y/N/NA)	28/4/4	28/4/4

[URID] Author, Year	Shingler et al. (2013)	Reichardt et al. (2012)
Sample Size	100	120 enrolled, 116 evaluable Four not valid for final analysis: missing response status (n = 1), did not complete any patient questionnaire (n = 1), enrolled in SUCCEED clinical trial (n = 1), and was too young (16.9 years old at survey completion) (n = 1).
Respondent Selection and Recruitment	Recruited from UK general public aimed to match census demographics. Participants were recruited through regional advertising	Consecutive recruitment by treating physicians at 25 sites across 9 countries
Inclusion/Exclusion Criteria	No formal inclusion/exclusion criteria reported	Included adults (≥18 years) with metastatic STS or bone sarcoma and favorable response (CR, PR, SD) to chemotherapy. Excluded SUCCEED trial participants
Response Rates to Instruments Used	No response rate detailed	Q1 of 3-item questionnaire: 97.4%Q2 of 3-item questionnaire: 99.1%Q3 of 3-item questionnaire: 98.3% missing EQ-5D - utility score: 114/116 (98.3%) EQ-5D - VAS score: 116/116 (100%)
Loss to Follow-up	Not applicable (cross-sectional study)	Not applicable (cross-sectional study)
Missing Data	No missing data detailed	Missing response status (n = 1) Did not complete any patient questionnaire (n = 1) Patients with missing EQ-5D data excluded from utility calculations. Missing values were not imputed as missing values appeared nonrandom.
Any Other Problems with the Study	Difficult to confirm the validity of vignettes. Members of the general public may overestimate lossess associated with certain states of health (hypothetical bias). Valuation exercise did not contain provision for estimating utilities associated with states worse than death. Sample was skewed towards being younger and more likely to be in full-time education than the UK general publica.	Possible bias in selecting healthier patients. No data on chemotherapy regimen or adverse events was collected

b) Please provide a scenario analysis using the Tikhonova et al. (2018) utilities?

Response: A deterministic scenario using the Tikhonova et al. (2018) utilities has been included in the company revised model. This scenario analysis resulted in an increased ICUR (ICUR = [REDACTED] per QALY in this scenario analysis within the company revised model [with PAS discount applied] compared to ICUR = [REDACTED]

per QALY in the base case analysis of the company revised base model [with the PAS discount applied]). As explained in **B16a**, the Tikhonova et al. (2018) utilities are subject to several limitations (i.e., only a single pre-progression utility input is available, masking the value of achieving better tumour responses); as such, the company's base case analysis that uses utilities from Shingler et al. (2013) is considered more suitable.

c) Please provide the results of any work conducted to check the face validity of the utilities included in the economic model. In particular the utility applied in progressive disease (0.26) was very low (similar to terminal care in oncology) and is applied for 41 years for BSC (Table 3.31) and the assumption of CR utilities equal to general population assumes that there are no lasting effects from desmoid tumours. Please comment on the face validity of these assumptions. Alternatively, please revise the assumptions made in the economic analysis.

Response: Given DT is a rare disease, there is limited information to inform long-term outcomes or the impact of subsequent treatment on post-progression survival. Furthermore, time in a health state is not tracked in the model, which is a common limitation and property of Markov models. The model design, which was validated with 3 clinical experts, does not allow patients to transition out of PD except for death; therefore, patients who enter the PD state will remain in PD until death. Markov models use a 'memoryless' assumption, meaning that patients incur specific health state utility values as long as they are in that health state, regardless of how long they have been in that health state.

Deriving mapped utilities from the DeFi study was associated with methodological challenges (e.g., PRO assessment time points did not fully overlap, no data for patients after they progress, and small sample size in the DeFi trial). Therefore, mapping utilities from the DeFi trial could not reliably produce valid health state utilities and, as such, literature-based utility values were considered the best available data source for informing the model. Shingler 2013 was considered the most appropriate literature source available to inform the PD utility value (see response to B16a). With respect to the CR utility value, the assumption that this is equal to the UK population norm was based on the fact that patients with CR no

longer have any tumours. This assumption was applied in the absence of any alternative sources of CR health state utility data and was validated with UK clinical advisors. A scenario analysis was also performed to test this assumption by applying a lower utility value (equal to PR health state utility) to the CR health state (Table 3.38 in company submission).

B17. A utility decrement of -0.095 was assumed to apply for ovarian dysfunction, for a [REDACTED]. A constant fraction of patients start to experience ovarian dysfunction each trial.

- a) In the trial, a portion of patients who start the treatment experience ovarian dysfunction. This problem resolves for some patients whereas other patients experience it for the duration of treatment. Please provide tabulated data on the length of time for which patients experience ovarian dysfunction.

Response: The tabulated data on the length of time patients experience ovarian dysfunction is provided below.

	Nirogacestat (N=27)	Placebo (N=0)	Total (N=27)
Duration of Ovarian Dysfunction Events (days) [1]			
m		0	
Mean (SD)			
Median			
Min, Max			

[1] Duration of event was calculated separately for each event; m was the total number of events.

- b) Please amend the model to reflect the data and assumptions outlined above.

Response: The company revised base case has been amended to include the costs and disutilities associated with ovarian dysfunction accrued for only a duration of [REDACTED], corresponding to the average duration of ovarian dysfunction as reported in **B17a** above.

- c) Does the current approach fully capture the impact of premature menopause?
If not, please include this as a separate utility decrement.

Response: Yes, the model captures costs and disutilities of ovarian dysfunction, and all cases of ovarian dysfunction resolved (without causing premature menopause) after treatment was stopped.

Cost and healthcare resource use identification

B18. Concomitant medication is not currently included in the analysis. Table 2.5 indicates that the majority of patients were receiving concomitant medications. Please report these costs in the submission and include them in the economic model.

Response: Concomitant medications were not included in the analysis as the concomitant medications received by patients in the DeFi trial were inexpensive and received by a relatively small proportion of patients; therefore, these were not expected to have an impact on the results of the analysis. In addition, patients in the placebo arm of the DeFi trial also received similar proportions of concomitant medications to patients in the nirogacestat arm, so the addition of concomitant medication costs is not anticipated to affect the results of the analysis given that they would apply equally to both the intervention and comparator arms.

B19. For the annual frequency of resource use, the company used Schut et al. (2023)(Schut et al. 2023a) for GP and specialist visits. For other resource use, monthly frequencies from Verboom et al. (2019)(Verboom et al. 2019) were used. In Verboom et al., hospitalisation was reported as “hospitalisation days,” whereas the company submission presents this as “per visit” (CS Table 3.24).

- a) The cost per hospitalisation visit is the weighted mean cost for non-elective inpatient long stay and short stay. Could the company justify why the “per visit” value was used as opposed to the “hospitalisation days” value from the source?

Response: The company agrees that the value for frequency of hospitalisation should represent a “per day” value, rather than a “per visit” value. **In the revised model that will be provided to NICE by 31st October, the cost for hospitalisation will**

be adjusted to represent the cost per day, rather than the cost per visit, to align with the frequency from Verboom et al. (2019).

Update: The company revised model has been amended to align the hospitalisation cost and frequency inputs. In the base case analysis of the company revised model, the per visit cost of hospitalisation input was maintained from the original submission (£2,597) while the frequency inputs were updated to reflect number of visits per year (rather than the number of days). The updated frequency inputs were 2.6 visits in SD/PR (as reported in the UK-specific study by Mytelka et al. (2018)) and 3.9 visits per year in PD (assuming that patients in the PD health state have 1.5-times the frequency of hospitalizations than in SD/PR). This revised model produced a deterministic base case ICUR of [REDACTED] per QALY in the company revised model (with PAS discount applied), which has increased compared to the deterministic base case ICUR of [REDACTED] per QALY in the original company submitted model (with PAS discount applied). Note that although other edits were made in this amended model (see **B17b** [ovarian dysfunction duration] and **B19** [wastage]), this change in hospitalisation inputs is driving the change in the base case ICUR between the company revised and originally submitted models.

However, to further assess the impact of these inputs (given the sensitivity of the model to the changes in this assumption from the originally submitted model), two additional deterministic scenarios were explored in the company revised model (with PAS discount applied). These consisted of (A) adjusting the per visit cost of hospitalisations (£2,597) to a per-day cost (£509.22, assuming a length of stay of 5.1 days, as reported by NHS England in Summary Table 8 “Count of critical care records and the average length of stay, by start day and discharge day, 2024-2025” (NHS England 2025)) but maintaining the original frequency inputs for SD/PR and PD from Verboom et al. (2019) and (B) adjusting the per visit cost of hospitalisations (£2,597) to a per-day cost (£509.22, assuming a length of stay of 5.1 days as described above (NHS England 2025)) and updating the frequency inputs to reflect the UK-specific study by Mytelka et al. (2018), which reported an annual frequency of 2 days for patients in SD/PR and between 5 and 20 days for patients in PD (model input assumed a weighted average of 6.18 based on information from the publication). It should be noted that both the frequency inputs by Verboom et al.

(2019) and Mytelka et al. (2018) were identified within the company's SLR, and while Verboom et al. (2019) provides a conservative assumption for the length of stay data (particularly for the PD health state), data from Mytelka et al. (2018), which presents UK-specific data, suggests that in the UK the length of hospital stay for patients with PD may vary considerably (given the range between 5 to 20 days) and also suggests that country-specific differences may exist. ICURs in scenarios (A) and (B) in the company revised model (with PAS discount applied) were [REDACTED] per QALY and [REDACTED] per QALY, respectively.

- b) Why did the company differentiate between nirogacestat and comparators for the stable disease number of GP visits and specialist visits.

Response: As noted on p114-115 of the company submission, HCRU was differentiated between treatment for the SD health state because the DeFi trial showed that, among participants with SD response in particular, nirogacestat was associated with significantly and clinically meaningful differences in patient reported outcomes (i.e., pain, DT-specific symptom burden, physical functioning, role functioning, and overall quality of life [QoL]) compared with placebo (Stacchiotti et al. 2024). Clinical advisors agreed that this was compelling data to support that nirogacestat patients in SD are different than placebo patients in SD and would, thus, have different HCRU assumptions. As such, the HCRU in the SD health state for nirogacestat was based on the frequency of GP and specialist visits for the 'intermediate symptoms – *low pain*' cluster while the HCRU in the SD health state for BSC/placebo was based on the 'intermediate symptoms – *high pain*', as reported by Schut et al. (2023b).

- c) Could the company clarify why there is a difference in stable disease resource use between nirogacestat and comparators, when no such difference was assumed in the partial response, complete response, or progressed disease health states?

Response: As described in the response to question B19-b above, there is evidence by Stacchiotti et al. (2024) to show a meaningful difference in pain levels between nirogacestat and placebo, specifically for patients in SD. Since there was no comparable data available for patients in other response levels, the model did not assume any pain/resource use differences in the PR, CR, or PD health states.

d) Please provide data on the number of hospitalisations and number of days spent in hospital by health state, year and arm in the DeFi trial including data from the OLE if available

Response:

Participant	Study Phase	Study Treatment	Hospitalization Study Days (Total)	Reason for Hospitalization	BOR	Response at Hospitalization
1						
1						
2						
3						
3						
4						
5						
5						
6						
6						
7						
8						
9						
10						
10						

- [REDACTED]
- [REDACTED]
- [REDACTED]
- e) Please justify the cost code used for hospitalisation or find one more appropriate to the main causes of hospitalisation for desmoid tumours

Response: Given the response above (to question B19d) indicating that hospitalisations for patients with DT are due to a wide range of comorbidities that are not consistent between individuals (as such, there is no “main” cause of hospitalisation), and the fact that hospitalisations are not directly due to DT itself, the average cost for all types of hospitalisation was used as a general cost estimate.

- f) The model assumes 1.96 specialist visits per year on nirogacestat and 2.24 on the comparator treatments. Clinical experts indicated that this would be an underestimate in the first year, where they would expect around 9 specialist visits. Please provide a rationale for the data provided and implement a scenario with a higher number of specialist visits.

Response: Schut et al. (2023b) provided HCRU information for a DT population. Therefore, the model used the frequency of specialist visits as reported by Schut et al. (2023b) as an average estimate of HCRU in any given year, and this was validated with UK advisors. Assuming 9 specialist visits per year for patients in the SD health state for both nirogacestat and comparator treatments, has very little impact on the results of the analysis (ICUR = [REDACTED] per QALY in this scenario analysis within the company revised model [with PAS discount applied] compared to [REDACTED] per QALY in the base case analysis of the company revised model [with PAS discount applied]).

B19. The model currently doesn't account for wastage. Please amend this by assuming that each patient throws away half a pack of each medicine they use.

Response: The company revised model has been amended to account for wastage as suggested, wherein it is assumed that half of a pack of nirogacestat is wasted when a patient discontinues treatment.

B20. Priority question: Please clarify whether the cost of the 150mg dose is equal to triple the cost of the 50mg dose and double the cost of the 100mg dose. If this is not the case the current application of RDIs is incorrect, please amend.

Response: Nirogacestat uses flat pricing across both 100 mg and 150 mg formulations (there is no 50 mg formulation of nirogacestat that will be commercially available). Drug costing in the model is based on the assumption that all patients use the 2 × 150 mg dose (in accordance with the SPC), and the trial-based RDI used in the model is consistent with the twice-daily 150 mg dosing schedule (with the RDI applied directly to the number of units per model cycle). As such, application of RDI within the model only applies to cost reduction with the 150 mg dosing, as the model does not account for dose reduction from 150 mg to 100 mg dose.

Exploring uncertainty

B21. In the probabilistic sensitivity analysis, the company have included the response rate for best supportive care and nirogacestat separately, then imposed perfect correlation by drawing the same random value in each arm. This is not an appropriate implementation. Please amend so that one treatment is treated as an anchor, then the other treatment is modelled using a treatment effect. Then use the uncertainty surrounding this treatment effect in the PSA, to ensure that the PSA represents the uncertainty observed in the clinical trial.

Response: As described in response to **B22** below, the company revised model has been updated to use independent random numbers and remove the concern related to perfect correlation across arms. Using independent random numbers is anticipated to produce similar results to the treatment effect approach, since the latter would still require random draws for both treatment effects and responses in the anchor group. Therefore, the company has not implemented a treatment effect approach, which would present implementation challenges given the 0% responses in both treatment arms at certain time points.

B22. In the probabilistic sensitivity analysis for health state utility values, the company has imposed perfect correlation by drawing the same random value in each arm. This is not an appropriate implementation. The company should treat

each health state utility value as a separate random variable. If there are issues with maintaining the order of health state utility values, the company should implement the method in Ren et al. (2018). (Ren et al. 2018)

Response: In the company submitted model, the same random value was drawn for each health state utility value in the probabilistic sensitivity analysis due to concerns with maintaining the order of health state utility values (given the small variation in utilities values between certain health states). To remove the concern related to perfect correlation across arms, the company revised model has been updated to use independent random numbers. To maintain the order of health state utility values, a stepwise approach was used (i.e., ordering the sample from random numbers from lowest to highest and then assigning these values to each health state).

Severity modifier

B23. Justify using different lifetables to calculate the severity modifier compared to the rest of the economic analysis. Alternatively, please update to use the latest source.

Response: Older life tables are used in the NICE Shiny app / DSU severity shortfall calculator (Excel), whereas the company submission model used 2021-2023 UK life tables. If the life table in the DSU calculator was updated to the latest dataset, the 1.2 weighting would still apply.

B24. In Section 3.6 of the company submission, it states that nirogacestat may qualify for a QALY severity weighting of 1.2. Please can you update this section to include the relevant details outlined in the severity section of the submission template, i.e. calculations and tables (for more information on severity see NICE's health technology evaluations manual section 6.2.12 to 6.2.22 and TSD 23: A guide to calculating severity shortfall for NICE evaluations). Please also clarify how the severity weighting has been incorporated into the cost effectiveness results. QALY weights should be applied to the incremental QALY gains, and ICERs should be presented with and without the severity modifier applied.

Response: Severity weighting was calculated using the DSU shortfall calculator/Shiny app from the NICE website (<https://sheffield.ac.uk/nice->

[dsu/tsds/severity-shortfall-tsd](#)). The base case deterministic results are shown without severity modifier applied; the PSA results were presented both with and without the severity modifier.

Section C: Textual clarification and additional points

C1. The submission refers to clinical expert consultation as the source for a large number of assumptions made in the economic model. Please provide details of how clinical consultation was conducted e.g. number of clinicians involved, their specialisms / level of experience, the types of centres they were from, how inputs were gained e.g. advisory board, telephone interviews, structured expert elicitation. Please provide minutes from any interviews conducted.

Response: The company sourced clinical expert opinion from three clinicians, both UK-based consultant medical oncologists, with a specialism in bone and soft tissue sarcomas. All clinicians work in specialist oncology units within hospitals. Inputs were gained via advisory boards (3 x 2-hour virtual advisory board meetings) as well as ad hoc follow-up communications.

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Appendix A: Company Revised Base Case Analysis

The new company revised base case model includes the following changes versus the original company submitted model:

- PAS discount applied
- Ovarian dysfunction duration capped at [REDACTED] (per **B17b**)
- Corrected hospitalisation inputs (per **B19a**)
- Assuming drug wastage (i.e., half of last pack of nirogacestat wasted; per **B19**)
- Independent random sampling (per **B22** and **B23**)

Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Sarcoma UK and Desmoid Aid UK
3. Job title or position	Policy and Public Affairs Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Sarcoma UK is registered as a charity in England and Wales (1139869) and in Scotland (SC044260), and as a company limited by guarantee in England and Wales (7487432). We are a national charity that funds research, offers specialist support for anyone affected by sarcoma cancer and campaigns for better treatments, and the only charity in the UK focusing on all types of sarcoma. The vast majority of our funding comes from donations and legacies. We currently employ 37 members of staff. Desmoid Aid UK is registered as a charity (1207309) all our funding to date comes from donations. We have 5 trustees, no employed staff.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Sarcoma UK has received funding from Merck (formerly Springworks), who brought forward this treatment to NICE for evaluation, in the past 12 months. On 1/11/2024, Merck awarded the value of £19,362. The sum was put towards funding our Support Line - a service offering advice and support for anyone affected by sarcoma or potentially affected by sarcoma, run by former or practicing sarcoma clinical nurse specialists - and specifically awarded to support patients with desmoid tumours. On 14/11/2024, Merck awarded the value of £2500. The sum was put towards hosting our annual awards ceremony for members of the sarcoma community, the Shining Star Awards. On 16/05/25, Merck awarded the value of £3000. The sum was put towards hosting our sarcoma community day event in June 2025. Desmoid Aid UK have not received any funding from the company bringing the treatment to NICE for evaluation or any comparator treatment companies in the last 12 months.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We do not have any direct or indirect links with, or funding from, the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have used four main evidence sources: • Patients and carers: evidence from patients and carers was gathered both through oral interviews and written statements. Patients and carers were identified and contacted through a number of sources: social media, including engaging with the community on Desmoid United Facebook group; recommendations from healthcare professionals within our networks that work regularly with desmoid patients; existing contacts of the charity through our Involvement Network. • Healthcare professionals: healthcare professionals were identified through our Healthcare Engagement Lead, who manages our networks of clinician contacts. We had informal discussions with healthcare professionals who work with desmoid patients to guide our areas of focus. We also received written evidence from sarcoma clinical nurse specialists and allied health professionals who work closely with desmoid patients and carers. • Academic literature: we also consulted existing academic evidence on the experiences of desmoid patients in the UK, primarily <i>Physical symptom burden in patients with desmoid-type fibromatosis and its impact on health-related quality of life and healthcare use</i>. (Schut AW et al., 2023) and <i>Desmoid fibromatosis through the patients' eyes: time to change the focus and organisation of care?</i> (Husson O et al., 2018). To inform our understanding of existing evidence, we also consulted the DeFi study, <i>Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors</i> (Gounder M et al., 2023). <i>Current management of Desmoid Tumors</i> (Kasper et al 2024). • Sarcoma UK Support Line: the specialist Support Line, run by former or practicing clinical nurse specialists, is a source of primary evidence for Sarcoma UK. It has had over 30,198 calls with 6,411 individuals since 2016. It receives daily phone and email enquiries, including regular contact with desmoid patients. In this consultation, we will refer directly to 3 people with DF tumours and 1 carer. • Sophie, a 35-year-old DF patient currently on nirogacestat. • Conor, a 40-year-old DF and FAP patient currently on nirogacestat • Inga 37-year-old DF patient had 4 lines of treatment to date.

	Jackie, carer to her partner, who is a DF patient. Please see the appendix for full statements of these and other patients and AHP/Nurse statement who kindly gave time to support our submission and whose lived experience we are sharing.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Desmoid-type fibromatosis (DF) is a rare, locally aggressive soft tissue tumour. Desmoid tumours do not metastasise but can recur at or around the site of the original tumour. Desmoid tumours are classified by WHO as intermediate tumours, not cancerous. Care for DF patients is provided by sarcoma specialist centres as people with DF require the expertise of the cancer services that deal with soft tissue tumours. Patients therefore must travel to one of the seventeen sarcoma specialist centres in the UK, with journey time disproportionately impacting those from rural areas and low-income households (Sarcoma UK, <i>Unique Among Cancers</i>, 2025). Approximately 5-6 in 1,000,000 people will develop DF. Physical symptom burden varies across patients (Schut et. al., 2023). For those with aggressive DF and high symptom load, desmoid tumours can affect all areas of life. The effects of living with desmoid tumours on patients and carers can be underestimated by both healthcare professionals and the public. The EQ5D measure is used here to demonstrate the wide effects of DF on some patients. Pain and discomfort: the ‘most debilitating’ effect of desmoid tumours for the patient is typically pain (Hussein et al, 2019). Sophie described the pain she experienced beginning as dull and consistent, before escalating to the point that she could no longer continue her daily activities, and poor sleep despite prescription of pregabalin and morphine from pain management services. She also experienced a bowel perforation because of the tumour in her abdominal wall, causing her ‘absolute agony’, describing to us screaming in pain in the hospital ward. Inga describes ‘forgetting what it’s like to live pain free, sleeping through the night and not waking up in pain feels like a luxury to me’ Pain can occur at any point in the growth of a desmoid tumour (Schut et. al., 2023). For some, comparator drugs and referral to pain management clinicians result in some improvement for a period; for others the effectiveness of other treatments is minimal, and they stay reliant on significant pain relief. Due to the ‘chronicity’ of desmoid tumours, clinicians raise concerns about consistent or lifelong use of pain medication leading to dependence and reduced effectiveness.

	• Mobility: mobility can be severely affected by DF. Sophie was left using a wheelchair and walking sticks in her late twenties and early thirties as a result of her pain, even when on morphine. Desmoid tumours can also limit mobility through size, location, or placement on a nerve, with patients reporting being unable to lean on the site of their tumour as one of their most common symptoms (Schut et. al., 2023). Inga struggles to stay physically active, with standing or sitting down for a period of time being difficult because of the DF. • Usual activities and self-care: DF can affect ability to undertake responsibilities and previously normal daily activities. Sophie recalled having to leave employment in retail due to the pain caused by her DF, side effects of ineffective treatments such as extreme fatigue, her need for mobility aids, and her medical needs. She was left reliant on her other part-time job, which she could perform from home and at irregular hours. Patients often have difficulties continuing their necessary responsibilities, including employment and caring for dependants (unable to bathe, dress or carry children), creating financial and social impacts. Patients can also lose their independence when unable to perform these tasks for themselves. In addition, desmoid tumours can prevent the body performing normal functions. Sophie's bowel perforation necessitated a stoma, and Jackie's husband was unable to maintain a normal diet of solid foods for three months. • Anxiety and depression: patients frequently experience depression and anxiety resulting from the chronic impacts of DF. ○ <i>Symptoms and side effects:</i> fatigue, pain and functional limitations can all directly impact the mental health of the patient. Robbie describes the constant symptoms being a reminder that the tumour is always there, he describes feeling out of control, and that he finds it hard now to socialise. Symptoms were described as limiting the ability to maintain employment, responsibilities, independence, and hobbies or other sources of joy. ○ <i>Body image:</i> appearance altering treatments and loss of mobility can change perception of self, with anorexia reported as a side effect of treatments, and difficulties for female patients feeling 'less feminine' as a result of surgery scars and disfigurements (Hussein O et al., 2018). Inga describes the disfigurement she lives with being the biggest challenge, 'my DF is 25 cm, imagine strapping a boulder to your hip and living with that' ○ <i>Relationships:</i> changes in body image, loss of libido and dependence on partner as a carer can put strain on relationships. Inga describes getting the diagnosis at 27 and how it dictates and influences every aspect of her life. It has restricted where she lives because of the need for specialist care, she remains single because of the impact of the disfigurement, has undergone IVF

	alone to keep future options open and her career has been impacted because of treatment and time off work. ○ <i>Isolation</i>: rare and unknown to the public, DF patients often struggle explaining their condition and experiences to others, whilst for some they receive the same chemotherapy as a cancer patient and have similar impacts because family and work colleagues don't understand DF they do not receive the same empathy and support. Sophie described her relief that her sister and friend also had desmoid tumours, since it gave her a community and support network, describing how alone she would feel without them. Conor described feeling isolated and the difficulty of explaining the nature of an intermediate and aggressive tumour that sometimes is dormant and manageable and other times he needs chemotherapy for, he describes feeling an 'imposter almost' when he goes to the cancer specialist centre and the support services. ○ <i>Medical isolation</i>: lack of awareness also extended to medical professionals, who can underestimate the effects of DF and treatment. In addition, medical indecision is common, due to lack of evidence-based treatments and expertise. This leaves patients often having to become an expert in their own condition. Patients spoke about the need to continually push to get seen by the specialist services and get to someone that knew anything about desmoid. ○ <i>Uncertainty</i>: patients must deal with the anxiety of an unpredictable condition, many living from scan to scan, unable to predict the progression or regression of their tumour. Jackie describes not being able to plan. The unpredictable nature of her husband's disease makes them anxious about booking holidays. Conor describes the uncertainty around the disease as being particularly hard to live with. ○ <i>Chronicity</i>: once aware of the current lack of effective treatments to manage their condition, many patients experience hopelessness at facing life in a constant state of pain and isolation. Patients face a 'life-changing and life-long' disease (Hussein et al., 2018). Studies have found that DF can leave patients with suicidal thoughts. Carers are impacted by the immense symptom load of this chronic condition on the patient. Practically, they typically have to take on the physical and organisational burden of both the medical needs of the patient and the functions that patients can no longer undertake. Jackie describes always being on red alert due to the unpredictable nature of her husband's DF and feeling powerless to help. Inga describes the impact on her parents, who have been her main support. The hope that they have with every start of a new treatment and how crushed they are every time the outcome failed. Inga and Conor describe the impact it has on their loved ones and that DF does not just impact the patients.

	Carers support DF patients often in addition to their own responsibilities, such as childcare and work, or those they may need to take on, such as extra employment to counter the financial impacts of desmoid on the patient and their dependents. They are also likely to provide emotional support to the patient. They can experience many of the same feelings as patients. The specialist nurses and physiotherapist we spoke to described carers as experiencing 'helplessness, restrictions on their life, feelings of no end in sight, and frustration as relationships can become tense and strained'. Physical and mental demands of caring can result in exhaustion and insomnia.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Nirogacestat is the first treatment to be specifically designed for DF - no other specialised treatment option is available. Available treatments for desmoid tumours are therefore limited and often ineffective in controlling tumour growth and reducing symptoms and not evidence-based. In addition, most have significant side effects. Clinicians describe the difficulty of clinical decision making due to the 'marginal clinical benefit of these treatments coupled with potentially serious adverse effects' (Hussein et al., 2018). The impact this combination has on patients should not be underestimated. At present, treatment options for desmoid tumours are: • Active surveillance ('watch and wait'): active surveillance is now established by global consensus guidelines as the first line of care for DF patients on diagnosis (The Desmoid Tumour Working Group, 2024). The use of active surveillance is the standard of care for patients newly diagnosed with DF and allows the medical teams to understand the nature of a persons DF. For patients, active surveillance is often 'associated with fear, stress and anxiety' between scans (Hussein et al., 2018). The Sarcoma UK Support Line reported how commonly they explain why surgery is not the first treatment option for desmoid patients. • Cryoablation: cryoablation is another treatment option for DF. It has been useful in some cases for managing symptoms and has minor side effects. The success of treatment depends on the size and location of the tumour. • Surgery: formerly the primary treatment for DF, surgery is now used thoughtfully and in specific situations DF patients (The Desmoid Tumour Working Group, 2020). It has 'high morbidity and postsurgical recurrence rates of up to 50 to 88%' (Gounder, M. et al., 2023). Surgery can be radical and

	often mutilating, leaving patients with significantly reduced function and cosmetic changes to their appearance. For patients, this can impact emotional wellbeing and social interaction. • Doxorubicin/ Liposomal Doxorubicin: one of the options for chemotherapy for DF patients, doxorubicin has documented severe side effects. Sophie described overwhelming fatigue that left her unable to work when combined with the symptoms of her DF. She described looking back at a photo herself from the period she was on the drug and feeling shocked at how she looked, wondering how she and her husband found the strength to make it through this time. For Sophie, the chemotherapy had no impact on her symptoms or the size of her tumour. • Vinorelbine: vinorelbine is another chemotherapy option for DF patients. Patients describe side effects including nausea, fatigue, vomiting, and mouth sores. Although easier to tolerate than doxorubicin, vinorelbine is still a chemotherapy drug with significant side effects and limited effectiveness. Inga describes the huge challenge of managing the side effects.
8. Is there an unmet need for patients with this condition?	There is an unacceptable unmet need for patients with desmoid fibromatosis. DF has no novel drugs and at present the options are scanty evidence based and reliant on drugs that are over 40 years old, Conor describes 'feeling left behind'. As described above, the currently available options for treatment come with significant side effects but have limited effectiveness. Angela, who is currently on surveillance, has described her unwillingness to begin treatment. She relayed that she would choose risking surgery over the other treatment options, telling us: 'I don't think I could go through with the chemo options which are truly terrible with horrible side effects, life limits and no guarantee... I couldn't mentally go through that unknown and still have the tumour.' Angela stressed the need for nirogacestat to provide alternatives to the current ineffective treatments with significant side effects.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	• Effectiveness: nirogacestat is highly clinically effective. Sophie had been through active surveillance, cryotherapy, vinorelbine and doxorubicin; after experiencing extreme pain and life disruption due to these treatments, none had controlled or regressed her desmoid tumour. Nirogacestat has been transformative. It has been highly effective, with her largest desmoid tumour approximately halving in size. The relief of scans showing sustained improvement after years of unsuccessful treatment has been immense. • Improvement of symptoms: unlike other treatments, nirogacestat is effective in controlling symptoms. For Sophie, the most unmanageable symptom was pain. Despite being on morphine, she had to use walking sticks or a wheelchair and give up one of her jobs. Having experienced extreme pain for such a sustained period, including when being treated with comparator drugs, she was surprised at the relief, describing it initially as 'weird'. Sophie told us 'it's literally been like day and night being on this. I'm just so happy I'm on it'. • Manageable side effects: when compared to comparator drugs, the side effects of nirogacestat are highly manageable. Having previously experienced the side effects of chemotherapy drugs on vinorelbine and doxorubicin, particularly extreme fatigue, Sophie was able to manage her fatigue through scheduling rest. Conor has found the side effects easier to tolerate than chemotherapy, he has found ways to manage the diarrhoea and fatigue. • Hope: Jackie told us that the approval of nirogacestat would give her and her partner a sense of hope for progress and management, as well as hope for the possibility of further treatments being developed in the future. The DF community have so far experienced no novel treatments for their condition. Facing a chronic condition with often life inhibiting symptoms, the development of nirogacestat could give patients a sense of hope. • Home administration: unlike chemotherapy, nirogacestat is taken twice daily in tablet form. Conor describes how it fits in with his daily life and routine. Our Support Line have heard that for patients, this is far less disruptive than travelling to hospital, often 2 hours away, to have a chemotherapy drug administered through a drip. It is also more cost effective for the patient and NHS.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	• Fatigue: the most common side effect described by patients was fatigue. This was described as manageable, particularly in comparison to comparator drugs. Patients spoke of using adjustments such as scheduling rest after particularly exerting days. • Amenorrhea: though no patients or carers we consulted raised this as a concern, it is worth noting that many female patients of childbearing age (75%) experience amenorrhea temporarily when taking nirogacestat (Gounder, M. et al., 2023). We heard that the patient's need to manage their condition came above concern over disruption to their menstrual cycle. Clinicians have anecdotally confirmed that thus far all patients' menstrual cycle has resumed by the latest 18 months after ending the drug. • Increased bowel output: the DEFI study notes diarrhoea as a side effect of nirogacestat. One patient with a stoma bag described increased high output stoma, which led to an infection. She now manages this symptom with loperamide and codeine. • Unknown side effects: as a new drug, Jackie raised concerns about long-term side effects. One clinician has also raised concern about possible effects on skin toxicity, aligning with the DEFI study note on skin effects, which they believe could be managed cost effectively through bi-annual dermatologist reviews.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are no expected variations in effectiveness between patient subgroups, including between patients with FAP and spontaneous desmoid tumours. A possible factor that may affect the decision to use the drug is the sex of the patient. As described above, amenorrhea is a predicted issue for female patients of reproductive age. This is reversible once a patient ceases to take the drug and does not affect effectiveness of the drug. We did not have any indication from female patients we spoke to that amenorrhea is likely to prevent them from choosing to use the drug.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• As above, female patients may experience amenorrhea. In comparison, there is no evidence of hormonal change for male patients. • Since DF comes under the care bracket of rare cancers, it should also be considered that DF patients face an inequality when compared to patients with common cancers who have access to novel treatments.

Other issues

13. Are there any other issues that you would like the committee to consider?	• Evidence: at present, there is very limited evidence base for the use of comparator treatments for DF. Their use is based not on clinical evidence, but the historic absence of other treatments. Nirogacestat is the first time that a drug has been developed and proven through a randomised, controlled trial for the treatment of DF. We hear that both patients and clinicians would be reassured through the availability of a drug that is clinically proven to be effective. • Quality of life: from a patient perspective, the effectiveness of nirogacestat must be assessed in terms of quality of life, not extension of life or improvement according to RECIST criteria. While DF is grouped under cancer care, the two conditions are distinct.
14. What medical therapies (licensed or off-label) are used for treating desmoid tumours? If tyrosine kinase inhibitors or chemotherapy is used, what drugs within these groups are used in clinical	Chemotherapy medications used for treating DF are: • Vinorelbine (licensed for use in NHSE). There are no randomised controlled trials for treatment of DF with vinorelbine. Evidence largely derives from retrospective data. • Doxorubicin (licensed for use in the NHSE). There are no randomised controlled trials for treatment of DF with doxorubicin. Evidence includes systemic reviews, retrospective data and case reports. Tyrosine kinase inhibitors used for treating DF are:

practice in the NHS? Is there clinical evidence to suggest these treatments are disease modifying?	• Sorafenib (not routinely funded in NHSE). Randomised controlled trial for treatment of DF suggests drug is disease modifying (Sorafenib for Advanced and Refractory Desmoid Tumors, 2018). • Pazopanib (not routinely funded in NHSE). Randomised trial for the treatment of DF with pazopanib compared with comparator drug suggests drug is disease modifying (DESMOPAZ pazopanib (PZ) versus IV methotrexate/vinblastine (MV) in adult patients with progressive desmoid tumors (DT) a randomized phase II study from the French Sarcoma Group, 2018). • Nirogacestat (not routinely funded in NHSE). Randomised, placebo-controlled clinical evidence presented in the DeFi study (Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors, 2023).
15. Do people with desmoid tumours have tyrosine kinase inhibitors through the compassionate use scheme. If so, how widely are they available through this scheme?	• Nirogacestat is currently available through the compassionate access scheme. • Pazopanib is accessible through individual patient request. The Sarcoma UK Support Line hears it is often declined, and that some patients have turned to self-funding. • Sorafenib is accessible through individual patient request. The Sarcoma UK Support Line hears that it is granted more often than pazopanib.
16. Are there any registries collecting data on desmoid tumours?	There is no national registry for data on DF in the UK. Sarcoma UK are aware that some sarcoma specialist centres keep in-house data on their DF patients.

Key messages

17. In up to 5 bullet points, please summarise the key messages of your submission.	- For some patients, DF significantly impacts quality of life. Patients can experience pain and loss of mobility that can result in inability to perform daily tasks or maintain employment and have mental health impacts as significant as suicidal thoughts. For patients with high symptom load, it may inhibit their ability to live a normal life. As an unpredictable and chronic condition, this may continue throughout the patient's life. - Existing desmoid treatments are of limited effectiveness and are being given with limited evidence. Nirogacestat is extremely effective and is the only drug currently available for treatment of DF supported by a randomised, controlled trial. - Existing treatments for desmoid have significant side effects that can limit patients' ability to continue daily activities and significantly affect their quality of life. The side effects of nirogacestat are manageable. - Due to the chronic nature of DF and its significant impact on patients' quality of life, nirogacestat must be evaluated by its effect on progression of symptoms and quality of life, not RECIST criteria alone. - Until this point, the DF community has had no specialised consideration of their care needs as unique from cancer care. Nirogacestat is the first drug developed specifically for desmoid tumours. This is a pivotal moment for the community that offers hope for care and treatments that meet their needs, and hope for those who are living with unmanageable DF.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES For more information about how we process your personal data please see our [privacy notice](#).

Appendix 1

Desmoid Patients and Carers Full Statements

Inga Written Statement

- What is it like to live with the condition?

On the day of getting the diagnosis of a desmoid tumour at the age of 27, I lost my freedom. This condition dictates and influences every single area of my life, from the physical side to the outcomes of my personal life. Starting with the physical, I forgot what it's like to live pain free. I am so used to being in pain that it's become normal for me. Sleeping through the night without waking up in pain feels like a luxury. Going through a day is a challenge too. Since it's on my hip, leg and glute muscle, even sitting down or standing up for too long can trigger pain which can be felt throughout my leg and the rest of my body. I struggle to stay physically active and can't do what other people of my age enjoy doing. The biggest challenge, however, is the disfigurement that I have to live with and hide every single day. I have done so for the past ten years. When I was first diagnosed, I was the only one who could see it, but as I was going through treatment after treatment, I had to watch it grow. First, it was the watch and wait approach, then I was on Tamoxifen and Naproxen, but it continued growing, and with agonising despair one day I had to admit to myself that I could no longer wear the clothes I wanted to wear. I didn't want to scare anyone at work, in local shops or anywhere else, so I started wearing baggy clothes so I could hide the disfigurement, which, I could tell, shocked even some medical professionals. After also being on Vinorelbin, Sorafenib, and having done the cryoablation procedure, it's still getting bigger even today, ten years on. It's still active, and it's already at 25cm. Imagine strapping a boulder to your hip and living with it. That's what it feels like.

While I'm grateful for the treatments I had access to, it's clear that none of them truly work. Some people, had more luck with them, but none of those treatments are considered to be a cure or even an approved treatment for this specific condition. I know there are so many patients like me, who struggle with the fact that nothing seems to work, especially patients with extra-abdominal disease. I lost count of how many times I heard "we don't know" from medical consultants, and how many times we had tough conversations because there wasn't much they could do as there wasn't anything effective enough to treat us with.

On top of the physical and treatment challenges, this condition dictates every other outcome of my life. I have to live in a location where I have access to specialists, so I can't move whenever I want. I am single, and I might never find a partner because of the disfigurement this condition has caused. I had to complete a cycle of IVF all by myself just to give myself a small chance of having a child in the future. I can't progress freely in my career because I have to align it with treatments. The financial burden it brings is also incredibly difficult. I had to take time off work in the past when starting treatments, which left me with questioning how I was going to afford to pay my rent and support myself during those months. Having to think about this whilst going through serious treatment is unfair. It adds a whole other layer of complexity to the situation.

Having Nirogacestat available on the NHS could bring us hope and a better solution to this devastating disease. It would be the first ever treatment specifically designed for desmoid tumour patients. I believe we finally deserve to have one so we can better manage this condition.

- What do carers experience when caring for someone with the condition?

My amazing parents have been very strong when caring for me. Together with me they were full of hope every time I started new treatments, and they were crushed everytime the outcome wasn't what it should have been. It's extremely challenging and isolating to be caring for someone with this condition. There isn't much support, and no answers from anyone. You are in the hands of luck. That's all. It's extremely tough to be in a position of wanting to help your child, and not being able to do anything. Bringing Nirogacestat to the NHS could be the answer all the carers have been hoping for.

- What do patients or carers think of current treatments and care available on the NHS?

There are hardly any treatments available, and the ones that are available are outdated and don't work in most cases:

Watch and wait: the approach has to be evaluated as it isn't suitable for everyone. In my case, this approach proved to make things much worse.

Tamoxifen and Naproxen: only works in 20% of cases. Hasn't worked for me at all.

Vinorelbin: only worked partially and for a very short time.

Sorafenib: worked partially for me, but it isn't available on the NHS, which is also unfair.

Cryoablation: works for some people but the success of the treatment very much depends on the size and location of the disease. In many cases it can only be used to treat a part of the affected area, which was also true for me.

In addition, all those treatments have significant side effects that are a huge challenge on their own. Managing those side effects costs the NHS money too. Nirogacestat is the next generation medication, which could present to be more manageable with less side effects.

It's also very tough for medical professionals, who are trying to find an answer, but hardly have any real treatment options available.

- Is there an unmet need for patients with this condition?

There is absolutely an unmet need for patients with this condition. The fact that we still haven't got a single approved treatment for aggressive fibromatosis in the 21st century is alarming. While having very limited treatment options, we've also been denied Sorafenib as it used to be funded by the NHS in the past, but isn't any longer because it was deemed to be an unapproved treatment specifically for desmoid tumours despite the fact it has helped many patients. The only reason I got access to Sorafenib was the compassionate use programme, and my application got approved because I tried every other treatment on the market.

Since we have a chance to have the first ever approved treatment for this condition in the form of Nirogacestat, I believe it would make a big difference to patients to have it available on the NHS.

- What do patients or carers think are the advantages of Nirogacestat ?

It's the only treatment that has a high efficacy rating of ~70%. It has the ability to shrink desmoid tumours, and it has already helped many patients who have participated in the trial. To my knowledge, it has less significant side effects compared to other treatments, which means a patient could potentially continue working without taking a sick leave while on this medication. It could have a lesser negative effect on patients' mental health and health of their carers too.

There is currently no cure for this disease, which is known to mostly affect young people, including children. I think having this new medication available on the NHS as the 1st treatment option is a necessity.

- What do patients or carers think are the disadvantages of Nirogacestat?

I don't think there are any as all current treatments haven't been working well.

Conor sent in voice messages, transcription directly from voice message.

What is it like to live with the condition- there's definitely physical mental aspects mentally it there's a lot of uncertainty associated with it. It's very challenging having to be under constant surveillance to understand as to whether you know you might be in a good place or might be the bad place and the tumour has grown.

I have FAP so it makes it even more challenging not just that but I have multiple desmoids. Physically on a day-to-day basis and it's difficult but I'd say that the tumours can be quite insidiously sometimes don't really know that there and so when you

actually then go and get scanned that you're like oh this is really a problem. Prior to starting Nirogacestat the tumour had grown aggressively had prevented me from eating properly it was causing me discomfort and was really noticeable.

What is the impact on carers and loved ones-I think for carers or loved ones it can be a lot of uncertainty for them, and I think there's a lot of helplessness associated with the condition. Especially then they themselves try and describe the condition to somebody else. It's quite hard to then be like it's not cancer but this is what it is and people tend to switch off from that. I think there is probably a lack of support for them and it's not just the patient who is affected by all of that. I think one of the issues for carers and loved one is supporting the patient through treatment and also having to mentally reassure them is challenging.

The problem always has been for me not just with FAP but also with a desmoid tumours is that you feel like a really rare statistic. As a result, you feel quite anxious to make sure that you've got the right care, it's difficult as well because there's not really one proven form of treatment, it seems like everybody responds in different ways. Trying to that balance the kind of intensity of treatment with quality of life for the patients is really important, which is why something like near Nirogacestat could really be a game changer.

I feel like there's a lot of unmet needs for patients with DF. You do often feel left behind an definitely out of the conversation sometimes around sarcoma but particularly when it comes to cancer and people just don't understand DF tumour as they are so rare. They don't understand something could be immediate aggressive and not aggressive go through periods of growth or subside. Also then having to feel like you are trialling different drugs that that can be a bit too intense something like chemotherapy and this is why Nirogacestat is really important because for most people it can be tolerated, and you can largely have a decent quality of life.

I've been Nirogacestat since end of March I had 3-month scan in July and the tumour had reduced by about 10 to 15%. This is really great news, it is quite remarkable. I'm obviously hopeful that as I continued to stay on the treatment that we're seeing big changes in terms of reduction of size for me, I'm really lucky that it seems to be having an effect. I take the drug twice a day as a tablet, I don't have to go to specialist care provider to have it administered, it fits in with my life and daily routine, I think that's one of the positives.

Nirogacestat side effects for me are improving over time- I had to take 5 weeks off work and then have a staggered return after starting the drug. I had intense fatigue. I think some of that fatigue was just dealing with the mental load. I didn't expect my tumour to grow so a lot of that was just dealing with that but apart from the fatigue it's

also the diarrhoea. I'm kind of used to that because of the FAP I've had a near total colectomy, so my bowel isn't as regulated as a normal person. I also get sinus issues and breathlessness. So even though it is having a positive impact it's still has an impact on my quality of life. No to the degree that chemotherapy does but I am always having to really second guess myself and what I'm capable of that day and making sure I don't overdo it. Making sure that I don't become more sick because maybe I've overexerted myself and it means stuff like going to the gym or eating and put on weight and keep calories up is really challenging. It is kind of a price that I accept, and I am willing to pay to reduce the size of the DF.

In terms of summarising any messages I would say living with DF is very isolating, it's very lonely you can feel misunderstood. It's really important that you get the correct medical team and I'm very lucky that I live relatively local to the Christie, I feel incredibly fortunate. That's not the same for everyone and so getting the correct team and information out to doctors, surgeons and the patients is so incredibly vital, I've seen many mistakes made where people have rushed to surgery and that does have dire consequences. It's really quite challenging place but it is really hopeful when there are these new drugs being made. I understand there's a big cost of them but due to the nature of a small population of people affected it does feel like an important price to pay and I'm sure I'm not the only one to say that I would rather have this treatment than have to have something far more toxic and have long lasting consequences like chemo.

Jaqui /Carer feedback and Robbie Patient DF sent in by email.

- What is it like to live with the condition?
- R: Horrible living with it as I have symptoms everyday. Knowing its there is always in the back of my mind wondering what it is doing. I feel out of control. It affects our decision whether to go on holiday or not due to possibility of it causing a bowel obstruction and the increased insurance costs makes it impossible to afford; it affects what I can or cannot eat and how a big a meal I can have and also how much work I do. I recently went from 4 days work to 5 and am finding it too much which affects us financially. Also nobody has heard of it and explaining its not cancer but not benign is quite difficult.

My symptoms get me down as it can be painful coughing so much and embarrassing. This stops me socialising. I've developed an umbilical hernia through coughing so much.

- What do carers experience when caring for someone with the condition?
- J: I feel like I am always on red alert in case there is an emergency. Any gastric symptoms send you in a spin in case it is related to a change in the tumour or is it just routine digestive problems. There is a lot of unknown. You feel powerless to

help. My husband lives with gastric symptoms everyday and we don't truly know if it's the tumour or a by product of the emergency surgery because of the tumour. The medical community can't decide either so there seems to be a lack of understanding or knowledge or just unknown. I think it affects his mental health a lot of the time as he gets quite low when he is coughing a lot.

- When his tumour was really active it was distressing as he couldn't eat any solid food for 3 months followed by surgery followed by chemotherapy. This also affected my mental health. As a couple it affected us financially as he didn't work for a year and we've never really got back to where we were.
- What do patients or carers think of current treatments and care available on the NHS?
- R&J: We have learnt that treatment is very much based on individual symptoms. The care around and management around the tumour from The Marsden is great but is only related to the tumour. So, associated gastric symptoms (cough, acid reflux, development of hiatus hernia and umbilical hernia) as a result of the tumour or surgery, are difficult to get resolved. GP services don't know seem to know enough about Desmoid tumours and they refer you back to The Marsden and The Marsden say its not directly linked (only as a result of) and to go back to GP. There is a lot on navigating and backwards and forwards.

- Is there an unmet need for patients with this condition?

Financial support when a patient cannot work in line with other diseases that are as debilitating. We did manage to secure PIP which has helped.

Practical support groups that offer solutions to problems, not just somewhere to let off steam (although that too is important)

- What do patients or carers think are the advantages of Nirogacestat?

It's a targeted treatment so gives a sense of progress and management

Hope for the patient that then improves their mental health

The potential for further treatments being developed off the back of the success of this one

An options that may be less traumatic than chemotherapy or invasive as surgery

- What do patients or carers think are the disadvantages of Nirogacestat?

Unknown long term effect

Unclear how long you may need to take the medication

Dealing with the side effects and the impact these may have on your everyday life

Cost of the drug

- . Please summarise the key messages (of your submission).

The key message is that aside from Nirogacestat the other treatment options appear to be trial and error and as a patient it can be hard to accept and go through not knowing if it will help. Living with the uncertainty of a Desmoid tumour is life impacting in so many ways; physical health, social, employment, financial and mental health. Every corner of your life can be affected. The more research into Desmoid tumours, a better understanding of the variety of symptoms and development of future treatment options would be beneficial to the Desmoid community.

Angela gave feedback via the Facebook United page

Happy to support any way I can as this drug should be available on the NHS here in the uk.

I haven't had any treatments yet. Was diagnosed with abdominal Desmoid in January this year and under watch and wait. I have researched and come across this drug over in the USA where it seems this drug actually shrinks and some cases actually kills the Desmoid, and this is what we need.

I had my diagnosis earlier this year but had other personal situations with the unexpected loss of my dad and my son being ill too with glandular fever. 2025 for us has been truly awful. So haven't had much time or head space to fully come to terms with my diagnosis.

With the Desmoid being so rare I have listened to the specialists and as it appears not to have grown yet I have let it be a watch and wait.

Although I really do worry about treatments if and when I do need, as know inevitably I will...surgery removal is a risk and other drugs out there are chemo drugs which will hammer your body and immune system and the results seems very mixed. I have started doing my own research. This drug seems to be the most effective from what I have read in actually success of reducing and killing the tumour.

If I needed treatment right now and without this available in the UK, given my age (I'm only 40) I would actually push for surgery removal, as I don't think I could go through the other chemo options which are truly terrible with horrible side affects, life limits and no guarantee it actually works as the results are so few and fair between for people. I couldn't mentally go through that unknown and still have the tumour.

With it removed the risk is it would return but not all the other uncertainty.

I don't think it understood how mentally it affects patients either having to live with a tumour and knowing it not beign (although my oncologist did refer to it as beign) but won't be removed and stays in your body.

If this drug was available and seeing the better success I would consider this option before removal.

When I mentioned this drug to my oncologist at clatterbridge after research I had done it was unknown to him other than what he heard about it being trialed in the USA. And passed it off as said only certain dispensation can be appealed to the drug companies so my initial options would be anti inflammatory drugs and the chemo drug that treats breast cancer should it start to show growth

I hope this information helps as we should have this available and as an option to treat Desmoids. Given how rare we should not have any option not available to us.

Feedback and Notes from Alison Dunlop Sarcoma /Desmoid CNS and Lucy Dean
Physio

- What is it like to live with the condition? What is the impact on quality of life for a person with desmoid?
- What do carers experience when caring for someone with the condition?
- What do patients or carers think of current treatments and care available on the NHS?
- Is there an unmet need for patients with this condition?

What is it like to live with the condition? What is the impact on quality of life for a person with desmoid?

All the issues these patient's face are interlinked. Site/Pain/Function. No one issue can be assessed in isolation. The quality of life is directly affected by these interlink issues.

Life-changing and life-long

Site

This disease can occur anywhere in the body, there is not one experience fits all. The site has a direct correlation to levels of pain, impact on function and quality of life. If the site is visible there are issues around body image and the perception of others.

Pain

Pain was the most debilitating symptom mentioned by all patients in RMH qualitative study.

The level of pain experienced can be variable within an hour, a day for some patients.

For some the pain is low level and they manage it without analgesia or using simple analgesic. For others the pain requires the skills and expertise of a specialist pain management team, to address the constant pressure and nerve pain.

Pain levels are not always reflected by the imaging we use, these tumours are often firm and feel hard.

The pain, and the effect of the medications used to manage it, can rob patients of their confidence, financial and personal independence, reduce the scope of their lives.

Impact on family and relationships. This can be really isolating.

The unrelenting nature of pain and its impact on patients' lives led to substantial psychological distress in the RMH study.

The impact of pain on quality of life is well documented.

Function:

The site of disease, if it is causing swelling, pressure and nerve pain, plays a significant role in how the individual manages the disease, what physical functions are affected and the impact it has on their quality life. Joint mobility and muscle function can be impaired by the tumour and/or associated pain. This can have a significant impact upon a persons movement, mobility, day-to-day activities, work, hobbies, exercise, and in turn, these affect a persons psychosocial wellbeing. People also talk about the impact on relationships and feeling understood – the challenges of a rare disease.

RMH study showed that DF patients experienced difficulty accomplishing their role in society. The side effects of treatment and long-term effects of the disease caused

relationship problems for several patients. Loss of libido affected sexual relationships and some reported break-down of their relationship or marriage. Patients did not want to feel as though they were a burden on their partner or family and tried to cope alone. DF patients also felt that their parental role was affected including difficulty breastfeeding, playing games with their children and depending on their partner or parent for childcare. Others felt guilty, as they did not want to burden their parents, siblings or children to the detriment of other family members. Suicidal thoughts were expressed by those who found the burden too much to bear

What do carers experience when caring for someone with the condition?

The impact on carers is affected by the site/pain/function. They experience the same as many carers, helplessness, restrictions on their life, feelings of no end in sight, frustration as relationships can become tense and strained. It is exhausting supporting hope and wellbeing in others. They maybe caring/ supporting other family members, children, siblings, older parents, friends. They may have to work, full or part time. Disruption to the patient's life, site/pain/function, may/can have a direct effect on the cares, lack of sleep, irritability, frustration, hopelessness ect.

What do patients or carers think of current treatments and care available on the NHS?

Diagnosis can be protracted.

Diagnosis may not be understood initially by the local team. Information may be good to poor.

Travel, which may be difficult, to Sarcoma Service and possible confusion over cancer.

Feeling like a fraud. Don't have Cancer taking a cancer slot.

Watch and wait policy, can be difficult for pt's and family, it needs to be clearly explained and reasons for.

Treatments which are effective may be limited/ not available/ on trial/ need to be applied for.

No ideal solution – this can feel hopeless when someone is living with the consequences of the disease.

Is there an unmet need for patients with this condition?

Do all pt's need to be followed up at a Sarcoma Centre?

Dedicated clinics, guideline consensus to allow shared care to be delivered safely in the local area were appropriate.

Easier access to OT, Physio, pain teams locally, psychological support especially for those where the current medication is not effective or tolerated.

A definite unmet need – this group often fall between the gaps in terms of support offerings (not cancer, but an often debilitating long term condition). People would benefit from more integrated multidisciplinary input to support them to live well and to tailor care.

Appendix 2

Desmoid Patients and Carers Full Statements

Sophie:

Sophie is a 35 year old woman from North Essex who lives with desmoid tumours. She was diagnosed with two desmoid tumours at aged 26. After initially being put on watch and wait, Sophie underwent cryoablation, then vinorelbine, before doxorubicin. None had lasting effects and were accompanied with disruptive side effects.

Diagnosis:

Sophie's first diagnostic difficulties were related to her FAP, which runs genetically in her family. Her dad experienced late diagnosed FAP. After this, he pushed for his daughters to get tested, but both Sophie and her sister were dismissed by GPs who told her she had piles or IBS, and could deal with her symptoms by eating more fibre. Her father had to ask St Mark's hospital to test both women before they received a diagnosis at aged 20.

Sophie's first major symptoms of her desmoid tumours were bowel obstructions, for which she visited A&E at [redacted, *hospital 1*]. A CT scan showed a 'shadow', but Sophie did not believe it was severe at this point. She was 26. She then mentioned it to a clinician at [redacted, *hospital 2*], who saw it as a red flag and requested the CT scan, which confirmed it was a desmoid tumour in her abdominal wall. At point of diagnosis, the tumour was roughly the size of an egg. Her local hospital were keen to operate- it took intervention from [redacted, *hospital 2*] to prevent this and get Sophie sent to the appropriate services.

From 2016 to 2018, Sophie's bowel obstructions began to increase in frequency from one every six months or so, to eventually occurring every month in line with her menstrual cycle. Clinicians were considering a stoma. In 2019, Sophie suffered a bowel perforation and had to have emergency surgery at [redacted, *hospital 2*]. Sophie describes the bowel perforation as being in 'absolute agony', recalling screaming in the hospital ward. Since this point, Sophie has been living with a stoma bag to avoid the monthly bowel obstructions, the bowel perforation having made the decision for her.

Sophie's desmoid tumour was being monitored, but not by specialist services. In 2019/2020, she was referred to [redacted, *hospital 3*], who continued to monitor the scan under a 'watch and wait' approach. Her scans showed her desmoid tumour was growing incrementally.

Comparator treatments:

In 2020, her consultant clinician made the decision that the desmoid should now be treated, and Sophie underwent cryoablation. She described the treatment as 'annoying'

and 'uncomfortable', but manageable. The surgeon remarked that it was the largest mass he had worked on. Sophie was left with a large, 'gnarly' scar across her side.

The cryoablation slowed growth for a while, but in 2023 Sophie began experiencing pains again. It began as a dull pain, which became constant. She adjusted to and tried to 'push on' with her normal life, but eventually, the pain became 'unbearable'. Sophie spoke to the pain management department and was put on pregabalin and MST morphine. Eventually, Sophie had to use crutches or a wheelchair due to her pain.

By October 2023, her scans showed considerable growth of the tumour. Clinicians considered it had become more aggressive. In November, she began vinorelbine and remained on it until January 2024. Sophie found vinorelbine tolerable but the side effects of nausea annoying, and struggled with the exhaustion.

Sophie came off vinorelbine in January 2024. She shortly afterwards began doxorubicin, which she described strongly as 'horrible', telling us how it affected her and her husband. She experienced overwhelming fatigue, frequently having to sleep, while also dealing with pain as a result of the desmoid. She describes these side effects combined as 'knocking [her] for six', recalling looking at a picture of herself from this period and being shocked at her appearance. She questioned how she was able to cope with these side effects at all to get through this period of her life.

Her symptoms affected her ability to work and consequently her income. Prior to this treatment, Sophie was working two part time jobs. She continued her job in retail for as long as she could but eventually was unable to due to her symptoms and the side effects of doxorubicin. She gave up her retail job but was able to continue her other part time job doing invoicing since she it was remotely performed from home, enabling her to rest periodically.

Sophie's tumour did not respond at all to the doxorubicin. After four or five rounds, her team made the decision to stop this treatment.

Nirogacestat:

A few months later, Sophie's team shared that they were aware of a drug that was licensed in the USA. After waiting for nirogacestat on compassionate access, she began the drug.

Sophie describes the side effects as similar to chemotherapy, but more manageable. The drug has increased her bowel output, which caused issues due to her ileostomy, leaving her dehydrated and with an infection, having to be hospitalised. Sophie also experienced fatigue- she describes this as manageable, and has learnt how to deal with it through listening to her body and pacing herself- for example, not scheduling a busy day after a day with a medical appointment in central London.

Sophie's desmoid tumour has responded positively to the nirogacestat. At present, it has reduced from approximately 26 cm wide to approximately 12 cm. Sophie has a review once monthly, where she is reviewed and has her bloods taken. She has an MRI every three months. She describes attending her scans with some hope that it would have shrunk, and being surprised by how much it had shrunk every scan.

More significantly for Sophie, her symptoms are improving, particularly her pain. She describes being surprised by the change, recalling findings it 'weird' how she was not in pain anymore. She no longer has to use walking sticks or a wheelchair due to her pain. She's incredibly grateful for the drug and wishes that she could have accessed it at the beginning of her treatment, rather than having to experience multiple unsuccessful treatments with unmanageable side effects. She shares that she wishes anyone who has a desmoid was able to access the drug without first exhausting all other options.

In her own words:

'It's brilliant having access to this drug. If I had access to Nirogacestat the beginning, back in 2023, and I didn't have to go through all of that treatment, that would have been amazing.'

The treatment available at the moment, it's either watch and wait, cryoablation and then chemo. I had no idea there was another drug possibly available as a last resort for treating Desmoid tumours, and to be able to have access to this- a potential last option for treatment, I'm really thankful for it. I really am. I just wish anyone who's got a desmoid had access to this sooner rather than having to go through jumping through all the hoops of the other treatments.'

'It's literally it's been like day and night being on Nirogacestat, I'm just so happy I'm on it and it's working!. I have annoying side effects (Exhaustion, nausea and high output) but I'd rather that than experiencing being on chemo, and the extra worry of has my tumour grown again.'

'The pain that I was in, I'd have to use walking sticks and wheelchairs for when I can't walk. And now I've not really needed to use them.'

When asking about how she feels about nirogacestat stopping her periods, and the possible ongoing implications, Sophie shared that she was offered IVF prior to chemotherapy, but has chosen not to have children due to her condition, which she does not want to pass on to children. Due to this, Sophie has no concern about any fertility issues and is happy not to have to deal with her periods, which used to be extremely painful. She dealt with pain for three weeks of the month, describing the one week after her period as the only pain free month. Her bowel perforations also aligned with her menstrual cycle, occurring shortly before her period. Her oncologist initially told her this was not connected, leaving Sophie feeling it was 'all in my head', before

recontacting her to share that there is evidence to connect her symptoms and condition to menstrual cycles.

Sophie has annoying side effects but would rather these than those on the comparator treatments she experienced previously. The biggest issues she has to manage are the exhaustion and her bowel output from her stoma. Her bowel output is the highest of any drug, but she is able to manage it since she is on loperamide and codeine.

Living with desmoid tumours:

Sophie described the challenges that living with desmoid has had on her emotional wellbeing. She described how having desmoid tumours is challenging due to their unpredictability- one month a scan could well and show no growth, and the next she could be in severe pain and unable to do anything about it. Sophie told us about the public ignorance and misconceptions about living with a desmoid tumour. She described the difficulty of having to explain desmoid tumours to others, telling us it often gets brushed off when people find out it is a sarcoma but not a cancer. It is also sometimes described as a **benign tumour in online information**, presenting them as liveable with. While this is the case, it does not align with the difficulty Sophie has experienced.

Sophie's twin sister also lives with desmoid tumours, which she described as helpful since she knows what she is experiencing. She also has another friend who has desmoid tumours too. She is thankful to have her sister and her friend (and an online Community on Social media), saying she would feel alone without the small community around her.



Nirogacestat for treating desmoid tumours [ID6453]

External Assessment Group (EAG) Report

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Abbreviations

AE	adverse event
BSC	best supportive care
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CS	company submission
CSR	clinical study report
CT	computed tomography
DT	desmoid tumours
EQ-5D	EuroQol five dimension
EAG	External Assessment Group
HRQoL	health-related quality of life
HTA	health technology assessment
HSUV	health state utility value
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
ITT	Intention-to-treat
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
ORR	objective response rate
OWSA	one-way sensitivity analysis
PD	progressed disease
PFS	progression-free survival
PR	partial response
PSA	probabilistic sensitivity analysis
QA	quality assessment
QALY	quality adjusted life year
RCT	randomised controlled trial
RDI	relative dose intensity

AE	adverse event
RECIST	Response Evaluation Criteria in Solid Tumors
SD	standard deviation
SLR	systematic literature review
SoC	standard of care
STS	soft tissue sarcoma
TA	Technology Appraisal
TKIs	tyrosine Kinase Inhibitors
vs	versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Section 1.3

Broadly speaking the key clinical issues related to the inclusion of chemotherapy as a relevant comparator and the uncertainty regarding the relative effectiveness of chemotherapy and nirogacestat. In terms of cost effectiveness issues, the EAG noted a number of issues regarding the way in which the company calculated progression and response transition probabilities, as well as unrealistic and unfounded assumptions about how patients' condition would evolve over the long term.

Table 1: Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1	Exclusion of chemotherapy as a comparator	Inclusion of an additional comparator	2.3.1 and 3.4.10
2	Uncertainty in relation to the indirect treatment comparison	Unknown	3.4.1
3	Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Expected to decrease the cost-effectiveness of nirogacestat compared to chemotherapy, impact versus BSC unknown	2.1.1, 3.3.4.1 and 3.4.1.1

ID	Summary of issue	Impact on results	Report sections
4	Calculation of progression risks during trial randomised period/first 2 years	Addressing this issue, combined with the below issue, led to a small reduction in the ICER compared with BSC	4.2.5.4
5	Calculation of response	See above	4.2.5.4
6	Extrapolation of progression	Removing progression after year 2 increased the ICER compared with BSC	4.2.5.4
7	Assumed stopping rule	Applying a 3 year stopping rule increased the ICER compared with BSC	4.2.5.2
8	Approach to discontinuation	Modelling premature discontinuation reduced the ICER compared with BSC	4.2.5.3
9	Health state utility values	Using different HSUVs increased the ICER compared with BSC	4.2.6

Abbreviations: BSC, best supportive care; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Comparators	Did not include chemotherapy as a comparator	Included chemotherapy as a comparator	4.2.5
Early discontinuation	Did not model premature discontinuation	Modelled the possibility of premature discontinuation, using data from DeFi	4.2.5.2
Stopping rule	The company assumed a two-year stopping rule	The EAG assumed a three-year stopping rule, with a two and four-year stopping rule tested as part of sensitivity analysis	4.2.5.2
Progression risks for first 2 years	Modelled progression risks assuming constant transition probabilities and	Amended errors in implementation of transition probabilities, modelled the possibility of premature discontinuation	4.2.5.4

	Company's preferred assumption	EAG preferred assumption	Report Sections
	no discontinuation and implemented 'calibration'	and did not implement 'calibration'	
Patient response	Did not accurately calculate transition probabilities regarding response	Calculated transition probabilities in relation to response using the level of patient response as Year 2, which was the best option given the available data.	4.2.5.4
Long-term progression risks	Assumed progression rate was constant over time	Assumed no further progression after Year 2.	4.2.5.4
Subsequent treatment	Doxorubicin used as subsequent therapy	Vinorelbine used as subsequent therapy, except after vinorelbine itself, where doxorubicin was used as subsequent treatment.	4.2.7.2
Utilities	Used HSUVs from Shingler 2013 (a vignette study in STS)	Used health state utility values from Reichardt 2012 for SD and PD health states. Used company base case PR and CR incremental utility applied to EAG base case SD for PR and CR utility	4.2.6
Ovarian dysfunction	Modelled ovarian dysfunction as an intermittent event lasting 28 days	Modelled ovarian dysfunction as a one-off event lasting for [REDACTED] days from initiation for 39% of patients	4.2.5.6
Resource use	Resource used was informed by Verboom 2019 and Schute 2023. No resource use in complete response health state.	Made minor changes to resource use, based on clinical opinion. Increased the number of specialist visits per annum in PR, SD and PD health states, added specialist visits in CR health state.	4.2.7.4

Abbreviations: EAG, external assessment group; HSUV, health state utility value; CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease; STS, soft tissue sarcoma

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Increasing the number of patients in partial response and complete response, improving quality of life
- Increasing the frequency and duration of ovarian dysfunction relative to best supportive care, reducing quality of life
- Decreasing the number of patients in progressed disease, improving quality of life
- Decreasing the mortality rate improving life years (minor impact)

Overall, the technology was modelled to affect costs by:

- Increasing the drug costs associated with treatment
- Reducing the number of patients in progressed disease reducing health-care resource use costs
- Increasing the number of patients in partial and complete response reducing health-care resource use costs
- Increasing the cost of adverse events relative to best supportive care

The modelling assumptions that had the greatest effect on the ICER were:

- Health state utility values had a large impact on the ICER
- Assuming patients do not progress after year two, in line with data from the De-Fi trial, had a large impact on the ICER.
- The stopping rule had a moderate impact on the ICER (company base case assumed two years, EAG base case assumed three years)

- Allowing patients to have a response in year 3 (in line with De-Fi) had a moderate impact on the ICER

1.3. The EAG's key issues

Key Issue 1: Exclusion of chemotherapy as a comparator

Report sections	Sections 2.3.1 and 3.4.10
Description of issue and why the EAG has identified it as important	The company only included BSC as a comparator in their submission and did not compare nirogacestat against other relevant treatments used in the NHS. The updated population addressed in the submission was adults with progressing DT <i>who require systemic treatment</i>. The systemic treatments offered to people with DT in the NHS were chemotherapy (vinorelbine or doxorubicin) or TKIs (sorafenib). Chemotherapy was used first-line and in later lines and, at the time of writing, was the primary systemic treatment for people with DT. TKIs (sorafenib) were only available for compassionate use, and as such, were less well-used. The EAG considered chemotherapy, as the primary systemic therapy for people with DT, to be a key comparator in this appraisal. TKIs would have been a comparator if they were available via routine funding. If they <i>were</i> available via routine funding rather than compassionate use, they would cost approximately [REDACTED] of the price of nirogacestat. The NMA found TKIs were more effective than chemotherapy for ORR, similar to nirogacestat for PFS, but also the least safe (Section 3.4.1).
What alternative approach has the EAG suggested?	At the clarification stage, the EAG requested the company conduct an ITC comparing nirogacestat to chemotherapy and use the results of the ITC to allow chemotherapy to be a comparator in the economic model. The company declined to complete an ITC and did not include chemotherapy as a comparator in the model. In the period after the clarification stage, the EAG completed pragmatic NMAs comparing nirogacestat to chemotherapy and utilised the results of the NMA to inform the inclusion of chemotherapy as a comparator in the economic model.
What is the expected effect on the cost-effectiveness estimates?	[REDACTED] The estimates of cost-effectiveness that could be provided were, however, highly uncertain due to the limited data available to the EAG for the NMA. Given lack of information provided by the company it is unclear if the best available data sources were used.
Could any additional evidence or analyses be provided to resolve this key issue?	This key issue could be resolved if chemotherapy were included as a comparator in the economic model. At the time of writing there was little robust evidence linking nirogacestat to vinorelbine, the primary chemotherapy that was used in people with DT in the NHS. However, the EAG did not consider a lack of robust evidence to be a legitimate reason not to address the most relevant comparator.

Abbreviations: CS, company submission; DT, desmoid tumours; EAG, External Assessment Group; ITC, indirect treatment comparison; NMA, network meta-analysis; TKIs, tyrosine Kinase Inhibitors.

Key Issue 2: Uncertainty related to the network meta-analysis

Report sections	Section 3.4.1
Description of issue and why the EAG has identified it as important	The EAG considered chemotherapy to be a key comparator (Key Issue 1) but no efficacy data was presented in relation to chemotherapy in the CS or after a request at the clarification stage. Therefore, the EAG conducted pragmatic NMAs to compare nirogacestat to chemotherapy to inform the inclusion of chemotherapy as a comparator in the economic model. However, the EAG noted a number of limitations to the NMAs conducted: • The network consisted of 3 small trials with a single trial for each comparison (3.4.1.1). • DESMOPAZ (chemotherapy versus TKIs) was a non-comparative phase 2 trial with only 24 participants on chemotherapy (3.4.1.2). • The chemotherapy evaluated in DESMOPAZ was not the chemotherapy used in the NHS (i.e. vinorelbine or doxorubicin; 3.4.1.1). • The trials had differing inclusion criteria related to their definition of <i>progressing</i> DT. Gounder 2018 potentially recruited people whose disease was not truly growing and this could have confounded the PFS reported in the trial. (3.4.1.2 and 3.4.1.8). • The baseline characteristics of the trial participants were inconsistently reported and, from the characteristics that were reported, there did appear to be differences between the trials. This included notable risk factors, such as extremity location, age, and size of tumour (3.4.1.3). • Two of the trials (De-Fi and Gounder 2018) had placebo arms where people received placebo alongside BSC. The placebo arm in Gounder 2018 performed substantially better than the placebo arm in De-Fi. It was unclear why this occurred, but it offered a large benefit to nirogacestat in ORR (3.4.1.7). • Each of the trials used RECIST v1.1 criteria to define progression in PFS but the De-Fi trial also used clinical progression in addition to RECIST (3.4.1.5). The EAG did not consider the uncertainties that arose from the NMA to clearly benefit any of the interventions but these uncertainties were in addition to the parameter uncertainty reflected in the wide confidence intervals in the NMA results. The EAG also considered the NMA for PFS to be too uncertain from which to draw any conclusions comparing nirogacestat to chemotherapy.
What alternative approach has the EAG suggested?	The approach recommended by the EAG was to conduct an NMA to support the inclusion of chemotherapy as a comparator in the appraisal. The EAG had very limited time post-clarification to do this and based their strategy on an NMA of RCTs published in 2024.¹ At the clarification stage (A14), the company conducted a SLR to determine the feasibility of an ITC. They concluded that an ITC between nirogacestat and vinorelbine was not appropriate due to

Report sections	Section 3.4.1
	methodological and data-related limitations, including study design and data collection issues. The company did not present their feasibility assessment and the EAG considered it inappropriate to exclude the most relevant comparator due to uncertainties related to the evidence base.
What is the expected effect on the cost-effectiveness estimates?	The direction of uncertainty surrounding the network meta-analysis results was not known, but there was some indication that the EAG base case may understate the benefits of chemotherapy. In the base case, the EAG have assumed the PFS for chemotherapy was equal to that of BSC. Clinicians have indicated nirogacestat may be superior, particularly in comparison to vinorelbine, which was the chemotherapy treatment in most regular use. They said they would not expect to see substantial improvements in PFS associated with chemotherapy. The EAG tested a scenario where the PFS for chemotherapy was aligned with nirogacestat. This yielded an increased ICER of [REDACTED] for nirogacestat versus chemotherapy in the fully incremental analysis ([REDACTED]), compared with the EAG base case. The EAG used the NMA result to inform the overall response for chemotherapy, which was similar to assuming equivalence with BSC as the effect size was close to 1. The EAG was not able to test the impact of improvements in pain associated with chemotherapy within the model provided by the company. This means that a key benefit of chemotherapy, according to clinical experts, may not be captured within this analysis. [REDACTED]
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG took a pragmatic approach to the ITC given the time pressures of the appraisal. The company may be able to conduct a more appropriate ITC given the extensive SLR they conducted. Other appropriate methodologies include conducting structured expert elicitation with clinicians to determine appropriate estimates for effect size for chemotherapy in the UK or seeking access to secondary data sets e.g. any registry data in order to be able to make a more robust comparison.

Abbreviations: BSC, best supportive care; CS, company submission; DT, desmoid tumours; EAG, External Assessment Group; ITC, indirect treatment comparison; NMA, network meta-analysis; PFS, progression-free survival; RCT, randomised controlled trial; SLR, systematic literature review.

Key Issue 3: Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain

Report section	2.1.1, 3.3.4.1 and 3.4.1.1
Description of issue and why the EAG has identified it as important	The EAG's experts explained that the primary benefit of chemotherapy is in reducing pain in people with DT rather than shrinking the tumour. A reduction of pain can be experienced without the tumour shrinking, and even in people with a tumour that is growing slowly, because treatment reduces inflammation/oedema. Therefore, a key output of this appraisal was assessing whether nirogacestat is more effective than chemotherapy in reducing pain. However, it was not possible to conduct an NMA as a connected network could not be established. Also, the efficacy of nirogacestat versus placebo (BSC) in reducing pain was unclear. In De-Fi, the LS mean difference in the BPI-SF worst pain intensity score at Cycle 10 (10 months) was -1.34. This was a statistically significant benefit ($p < 0.001$) of nirogacestat over placebo. However, it was not a clinically meaningful benefit when judged against an MID, (± 2 points) estimated using best-practice methodology. It was not clear to EAG whether this was an indicator that nirogacestat did not have a benefit over BSC in terms of pain, or whether it was due to many participants in De-Fi not having uncontrolled pain at baseline.
What alternative approach has the EAG suggested?	It would have been appropriate for the company to conduct an ITC comparing nirogacestat to chemotherapy for reduction in pain related to DT. If chemotherapy is found to improve pain outside of tumour response then this should be included in the economic analysis. In terms of the efficacy data from De-Fi, the company could present subgroup analysis in people who are in pain at baseline to establish whether nirogacestat offers a clinically meaningful benefit over placebo.
What is the expected effect on the cost-effectiveness estimates?	There is no direct link between pain scores and the model results, because pain was not explicitly included within the model. However, this is linked to the uncertainty surrounding the appropriate utility value for patients with progressed disease and the appropriate method for comparison to chemotherapy.
Could any additional evidence or analyses be provided to resolve this issue?	The alternative approach suggested above could help to resolve this issue. If additional information is identified to allow a comparison to chemotherapy for either pain or quality of life the weak correlation between response and pain may warrant inclusion of treatment-specific utilities to allow the full benefits of chemotherapy to be captured.

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; BSC, best supportive care; CS, company submission; EAG, External Assessment Group, LS, least squares; MID, minimally important difference

Key Issue 4: Calculation of progression risks during trial randomised period/first 2 years

Report sections	4.2.5.4
Description of issue and why the EAG has identified it as important	The company took an inappropriate approach to calculating progression risks within the model. The company calculated the probability of maintaining progression free survival for one year, conditional on having achieved stable disease only and on receiving one or two years of treatment, without early discontinuation. This approach did not account for the fact that some patients never achieved disease control within the trial, it inappropriately disregarded patients who discontinued treatment prematurely (in the nirogacestat arm) and it assumed that transition probabilities were constant through time, which did not reflect trends in the trial data in the randomised period in which progression plateaus from Month 18 onwards. Overstating the extent of progression after Month 18 potentially overstated the value of nirogacestat. The company then observed that the modelled proportion of progressed patients, did not align with the number of progression events by Month 24 for nirogacestat (Month 15 for placebo) divided by the number of patients who entered the trial at baseline. The company used this as justification to 'calibrate' the transition probabilities, so that the modelled number of progressed patients at these time points, aligned with the number progression events divided by the number of patients at baseline. However, this was a misinterpretation of the progression rate, as the number of patients at risk at Month 15 and Month 24, was different to the number of patients at risk at baseline. This was a result of censoring and is explained in detail in the relevant section. Therefore, the calibration process served to introduce unnecessary bias. Implementing calibration reduced the company's base case ICER from [REDACTED] to [REDACTED].
What alternative approach has the EAG suggested?	The EAG preferred to calculate progression risk separately for Year 1, Year 2 and Year 3+, to account for the varying progression rates observed in the trial data. The EAG preferred to incorporate the possibility of premature discontinuation when modelling progression rates and allow for the fact that some patients never achieved disease control. The EAG demonstrated that its approach provided a much closer representation of progression rates observed in the De-Fi trial.
What is the expected effect on the cost-effectiveness estimates?	Removing calibration increased the ICER. Addressing this issue, along with the next one, increased the ICER for nirogacestat versus BSC, compared with the company base case, from [REDACTED] to [REDACTED]. This was primarily as a result of the severity modifier no longer applying.
Could any additional evidence or analyses be provided to resolve this key issue?	Longer term data on patients' progression rates for nirogacestat and BSC.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

Key Issue 5: Calculation of response

Report sections	4.2.5.4
Description of issue and why the EAG has identified it as important	The company modelled response using the Best Overall Response Rate (BORR) observed in the trial. Clinicians informed the EAG that measurements can vary, and therefore measured response fluctuates. This meant that using the Best Overall Response Rate could result in a bias that favoured the treatment. The EAG requested that the company provide actual response data so that the EAG could use this to validate the Best Overall Response data. The company provided these data at the clarification stage, but they appeared to be erroneous (they were more favourable than the Best Overall Response data, which is impossible) and the EAG did not use them. The company also made an error when implementing these data in the model. They adjusted the annual probability of transitioning from stable disease to complete response (and partial response) to a monthly probability, without accounting for the fact that patients were also transitioning from stable disease to progressed disease during that time point. This resulted in a bias that was not favourable to nirogacestat. This was complicated by the fact the company then implemented calibration, which somewhat reversed the impact of the bias.
What alternative approach has the EAG suggested?	The EAG continued to use the best-overall-response rate as the actual response data provided were erroneous. The EAG corrected the errors that the company made in converting annual transition probabilities to monthly transition probabilities.
What is the expected effect on the cost-effectiveness estimates?	The calculation error described here and the error described in the previous key issue were addressed simultaneously and the results are reported in the key issue above. This was necessary based on the data available to the EAG. The EAG did not have access to accurate data on actual response, so could not test the impact of including these data, but it is known ex ante that these data would yield a higher ICER for nirogacestat compared with BSC.
Could any additional evidence or analyses be provided to resolve this key issue?	Decision uncertainty would be reduced if the company provided correct actual response data.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio

Key Issue 6: Extrapolation of progression

Report sections	4.2.5.4
Description of issue and why the EAG has identified it as important	The company assumed that the rate of progression observed within the 2-year randomised period in the De-Fi trial would continue for the rest of the patient's life. This resulted in over [REDACTED] of patients having progressed in the BSC arm by Year 5. This was in contrast with the trend observed in the trial in which [REDACTED] patient progressed after

Report sections	4.2.5.4
	Month 18 in the Nirogacestat Arm and █████ progressed after Month 18 in the placebo arm. Clinicians also advised the EAG that a substantial portion of patients experience disease stabilisation or spontaneous regression.
What alternative approach has the EAG suggested?	The EAG assumed that no additional progression occurred after Year 2.
What is the expected effect on the cost-effectiveness estimates?	This change led to the ICER for nirogacestat versus BSC increasing to █████, compared with the EAG corrected base case of █████. Chemotherapy remained █████ in the fully incremental analysis.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could provide data on the long-term outcomes achieved by patients receiving best supportive care (and chemotherapy), for example as part of a registry study.

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio

Key Issue 7: Assumed stopping rule

Report sections	4.2.5.2
Description of issue and why the EAG has identified it as important	The company assumed that all nirogacestat patients stop treatment after two years of treatment. The company noted in the CS that the optimal duration of treatment with systemic treatments in people with DT remains to be determined. When the EAG asked clinicians, they said they would broadly support a two-year stopping rule, if they had the flexibility to keep patients on treatment past two years, if their tumour was continuing to shrink in size and had not plateaued. They would also like to be able to restart patients on treatment, if they stopped due to adverse events, or their tumour starting to grow again. The proportion of patients who would discontinue treatment after two years was not clear, based on the evidence provided. Data suggested that new patients continued to respond in the third and fourth year of treatment meaning that it is unlikely that all patients would be suitable to stop treatment at year two.
What alternative approach has the EAG suggested?	The EAG assumed a three-year stopping rule in the base case, with a two, four and five-year stopping rule tested in sensitivity analysis.
What is the expected effect on the cost-effectiveness estimates?	This increased the ICER, as patients stay on treatment for longer and accrue the associated costs. The EAG base case, with a 3-year stopping, had an ICER of █████ for nirogacestat versus BSC. This reduced to █████ for a 2-year stopping rule in a scenario. It increased to █████ for a 4-year stopping rule and █████ for a 5-year stopping rule. The stopping rule was not modelled to impact patient outcomes.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could conduct a real-world study to determine how long patients stay on treatment in practice. They could also develop a

Report sections	4.2.5.2
	clear definition of tumour size plateauing, to inform a clinically viable stopping rule.

Abbreviations: CS, company submission; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio

Key Issue 8: Approach to early discontinuation

Report sections	4.2.5.3
Description of issue and why the EAG has identified it as important	In the base case, the company assumed that all nirogacestat patients continued treatment to 2 years, then stopped treatment, unless they experienced progression. This does not represent the DeFi trial data in which █ patients discontinued nirogacestat before 2 years due to TAEs and █ discontinued BSC prematurely due to TAEs.
What alternative approach has the EAG suggested?	The EAG prefers to assume that discontinuation was aligned with the trial data. The data suggested that discontinuation was fairly constant through time, so the EAG assumed a constant rate by averaging the data across the four years.
What is the expected effect on the cost-effectiveness estimates?	This change led to a small increase in the ICER. The ICER for nirogacestat vs BSC increased from █ to █ in a head-to-head comparison. This was in part a product of the way in which the EAG modelled the health outcomes for patients off treatment which were assumed to be the same as those on treatment. This was a necessary consequence of the EAG not having separate data on the outcomes achieved by these patients. This may skew the results of implementing early discontinuation in isolation but is not expected to skew the results overall.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could have provided separate data on the response and progression outcomes of patients stopped treatment prematurely and patients who remained on treatment. This should be best overall response and actual response at Year 1 and Year 2 by whether patients are on and off treatment at those time points. State membership at Year 2 should also be divided by patients state membership at the end of Year 1. Further real-world data collection would reduce uncertainty about the rate at which premature discontinuation would occur.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio

Key Issue 9: Health state utility values

Report sections	4.2.6
Description of issue and why the EAG has identified it as important	The company used health state utility values from Shingler 2013. This meant assuming that patients with progressive disease experience a health state utility value of 0.263. This was not credible as it was in line with the utility values experienced by patients receiving terminal care for cancer. Further, clinicians advised us that not all patients with a progressing desmoid tumour will experience

Report sections	4.2.6
	pain or mobility issues, as it is dependent on the location of the tumour. The source which the value came from was not thought to be a suitable analogue because it was from soft tissue sarcoma which is a more severe condition and it was a time trade off (TTO) study that used vignettes which is not in line with the NICE Reference Case.
What alternative approach has the EAG suggested?	The EAG preferred to use estimates from ² Reichardt et al, 2012 as they were estimated from patients with STS in a clinical trial setting using the EQ-5D as opposed to using vignettes. Reichardt 2012 was identified in the company economic evaluation SLR for STS.
What is the expected effect on the cost-effectiveness estimates?	Changing the utility source increased the ICER for nirogacestat versus BSC to [REDACTED] in the fully incremental analysis, compared with the EAG corrected base case ICER of [REDACTED] as the health state utility value for PD was higher in the EAG base case. It also removed the severity modifier. In the EAG base case, the utility value for PD patients would need to be reduced to [REDACTED] for the severity modifier to apply. In the company base case, the utility value for progressed disease needs to be [REDACTED] or lower for the severity modifier to apply (if chemotherapy is included as a comparator).
Could any additional evidence or analyses be provided to resolve this key issue?	The company mapped utility data on the EORTC scale taken from their clinical trial (De-Fi) to EQ-5D. The company chose not to present this data, on the basis that they did not believe the data, and the mapping, were robust. Nevertheless, the EAG would like to have seen the data as they represented the only utility data available for a desmoid tumour population.

Abbreviations: EAG, External Assessment Group; SLR, systematic literature review; STS, soft tissue sarcoma; TTO, time trade off.

1.4. Secondary issues identified by the EAG

Issue 1: Conduct of the De-Fi trial

Report section	3.2.9
Description of issue and why the EAG has identified it as important	In the critical appraisal of De-Fi, the EAG had some concerns over differences between the treatment arms in baseline characteristics, concerns about inadequate disease assessment primarily in the nirogacestat arm, and the different way PFS was measured in the De-Fi trial in comparison to other trials in the desmoid tumour population. The EAG noted that the direction of bias favoured nirogacestat in each case. A further concern was raised at the clarification stage (11b) where the company stated that there was no further data collection when a participant discontinued from De-Fi. The EAG understood it to be standard practice in trials to collect data related to subsequent treatments after they have discontinued from the trial treatment. The economic evaluation in this appraisal used lifetime horizons, so costs and benefits after discontinuation were included. These data would have offered more robust estimate of future treatment costs. Not collecting these data resulted in the company making some assumptions in relation to subsequent treatments in the economic model. In the model, the company assumed all patients received doxorubicin as subsequent therapy if they progressed. However, the EAG's clinical experts clarified that the chemotherapy treatment in most frequent use was vinorelbine.
What alternative approach has the EAG suggested?	No alternative approaches could address the conduct of De-Fi. In the respect of subsequent therapies, the EAG preferred to apply vinorelbine as subsequent treatment, except in the chemotherapy arm, in which doxorubicin was used as subsequent treatment.
What is the expected effect on the cost-effectiveness estimates?	The impact of the conduct of the trial was unclear but the direction of bias favoured nirogacestat. The impact of the EAG's updated assumptions around subsequent treatments was small, as it only effected costs and not health benefits, and the costs of the different chemotherapy options were similar.
Could any additional evidence or analyses be provided to resolve this issue?	The company could seek access to secondary data sets e.g. any registry data in order to better assess subsequent treatments.

Abbreviations: EAG, External Assessment Group.

Issue 2: The company did not present any details of the studies included in the clinical SLR outside of the title each paper and the study it reported on

Report section	Section 3.1
Description of issue and why the EAG has identified it as important	The company undertook an SLR, present in Appendix B of the CS. The SLR included RCTs, non-randomised studies, and single-arm studies investigating all the relevant treatments for people with DT. The company included 104 papers reporting 69 studies in the SLR. However, no data extraction or even summary, of these papers was presented. Instead, the 104 papers were presented as a list, subdivided by the study they were reporting (Table 5, Appendix B).
What alternative approach has the EAG suggested?	If the company could report an included studies table that summarises the key characteristics of each study, such as the author/year, study design, population, interventions, comparators, outcomes, and sample size. Clearly presenting the evidence related to chemotherapy for DT might have allowed the EAG to assess whether a more appropriate ITC could have been conducted.
What is the expected effect on the cost-effectiveness estimates?	Not quantifiable. Lack of a clear evidence base for the comparison to chemotherapy increases the level of uncertainty in the comparison.
Could any additional evidence or analyses be provided to resolve this issue?	The company could also more formally report the feasibility analysis on whether a robust ITC comparing nirogacestat to chemotherapy could be performed. In doing this they could offer more detail related to their conclusion that, for example, a population-adjusted indirect comparison (PAIC), would not offer a robust estimate.

Abbreviations: CS, company submission; EAG, External Assessment Group, DT, desmoid tumours; ITC, indirect-treatment comparison; RCT, randomised controlled trial; SLR, systematic literature review.

Issue 3: Assumed health related resource use

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	The company did not include any resource use for patients in the CR health state. The company assumed treatment specific levels of GP and specialist visit resource use for patients in SD health state. The company underestimated the specialist visits in PD health state. The company underestimated specialist visits in SD and PR health state.
What alternative approach has the EAG suggested?	Based on clinical expert opinion, patients would receive two specialist visits per year for five years post treatment in the CR health state. The EAG considered resource use for patients in SD to be equal despite alternative treatment arms, validated by clinical opinion. EAG clinical experts stated six specialist visits per year in the PD health state, four per year in the SD health state and two per year in the PR health state is a more reasonable estimate of resource use.
What is the expected effect on the cost-effectiveness estimates?	This reduced the ICER nirogacestat versus chemotherapy from [REDACTED] in the EAG corrected case to [REDACTED].
Could any additional evidence or analyses be provided to resolve this issue?	Analysis of patient resource use in the De-Fi trial could provide a more robust estimate of healthcare resource utilisation Clinical consultation or analysis from a UK data source to inform estimates, however currently the EAG is unaware of any suitable data sources.

Abbreviations: CR, complete response; EAG, External Assessment Group; PD, progressive disease; PR, partial response; SD, stable disease.

1.5. Company's modelling errors identified by the EAG

The EAG identified a few fairly modest errors. Overall, the company model had an appropriate lay out and formatting, and the model functionality was fit for purpose.

The company did not implement a probabilistic base case. The EAG attempted implementing a probabilistic base case, in line with NICE guidance. However, the run time for the probabilistic analysis was impractically long, so the EAG opted for a deterministic base case. The alignment between the deterministic and probabilistic results in the EAG base case, mean that the EAG do not consider this a key area of uncertainty.

The company's implementation of response rates was incorrect, in a way that impacted response rates and progression rates. The company adjusted the annual probability of achieving a response conditional on having stable disease to a monthly probability of response, without accounting for the impact of progression on the number of patients with stable disease.

The company implemented ovarian dysfunction as a one-off event with a constant risk each cycle. This did not reflect the fact that ovarian dysfunction was a one-off long-term event (as the company acknowledged in their submission). The company attempted to rectify this area at clarification stage but were not successful. The EAG amended this error by modelling ovarian dysfunction as a one-off event that applied for the average duration observed in the trial.

The company implemented the cost of doxorubicin incorrectly at £4.08 per unit. The correct price is £4.20 per unit. The EAG amended this.

These issues are also described in Section 5.2.1.

1.6. Summary of EAG's preferred assumptions and resulting ICER

Table 3 presents the fully incremental analysis of the EAG's preferred assumptions, with the 1.2x severity modifier applied where relevant.

The company submitted an initial base-case analysis comparing nirogacestat with BSC/placebo. In the company base case, the total costs were [REDACTED] for nirogacestat and [REDACTED] for BSC/placebo, with total QALYs of [REDACTED] respectively. This resulted in an ICER of [REDACTED] per QALY gained for nirogacestat vs BSC/placebo when a 1.2x severity modifier was applied.

The EAG identified a series of corrections to the company model. These included a correction to the price of doxorubicin, the timing of progression, the transition probabilities calculated based on best overall response, the implementation of mortality values and the implementation of ovarian dysfunction as an adverse event. Incorporating these corrections produced the EAG-corrected company base case. Under the corrected specification, the total costs were [REDACTED] for nirogacestat and [REDACTED] for BSC/placebo, and total QALYs were [REDACTED] respectively. The resulting ICER was [REDACTED] per QALY. The correction that had the largest impact on the company base case was the correction to the transition probabilities that were calculated based on best overall response, which created an ICER of [REDACTED] as the severity modifier no longer applied. This was also true in the EAG corrected base case.

The EAG then applied its preferred assumptions, which included matching premature discontinuation to DeFi, using a three year stopping rule, no patients progressing after year two in line with DeFi, patients receiving a response in year three in line with DeFi, utilities values derived from Reichardt et al. (2012),³ alternative HCRU assumptions and using vinorelbine as a

subsequent therapy. Applying these assumptions generated the EAG base case. In its base case, the EAG included chemotherapy as a comparator, selecting vinorelbine based on clinical expert advice that it is commonly used for this patient group. A scenario analysis was also conducted with doxorubicin and methotrexate with vinblastine as chemotherapy alternatives assuming similar effectiveness across chemotherapies.

In the EAG base case, the total costs for nirogacestat [REDACTED] [REDACTED] for vinorelbine and BSC/placebo respectively. Total QALYs for nirogacestat were [REDACTED] compared to [REDACTED] for vinorelbine and [REDACTED] for BSC/placebo. The ICER per QALY gained was [REDACTED] for nirogacestat vs BSC/placebo and [REDACTED] for nirogacestat vs vinorelbine. The severity modifier did not apply in the EAG base case, or when any of the EAG base case changes were applied to the EAG corrected base case individually.

The changes which had the greatest impact within the EAG base case were the use of utility data from patient EQ-5D data rather than vignettes, the application of a 3 (rather than 2) year stopping rule and the assumption that no progression occurs after year 2 in line with the De-Fi trial.

The EAG was not able to test the impact of improvements in pain associated with chemotherapy within the model provided by the company. This means that a key benefit of chemotherapy, according to clinical experts, may not be captured within this analysis.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 3: Summary of EAG's preferred assumptions and ICER fully incremental vs multiple comparators

Report section	EAG correction /assumption	Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	ICER vs nirogacestat (% change from company base case)
5.1	Company base case with chemotherapy included*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
5.2	EAG correction to doxorubicin price*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
5.2	Correction to mortality probabilistic values*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
5.2	Ovarian dysfunction applied as a one-off event, instead of intermittent*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
4.2.4.4	Transition probabilities calculated based on best overall response at 2 Years*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
5.2.2		Vinorelbine	██████	██████	██████	██████	██████	██████

Report section	EAG correction /assumption	Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	ICER vs nirogacestat (% change from company base case)
	EAG corrected company base case*	BSC/placebo						
		Nirogacestat						
4.2.4.3	Premature discontinuation included (to match De-Fi)*	Vinorelbine						
		BSC/placebo						
		Nirogacestat						
4.2.4.2	3-Year stopping rule*	Vinorelbine						
		BSC/placebo						
		Nirogacestat						
4.2.4.4	No progression after Year 2 (matches De-Fi)	BSC/placebo						
		Vinorelbine						
		Nirogacestat						
4.2.4.4	Patients can achieve a response after Year 2 (matches De-Fi)*	Vinorelbine						
		BSC/placebo						
		Nirogacestat						
5.2	Utilities taken from Reichardt 2012	Vinorelbine						
		BSC/placebo						
		Nirogacestat						
5.2		Vinorelbine						

Report section	EAG correction /assumption	Intervention	Total costs	Total QALYs	Incremental costs	Increment al QALYs	Fully incremental ICER	ICER vs nirogacestat (% change from company base case)
	Alternative HCRU assumptions (monitoring complete responders and more specialist visits)*	BSC/placebo	██████	██████	██████	██████	██████████	██████
		Nirogacestat	██████	██████	██████	██████	██████	
5.2.3	Vinorelbine as subsequent therapy*	Vinorelbine	██████	██████	██████	██████	██████	██████
		BSC/placebo	██████	██████	██████	██████	██████████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████
5.2.3	EAG base case	BSC/placebo	██████	██████	██████	██████	██████	██████████
		Vinorelbine	██████	██████	██████	██████	██████████	██████
		Nirogacestat	██████	██████	██████	██████	██████	██████

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Note: *A severity modifier of x1.2 has been applied to the QALYs in these scenarios, in all other scenarios no severity modifier was applied

1.7. Outline of confidential comparator or subsequent treatment prices

No included comparators had confidential price discounts so there is no confidential appendix.

2. BACKGROUND

This report critiques the company submission (CS) for nirogacestat (Ogsiveo®) for treatment of desmoid tumours (DT) in adults.

2.1. Critique of the company's description of the underlying health problem

The company presented a comprehensive summary of the health condition in their submission and the EAG has presented additional information relevant to the decision problem highlighted by their clinical experts.

Desmoid tumours are rare, noncancerous (benign) growths that develop in the body's connective tissues, such as muscle, fat, and bone. Also called aggressive fibromatosis, these intermediate tumours are characterized by their tendency to grow locally and invade surrounding tissues, though they do not spread to distant parts of the body (metastasize). People can die from desmoid tumours, though it is rare.⁴

There are two types of DT: sporadic tumours, which form the majority of all DT (85 to 90%) and harbour somatic β -catenin (CTNNB1) gene mutations; the remainder of DT (10 to 15%) occur in people with mutations in the adenomatous polyposis coli (APC) gene, including people with familial adenomatous polyposis (FAP), a tumour predisposition syndrome.⁵ FAP associated desmoid tumours are most commonly found within the abdomen and may be larger and multifocal. Approximately 10-25% of FAP affected individuals will develop a desmoid tumour in their lifetime. It has been estimated that DTs are 800 to 1,000 times more common in FAP individuals than in the general population, but the exact incidence has not been determined due to the lack of a dedicated surveillance regimen.⁶

The company stated that people with DT experience substantial pain, symptom burden, and functional limitations that are influenced by tumour location and size. The EAG's clinical experts agreed that a proportion of people with DT do experience substantial pain, symptom burden, and functional limitations, but in many people the symptoms are minor and less commonly a person has a significant morbid lesion.

The company quoted a paper by Gounder et al. (2020)⁷ where the most frequently reported symptoms across tumour locations were disfigurement (81%), nerve pain (71%), decreased range of motion (68%), and muscle pain (65%). However, the paper by Gounder et al. was not

designed to make an assessment of the proportions of people with specific DT symptoms, it was a qualitative study that used concept elicitation (CE) interviews with 30 people with DT to explore their perspectives on key disease-related symptoms and impacts. It was used to develop the Gounder/DTRF Desmoid Symptom/Impact Scale (GODDESS). Therefore, the EAG do not accept the proportions listed above to be an accurate reflection of all people with DT, or indeed progressing DT as that is the population of interest for this appraisal. Instead, based on feedback for their clinical experts, the EAG understand that people with DT do experience these frequently reported symptoms, but their impact and severity can vary greatly from person to person. For example, a person with a small abdominal DT may experience disfigurement, but it is a very different experience to a person with a DT on their cheek. The same is true of pain, where some people cannot walk or extend their arms, whereas others have occasional pain and/or discomfort that can be well managed.

In the CS, the company noted that in some cases, people with DT experience more severe symptoms such as bowel obstruction and perforation, organ dysfunction, and sepsis. Both of the EAG's clinical experts stressed that these are rare complications, one noting that in four years he had seen three or four cases of bowel obstruction and perforation.

The EAG's clinical experts did agree with the company that DT have an unpredictable clinical course marked by periods of rapid progression, spontaneous regression, and stability, which can influence symptom burden and contribute to impaired health-related quality of life (HRQoL). The natural history of a desmoid tumour is to rapidly progress in the initial period but then to regress spontaneously or remain stable after two to three years. An EAG expert explained that DT are likely caused by an aberrant repair process and the body has a high propensity to overcome that given enough time i.e. two to three years.

2.1.1. Treatment

The EAG's experts stated the most relevant clinical guideline for people with DT is the consensus-based guideline first published in 2020 and updated in 2024.^{9,10} These have been summarised in Section 1.3.7 of the CS. The key to understanding the treatment pathway for DT is understanding the natural history of DT. As stated in the previous section, the natural history of a desmoid tumour is to rapidly progress in the initial period but then to regress spontaneously or remain stable after two to three years. Therefore, the goal of treatment is to control symptoms and preserve function, not to "cure" the tumour at all costs as the body will often achieve stable disease and complete resolution without treatment. This means the initial strategy is most

commonly active surveillance, and that surgery is not commonly used unless the tumour is imminently life-threatening to the person. The EAG's experts also noted that the treatment pathway was the same whether or not a person has FAP.

The people who are offered systemic treatment are either very symptomatic at diagnosis and have signs of rapid growth, either clinically or radiologically, before coming to clinic, or people who develop worsening symptoms or have radiologic growth while on active surveillance. Treatment prior to active surveillance is only for life threatening situations or a history of rapid growth.

The EAG's experts advised that people on active surveillance are given imaging scans and an assessment every six week or three months depending on their history. The decision of whether to offer systemic treatment is based on these assessments. If the tumour is convincingly larger on sequential imaging scans, then systemic treatment would be considered. While the percentage increase in size would be noted the decision is not solely based on progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. For example, progression may be diagnosed on only a modest increase in the size of the tumour, aligned to the development of a new pain.

The initial systemic treatment in the NHS was chemotherapy. The primary chemotherapy agent offered was vinorelbine though low dose doxorubicin can also be used. Tyrosine kinase inhibitors (TKIs) were also effective treatments but at the time of writing were available for compassionate use only, and as such, were less available than chemotherapy. They were therefore only used at second line or later in the NHS. Whilst each of the systemic treatment options were considered effective, they each come with a different safety profile and monitoring needs.

Pain management is a key aspect of symptom control, and its reduction depends on multiple factors. Systemic treatment can reduce the size of a tumour, and in doing so this may reduce pain, through reduced compression of nerves or reduced pressure on blood vessels and organs. However, a reduction of pain can be experienced without the tumour shrinking, and even in people with a tumour that is growing slowly, because treatment reduces inflammation/oedema in the tumour making the tumour less, in the words of an expert, "angry, hot, and cross".

2.1.2. Ongoing assessment

The EAG's clinical experts do not limit their assessment to the change in tumour size given by the imaging scans. They combine that assessment with an assessment of patient-reported outcomes, such as pain. This is because the dominant symptoms will, in most cases, be pain and a reduced ability to move across a joint. If these symptoms are reduced by treatment, then it may be immaterial whether they had complete response, partial response, or stability.

In addition, there are limitations to RECIST criteria for DT. One limitation is that desmoid tumours' irregular, non-spherical shapes can make one-dimensional measurements inaccurate. A second limitation relates to changes of fibrous and myxoid (gelatinous) content that can occur inside a DT. When MRI T2-weighted images are taken, they can reveal how much of a tumour is hyperintense, with areas of higher water content that indicate increased cellularity or myxoid stroma, and how much of the tumour is hypointense, denser, more fibrotic regions with less water. Desmoid tumours with $\geq 90\%$ hyperintensity are more likely to progress.¹¹ The study found that people in the $\geq 90\%$ group ($n=20$), 1-year progression-free survival (PFS) was 55%, compared to 94% in the $<90\%$ group ($n=17$). The limitation of RECIST is that a tumour may stay the same size, i.e. be classed as stable and continue to raise concerns that it may progress, but MRI T2-weighted images could find it was hypointense and very unlikely to progress again. In current NHS practice, MRI T2 weighted images can be used to further inform the care a person is offered.

2.1.3. Monitoring and stopping treatment

The EAG's clinical experts explained that the decision to discontinue systemic treatment is based on the symptoms of the DT, experience with the side-effects of treatment, and the tumour's response to treatment.

If a person has complete response (CR) then systemic treatment can be discontinued. An expert noted that, while he understood it was possible, he had never seen recurrence after CR. Alternatively, if the treatment was ineffective then treatment could also be discontinued.

When the treatment offers a positive effect that is short of CR, it is appropriate to stop when symptoms have been addressed, and the person has reached a "radiological plateau". A radiological plateau is stability for at least three to six months. However, if a person's symptoms have been addressed but their tumour continues to shrink i.e. not reached ongoing stability, they may decide not to continue experiencing the side-effects of treatment and discontinue. The

EAG's experts explained that this is a reasonable decision because, when a person's DT is shrinking, it will often continue to shrink after systemic treatment is discontinued. As noted previously, after a person has had DT for two to three years, it can quite commonly spontaneously regress or have ongoing stability without treatment.

Both experts consulted by the EAG agreed that the decision to stop treatment could be made earlier when it were possible to re-challenge if the person subsequently progressed. At the time of writing, practice was for regular monitoring to continue for five years after treatment was discontinued.

2.1.4. Positioning

The two systemic therapies offered in the NHS were chemotherapy (vinorelbine or doxorubicin) and TKIs (sorafenib). The only option first-line was off-label vinorelbine (chemotherapy). At second-line or later, people may be offered TKIs (sorafenib) or doxorubicin (chemotherapy). The EAG's experts explained that they would expect nirogacestat to be offered first-line or later, i.e. alongside chemotherapy (vinorelbine or doxorubicin) at all lines, and alongside TKIs (sorafenib) 2nd line onwards.

2.2. Critique of the company's overview of current service provision

The company summarised the treatment pathway based on recent consensus guidance in Section 1.3.7 of the CS.¹¹ Based on expert advice, the EAG considered this guideline to offer an accurate picture of the most appropriate care currently available for people with DT. Based on this guideline and the advice of their experts on their current service provision, the EAG considered chemotherapy (off-label) and TKIs (off-label, compassionate use) to be the other systemic treatments given in current practice in the NHS.

Table 4: Comparability of intervention with current comparators

Comparison	Nirogacestat	Vinorelbine (chemotherapy)	Sorafenib (TKI)
International non-proprietary name (Brand)	Ogsiveo	Navelbine / generic versions	Nexavar / generic versions
Commissioning status	Not yet commissioned for routine NHS use	Not commissioned for use for DT. Its use for this indication is therefore off-label and managed through local or regional protocols	Not commissioned for use for DT. It is available via compassionate use.

Comparison	Nirogacestat	Vinorelbine (chemotherapy)	Sorafenib (TKI)
		rather than a national mandate.	
Available formulation(s), strength(s)	Oral administration of 150 mg of nirogacestat twice daily.	Oral administration of 90 mg on days 1, 8, and 15 of a 28-day cycle	Oral administration of 400 mg PO once daily
Principle pharmacological action and therapeutic class	Nirogacestat, blocks the activity of an enzyme (a type of protein) called gamma secretase. This enzyme normally activates a protein called NOTCH, which is found on the surface of cells and is involved in cell growth. By blocking gamma secretase, nirogacestat prevents NOTCH activation and slows down the growth of tumours.	Vinorelbine is a nonmutagenic cytotoxic agent. It has a cytostatic / anti-proliferative effect by inhibiting microtubule polymerization. This suppresses proliferation of fibroblastic cells that drive tumour growth.	Sorafenib blocks two cellular pathways which are critical for cell proliferation, invasion, and growth. This blocks signal transduction that drives desmoid tumour growth. As a multi-kinase inhibitor, sorafenib can also interfere with the development of new blood vessels (angiogenesis) that supply tumours.
Course of treatment	The draft SmPC states that treatment should be continued until disease progression or unacceptable toxicity. The company used a 2-years stopping rule in the economic model.	Experts advised that a standard course is 18 weeks. Treatment can continue if people have not experienced serious toxicity for up to 12 treatments total.	Treatment can continue for two years or more depending on toxicity
Proposed/approved indications	Adults with progressing desmoid tumours who need systemic treatment	Off-label: Adults with progressing desmoid tumours who need systemic treatment	Off-label: Adults with progressing desmoid tumours who need systemic treatment
Toxicities (or other characteristics) that may result in differences in use	Grade III: diarrhoea, folliculitis, maculopapular rash, hidradenitis, hypophosphataemia, hypokalaemia, ALT/AST ≥ 3 to $5 \times$ ULN, would result in discontinuation until resolved followed by reduced dose (100 mg twice daily). ALT/AST $> 5 \times$ ULN, anaphylaxis or other severe hypersensitivity, leads to permanent discontinuation.	Grade $\geq$ III neutropenia, febrile neutropenia, Grade ≥ 2 neuropathy, Grade ≥ 2 mucositis, Grade ≥ 3 GI toxicity discontinuation until resolved followed by reduced dose. Discontinue treatment after hepatic dysfunction or hypersensitivity.	Grade III: neutropenia, thrombocytopenia, neutropenic fever, diarrhoea, hepatic dysfunction, persistent or symptomatic hypertension would result in discontinuation until resolved followed by reduced dose. Discontinue treatment after GI perforation, Grade 4 hepatic dysfunction, Grade 4 hypertension, myocardial ischemia:

Comparison	Nirogacestat	Vinorelbine (chemotherapy)	Sorafenib (TKI)
Any differences that may result in different populations using the medicine	Nirogacestat is contraindicated in pregnant women and in women of childbearing potential not using highly effective contraception. Men with female partners of childbearing potential should be advised to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat.	Pregnant individuals and those planning pregnancy should also avoid vinorelbine due to risks to the fetus and should discuss contraception options with their doctor.	Sorafenib should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus. Women of childbearing potential must use effective contraception during treatment.
Any differences that may result in growth in the market	None	None	Sorafenib-induced cardiovascular toxicity can be addressed with losartan, captopril, or sildenafil.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DT, desmoid tumours; HFSRs, hand-foot skin reaction; SAEs, serious adverse events; TKI, tyrosine kinase inhibitor; Committee for Medicinal Products for Human Use (CHMP)

2.3. Critique of company's definition of decision problem

The company's decision problem, along with the EAG's commentary, is presented in Table 5. The EAG considered the population, intervention, outcomes, and subgroups addressed in the CS were well-aligned to the final scope issued by NICE. The company did not address the economic analysis in the decision problem table but the economic analysis was in line with the decision problem, other than the exclusion of a relevant comparator (chemotherapy).

2.3.1. Comparators

The comparators addressed in the CS were not well aligned with the final scope issued by NICE. The company only addressed best supportive care (BSC) in the submission and argued that established clinical management using medical therapies, such as chemotherapy or tyrosine kinase inhibitors (TKIs) were not relevant comparators. The EAG did not consider their rationale to be well-founded and noted that in Section 1.3.7 of the submission, the company quoted from the 2024 guideline update⁹: "Medical therapy (including TKIs and chemotherapy) is recommended as one of the first-line treatment options for patients who require treatment for a DT in the abdominal wall, mesentery, retroperitoneum, pelvis, extremities, girdles, or chest wall".

Indeed, Ou et al. (2024) published a Bayesian network meta-analysis (NMA) of RCTs comparing chemotherapy (methotrexate–vinblastine), TKIs (sorafenib/pazopanib), and nirogacestat.¹

Best supportive care

BSC was a comparator in the scope and despite the updated population being adults with progressing DT *who require systemic treatment*, and BSC not being systemic treatment, the EAG understood that BSC was the comparator in De-Fi and was potentially permitted because their DT was not immediately life-threatening and participants could cross over to active treatment if progression occurred. In addition, the EAG’s clinical experts stated that not everyone is suitable for systemic treatment or would choose to take it given current options. Therefore, the EAG accepted BSC as a relevant comparator for this appraisal.

Chemotherapy

Chemotherapy works by interfering with DNA synthesis or cell division, affecting rapidly dividing cells. An EAG expert explained that the main benefit of chemotherapy is to reduce pain. He noted that it can shrink the tumour but he had no expectations that it would extend a person’s life, and he was unclear how it would affect time to progression.

In Section 1.3.7.1 of the CS, the company stated that chemotherapy was used off-label for DT and was considered a treatment option largely due to the lack of alternative options available in clinical practice. The EAG’s experts agreed that chemotherapy was used off-label for DT and there were limited systemic treatment options first-line for people with DT. However, in their experience it was effective and in the majority of people the toxicity could be managed. Therefore, given the limited systemic treatments available, this was the primary treatment given to adults with progressing DT who require systemic treatment, and as such was a key comparator in this appraisal. At the clarification stage (A14), the EAG requested the company present an indirect treatment comparison (ITC) comparing chemotherapy (vinorelbine) to nirogacestat with the intention of including chemotherapy as a comparator in the economic model. The company did not present an ITC and stated it was not appropriate due to methodological and data-related limitations, including study design and data collection issues. The company did not provide a comprehensive feasibility analysis (Secondary Issue 2). The EAG considered chemotherapy an important comparator and conducted a pragmatic NMA presented in Section 3.4.1.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) block specific tyrosine kinase enzymes involved in signalling pathways that drive cell proliferation and angiogenesis. They inhibit multiple different pathways at the same time and in some tumours inhibit a pathway that is active. This will slow the growth of the tumour and may move it towards stability. This is different to nirogacestat which was developed based upon the specific intracellular and intercellular communication pathways in DT. Therefore, it is more targeted than TKIs to the likely pathways active in DT.

The company addressed TKIs in Section 1.3.7.1 of the CS and correctly stated that TKIs may be prescribed off-label for the management of DT to a very limited population through compassionate use programs in the UK. The EAG's clinical experts explained that limiting TKIs to compassionate use means they cannot be used first-line and are instead utilised at 2nd line onwards. However, the EAG's clinical experts both stated that in their experience TKIs are effective and would be used more often if they were available through routine funding. There was also an RCT published which found sorafenib significantly prolonged PFS and induced durable responses.¹² Therefore, given the place TKIs occupy in the treatment pathway in the consensus-based guideline and their use in the NHS as detailed by the EAG's clinical experts, the EAG considered TKIs would be a relevant comparator if made available through routine funding. However, given that at the time of writing they were only available via compassionate care, the EAG has not included TKIs as a comparator in this appraisal.

2.3.2. Highly specialised technology assessment

The company applied to be evaluated through the Highly Specialised Technologies (HST) process but were not considered to meet the criteria. The HST Programme evaluates technologies for very rare and severe diseases that require specific considerations and flexibilities permitted by the programme. NICE applied four criteria to determine the eligibility of technologies to be evaluated under the HST Programme. The final routing criteria for the Highly Specialised Technologies Programme are:

- 1) The disease is very rare – defined as 1:50,000 population in England.
- 2) Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications.
- 3) The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life.

- 4) There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.

The Prioritisation Board made a decision on nirogacestat for treating DT in [2025](#). The board agreed that criteria 1 and 4 of the highly specialised technology framework were not met, and that therefore the treatment should be routed to the technology appraisals programme.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults (aged 18 years and over) with DT	Adult patients (aged 18 years and over) with progressing DT who require systemic treatment	Align to population in market authorisation application	The EAG considered that, given the treatment pathway, adults with progressing DT who require systemic treatment, was a more appropriate population than all adults with DT. This was the population addressed in the pragmatic NMA conducted by the EAG (Section 3.4.1.2) but there were notable differences in the inclusion criteria for each of the included trials.
Intervention	Nirogacestat monotherapy	Per final scope	N/A	As per the scope.
Comparator(s)	- Established clinical management using medical therapies. This may include chemotherapy or TKIs. - Best supportive care	Best supportive care	TKIs and chemotherapy were not included as relevant comparators in this submission as they do not reflect the current SoC in UK clinical practice (further details are provided in Section 1.3.7 of the CS). TKIs are not licensed or reimbursed for DT (only available via compassionate use programmes) nor are they routinely used in UK clinical practice for the treatment of DT, as they are difficult to access based on feedback from UK advisers¹³ and are associated with considerable treatment	As stated in Section 2.3.1, the EAG accepted that BSC was a relevant comparator, but also noted that the updated population was adults with progressing DT <i>who require systemic treatment</i> . The systemic treatments used in the NHS were chemotherapy and TKIs. The EAG considered chemotherapy, available off-label through routine

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			discontinuation due to toxicity and disease progression¹⁴⁻¹⁷. Chemotherapy treatment is used more frequently than TKIs and is included in the current clinical practice guidelines as an option for patients (largely due to lack of alternative options approved for use in DT⁹); however, it is not considered the SoC and is associated with significant toxicity issues,¹⁷ which can affect patients' QoL, adherence/persistence, and treatment preference. Furthermore, there is no robust high-quality evidence generated from randomised clinical trials on which to assess efficacy and/or compare chemotherapy to nirogacestat, with outcomes data in adults limited to retrospective studies and a single-arm trial.^{5,17-20} Thus, best supportive care is the only appropriate comparator for nirogacestat as it most accurately reflects UK SoC in the treatment of DT.	funding, a relevant comparator, but accepted that TKIs were only available via compassionate care and were not an appropriate comparator.
Outcomes	• Response rates (for example: partial or complete response) • Duration of response • Improvement in symptoms, including pain	• Response rates • Duration of response • Improvement in symptoms, including pain	Transition between health states was calculated by combining data on PFS, with the level of tumour response achieved by patients who did not progress during the trial (e.g., stable disease, partial response, complete response, progression), as defined by the	The EAG's experts agreed these were the appropriate outcomes. They noted that while tumour size is the key measure reported in trials there are limitations to RECIST v1.1 criteria

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	- Adverse effects of treatment - HRQoL - PFS - Mortality	- Adverse effects of treatment - HRQoL - PFS - Mortality	RECIST, version 1.1), is an outcome that can demonstrate the disease-modifying effect of treatment for these patients and was therefore selected for the model. PFS has also been used to validate the model.	(Section 2.1.2). In addition, the size of a tumour is less important than the location of the tumour for tumour symptoms such as disfigurement, nerve pain, decreased range of motion, and muscle pain. Also, in relation to mortality, people can die from desmoid tumours, but it is rare.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator	The company presented a cost-utility analysis, using quality-adjusted life years. The analysis used a life-time horizon. Costs were considered from an NHS and Personal Social Services perspective. Confidential price discounts were provided as clarification stage and were incorporated into the economic model.	There were no differences from the final NICE scope relevant to the economic analysis specifically, issues regarding exclusion of a relevant comparator are discussed above.	The economic analysis was in line with the Reference Case, except for the exclusion of a relevant comparator which is discussed above and the use of and a source of utility data which does not align with the Reference Case (a vignette study in soft tissue sarcoma).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	• People who have not had previous treatment and people whose DT is relapsed or refractory to treatment • Subgroups based on tumour site such as people with intra-abdominal or extra-abdominal DT • People with FAP	Per NICE final scope	N/A	The relevant subgroup analysis was presented in the clinical effectiveness results but not in the economic analysis. The subgroup analysis was underpowered, limiting the ability to detect statistically significant differences between treatment arms.
Special considerations including issues related to equity or equality	None stated	None stated	N/A	The EAG's experts did not raise any special considerations related to equity or equality.

Abbreviations CS, company submission; DT, desmoid tumours; EAG, External Assessment Group; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care; TKIs, tyrosine kinase inhibitors; UK, United Kingdom.

3. CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Section 3.4 covers additional work done by the EAG.

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) of clinical evidence and presented it in Appendix B of the CS. In Section 1.1 of Appendix B the company stated that a formal protocol was not developed for the SLR, but the EAG were able to ascertain that the methods used were appropriate.

The search process was well described in Appendix B. The company searched Embase, MEDLINE, Cochrane CENTRAL and the Cochrane Database of Systematic Reviews. There was an original review in 2022 and update in 2024 and, finally, May 2025. Searches were performed on the Ovid platform and all via a single search strategy that combined the searches for each of the four databases. While there is always a slight concern with such an approach – because of uncertainties around thesaurus term mapping – the strategies were comprehensive and the EAG deemed them appropriate given the decision problem. Supplemental to the database searches, the company also performed manual grey literature searching for five conferences.

While the search methods did appear to be appropriate, the company did not follow them through and conduct an SLR. In the PRISMA diagram presented in Figure 3 (Appendix B), the company stated that 69 studies were included in the review but no data extraction or even summary of these papers was presented. All that is presented is a list of 104 papers subdivided by the study they were reporting on (Table 5, Appendix B). At a very minimum it would have been valuable for the EAG, and indeed the Committee, if the company had presented the study designs and the drugs being tested in each of the included studies. This would have provided a fuller picture of the evidence base on which evidence could be drawn for this appraisal.

Table 6: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix B (Pages 1-34)	The described search strategies for the four databases and five conferences were considered appropriate and well reported. Publication type filters were fully referenced.
Inclusion criteria	Appendix B (Pages 35-36)	Broad inclusion criteria were adopted
Study selection	Appendix B (Pages 34-35)	Adequate double blind assessment at title and abstract and full-text
Data extraction	Appendix B (Page 36)	Data extraction by a single reviewer and validated by a second reviewer. However, the company did not present any of the data they extracted.
Quality assessment	Appendix B (Page 36)	The company stated that checklists recommended by NICE were used
Evidence synthesis	NA	No evidence synthesis was presented

Abbreviations: CS, Company submission; EAG, External Assessment Group

3.2. Critique of the methods of the trials of the technology of interest

The company detailed one trial of nirogacestat in the submission (De-Fi). Details of the study are given below in Table 7.

Table 7: Clinical effectiveness study of nirogacestat

-	De-Fi
Role in this evaluation	The De-Fi trial has been used to inform key model inputs including baseline patient characteristics, transition between health states, treatment discontinuation and safety for nirogacestat and best supportive care.
Study type	Phase 3, multicentre, double-blind, randomized, placebo-controlled trial
Patient group	Adults with progressing ($\geq 20\%$ within 12 months) desmoid tumours according to the Response Evaluation Criteria in Solid Tumours, version 1.1.
Subgroups	• People who have not had previous treatment and people whose DT is relapsed or refractory to treatment • Subgroups based on tumour site such as people with intra-abdominal or extra-abdominal DT • People with familial adenomatous polyposis
Exclusion criteria (Table 2.2, CS)	• Known malabsorption syndrome or pre-existing gastrointestinal conditions • Various severe CVD conditions/events • Abnormal QT interval
Intervention	Oral administration of 50 mg tablets (3 tablets; 150 mg) of nirogacestat twice daily
Comparator	Oral administration of 50 mg tablets (3 tablets; 150 mg) of placebo twice daily
Stopping treatment	Participants continued to receive nirogacestat or placebo until one of the following events or circumstances occurred: • Death • Trial completion • Imaging-based or investigator-determined clinical progression • An intolerable adverse event • Circumstances that prevented the participant from adhering to the trial protocol • Participant or investigator request for discontinuation Dose reduction to 100 mg twice daily was mandated by the protocol for the management of selected, persistent adverse events of grade 3 or higher (diarrhoea, nausea, vomiting, skin toxic effects, hypophosphatemia, and hematologic or nonhematologic toxic effects) and was optional for grade 2 ovarian dysfunction.
Duration	The median duration of exposure was 20.6 months (range, 0.3 to 33.6) among the patients receiving nirogacestat and 11.4 months (range, 0.2 to 32.5) among those receiving placebo. The double-blind phase lasted approximately 20 months (August 2020 to April 2022) and the OLE had a database lock date of December 2024, potentially offering data on participants after more than four years of treatment with nirogacestat.
Location	This study was conducted at 52 sites in Canada, the US, and Europe, with 37 sites randomising at least 1 participant

Abbreviations: CS, Company submission; CVD, cardiovascular disease; DT, desmoid tumours; EAG, External Assessment Group.

3.2.1. Study design

The De-Fi (Desmoid Fibromatosis) trial was a phase 3, international, double-blind, randomized, placebo-controlled trial to determine the efficacy and safety of nirogacestat in adults with progressing desmoid tumours.

3.2.2. Population

3.2.2.1. Trial eligibility criteria

The EAG's experts considered the De-Fi trial eligibility criteria, as detailed in Table 2.2 of the CS to be standard for trials in people with DT. The trial recruited adults with a histologically confirmed DT (by local pathologist prior to informed consent) that had progressed by $\geq 20\%$ as measured by RECIST v1.1 within 12 months of the screening visit scan.

They could be:

- Treatment naïve, measurably progressing DT that was deemed not amenable to surgery without the risk of significant morbidity.
- Recurrent, people with a prior line of therapy and a best overall response of complete response (CR) or partial response (PR) prior to randomisation.
- Refractory, measurably progressing DT following at least 1 line of therapy and no response to treatment.

3.2.2.2. Baseline characteristics

The company presented baseline demographics of the participants in De-Fi in Table 2.4 in the CS. The EAG noted a higher proportion of white people in the nirogacestat arm (91% versus 75%), a higher proportion with a healthy weight in the nirogacestat arm (51% versus 39%), and more people in the ≥ 46 years aged quartile in the nirogacestat arm. No subgroup analysis was presented on these subgroups in the CS. However, the EAG's clinical experts did not suggest these imbalances would overtly bias the trial results in any specific direction.

The company presented the baseline disease characteristics of the participants in De-Fi in Table 2.5 in the CS. The EAG noted differences between the two treatment arms. A higher proportion of participants in the placebo arm (76.4%) were refractory to treatment compared to 61.4% in the nirogacestat arm. The EAG's experts explained that people who are refractory to treatment are less likely to respond to a new treatment and this imbalance favoured the nirogacestat arm. This was not entirely supported by the subgroup analysis in De-Fi (Section

3.3.8) but the trial was too small to offer any convincing differences in the efficacy of nirogacestat in the subgroups of interest.

3.2.3. Intervention

The intervention was 150 mg of nirogacestat twice daily. In Section 3.3.1 of the CS, the company noted that the optimal duration of treatment with systemic treatments in people with DT remains to be determined.

3.2.4. Comparator

The comparator was 150 mg of placebo twice daily.

3.2.5. Concurrent treatment

Both treatment arms received best supportive care (BSC) in addition to the intervention/comparator treatment. At the clarification stage (A7), the company provided a description of what treatments were, and were not, permitted. However, this concentrated on the medications not permitted, medications that addressed intervention side effects, and medications that should be avoided if possible. The company did not provide a summary of the BSC people in each arm receive in the submission and it was not available in the De-Fi trial publication.

3.2.6. Statistical analysis and definition of study groups

3.2.6.1. Study groups

The study groups of interest in relation to the results in this report were the intention-to-treat (ITT) population and the safety population.

The ITT population was all participants who were enrolled and randomised to receive treatment in the study (nirogacestat or placebo). Participants were analysed according to the treatment they were randomised to and the strata (intra-abdominal/extra-abdominal) to which they were assigned. This included participants who were randomised but did not subsequently go on to receive study treatment.

The safety population was all participants randomly assigned to study treatment and who took at least 1 dose of study treatment. However, participants were analysed according to the treatment they actually received.

3.2.6.2. Statistical analysis

The company presented details of the statistical analysis in De-Fi in Table 2.7 in Section 2.4 of the CS. The stated null hypothesis for testing the primary efficacy outcome was that the PFS for nirogacestat and placebo was equal.

The primary and secondary efficacy endpoints were tested in a hierarchical stepdown procedure in the following order: PFS, ORR, pain, disease symptoms, disease impact, and HRQoL evaluations of GHS/QoL, physical functioning, and role functioning, by PRO. If the null hypothesis was rejected at the 1-sided significance level of 0.025 the testing could proceed to the next endpoint, but if the null hypothesis was not rejected, all subsequent results were considered descriptive only.

Progression-free survival

A 1-sided stratified log-rank test was performed to compare the distributions between nirogacestat and placebo at alpha level of 0.025. Kaplan-Meier methods were used to summarise PFS data. A Cox proportional hazards model was used to estimate HR and the 2-sided 95% CIs controlling for the stratification factor to which the participant was assigned at randomisation (target tumour(s) location – intra-abdominal vs. extra-abdominal). At the clarification stage (A9), the company presented a log-log plot, Schoenfeld residual plot, and Schoenfeld residual test. The plots and Schoenfeld residual test did not indicate a violation of the proportional hazards assumption.

3.2.6.3. Data management, participant withdrawals

The company presented details of the data management and how participant withdrawals were managed in De-Fi in Table 2.7 in Section 2.4 of the CS.

Missing data

The company stated that, “in general, there were no substitutions made to accommodate missing data points”.

They did go on to say that in case of missing patient reported outcome (PRO) items, the scale and total scores were calculated as indicated in the scoring manual for the PRO instrument for the existing instruments.

- For GODDESS, all items for a given total or domain score should be present in order to create the total or domain score.
- Weekly scores (GODDESS and BPI-SF) were calculated only if there were 4 or more days of assessments with non-missing data within the respective week.
- Missing PRO data was assumed to be missing at random in general and was analysed using the Mixed Model for Repeated Measures (MMRM) analysis when appropriate. To address the possibility that missing data was not missing at random, sensitivity analysis with pattern mixture model was planned.

Discontinuations

- Participants who were withdrawn or discontinued from the study were not replaced.
- In situations where study participants were discontinued early from the study by investigators for clinical progression but could not be verified as qualified events, they were considered as dropouts and were censored for the primary analysis. Similarly, participants who did not progress or die were censored at the date of the last valid CT/MRI assessment.

3.2.7. Outcomes

The outcomes reported in De-Fi were:

- Progression-free survival (PFS)
- Objective response rate (ORR)
 - Complete response (CR)
 - Partial response (PR)
- Duration of objective response
- Disease Control Rate (DCR)
- Patient reported outcomes
 - BPI-SF API score
 - Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
 - Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
 - EORTC QLQ-C30 GHS/QoL
 - EORTC QLQ-C30 Physical Functioning
 - EORTC QLQ-C30 Role Functioning

- PROMIS questionnaire
- Safety

Progression-free survival

Time from randomisation until the date of assessment of progression or death by any cause. Progression was determined radiographically using RECIST v1.1 criteria or clinically as assessed by the investigator and qualified via blinded independent central review. Clinical progression was defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g. radiotherapy, surgery, or systemic therapy including chemotherapy or TKIs) for DT.

The analysis was performed on the ITT Population, defined as all participants who were randomized to study treatment. PFS was summarised with Kaplan-Meier methodology (Table 8). A total of 51 events was estimated to provide 90% power and a 1-sided type 1 error rate of 0.025 (1-sided hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat arm was 20 months and 8 months in the placebo arm (corresponding to a HR of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, the company calculated that 118 participants would be needed to be randomised in a 1:1 ratio to observe the estimated number of events.

Table 8: Primary PFS Censoring Methodology (reproduced from Table 5, De-Fi protocol)

Situation	Date of Censoring of Event	Outcome
No adequate disease status assessment Date of randomization Censored	Date of randomization	Censored
No documented progression or death	Date of last adequate disease status	Censored
Progression that has been verified by the central imaging review using RECIST v1.1 with ≤ 1 missing consecutive scheduled disease status assessment before progression	Date of the earliest assessment that results in a finding of progression	Event
Early discontinuation by study investigator due to clinical progression that has been verified as qualified event by the independent Event Adjudication Committee (EAC) for primary analysis	Earliest date of onset or worsening of symptoms resulting in a global deterioration of health status as documented by the date of clinical progression in the case report form	Event
Early discontinuation by study investigator due to clinical progression that does not meet the definition of a qualified event per protocol as judged by the EAC.	Date of last adequate disease status assessment	Censored
Death before progression being documented with ≤ 1 missing scheduled disease status assessment before death	Date of death	Event
New anticancer therapy or procedure started prior to documented radiographic or clinical progression	Date of last adequate disease status assessment before the new therapy	Censored

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors.

Objective response rate

Objective response rate, defined as the proportion of participants with complete response (CR) or partial response (PR) assessed via central reader using RECIST v1.1 criteria. A complete response (CR) according to RECIST 1.1 is the disappearance of all "target" lesions. A partial response (PR) by the RECIST version 1.1 criteria is defined as at least a 30% decrease in the sum of the diameters of all target lesions compared to the baseline measurement.

Duration of objective response

Duration of Objective Response (DoOR) was defined as the duration in months from the time measurement criteria were met for CR or PR (whichever came first) until the date of progression or death (whichever came first).

Best overall response

The company presented best overall response (BOR) which was the number of people whose best response during the trial was either complete response, partial response, stable disease, progressive disease, or not evaluable.

Disease Control Rate

Disease Control Rate (DCR) was calculated as the number of people with who experience CR or PR or stable disease (SD) at some point during the trial.

Patient reported outcomes

The patient reported outcomes (PROs) detailed in the CS were:

- Mean change from baseline at Cycle 10 in Brief Pain Inventory-Short Form (BPI-SF) Average Pain Intensity (API) score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- Mean change from baseline at Cycle 10 in EORTC QLQC30 Physical Functioning
- Mean change from baseline at Cycle 10 in EORTC QLQC30 Role Functioning

Change from baseline during the double-blind phase in PRO scores was analysed using a Restricted Maximum Likelihood (REML) based repeated measures approach (MMRM) in a primary analysis. They did not impute data but handled missing data under the assumption of Missing At Random (MAR). This can be unrealistic as missingness often relates to unmeasured factors (e.g., worsening symptoms, adverse events), which violates MAR.

The company stated in Section 2.4 of the CS that sensitivity analysis was conducted using a Pattern Mixture Model (PMM). PMM does not assume MAR; instead, it acknowledges that missingness may relate to unobserved outcomes. By varying assumptions about how missing

patterns relate to outcomes (e.g., assuming worse outcomes for early dropouts), PMM can explore Missing Not At Random (MNAR) scenarios and can make assumptions explicit rather than hidden in the MAR assumption. However, the EAG could not find any sensitivity analysis of the PROs reported in the CS, or in the De-Fi CSR.

3.2.8. Safety

Safety analyses were conducted using the Safety Population. The Safety Population consisted of all participants randomly assigned to study treatment and took at least 1 dose of study treatment. Participants were analysed according to the treatment they actually received.

Study Drug Exposure and Compliance

Exposure was summarised using multiple measures detailed in Section 4.4.1 of the De-Fi protocol. It included duration of exposure, actual dose intensity, and relative dose intensity.

Adverse events

All adverse events (AEs) were coded using the [MedDRA coding system](#) version 24.0 or later. Analyses of AEs was performed for those events that were considered treatment-emergent adverse events (TEAEs), where treatment-emergent was defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. AE severity was classified according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.²²

3.2.9. Critical appraisal of the design of De-Fi

The company presented a critical appraisal of De-Fi in Section 1.3 of Appendix B using the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs detailed in the NICE STA methods document.²³ The company considered De-Fi to be at low risk of bias for six of the seven items on the checklist but noted an imbalance in the dropouts between treatment arms. The company did not present an overall measure of the quality of the trial as they would if they had used the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).²⁴ The EAG undertook an assessment of PFS in De-Fi using the RoB 2 tool to offer a fuller assessment than that presented in the CS. The EAG was not able to complete RoB 2 assessments for the other trial outcomes within the timescale of the appraisal. In sum, the EAG had some concerns over the risk of bias related to the differences between the treatment arms in baseline characteristics, concerns about inadequate disease assessment primarily in the

nirogacestat arm, and the different way PFS was measured in the De-Fi trial in comparison to the RCT of sorafenib.¹² Overall, the EAG did not consider this to be a high risk of bias but the Committee should be made aware that the direction of bias favoured nirogacestat in each case.

Table 9: RoB 2 assessment of PFS in the De-Fi trial

Domain	Judgment	Rationale
1. Randomization process	Some concerns Favours intervention arm	Allocation was concealed and appeared to be adequately randomised using interactive response technology. However, there were differences in baseline characteristics between the treatment arms (Section 3.2.2.2). A key difference being a higher proportion of participants in the placebo arm (76.4%) were refractory to treatment compared to 61.4% in the nirogacestat arm.
2. Deviations from intended interventions	Low risk	During the double-blind phase, neither the participants nor any clinical site personnel knew whether the patient was receiving nirogacestat or placebo. RDI was above 85% in both arms. Restricted concomitant medications were used by similar proportions in each treatment arm (6%/7%).
3. Missing outcome data	Some concerns Favours intervention arm	The company presented reasons for censoring in Table 12 of the CSR. ²¹ Four people in the nirogacestat arm and one person in the placebo arm were censored due to no adequate disease status assessment and one person in the nirogacestat arm due to early discontinuation by study investigator and not adjudicated as qualified event. If all these people had progressed but were not reported as such then this would favour the nirogacestat arm.
4. Measurement of the outcome	Some concerns Favours intervention arm	The method of measuring PFS combined imaging-based progression according to RECIST, version 1.1 with investigator-determined clinical progression. This was different to the 2018 RCT of sorafenib ¹² that judged PFS imaging-based progression according to RECIST, version 1.1. Both trials were overseen by Dr M Gounder as principle investigator. This difference in definition favoured nirogacestat (Table 10).
5. Selection of the reported result	Low risk	Outcome reported as described in the protocol
Overall Risk of Bias	Some concerns Favours intervention arm	The EAG had some concerns over the risk of bias related to the differences between the treatment arms in baseline characteristics, concerns about inadequate disease assessment primarily in the nirogacestat arm, and the different way PFS was measured in the De-Fi trial in comparison to the RCT of sorafenib. ¹²

Abbreviations: CS, Company submission; CSR, clinical study report; EAG, External Assessment Group; PFS, progression-free survival; RCT, randomised controlled trial; RDI, relative dose intensity; RECIST, Response Evaluation Criteria in Solid Tumors.

3.3. Critique of the results of the trials of the technology of interest

The results of De-Fi are presented in the following sections.

3.3.1. Progression-free survival

The overall median follow-up was [REDACTED] months (range [REDACTED]) months in the nirogacestat arm and [REDACTED] (range [REDACTED]) months in the placebo arm. Nirogacestat was associated with a statistically significantly improved PFS compared with placebo (HR: 0.29; 95% CI: 0.15, 0.55; $p < 0.001$). The probability of being event-free after two years was [REDACTED]% (95% CI: [REDACTED]) in the nirogacestat arm, and [REDACTED]% (95% CI: [REDACTED]) in the placebo arm.

At the clarification stage (A10), the company presented Table 10, below. This table details censoring for PFS and the number of progression events determined radiographically using RECIST v1.1 criteria or clinically as assessed by the investigator and qualified via blinded independent central review. The EAG noted that [REDACTED] in the nirogacetstat arm compared to [REDACTED] in the placebo arm were censored due to no adequate disease status assessment. This inadequate assessment may have favoured nirogacetstat. Also, six people in the placebo arm had clinical progression compared to one person in the nirogacetstat arm. The EAG considered it notable that both the censoring in the trial and the addition of a clinical assessment for progression appeared to favour the nirogacestat arm. However, the EAG agreed that, with or without the benefit of censoring and clinical progression, nirogacestat offered a clinically important benefit over placebo for PFS. This outcome was mainly based on progression as only one person died prior to progression.

Table 10: Events and censoring for progression-free survival

	Nirogacestat (N = 70)	Placebo (N = 72)
Number of participants with event, n (%)	12 (17)	37 (51)
Type of event		
Progression	12 (17)	36 (50)
Radiographic progression	11 (16)	30 (42)
Qualified clinical progression	1 (1)	6 (8)
Death before progression	0	1 (1)
Number of participants censored, n (%)	58 (83)	35 (49)
Reason for censoring		
████████████████████	██	██
████████████████████	██	██
████████████████████	██	██
████████████████████		
████████████████████	██	██

3.3.2. Hyperintensity

The EAG's experts noted the benefit of MRI T2 weighted images when assessing a tumour (Section 2.1.2). Desmoid tumours with $\geq 90\%$ hyperintensity are more likely to progress and $< 90\%$ are unlikely to progress. The hyperintensity in De-Fi was reported by Alcindor et al. (2023)²⁵ in a poster at the American Society of Clinical Oncology (ASCO) 2023 Annual Meeting.

At baseline, similar proportions of participants in each arm had a T2 hyperintensity ratio $\geq 90\%$ (95% vs 97%). The proportion of people who had $< 90\%$ at any time during the double-blind treatment period (~ 20 months) was 34% in the nirogacestat arm and 15% in the placebo arm. This result reiterates the benefit of nirogacestat over placebo in terms of progression.

3.3.3. Other efficacy outcomes

The company reported secondary efficacy items in Table S2 in the De-Fi appendix and this has been reproduced in Table 11. De-Fi found nirogacestat to have a statistically significant benefit over placebo in objective response rate. This was primarily PR but five participants in the nirogacestat arm did have a complete response compared to zero participants in the placebo

arm. Median time to response was notably faster in the nirogacestat arm (5.6 months) compared to the placebo arm (11.1 months) but the Kaplan-Meier median duration of response could not be estimated for either treatment arm due to the small number of progression events after response. Response was maintained in 28 of 29 participants (97%) who had had a response in the nirogacestat arm and 5 of 6 participants (83%) who had had a response in the placebo arm. Best overall response (BOR) was substantially better for the nirogacestat arm than the placebo arm with 29 people (42.0%) of people having either a CR or PR, compared to 6 people (8.3%) in the placebo arm. There was a minor discrepancy in the table with 70 participants in the nirogacestat arm, but BOR was only presented for 69 participants. It was not clear why one person was not included given the definition of the ITT population (3.2.6.1). The company also presented the disease control rate (DCN) which is the number of people achieving CR, PR, or SD at some point during the trial. The DCN was only slightly better for nirogacestat than placebo, and while it does not account for the differences in the level of control (CR/PR/SD), it is an indicator that BSC can offer control over a person's DT.

Table 11: Confirmed tumour response (adapted from Table S2 in the De-Fi supplementary appendix²⁶)

	Nirogacestat (n=70)	Placebo (n=72)
Objective response rate, n (%) [95% CI]	29 (41) [29.8, 53.8]	6 (8) [3.1, 17.3]
P value	<0.001	
Time to response, months, median (range)	5.6 (2.6, 19.4)	11.1 (2.8, 16.4)
Kaplan-Meier estimate of duration of response, months, median (95% CI) ^a	NE (NE, NE)	NE (8.3, NE)
Best overall response, n (%)		
Complete response	5 (7.2)	0
Partial response	24 (34.8)	6 (8.3)
Stable disease	35 (50.7)	55 (76.4)
Progressive disease	1 (1.4)	10 (13.9)
Not evaluable	4 (5.8)	1 (1.4)
Disease control rate, n (%)	64 (92.8)	61 (84.7)

Abbreviation: CR, complete response; NE, not estimable; PR, partial response.

^aDuration of objective response was defined as duration in months from the time CR or PR (whichever came first) was met until the date of progression or death.

3.3.4. Patient reported outcomes

The results of PROs in De-Fi were reported in Section 2.6.5 of the CS.

3.3.4.1. Brief Pain Inventory

The Brief Pain Inventory (Short Form; BPI-SF) is a self-administered questionnaire used to assess the severity of a person's pain and how it interferes with daily life. It includes questions about pain intensity (at its worst, least, average, and current) and how it affects activities like general activity, mood, sleep, and enjoyment of life. The score uses an 11-point numeric scale (0 = no pain, 10 = worst imaginable pain).

The least squares (LS) mean difference in worst pain intensity score at Cycle 10 (10 months) was -1.34 (standard error [SE] 0.40) $p < 0.001$. The company stated that the [REDACTED], however the EAG were unable to confirm this.

The company did not report a minimally important difference (MID) for BPI-SF and it was unclear to the EAG whether a mean reduction of -1.34 offered a meaningful benefit. The EAG sourced a paper which utilised both anchor-based, and distribution-based, methods to determine an MID of two points for BPI-SF worst pain rating.²⁷ Using two points as the MID for BPI-SF worst pain rating, then nirogacestat did not demonstrate a clinically meaningful benefit over placebo for pain. However, the EAG were concerned that this apparent lack of benefit over placebo could have been due to a substantial proportion of participants in De-Fi not having uncontrolled pain at baseline. The baseline disease characteristics reported in Table 2.5 in the CS reported 58 (40.8%) of participants had uncontrolled pain, defined as a BPI-SF worst pain intensity score of more than 4. Therefore, 84 (59.2%) participants were in less pain than this with some potentially in no pain, or very little pain. With this uncertainty in mind, the EAG cannot conclude that De-Fi found nirogacestat offered a clinically important benefit in pain over placebo, but the EAG would encourage the company to present subgroup analysis in people who are in pain at baseline.

At the clarification stage (A13), the EAG requested pain scores by response level by timepoint for both arms in De-Fi. The tables presented by the company is the clarification response displayed a weak correlation of response status and pain. At a number of timepoints participants with partial response were in more pain than participants with stable disease. This reflected the EAG's expert advice that pain reduction depends on multiple factors and a reduction of pain can be experienced without the tumour shrinking, and even in people with a tumour that is growing slowly, because treatment reduces inflammation/oedema in the tumour (Section 2.1.1).

The company only reported an analysis of the worst pain intensity score in the CS (Section 2.6.5.1) and it was unclear to the EAG whether different conclusions could be drawn from the least pain, average pain, or current pain, had they been reported.

3.3.4.2. GODDESS DTSS and DTIS

The GODDESS tool, which comprises the Desmoid Tumor Symptom Scale (DTSS) and Desmoid Tumor Impact Scale (DTIS), measures signs and symptoms of DT and their impact on peoples' lives. Scores in the DTSS total symptom score range from 0 to 10, with higher scores indicating more severe symptom burden; scores in the DTIS physical functioning domain score are measured on a 5-point Likert scale, ranging from 1 to 5 with higher scores indicating worse function. The company presented research that for DTSS the between-group MID was 1.0 and the between-group MID for DTIS was 0.5.²⁸ The EAG agreed that these MIDs were appropriately estimated.

The De-Fi trial found nirogacestat offered a [REDACTED] placebo for [REDACTED] the DTSS total symptom score [REDACTED] and the DTIS physical functioning domain score [REDACTED] at [REDACTED]. Therefore, the De-Fi trial found nirogacestat [REDACTED] placebo in symptoms (pain, fatigue, stiffness/mobility issues, swelling or pressure, other localised symptoms) and physical functioning. It was unclear whether this represented a clinically important difference between the treatment arms.

The EAG understood that DTSS and DTIS overlap conceptually but complemented each other in the GODDESS framework:

- DTSS: What symptoms do you have and how bad are they?
- DTIS: How do those symptoms affect your daily life and well-being?

The company only presented one of three domains of DTIS and a fuller picture would have been given if they had presented the sleep (trouble falling asleep, getting comfortable in bed, staying asleep) and emotional impact (fear of future diagnostic tests or tumour recurrence/growth, hopelessness, anger, anxiety, frustration) domains, in addition to physical functioning.

Overall, the EAG concluded that these results indicated nirogacestat with BSC likely offers a well-rounded benefit over BSC alone across multiple DT domains. However, the company

would have made a stronger case if they had also presented the sleep and emotional impact DTIS domains.

3.3.5. Health-related quality of life

3.3.5.1. EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) is a 30-item, cancer-specific, PRO measure designed to assess health-related quality of life (HRQoL) in people with cancer across different tumour types and treatment settings. The EORTC QLQ-C30 is widely validated across many cancer types and stages, but it has not been specifically validated in people with desmoid tumours.

Scores range from 0 to 100, with higher scores on functional scales and Global Health Status/quality of life (GHS/QoL) representing better functioning or QoL and high scores on a symptom scale representing greater symptomology. The company quoted an MID of at least 5 to 10 from an analysis of women with breast cancer conducted in 1998.²⁹

The EAG understood that the EORTC QLQ-C30 produces 15 scores:

- 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning)
- 1 global QoL scale
- 3 symptom scales (fatigue, pain, nausea and vomiting)
- 6 single-item symptom measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties)

The company reported three of these scores in the submission: physical functioning, role functioning, and GHS/QoL. The EAG agree these were relevant scales and that pain was appropriately measured through BPI-SF.

The De-Fi trial found nirogacestat offered a statistically significant benefit over placebo for physical functioning (██████████), role functioning (██████████), and for GHS/QoL (██████████). This was a clinically important benefit if judged using the MID or “at least 5 to 10”. The EAG considered the EORTC QLQ-C30 results reported in De-Fi suggested people treated with BSC with nirogacestat had improved physical functioning, role functioning, and quality of life. However, the EAG noted that the GHS/QoL was scored

based on two questions, where a person rates 1 (very poor) to 7 (excellent): “How would you rate your overall health during the past week?” and “How would you rate your overall quality of life during the past week?” This was simplistic in comparison to the EQ-5D, NICE’s preferred quality of life measure.

3.3.5.2. PROMIS PF10a

The company reported Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) as an exploratory outcome in Section 2.6.6.1 of the CS. PROMIS PF was a tool to measure health outcomes across physical, mental, and social domains and physical function (PF) refers to a person’s self-reported capability (not actual performance) to carry out physical activities in daily life. The company stated that participants treated with nirogacestat reached the average PROMIS PF Short Form 10a (PROMIS PF10a) score observed in the general US population by Cycle 4, while the placebo group did not. However, no change scores or measures of variability were presented.

3.3.6. Long term outcomes

The randomized treatment period of De-Fi was up to 2 years for the primary analysis, with participants continuing treatment beyond that in an open-label extension. Data were available on people who were randomised to nirogacestat and continued treatment for up to four years.³⁰ Of the 70 participants randomised to nirogacestat, 39 continued in the open-label extension (OLE). Overall, 33 and 15 people received nirogacestat for at least 3 and 4 years, respectively.

3.3.6.1. Tumour Response

No additional events (progression or death) occurred with additional exposure after year 2. This lead to a consistent probability of being event free of 78.8% (65.6% to 87.4%) at the end of years 2, 3, and 4. The details on the response after three and four years of treatment were presented in the data supplement and have been reproduced in Table 12. The number of people with CR increased by three over years 3 and 4 while the number with PR and PD stayed the same. It does demonstrate they people can experience an improved response after treatment with nirogacestat for more than two years. However, the natural history of a desmoid tumour is to rapidly progress in the initial period but then to regress spontaneously or remain stable after two to three years, so potentially this would have occurred whether or not the participants were on nirogacestat. There was no control arm for the treatment period after two years so there was no counterfactual with which to test this.

Table 12: Long term response

Nirogacestat (N=70)				
	Up to 1 year	Up to 2 years	Up to 3 years	Up to 4 years
Best overall response^a				
CR	3 (4.3)	5 (7.1)	7 (10.0)	8 (11.4)
PR	21 (30.0)	24 (34.3)	24 (34.3)	24 (34.3)
SD	39 (55.7)	34 (48.6)	32 (45.7)	31 (44.3)
PD	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Not evaluable	5 (7.1)	5 (7.1)	5 (7.1)	5 (7.1)
Missing	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
ORR^b				
n (%)	24 (34.3)	29 (41.4)	31 (44.3)	32 (45.7)
95% CI ^c	23.3 to 46.6	29.8 to 53.8	32.4 to 56.7	33.7 to 58.1
Time to response				
Median (range), months	5.6 (2.6 to 9.3)	5.6 (2.6 to 19.4)	5.7 (2.6 to 24.4)	5.9 (2.6 to 33.1)

Abbreviations: CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

^a Best overall response was defined as the best response obtained across all assessments per independent central review up to the landmark year. PR and CR required confirmation by subsequent scans.

^b ORR was defined as the proportion of patients having a best overall response of CR or PR by RECIST v1.1.

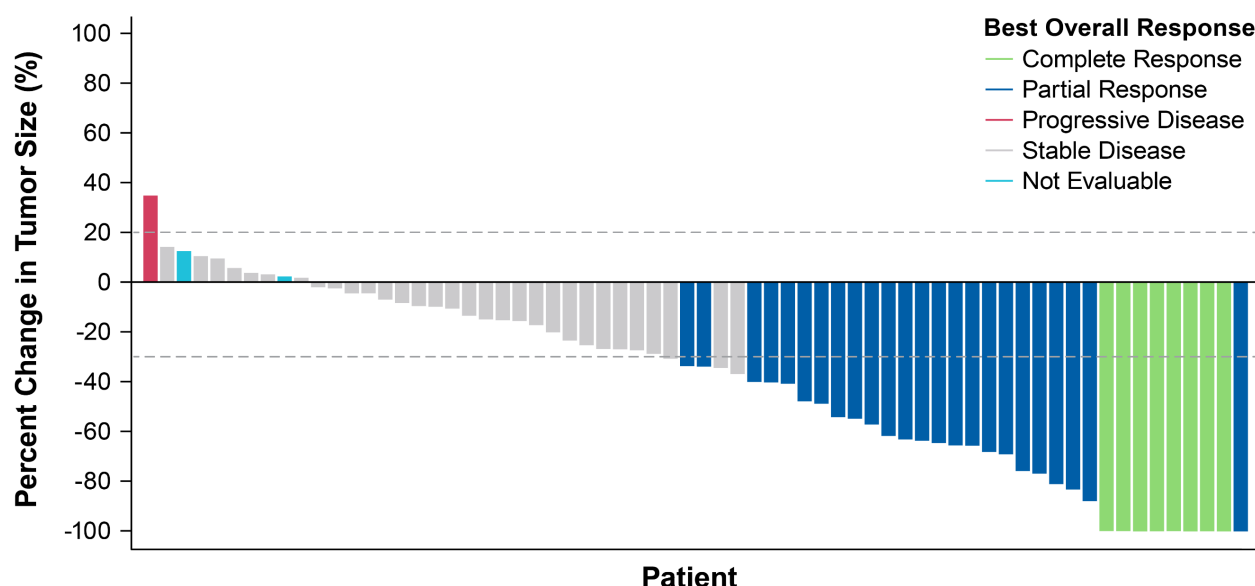
^c Obtained using exact method (Clopper-Pearson) based on binomial distribution.

3.3.6.2. Tumour size

The EAG was aware that a high proportion of participants best response was SD, and SD included people whose tumours shrunk, but not by enough to be called a PR (<30%), and grew, but not by enough to be called PD (<20%). It was therefore possible that a participant's tumour could grow by 15% at each assessment and still be categorised as having stable disease.

Alternatively, a participant's tumour could shrink by 25% at each assessment and they could be categorised as having stable disease. The investigators presented Figure 1, detailing the confirmed best overall response in percent change in tumour size, in people on nirogacestat with up to four years treatment in the paper reporting efficacy and safety of long-term treatment.³⁰ This showed that most of the people on nirogacestat, whose best response was SD, experienced tumour regression for at least one assessment. The EAG's clinical experts advised that, in their experience, once a tumour stops growing and begins to shrink it is unlikely to rapidly progress again. Once they have ceased rapidly progressing, they are much more likely to regress whether on or off systemic therapy. Therefore, most of the participants on nirogacestat whose best response was SD were unlikely to rapidly progress again. Also, the positive long-term efficacy of nirogacestat can be seen in the PROs reported in the following section where the early positive effect was sustained for at least four years.

Figure 1: Best^a percent change from baseline in target tumour size by confirmed best overall response^b with up to 4 years of nirogacestat treatment (n=66^c)



Abbreviations: CR, complete response; DB, double-blind; OLE, open-label extension; PR, partial response.

^a Best was defined as the lowest value of percent change and was calculated as the sum of lesions read by the central reviewer who continued to read during the OLE phase unless the assessments were adjudicated. In adjudicated cases, the adjudicated sum record was used in the DB phase. In the OLE phase, the sum of lesions was used based on central assessment. In cases where the OLE phase assessment was read by a different reviewer than the adjudicated DB phase assessment, the OLE phase percent change was recalculated using the DB phase baseline value. If there was no adjudication and no OLE data, then the averaged lesions in the DB phase were used.

^b Best overall response was defined as the best response obtained across all assessments per independent central review. PR and CR required confirmation by subsequent scans.

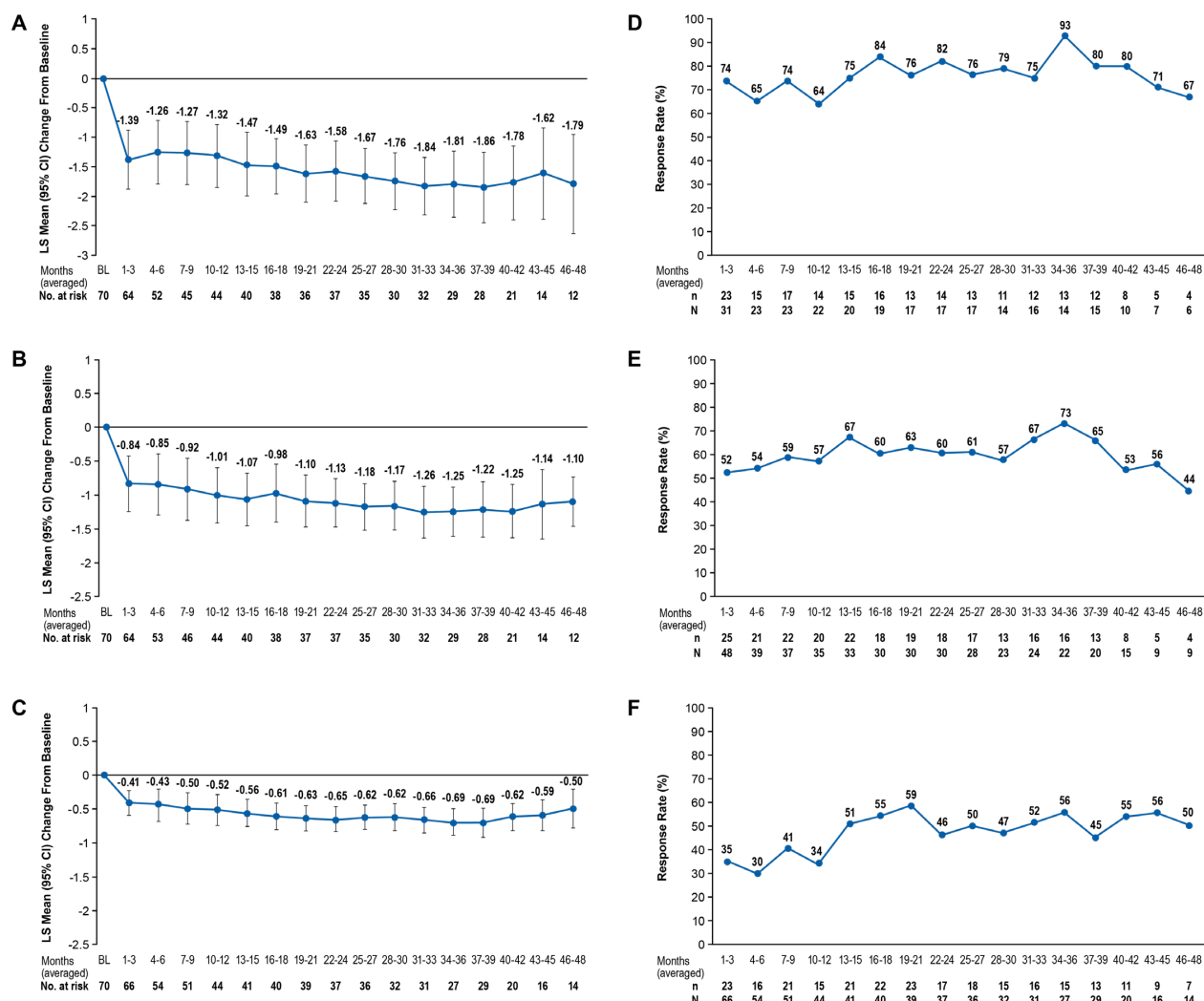
^c 1 patient had no tumour size assessments and 3 patients had missing postbaseline tumour size measurements.

3.3.6.3. Patient-Reported Outcomes

The investigators presented the patient-reported outcomes after as long as four years treatment with nirogacestat, reproduced in Figure 2. There was an initial benefit in BPI-SF average worst pain intensity score (A), DTSS total symptom score (B), and DTIS physical functioning domain score (C) after three months and this benefit was largely maintained until 48 months. The company also presented dichotomised BPI-SF (D), DTSS (E) and DTIS (F). The initial BPI-SF benefit was maintained for four years, there were potentially a small increasing benefit in DTSS, and DTIS continued to improve for 20 months and then plateaued. The overall message from these results was that the benefits of nirogacestat were maintained when treatment was continued until at least four years. It would have been useful to understand whether the benefits were maintained after treatment with nirogacestat was discontinued.

Figure 2: Long term patient-reported outcomes

- Change from baseline in BPI-SF average worst pain intensity score;
- Change from baseline in GODDESS DTSS total symptom score;
- Change from baseline in GODDESS DTIS physical functioning domain score;
- Response rate in BPI-SF average worst pain intensity score with MCT of ≤ -2.0 ;
- Response rate in GODDESS DTSS total symptom score with MCT ≤ -1.4 ;
- Response rate in GODDESS DTIS physical functioning domain score with MCT ≤ -0.8 .



Panels A-C show LS mean change from baseline over time in PRO. In panels D-F, N is the total number of patients with non-missing data at each 3-month interval, and n is the number of patients with a response in each interval. PRO data were averaged in 3-month intervals including DB and OLE data combined. For patients with DB phase last dose and OLE phase first dose gap >5 days, the gap was adjusted. The vertical bars indicate 95% CIs. LS Mean and 95% CIs were derived from a mixed model with repeat measures. Scheduled visits with less than 10 patients and unscheduled visits were not included in the model.

3.3.7. Subsequent treatments

The company stated in Section 2.7 of the CS that no subsequent treatments were used in De-Fi. The EAG requested clarification on this (Q11b) and the company responded saying that after a participant experienced a progression they attended an end of treatment (EOT) visit and were discontinued from the study. The company clarified that there was no further data collection when a participant discontinued from the study. The EAG understand it to be standard practice in trials to collect data related to subsequent treatments after they have discontinued from the trial treatment. It was concerning these data were not collected in De-Fi and it raised questions related to the overall quality of the trial.

3.3.8. Subgroup analyses

The company presented subgroup analyses in Appendix C of the CS. The subgroups of interest detailed in the Final Scope issued by NICE were people who have not had previous treatment and people whose DT is relapsed or refractory to treatment, subgroups based on tumour site such as people with intra-abdominal or extra-abdominal DT, and people with familial adenomatous polyposis (FAP). In line with the scope, the EAG intended to concentrate their analyses on those subgroups of interest.

3.3.8.1. Progression-free survival

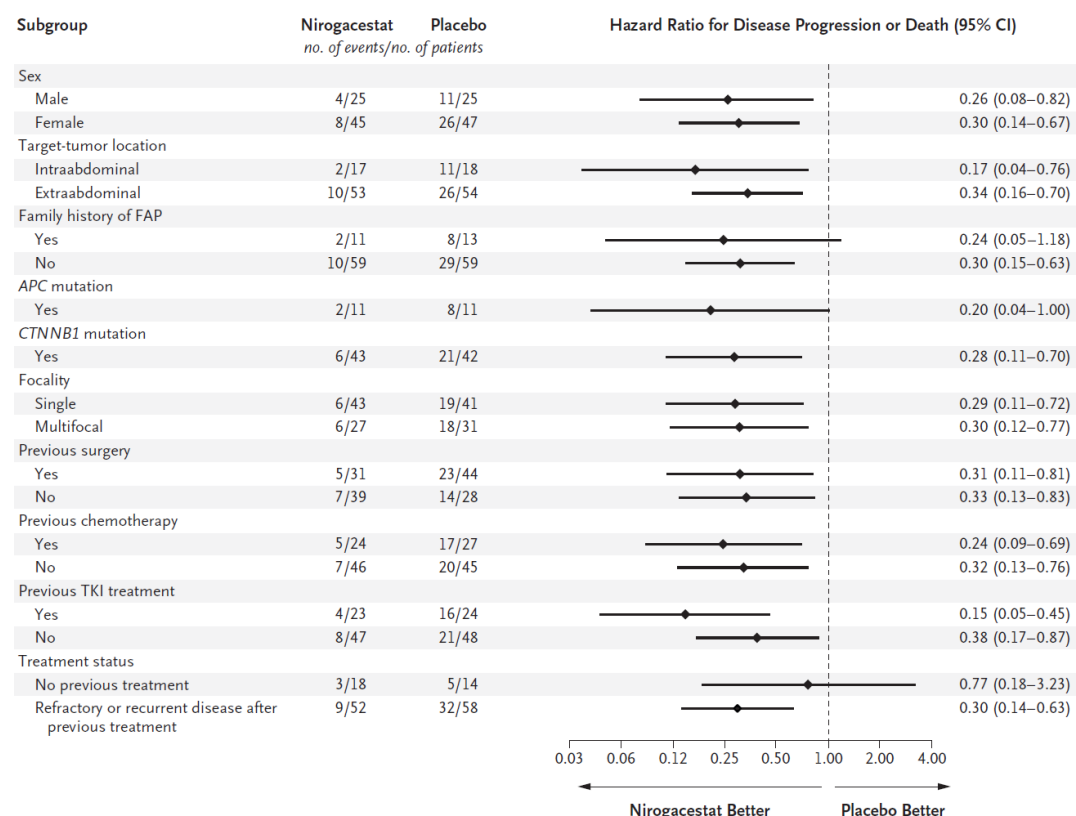
The company presented a forest plot of PFS in the pre-specified subgroups and this has been reproduced in Figure 3. The company presented subgroup analysis in participants with either intra-abdominal or extra-abdominal DT, and found a statistically significant benefit for nirogacestat over placebo in both. The effect estimate was slightly stronger in the intra-abdominal subgroup but only 35 participants (24.6%) had intra-abdominal DT.

The subgroup analysis of participants with or without a family history of FAP found a similar effect estimate for both arms. The estimate was not statistically significant in participants with a family history of FAP but the subgroup was small; 24 participants (16.9%).

The subgroup analysis of participants who have not had previous treatment versus participants whose DT is relapsed or refractory to treatment had quite different effect estimates. De-Fi found a statistically significant (HR: 0.30; 95% CI: 0.14, 0.63) benefit for nirogacestat over placebo in 110 (77.5%) participants whose DT was relapsed or refractory to treatment. The 32 (22.5%) participants who have not had previous treatment (HR: 0.77; 95% CI: 0.18, 3.23) appeared to have a moderate, but very uncertain, benefit versus placebo. However, there were only eight

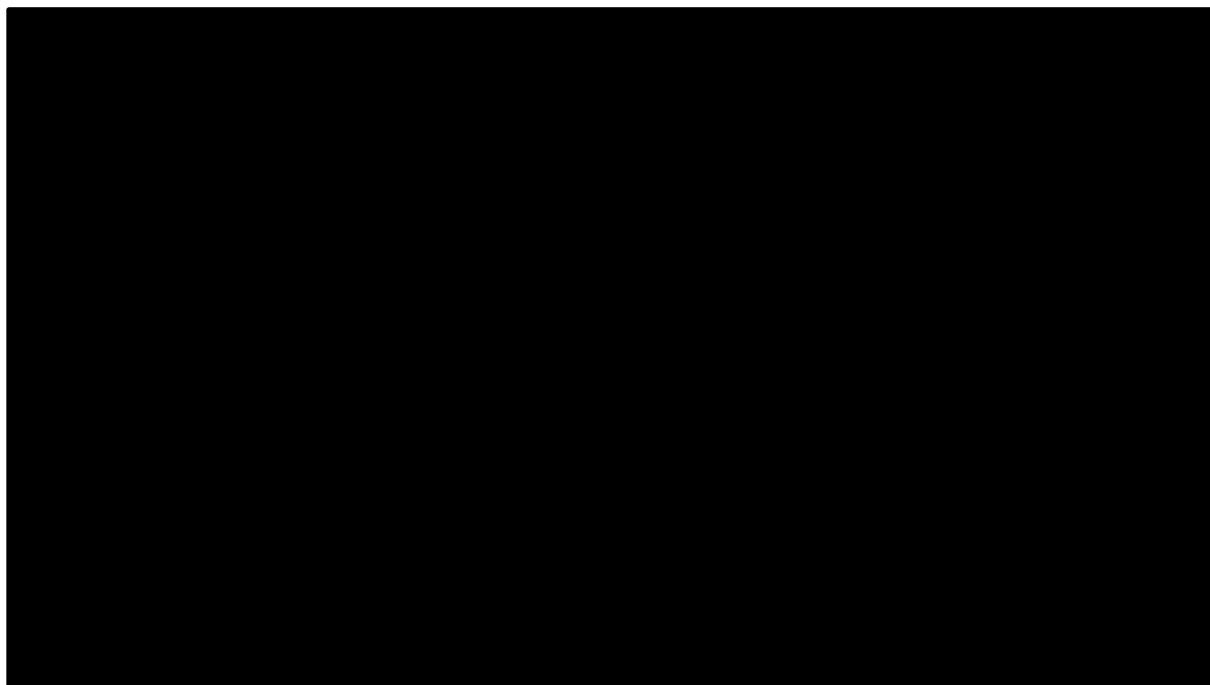
events in this subgroup analysis and this was too few from which to conclude a robust estimate of effect.

Figure 3: PFS in prespecified subgroups



3.3.8.2. Objective response rate

The company presented a forest plot of ORR in the pre-specified subgroups and this has been reproduced in Figure 4. The effect estimates were [REDACTED] for tumour location subgroups (intra-abdominal/extra-abdominal). The subgroup estimates for participants with or without a family history of FAP were [REDACTED]. However, they were based on only [REDACTED] events in the participants with a family history of FAP subgroup, and as such, were not considered robust estimates by the EAG. The subgroup analysis based on treatment status (recurrent/refractory/no previous treatment) were [REDACTED] but each quite uncertain and based on small numbers of events.

Figure 4: ORR in prespecified subgroups**3.3.8.3. Subgroup conclusion**

The EAG considered the trial too small to offer any convincing differences in the efficacy of nirogacestat in the subgroups of interest detailed in the Final Scope issued by NICE. Where there did appear to be differences between the subgroups it was too uncertain given the [REDACTED] or [REDACTED]. In sum, the EAG did not consider this to be good evidence of an absence of difference in efficacy between the subgroups, but an absence of evidence from which to draw any conclusions.

3.3.9. Extent of exposure

The company presented extent of exposure in Section 2.11.1 of the CS and detailed exposure in Table 2.11 (reproduced below in Table 13). Participants received nirogacestat for a median [REDACTED] months and placebo for a median [REDACTED] months. The mean (SD) relative dose intensity (RDI) was [REDACTED]% ([REDACTED]) for nirogacestat and [REDACTED]% ([REDACTED]) for placebo. An RDI of $\geq$ [REDACTED]% has been considered the optimal target maintaining efficacy.^{31,32} Dose modifications occurred in the majority ([REDACTED]%) of participants in the nirogacestat arm and [REDACTED]% in the placebo arm.

Table 13: Study treatment exposure, De-Fi trial (safety population, double-blind phase)
(adapted from Table 2.11 in the CS and Table 16 in the De-Fi CSR)

	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Duration of study drug exposure (months) ^a			
Mean (SD)			
Median			
Min, max			
Participants who received study treatment for at least:			
1 cycle, n (%)			
2 cycles, n (%)			
3 cycles, n (%)			
4 cycles, n (%)			
5 cycles, n (%)			
6 cycles to <13 cycles, n (%)			
13 cycles or longer, n (%)			
Actual dose intensity (mg/day) ^b			
Mean (SD)			
Median			
Min, max			
Relative dose intensity (%) ^c			
Mean (SD)			
Median			
Min, max			
Dose modifications			
Number of participants with a dose modification, n (%) ^d			
Adverse event			
COVID-19			
Other			

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

A cycle was 28 days.

3.3.10. Adverse events

Adverse events in De-Fi were reported in Section 2.11 of the CS.

3.3.10.1. Summary of adverse events

The EAG have summarised the treatment-emergent adverse events (TEAEs) in Table 14. The overall proportion of people experiencing an adverse event of any grade was very high in both treatment arms. Grade ≥ 3 TEAEs were experienced by a higher proportion of participants in the nirogacestat arm (██████████%) than the placebo arm (██████████%). TEAEs resulting in death were observed in █ (██%) participants in the nirogacestat arm and █ (██%) participant in the placebo arm, and TEAEs leading to treatment discontinuations were observed in █ (██%) participants in the nirogacestat arm and █ (██%) participants in the placebo arm.

Table 14: Summary of treatment-emergent adverse events, De-Fi trial (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Adverse events (any grade)	██████████	██████████	██████████
TEAEs	██████████	██████████	██████████
Maximum grade			
Grade 1	██████████	██████████	██████████
Grade 2	██████████	██████████	██████████
Grade 3	██████████	██████████	██████████
Grade 4	██████████	██████████	██████████
Grade 5	██████████	██████████	██████████
Grade ≥ 3 TEAEs	██████████	██████████	██████████
TEAEs leading to death	██████████	██████████	██████████
TEAEs leading to study treatment discontinuation	██████████	██████████	██████████

Abbreviations: TEAE, treatment-emergent adverse event.

3.3.10.2. Grade ≥ 3 treatment-emergent adverse events

Grade ≥ 3 TEAEs were experienced by █ (██%) participants in the nirogacestat arm and █ (██%) of participants in the placebo arm. The most commonly occurring Grade ≥ 3 TEAEs are reported in Table 15.

Table 15: Grade ≥3 TEAEs occurring in ≥4% of participants in either arm (safety population)

Category, n (%)	Nirogacestat (n=69)	Placebo (n=72)	Total (N=141)
Diarrhoea	11 (16)	1 (1)	12 (9)
Folliculitis	■	■	■
Rash maculopapular	■	■	■
Stomatitis	■	■	■
Sepsis	■	■	■

Abbreviations: TEAE, treatment-emergent adverse event.

3.3.10.3. Adverse events leading to dose reduction, dose interruption, and treatment discontinuation

Dose modifications, including dose interruptions and/or reductions, were experienced by ■■■■■ in the nirogacestat arm and ■■■■■ in the placebo arm. ■■■■■
■■■■■
■■■■■²¹

Discontinuation of the study treatment due to TEAEs occurred in ■■■■■ participants in the nirogacestat group and ■■■■■ participants in the placebo group.²¹ ■■■■■

■■■■■ The TEAEs that led to the discontinuation of study treatment by more than one participant in the nirogacestat arm were ■■■■■
■■■■■.

3.3.10.4. Adverse events of special interest

The company reported on specific adverse events in Section 2.11.5 of the CS.

Diarrhoea

The company noted that diarrhoea, the most prevalent adverse event, tended to occur soon after treatment was started (median nine days) and led to a dose reduction in 10% of participants and treatment discontinuation in 7% participants in the nirogacestat arm. No data were presented on the speed of resolution of Grade 3 diarrhoea.

Ovarian dysfunction

The CS stated that ovarian dysfunction (OD; amenorrhea, premature menopause, menopause, and ovarian failure) occurred in 75% (27/36) of women of reproductive potential who received nirogacestat and no participants (0/37) who received placebo. The median time to first onset of OD was 8.9 weeks (range 1 day-54 weeks), and the overall median duration was 18.9 weeks (range 11 days-215 weeks). OD was resolved in 79% of women of childbearing potential during treatment.

At the clarification stage (A6), the company detailed the mechanism by which nirogacestat may trigger OD, including premature menopause. In further response to question A6, the company stated that 30.6% (11/36) of women of reproductive potential who received nirogacestat experienced premature menopause but noted that no Grade 3+ adverse events related to OD were experienced.

The EAG's experts explained that chemotherapy could also cause ovarian dysfunction. Prior to treatment this risk would be explained to women of childbearing potential, and they would be offered ovarian preservation. They would expect the same process to be put in place for nirogacestat.

Non-melanoma skin cancers

Non-melanoma skin cancers were reported at a higher incidence in participants receiving nirogacestat than in those receiving placebo in the double-blind phase of the De-Fi study, including squamous cell carcinoma (3% vs. 0%) and basal cell carcinoma (1% vs. 0%), with one participant reporting both types of non-melanoma skin cancer. An additional 2 cases of non-melanoma skin cancer were reported outside of the double-blind phase of the De-Fi study.

At the clarification stage (A12), the EAG asked whether there is a mechanism by which nirogacestat is linked to non-melanoma skin cancer. The company noted that the Notch signalling may have a tumour suppressor role in non-melanoma skin cancers and provides mechanistic supports for how gamma-secretase inhibition might increase the incidence of non-melanoma skin cancers in humans. The company go on to say that data from the latest datacut (December 2024) [REDACTED]

[REDACTED]

[REDACTED]

The EAG's experts stated that non-melanoma skin cancer can be treated with cryotherapy or cream and as long as it's detected early, and is not a big ulcer, it is not a big concern. It can be detected early because physicians check for non-melanoma skin cancer at their check-ups and make the person aware of the increased risk and what to look out for.

Bone fracture

In the double-blind phase of the De-Fi study, bone fractures were reported in 6% of participants receiving nirogacestat compared with no participants receiving placebo. All reports of bone fracture were non-serious and Grade 1 or Grade 2. [REDACTED]. Bone fracture events did not lead to dose reduction or treatment discontinuation in any participants receiving nirogacestat.

3.4. Additional work on clinical effectiveness done by the EAG

3.4.1. Network meta-analysis

The EAG were aware of the importance of a comparison versus chemotherapy as that was the primary systemic treatment used in the NHS and the updated population in the appraisal was adults with progressing DT *who require systemic treatment*. Therefore, the EAG conducted pragmatic network meta-analyses to support the committee in understanding where nirogacestat sat in comparison to chemotherapy.

3.4.1.1. Methodology of the indirect comparisons

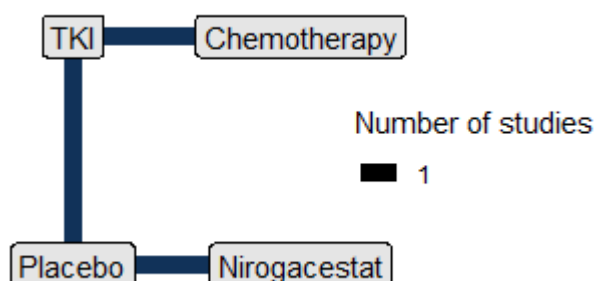
NMAs were conducted by the EAG to compare nirogacestat with chemotherapy via tyrosine kinase inhibitors (TKIs) using indirect comparisons. As noted in Section 3.1, the company did not present anything beyond a list of 104 papers for the SLR they conducted. Therefore, the evidence base was unclear and, given the short timescale, the EAG took a pragmatic approach to the NMA. The EAG took an NMA published in 2024 by Ou et al.¹ as a starter point for the relevant RCTs in people with DT. This NMA linked nirogacestat to chemotherapy using three RCTs and the EAG took advice from their clinical experts and undertook informal searches to ascertain there were no other relevant RCTs.

The NMA used three RCTs, De-Fi (nirogacestat versus placebo), Gounder et al. 2018 (sorafenib versus placebo), and DESMOPAZ (pazopanib versus methotrexate plus vinblastine). Methotrexate plus vinblastine was chemotherapy, at the time of writing, was not commonly used in the UK. As noted in Section 2.1.1, vinorelbine and low dose doxorubicin were more

commonly used in the UK but the EAG were not aware of any high quality evidence for those treatments in people with DT. Sorafenib and pazopanib were TKIs and were both effective in people with DT.¹⁵ The EAG's clinical experts noted that sorafenib was more commonly used in the NHS for DT but that both TKIs could be considered similarly effective. The network diagram of treatment comparisons for the three studies of interest is given in Figure 5.

While vinorelbine and vinblastine are both vinca alkaloids and share a mechanism, the addition of methotrexate to vinblastine offers a further mechanism not present in the monotherapy. The EAG were not aware of any studies comparing vinorelbine to methotrexate with vinblastine and they relied on their expert's experience and knowledge of the treatments. Both of the EAG's experts agreed that vinorelbine was safer than methotrexate with vinblastine. However, they differed on similarity of effect with one expert indicating very similar efficacy and another that vinorelbine was less effective. Despite differences in safety and uncertainty related to the similarity of effect, the EAG considered it reasonable to translate the results of methotrexate with vinblastine to vinorelbine given the limited evidence base. As previously noted, the company did not provide the data extracted from the SLR that might have offered a more appropriate route to a comparison of nirogacestat to chemotherapy.

Figure 5: Network diagram of treatment comparisons for the included studies



Abbreviations: TKI, Tyrosine Kinase Inhibitor

The outcomes of interest for this NMA were chosen to be ORR, PFS and Grade 3 or higher adverse events as these outcomes were considered to be of most relevance to a cost-effectiveness analysis of nirogacestat relative to its key comparators. Pain was also an important outcome and the EAG investigated performing an NMA using the three trials in the network. However, despite the Gounder 2018 trial reporting that the BPI-SF was collected, the results were not reported and a connected network could not be established.

The outcomes of ORR and Grade 3 or higher adverse events were compared between treatments using odds ratios (ORs), while PFS was compared between treatments using hazard ratios (HRs).

NMA models were fitted to trial-level reported data for these outcomes on the basis of the network graph in Figure 5 using the Bayesian approach to inference. For PFS, this was done under the assumption of proportional hazard functions for different treatment arms. A justification for making this assumption is given in Section 3.4.1.6. For the DESMOPAZ trial, an estimate of the HR for PFS was not reported and so this HR and its standard error were obtained by digitising the Kaplan-Meier curves of PFS that were presented in Toulmonde et al. 2019 and then fitting a Cox proportional hazards model.

For all analyses, the NMA models were fitted under the assumption of fixed treatment effects as fitting random effects models was not possible given the nature of the trial data being analysed. Non-informative prior distributions were used for the main treatment effects. Model fit and algorithm convergence were checked using standard methods.

3.4.1.2. Characteristics of trials identified and included in the indirect comparisons

Characteristics of the three trials included in the network meta-analysis are presented in Table 16. As expected, given the rarity of the condition, they were small trial. De-Fi and Gounder 2018 were double-blind phase 3 trials, and DESMOPAZ was an open-label phase 2 trial. The paper reporting DESMOPAZ stated that it is a non-comparative, randomised trial. The methotrexate–vinblastine arm was used to gather additional data, but the results were not intended to support formal comparative conclusions. This is typical in non-comparative phase II trials, which often aim to assess activity or feasibility rather than comparative effectiveness. However, as noted by the company in their clarification response (A14), there were limited relevant studies in the DT population, and it would not have been possible to form a network without including this trial.

Each of the trials recruited adults with progressing DT but the definition of progressing varied. De-Fi recruited people whose DT had progressed by at least 20% over a twelve month period leading up to the trial and Gounder 2018 recruited people whose DT had progressed by at least 10% over a six month period. The EAGs experts considered they were similar populations, with growing disease. However, Gounder 2018 might have recruited a few participants whose disease was not truly growing, given the shorter time and lesser degree of increase in size. DESMOPAZ recruited people with progressing DT through two imaging assessments by RECIST v1.1 (progressed by at least 20%) within six months. There were potentially a higher

proportion of participants in DESMOPAZ who had faster progression, and faster progression can indicate a more aggressive biology, which can lead to greater local tissue involvement and higher symptom burden. However, as noted in Section 3.4.1.3, this difference was not clear from the baseline characteristics reported.

Table 16: Key studies with clinical and technological evidence

Study name, design and location	Interventions and comparator	Participants and setting length of follow-up	Relevant outcomes for the NMA EAG comments
De-Fi ²⁶ NCT03785964 Double-blind, phase III, RCT 52 sites in Canada, the US, and Europe. Gounder 2023	Nirogacestat (n=70) versus placebo (n=72)	N=142 Adults with a progressing DT (≥20% as measured by RECIST v1.1 within 12 months) ECOG performance status 0–2. They could be treatment naïve, have recurrent DT, or be refractory to treatment.	• PFS • ORR • Grade ≥3 AEs
DESMOPAZ ¹⁷ NCT01876082 Non-comparative ^a , open-label, phase 2, randomised trial. 12 centres in France Toulmonde 2019	Pazopanib (n=48) versus methotrexate–vinblastine (n=24)	N=72 Adults with a progressing DT (two imaging assessments by RECIST v1.1 ^b within 6 months). ECOG performance status 0–1. Treatment naïve and previously treated people included.	• PFS • ORR • Grade ≥3 AEs
Gounder 2018 ¹² NCT02066181 Double-blind, phase III, RCT 150 centres in US and Canada	Sorafenib (n=50) versus placebo (n=37)	N=87 Adults with a progressing DT (≥10% as measured by RECIST v1.1 within 6 months) They could be treatment naïve, have recurrent DT, or be refractory to treatment. ECOG performance status 0–1.	• PFS • ORR • Grade ≥3 AEs

Abbreviations: AEs, adverse events; BSC, best supportive care; DT, desmoid tumours; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, progression-free survival; RCT, randomised controlled trial.

^a Treatment assignment was randomly allocated but each treatment arm was analysed independently without any formal statistical comparison between them.

^b Progressive disease under RECIST 1.1 criteria was defined by either a significant increase in the size of existing tumours or the appearance of new ones. The sum of the longest diameters of target lesions must show at least a 20% increase, with an absolute increase of at least 5 mm, compared to the smallest sum recorded previously (the nadir). Alternatively, progression is confirmed by the appearance of one or more new lesions.

3.4.1.3. Participants recruited to the included trials

The baseline and disease characteristics of participants recruited to the three trials in the NMA are presented in Table 17. The reporting of the characteristics was inconsistent and it was not possible to understand entirely how similar or different the participants were and whether participants in one trial were more difficult to treat than another. A paper published in 2021 assessing risk factors that “warrant consideration” when deciding the treatment strategy for a person with DT, and concluded that young people, extremity location, or large tumours were at increased risk of recurrence.³³ The participants in De-Fi were slightly younger than those in DESMOPAZ or Gounder 2018. A higher proportion of participants in De-Fi had extra-abdominal tumours i.e. extremities (arms, legs), chest wall, shoulder girdle, and head and neck region. The target tumours were larger at baseline in De-Fi than those in Gounder 2018, the size was not reported in DESMOPAZ. While the differences between trials were small, each of the differences indicated participants in De-Fi were harder to treat. However, it was unclear from the research whether these were prognostic factors or treatment effect modifiers and the De-Fi trial was too small to offer meaningful subgroup analysis (Section 3.3.8.3) to inform this.

Table 17: Baseline and disease characteristics of participants in the included trials

	De-Fi		DESMOPAZ		Gounder 2018	
	Nirogacestat (n=70)	Placebo (n=72)	Pazopanib (n=48)	Methotrexate and vinblastine (n=24)	Sorafenib (N = 50)	Placebo (N = 37)
Age (year), median (range)	33.5 (18, 73)	34.5 (18, 76)	35 (18, 78)	42 (21, 79)	37 (18, 72)	37 (21, 67)
Female, n (%)	45 (64.2)	47 (65.3)	31 (64.6)	15 (62.5)	34 (68.0)	26 (70.2)
Non-Hispanic or Latino, n (%)	67 (95.7)	55 (76.4)	NR	NR	NR	NR
CTN NB1 Somatic mutation, n (%)	43 (61)	42 (58)	32 (67)	16 (67)	NR	NR
Time since diagnosis to randomisation (months), mean (SD)	59.3 (72.9)	61.7 (77.0)	NR	NR	NR	NR
Desmoid tumour treatment status, n (%)						
Treatment naive	18 (25.7)	14 (19.4)	NR	NR	26 (52.0)	19 (51.4)
Refractory	43 (61.4)	55 (76.4)	NR	NR	NR	NR
Recurrent	9 (12.9)	3 (4)	NR	NR	22 (44.0) ^a	18 (48.6) ^a
Lines of therapy, n (%)						
0	NR	NR	11 (22.9)	6 (25.0)	NR	NR
1	NR	NR	17 (35.4)	13 (54.2)	NR	NR
2	NR	NR	13 (27.1)	1 (4.2)	NR	NR
3	NR	NR	7 (14.6)	4 (16.7)	NR	NR
Median no. of lines of previous therapy (range)	2 (0, 14)	2 (0, 19)	NR	NR	NR	NR
Number of target tumours, median (min, max)	1.0 (1, 4)	1.0 (1, 5)	NR	NR	NR	NR
Target tumour location(s), n (%)						
Intrabdominal	17 (24.2)	18 (25)	13 (27.1)	13 (54.2)	14 (28.0)	16 (43.2)
Extraabdominal	53 (75.7)	54 (75)	35 (72.9)	11 (45.8)	32 (64.0)	18 (48.6)
Both abdominal and extraabdominal	NR	NR	NR	NR	4 (8.0)	3 (8.1)

	De-Fi		DESMOPAZ		Gounder 2018	
Mean (SD) baseline target tumour size per RECIST (mm)	111.2 (70.6)	121.2 (66.4)	NR	NR	76 (26, 265) ^b	84 (12, 193) ^b
ECOG performance-status score						
0	51 (72.9)	52 (72)	34 (70.8)	18 (75.0)	35 (70.0)	22 (59.5)
1	18 (25.7)	20 (28)	14 (29.2)	6 (25.0)	15 (30.0)	15 (40.5)
2	1 (1.4)	0	0	0	0	0
Uncontrolled pain, n (%)	27 (38.6) ^c	31 (43) ^c	NR	NR	9 (18.0) ^d	12 (32.4) ^d

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; mm, millimetres; NR, not reported; RECIST, Response Evaluation Criteria for Solid Tumours; SD, standard deviation.

^a People with both refractory and recurrent disease

^b Median sum of target lesions at randomization (range) — mm

^c Uncontrolled pain was defined as a Brief Pain Inventory–Short Form average worst pain intensity score of more than 4 (range 0-10 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.

^d BPI worst pain score of more than 6 at randomization — no. (%)

3.4.1.4. Treatments not permitted

The EAG noted differences in the efficacy in the placebo arms of De-Fi and Gounder 2018. The placebo arm in De-Fi trial performed much worse in terms of ORR (Table 19), and slightly worse in PFS (Table 21), than the placebo arm in Gounder 2018. The EAG considered this might be related to the BSC treatments they were eligible to receive. The company did not detail what treatments, outside of the study treatments, participants in De-Fi received. However, they did detail the treatments were not permitted and the EAG sourced the treatments not permitted in Gounder 2018 (Table 18). It was not clear to the EAG's experts that the difference in ORR and PFS between the two placebo arms could be explained by treatments not permitted.

Table 18: Treatments not permitted prior to discontinuation in the included trials

De-Fi	DESMOPAZ	Gounder 2018
• Other antineoplastic therapy, including cytotoxic agents, targeted agents, endocrine therapy, TKIs, or other antibodies • Chronic daily use of NSAIDs for treatment of DT • Potentially curative radiotherapy • Surgical resection of DT tumours • Strong/moderate CYP3A4 inhibitors and strong CYP3A4 inducers • CYP3A substrates with a narrow therapeutic index • CYP3A substrates with a narrow therapeutic index • Gastric acid reducing agents such as proton pump inhibitors • Gastric bypass, lap band, or other gastric procedures that would alter absorption • Antiarrhythmic medications that are known to prolong the QT/QTcF interval	Not reported	• Alternative therapies (e.g., hormonal blockade, cytotoxic chemotherapy, or other tyrosine kinase inhibitors) • Radiation therapy or surgery • Strong inhibitors of CYP3A4 • Therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g., clopidogrel)

Abbreviations: AEs, adverse events; BSC, best supportive care; DT, desmoid tumours; ECOG, Eastern Cooperative Oncology Group; NSAIDs, non-steroidal anti-inflammatory drugs; TKI, tyrosine kinase inhibitors.

3.4.1.5. Outcome definitions

Progression-free survival

For each trial, PFS was defined as the time from randomisation until the date of assessment of progression or death by any cause. All three trials used the RECIST v1.1 criteria to define progression but De-Fi used clinical progression in addition to RECIST v1.1 criteria. Clinical progression was defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g. radiotherapy, surgery, or systemic therapy including chemotherapy or TKIs) for DT. Seven progressions (one in the nirogacestat arm and six in the placebo arm) were “clinical” progression (Table 10).

Objective response rate

For each trial ORR was defined as the proportion of participants with CR + PR assessed using RECIST v1.1 criteria.

Grade 3 or higher adverse events

Adverse events were graded according to National Cancer Institute Common Terminology criteria for Adverse Events (NCI-CTCAE). De-Fi used version 5.0 while DESMOPAZ and Gounder 2018 used version 4.0. It was unclear to the EAG whether this difference influenced the AEs reported in the trials.

3.4.1.6. Investigation of the proportional hazards assumption

The proportionality of hazard functions for PFS between the arms of each of three trials included in the NMA was investigated in the standard way by using plots of non-parametric estimates and 95% confidence bands of the logarithm of the hazard ratio over time. These plots were supplemented by chi-squared tests of the correlation of the Schoenfeld residuals over time and log cumulative hazard plots (also known as log minus log survival plots) of each treatment. The individual patient survival data that was required for these analyses was obtained by digitising Kaplan-Meier curves for the relevant outcome that appeared with the published trial results using the R package IPDfromKM (<https://CRAN.R-project.org/package=IPDfromKM>).

The results of the analysis of the proportional hazards (PH) assumption for PFS are given in Appendix A. For the De-Fi trial and the Gounder et al. (2018) trial, the plots of the estimated

logarithm of the hazard ratio of PFS over time were consistent with the hazard ratio being a constant, since this hypothesis lay within the 95% confidence bands of the estimated log hazard ratio function. This graphical analysis was supported by the P values for the chi-squared tests of the correlation of the Schoenfeld residuals over time, which for both of these trials were substantially greater than 0.05. Also, for the De-Fi trial and the Gounder et al. (2018) trial, the plots of the log cumulative hazard functions were reasonably parallel between treatment groups, which suggested that the proportional hazards assumption was appropriate. In summary, none of the analyses that were conducted indicated that the PH assumption for PFS was invalid for these two trials.

By contrast, for the DESMOPAZ trial, the plots of the estimated logarithm of the hazard ratio for PFS over time suggested that the hazard ratio was approximately constant rather than strictly constant. However, the P values for the chi-squared test of the correlation of the Schoenfeld residuals over time was greater than 0.05 ($P=0.069$) and the plots of the log cumulative hazard functions did not provide strong evidence to suggest that the proportional hazards assumption was inappropriate. In summary, when all these analyses were considered together, there were grounds for concluding that the PH assumption for PFS was also adequate for the DESMOPAZ trial. Also, there were too few events to sensibly do an analysis assuming non PH.

3.4.1.7. Objective response rate

A summary of the trial data used in the NMA analysis of ORR is given in Table 19. The EAG noted the large difference in the efficacy of placebo between De-Fi and Gounder 2018. Twenty percent of people responded in Gounder 2018, while only 8.3% responded De-Fi. The reason for this difference was unclear to the EAG but differences in the inclusion criteria and BSC provided may have been factors. Whatever the reason for this was, it did benefit nirogacestat in the NMA for ORR.

The ORR results from the methotrexate with vinblastine arm was 26.3%. The EAG checked a retrospective review of people treated with vinorelbine from January 2004 to July 2019 where the ORR was 20.7%.¹⁸ Methotrexate with vinblastine being slightly more effective than vinorelbine was in line with the advice received from the EAG's experts.

Table 19: Objective response rate

Study	Intervention	Comparator	Median follow-up	No. of events (% of patients)	
				Intervention	Control
De-Fi	Nirogacestat	Placebo	15.9 months ^a	29 (41.4)	6 (8.3)
Gounder et al. (2018)	TKI (sorafenib)	Placebo	27.2 months	16 (32.7)	7 (20.0)
DESMOPAZ	TKI (pazopanib)	Chemo (meth+vinb)	23.4 months	17 (37.0)	5 (26.3)

Abbreviations: Chemo, chemotherapy; meth, methotrexate; NMA, network meta-analysis; ORR, objective response rate, TKI, tyrosine kinase inhibitors; vinb, vinblastine

^a The median follow-up for ORR was not presented in the CS. The EAG would not expect the follow-up for ORR to differ substantially from the follow-up for PFS and the value entered here was the median follow-up time for PFS in De-Fi.

The results of the NMA analysis of ORR are detailed in Table 20. The NMAs demonstrated that nirogacestat offers a statistically significant benefit over placebo (OR: 8.40; 95% CrI: 3.30, 23.9) and chemotherapy (OR: 7.28; 95% CrI: 1.14, 49.3), with a numerical benefit that was close to statistical significance over TKIs (OR: 4.19; 95% CrI: 0.99, 17.8). While there are many uncertainties related to the NMAs in terms of differences in the participants recruited to each trial, and the small size of each trial, the EAG had expert advice that the benefit was plausible given the mechanisms of action and expected effect of treatment. Chemotherapy was primarily expected to reduce pain rather than shrinking tumours and nirogacestat was designed to target relevant pathways active in DT than TKIs. The EAG's experts also stated that this result broadly tallied with their experience of using nirogacestat, chemotherapy, and TKIs. In sum, there is evidence to suggest that the ORR is higher for nirogacestat than for chemotherapy and less certain evidence to suggest that the ORR is higher for nirogacestat than for TKIs.

Table 20: Estimates of OR for the Objective Response Rate with 95% credible intervals

	Nirogacestat	TKIs	Chemotherapy	Placebo
Nirogacestat	-	4.19 (0.99, 17.8)	7.28 (1.14, 49.3)	8.40 (3.30, 23.9)
TKIs		-	1.74 (0.54, 6.15)	2.01 (0.72, 5.84)
Chemotherapy	0.14 (0.02, 0.88)	0.58 (0.16, 1.85)	-	1.15 (0.23, 5.59)
Placebo	0.12 (0.04, 0.30)	0.50 (0.17, 1.38)	0.87 (0.18, 4.40)	-

Statistical method: Fixed effect network meta-analysis.

Abbreviations: OR, Odds Ratio; ORR, Objective Response Rate; TKIs, Tyrosine Kinase Inhibitors.

Note: Odds ratios greater than one indicate higher odds of an objective response, i.e. a complete or partial response, for the row-forming treatment compared to the column-forming treatment

3.4.1.8. Progression-free survival

A summary of the trial data used in the NMA analysis of PFS is given in Table 21 with the Kaplan-Meier (KM) curves for PFS in each trial in Figure 6, Figure 7, and Figure 8. The median follow-up time for the De-Fi study (15.9 months) was notably shorter than for the other two studies (23.4 and 27.2 months) but, as visualised in the KM curves, there were few events after 15 months. The KM curve for TKI (pazopanib) in DESMOPAZ plateaued at around 67% and TKI (sorafenib) in Gounder 2018 plateaued at around 82%. The KM curve for placebo in De-Fi plateaued at around 42% and placebo in Gounder 2018 plateaued at around 26%. The difference between the proportion progressing was an indicator of dissimilarity between the participants recruited to each of the trials.

Table 21: Summary of the PFS trial data used in the NMA

Study	Intervention	Comparator	Median follow-up	No. of events (% of patients)	
				Intervention	Control
De-Fi	Nirogacestat	Placebo	15.9 months	12 (17.1)	37 (51.4)
Gounder et al. (2018)	TKI (sorafenib)	Placebo	27.2 months	7 (14.3)	22 (62.9)
DESMOPAZ	TKI (pazopanib)	Chemo (meth+vinb)	23.4 months	12 (26.1)	4 (20)

Abbreviations: Chemo, chemotherapy; meth, methotrexate; NMA, network meta-analysis; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; vinb, vinblastine.

Figure 6: Kaplan-Meier curve for progression-free survival in De-Fi

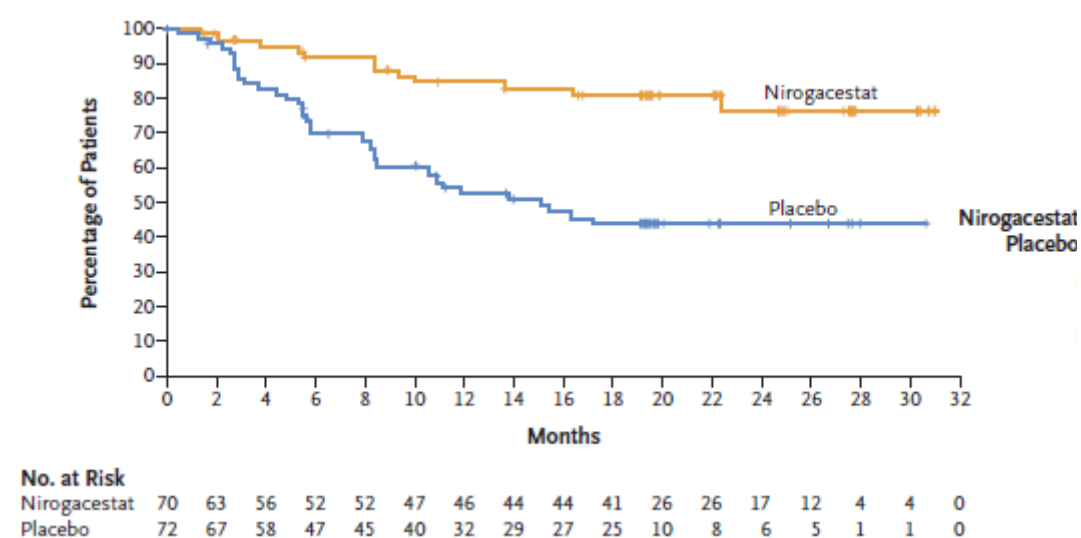
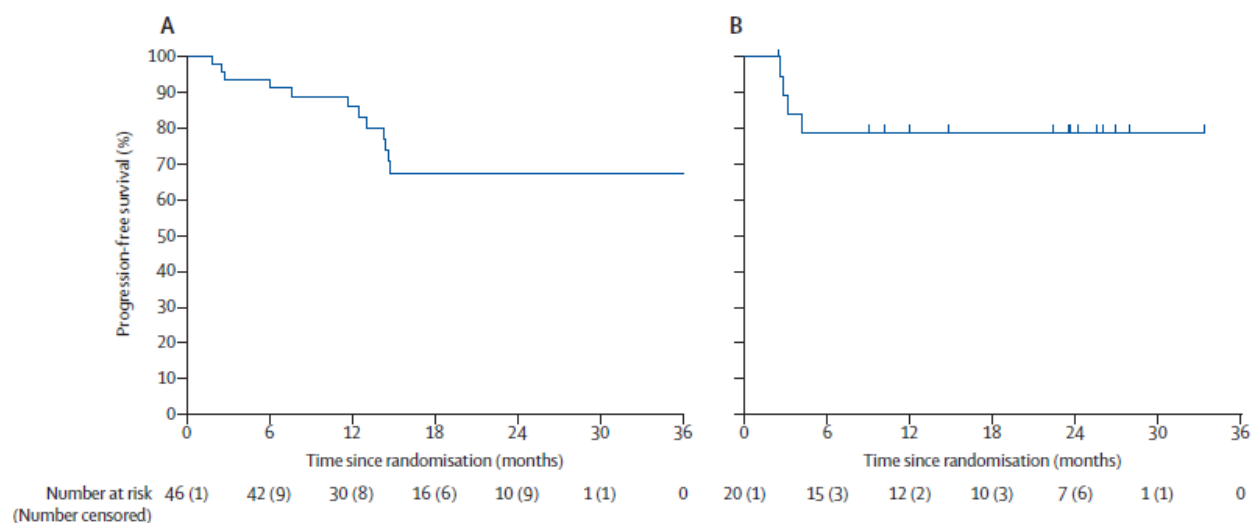
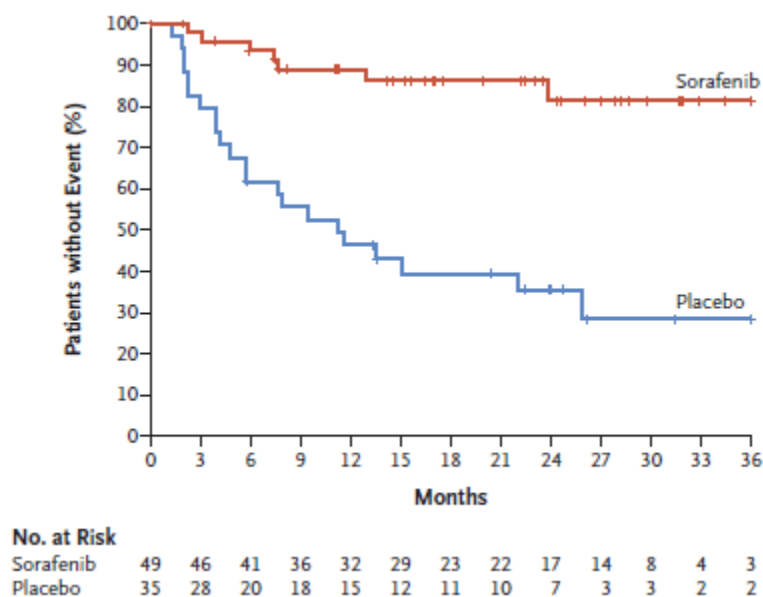


Figure 7: Kaplan-Meier curves for progression-free survival in DESMOPAZ



(A) Progression-free survival in the pazopanib group (n=46). (B) Progression-free survival in the methotrexate-vinblastine group (n=20).

Figure 8: Kaplan-Meier curve for progression-free survival in Gounder 2018



The results of the NMA analysis of PFS are detailed in Table 22. The NMA found that nirogacestat offers a statistically significant benefit over placebo (HR: 0.29; 95% CrI: 0.15, 0.55). However, it was numerically worse than chemotherapy (HR: 2.74; 95% CrI: 0.56, 13.5) and TKIs (HR: 2.23; 95% CrI: 0.72, 6.86). However, the EAG had concerns related to the PFS NMA. As

noted in the previous section, quite different proportions progressed in the placebo arm of De-Fi and the placebo arm of Gounder 2018, and quite different proportions progressed in the TKI arm of DESMOPAZ than the TKI arm of Gounder 2018. This was an indicator of dissimilarity of populations recruited. An EAG clinical expert noted a possible reason for this in relation to Gounder 2018 where participants were recruited who had 10% growth over a 6 month period. The 10% change was relatively small and a proportion of participants whose disease was not truly growing were potentially recruited (Section 3.4.1.2). Recruiting people without growing disease would confound the results because it did not matter to which arm they were assigned, their tumour was not going to progress whether they were, or were not, on systemic treatment. The EAG were also concerned that there were only four events in the chemotherapy arm of DESMOPAZ and one additional or one fewer events could have a large impact on the estimate of effect.

In addition, the results of the NMA did not tally with an EAG's experts experience of using chemotherapy. In his experience, the main benefit of chemotherapy was to reduce pain and while it can occasionally shrink the tumour that was not the primary benefit of treatment.

In sum, the EAG considered the NMA for PFS to be too uncertain from which to draw any conclusions comparing nirogacestat to chemotherapy. The comparison of nirogacestat to TKIs did not heavily rely on the non-comparative DESMOPAZ trial but still relied on the Gounder 2018 where a proportion of participants potentially did not have truly growing disease (Section 3.4.1.2). Given the limitations of Gounder 2018, the EAG considered interpreted the NMA as very uncertain evidence of similarity of effect for PFS between nirogacestat and TKIs.

Table 22: Estimates of HR for PFS with 95% credible intervals

	Nirogacestat	TKIs	Chemotherapy	Placebo
Nirogacestat	-	2.23 (0.72, 6.86)	2.74 (0.56, 13.5)	0.29 (0.15, 0.55)
TKIs	0.45 (0.15, 1.38)	-	1.23 (0.39, 3.87)	0.13 (0.05, 0.32)
Chemotherapy	0.37 (0.07, 1.80)	0.81 (0.26, 2.58)	-	0.11 (0.02, 0.46)
Placebo	3.35 (1.80, 6.64)	7.68 (3.08, 19.1)	9.46 (2.19, 40.7)	-

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Abbreviations: HR, Hazard Ratio; TKIs, Tyrosine Kinase Inhibitors; PFS, Progression-Free Survival.

Note: The comparison is the row-forming treatment against the column-forming treatment.

3.4.1.9. Grade 3 or higher adverse event results

A summary of the trial data used in the NMA analysis of grade 3 or higher adverse events (grade ≥ 3 AEs) is given in Table 23. Similar proportions (46.9% to 56.3%) of participants in the intervention arms of each of the trials, and placebo arms (16.7% and 25.0%), had a Grade 3 or higher adverse event. However, 77.3% of the participants in the comparator arm in DESMOPAZ (methotrexate and vinblastine) had at least one Grade 3 or higher adverse event. Given the number of participants in the chemotherapy arm, it was not clear to the EAG whether this was a true reflection of the toxicity of methotrexate and vinblastine. Also, the EAG understood the chemotherapy commonly used in the NHS was vinorelbine and their experts stated that vinorelbine has less adverse events than TKIs and methotrexate and vinblastine.

The EAG checked a retrospective review¹⁸ of people treated with vinorelbine from January 2004 to July 2019 where no Grade ≥ 3 side effects or any serious complications due to treatment were recorded. One patient (4.2%) had a dose reduction that was to ensure tolerability due to Grade 2 nausea and Grade 2 abdominal pain. Side effects were mostly gastrointestinal and self-limiting. Methotrexate with vinblastine being more toxic than vinorelbine was in line with the advice received from the EAG's experts.

Table 23: Summary of the trial data for Grade ≥ 3 AEs used in the NMA

Study	Intervention	Comparator	Median follow-up	No. of events (% of patients)	
				Intervention	Control
De-Fi	Nirogacestat	Placebo	NR	38 (55.1)	12 (16.7)
Gounder et al. (2018)	TKI (sorafenib)	Placebo	NR	23 (46.9)	9 (25.0)
DESMOPAZ	TKI (pazopanib)	Chemo (meth+vinb)	23.4 months	27 (56.3)	17 (77.3)

Abbreviations: Chemo, chemotherapy; grade ≥ 3 AEs, grade 3 or higher adverse events; meth, methotrexate; NMA, network meta-analysis; TKI, tyrosine kinase inhibitors; vinb, vinblastine

The results of the NMA analysis of Grade ≥ 3 AEs are detailed in Table 24. It can be seen that the estimate of the OR of Grade ≥ 3 AEs favours nirogacestat having higher rates of such adverse events than TKIs (OR: 2.31; 95% CrI: 0.66, 8.02) but lower rates of such adverse events than chemotherapy (OR: 0.81; 95% CrI: 0.14, 4.39). However, the differences in the OR of Grade ≥ 3 AEs between nirogacestat and TKIs and between nirogacestat and chemotherapy were not statistically significant. In summary, there is weak evidence to suggest that the rate of

Grade ≥ 3 AEs is higher for nirogacestat than for TKIs and is weak evidence to suggest that the rate of Grade ≥ 3 AEs is lower for nirogacestat than for chemotherapy. However, as noted, the primary chemotherapy used in the NHS was single agent vinorelbine and in the EAG's experts experiences it leads to fewer adverse events than sorafenib (TKI) or the combination chemotherapy used in the NMA.

Table 24: Estimates of OR for grade 3 or higher adverse events with 95% credible intervals

	Nirogacestat	TKIs	Chemotherapy	Placebo
Nirogacestat	-	2.31 (0.66, 8.02)	0.81 (0.14, 4.39)	6.34 (2.95, 14.4)
TKIs	0.43 (0.12, 1.51)	-	0.35 (0.10, 1.07)	2.75 (1.07, 7.35)
Chemotherapy	1.23 (0.23, 7.08)	2.84 (0.93, 9.81)	-	7.82 (1.81, 37.2)
Placebo	0.16 (0.07, 0.34)	0.36 (0.14, 0.93)	0.13 (0.03, 0.55)	-

Statistical method: Fixed effect network meta-analysis.

Abbreviations: OR, Odds Ratio; TKIs, Tyrosine Kinase Inhibitors

Note: The comparison is the row-forming treatment against the column-forming treatment.

3.5. Ongoing trials

The De-Fi was completed and the final data cutoff of the OLE was December 19, 2024, and was used for this appraisal.

3.6. Conclusions of the clinical effectiveness section

A DT is a rare, locally aggressive tumour that develops in the body's connective tissue and is also known as aggressive fibromatosis. The natural history of a desmoid tumour is to progress in the initial period but then to regress spontaneously or remain stable after two to three years. However, many people with DT experience disfigurement, nerve pain, decreased range of motion, and muscle pain. People who experience these symptoms, or have tumours that continue to rapidly grow, may be offered systemic treatment. At the time of the writing, the goal of systemic treatment was to control these symptoms and preserve function, not to "cure" the tumour at all costs as the body would often achieve stable disease and complete resolution with or without treatment.

The systemic treatments used in the NHS were off-label chemotherapy (vinorelbine or doxorubicin) via routine commissioning, given at first and later lines, and TKIs (sorafenib) via compassionate use, at later lines. Nirogacestat could sit alongside chemotherapy as an

alternative systemic therapy for people with progressing DT at any line of treatment. Therefore, the relevant comparators for an appraisal of nirogacestat were best supportive care, and chemotherapy, as it was available for routine commissioning and was used in all lines of treatment (Section 2.3.1).

De-Fi, the company's trial of nirogacestat versus placebo (BSC alone), found nirogacestat offered a clinically important benefit over placebo in PFS (Section 3.3.1) and ORR (Section 3.3.3). PROs collected in De-Fi indicated nirogacestat offered benefits in excess of placebo in reducing symptom severity, improving function, reducing pain, and increasing quality of life (Section 3.3.4). However, it was not clear if these were clinically important benefits, perhaps due to the small sample size or perhaps due to, for example, low pain at baseline. It can be hard to detect a benefit in a sample of people when the impact and severity of symptoms vary greatly from person to person. Also, reducing pain is not solely achieved by reducing the size of the tumour, it can also be achieved with a stable tumour (Section 2.1.1). This was reinforced when the company presented pain scores by response level by timepoint (Section 3.3.4.1).

De-Fi also demonstrated the toxicity of nirogacestat with Grade ≥ 3 TEAEs experienced by █ (█%) participants in the nirogacestat arm. █ (█%) participants had TEAEs that led to treatment discontinuation and █ (█%) participants had a dose modification.

The EAG's critical appraisal raised some concerns related to De-Fi. There were differences between the treatment arms in baseline characteristics, concerns about inadequate disease assessment primarily in the nirogacestat arm, and the different way PFS was measured (Section 3.2.9). The direction of bias favoured nirogacestat in each case.

De-Fi had an open label extension where people in the nirogacestat arm, who did not discontinue due to adverse events or progression, were on treatment for up to four years. There were people who improved to complete response after more than two years of treatment. However, it was unclear if this response was due to ongoing treatment with nirogacestat or whether it would have occurred without treatment as the DT followed its natural history (Section 3.3.6). The EAG's experts stated that it was appropriate to stop treatment when symptoms have been addressed, and the person has reached a "radiological plateau" (Section 2.1.3). Their expectation was that ~90% of people would stop nirogacestat treatment by two years. They also stated that the decision to stop treatment can be made earlier if it is possible to re-challenge if the person subsequently progressed.

The company chose not to compare nirogacestat to chemotherapy in the CS due to methodological and data-related limitations, including study design and data collection issues. However, they did not supply their feasibility assessment. The EAG did not consider it was appropriate to exclude the primary systemic treatment utilised in the NHS (Key Issue 1) and undertook the comparison without support from the company.

The EAG took a pragmatic approach to assessing the efficacy of nirogacestat versus chemotherapy and ran NMAs using three RCTs (Section 3.4.1.1). There were insufficient data reported to run an NMA for pain. The results of the NMAs indicated a benefit for nirogacestat over chemotherapy for ORR but no conclusion could be drawn for PFS due to differences between the trials with respect to that outcome. Nirogacestat appeared to be a little safer than chemotherapy in terms of Grade 3 or higher AEs. However, the EAG's experts did clarify that vinorelbine, the primary chemotherapy used in the NHS, was safer than methotrexate with vinblastine and this was reflected in available single arm data. The NMA found a benefit for nirogacestat over TKIs for ORR and a similar, but very uncertain, effect for PFS. The NMA also found nirogacestat led to more Grade 3 and higher adverse events, though the results were very uncertain.

The EAG noted a number of limitations of the NMA in Key Issue 2. These limitations primarily related to the very small size of the trials, one of which was a non-comparative phase 2 trial. The poor performance of the placebo arm in De-Fi benefited nirogacestat in the NMA and the chemotherapy drug evaluated in DESMOPAZ was not the chemotherapy used in the NHS i.e. not vinorelbine or doxorubicin. However, given the timespan of the appraisal and the evidence available, the EAG considered the NMA offered an important insight into the comparative efficacy and safety of nirogacestat in comparison to chemotherapy.

In sum, nirogacestat was developed based upon the specific intracellular and intercellular communication pathways in DT. The De-Fi trial found it to be more effective than placebo (BSC alone) in shrinking desmoid tumours, and to offer benefits in addressing the symptoms of DT, including pain. The NMA indicated that it was superior to chemotherapy for ORR, and similarly safe. No conclusions could be drawn on PFS.

4. COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation.

4.1. Critique of the review of cost-effectiveness evidence

The company conducted an SLR to identify economic evaluations, costs and healthcare resource use (HCRU) of any treatment for people with DT. Given the rareness of DT, the company also performed a second SLR on soft tissue sarcoma (STS), based on its similarity to DT, which they used to inform key parameters of the economic model and expand the evidence base. The company stated that STS was an appropriate analogue condition due to the similar presentation, diagnostic pathways and treatment approaches. Clinical experts advised the EAG that desmoid tumours are rarely as serious as STS and that patients with side effects as a result unsuccessful of hip or knee surgery would be a better analogue. The methods and results are presented in Appendix E of the company submission.

The company searched the same four databases as for the clinical search (Embase, MEDLINE, Cochrane CENTRAL and the Cochrane Database of Systematic Reviews), using the same style of a merged search strategy in the Ovid platform. The same five conferences were also searched manually, although only for DT terms. The initial DT search was performed in 2022 with updates in 2024 and May 2025. The STS search was first performed in 2024, with an update search in May 2025. The searches and search process were well described and considered appropriate, given the decision problem.

The SLR for people with DT identified eight studies, but data were not extracted regarding economic evaluation as no studies detailed an economic evaluation, however they did report cost data and HCRU. Of the 23 studies included in the STS SLR, six were identified as economic evaluations. The results of the SLR specifically for costs and HCRU are detailed in Appendix F of the company submission.

It should be noted that the inclusion criteria for the STS SLR and DT SLR are not identical. The timeframe in the DT SLR was November 2011 - May 2025 compared to January 2014 - May 2025 in the STS SLR and the STS SLR included QALYs as an outcome, whereas the DT SLR did not.

Of the six economic evaluations identified in the STS SLR, two were based in the UK, Amdahl et al (2014),³⁴ and Tikhonova et al (2018).² Only the utility estimates from the economic evaluation SLR were used in the company base case. Utility estimates from Amdahl 2014 were used in the company base case. The utility data source in Amdahl 2014 was Shingler et al (2013).³⁵

While the EAG considered it broadly appropriate that STS economic evaluation data is suitable to be used to inform the base case of the analysis given noted similarities in disease characteristics and clinical expert opinion, the EAG considered the utility data source in Tikhonova et al (2018), which was Reichardt et al. (2012)³, to be more appropriate. No justification for the exclusion of the Reichardt 2012 utility data was provided by the company nor any scenario analyses using the Reichardt 2012 utility data was performed in the company submission. Upon clarification the company provided a scenario analysis using Reichardt 2012.

Detailed discussion of the health-related quality of life estimates used by the EAG and company are presented in section 4.2.6

Table 25. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix E (Pages 1-21)	The described search strategies for the four databases and five conferences were considered appropriate and well reported. Publication type filters were fully referenced.
Inclusion criteria	Appendix E (Page 21)	Appropriate broad inclusion criteria applied
Screening	Appendix E (Page 21)	Double blind assessment at title, abstract and full text
Data extraction	Appendix E (Page 22)	Data extraction by a single reviewer and validated by a second reviewer
QA of included studies	Appendix E (Page 35)	The company used the Drummond and Jefferson checklist

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The company conducted an SLR to identify health related quality of life (HRQoL) data for people with DT. The methods and results are presented in Appendix F of the company submission. As

with the economic evaluation SLR, the company reported there was limited HRQoL data from published sources, so it used an analogue condition. In the HRQoL the company stated that chronic neuropathic pain (CNP) is an appropriate analogue condition for HRQoL for people with DT. Clinical experts advised the EAG that patients with side effects as a result unsuccessful of hip or knee surgery would be a better analogue. The described search strategies for the four databases and five conferences were considered appropriate and well reported. Publication type filters were fully referenced.

None of the included studies from the DT HRQoL SLR reported utility values for patients with DT, three of the included studies reported HRQoL data. 22 of the studies in the CNP SLR reported utility values developed using EQ-5D.

The EAG noted that this is a different analogue condition to the economic evaluation and HCRU SLRs, and the company did not use the outcomes of the HRQoL SLR in its base case analysis despite the company stating that CNP is significantly similar in regard to symptom burden and functional impairments. Of the six CNP HRQoL studies that were UK based, two studies, Eldabe et al (2020)³⁶ and Eldabe et al. (2023),³⁷ were based on the same clinical trial, TRIAL-STIM. EQ-5D was collected directly from patients at baseline, 3 months, 6 months and at 36 month follow up. The trial studied the impact of screening patients who were undergoing spinal cord stimulation implantation. The EAG considered patients undergoing chemotherapy for STS identified in Reichardt et al. (2012)³ as a more appropriate source of utility estimates given the patient experience of receiving pharmacological treatment for STS is likely to be more similar to a pharmacological intervention for DT than patients undertaking spinal cord stimulation in chronic neuropathic pain.

The EAG also noted the inclusion criteria for the DT HRQoL SLR and the CNP HRQoL SLR were different. The outcomes in the CNP HRQoL SLR contained EQ-5D and QALYs as an included outcome, whereas the DT HRQoL SLR outcomes were specific instruments (DTF-QOL and GODDESS) and “HSUVs”.

Table 26. Summary of EAG’s critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix F (Pages 1-20)	The described search strategies for the four databases and five conferences

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		were considered appropriate and well reported. Publication type filters were fully referenced.
Inclusion criteria	Appendix F (Pages 21-22)	Appropriate broad inclusion criteria applied
Screening	Appendix F (Page 21)	Double blind assessment at title, abstract and full text
Data extraction	Appendix F (Pages 22-23)	Data extraction by a single reviewer and validated by a second reviewer
QA of included studies	Appendix F (Page 23)	Company used the NICE quality assessment checklist for health state utility values for the assessment of risk of bias in utility studies.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The identification of evidence for resource use and costs used the same search and inclusion criteria as described above for cost-effectiveness studies (described by the company in Appendix E). Of the identified studies in DT, four costing studies were identified that reported data in DT, and four healthcare resource use studies were identified that reported data in DT. Of the four healthcare resource use studies in DT, one had UK patients, Schut et al. (2023).³⁸ Schut 2023 is based on the QUALIFIED clinical trial, analysing healthcare resource use in patients with DT. Schut 2023 was used to inform the number of GP visits and specialist visits per annum in the company economic model.

The STS SLR identified 23 studies that reported resource use and costs, with all studies being based in Europe including 11 studies with at least one UK site. Given Schut 2023³⁸ analysed only GP visits and specialist visits, a second source was used by the company from the STS healthcare resource use SLR. To estimate hospitalisations, lab tests and imaging, Verboom et al. (2019)³⁹ was used to inform the company economic model. The EAG considers this method appropriate as Verboom 2019 contained pre progression versus post progression healthcare resource use, however upon clinical expert validation the estimates were deemed to be lower than what would be considered UK clinical practice for DT patients. Further discussion regarding the company and EAG healthcare resource use assumptions are presented in section 4.2.7.

4.2. Critique of the submitted economic evaluation

The EAG critique focusses on the economic model submitted by the company at clarifications stage. One of the main issues was the way in which transition probabilities were calculated, particularly progression risks. There were also important issues with the health state utility values that the company used, so the EAG has used an alternative source.

4.2.1. NICE reference case checklist

Table 27: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Direct health effects for patients were included in the base case which is appropriate for this condition. A scenario was included in which carer disutilities were included.
Perspective on costs	NHS and Personal Social Services	In line with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company only compared to BSC (which would not require a fully incremental analysis) but chemotherapy was also a relevant comparator, so a fully incremental analysis was added by the EAG.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Time horizon runs to age 100, by which point there were [REDACTED] of patients alive in the nirogacestat arm in the EAG corrected company base case.
Synthesis of evidence on health effects	Based on systematic review	In line with reference case for the comparison for the comparison with BSC. Chemotherapy was not included as a comparator and the results of the companies systematic literature review were not presented, even though it was a relevant comparator.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The De-Fi trial did not collect EQ-5D data. The company explored mapping EORTC scores but determined these were not suitable for use. The EAG did not agree that it was appropriate withhold the results of

Attribute	Reference case	EAG comment on company's submission
		this analysis and the justification for this was not sufficient. Health state utility values were taken from published literature identified in the company economic evaluation SLR in STS. They were informed by Shingler 2013.³⁵ This was a time trade off (TTO) study that used vignettes for patients with soft tissue sarcoma. The use of vignette studies does not comply with the NICE Reference Case.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	No, vignettes were informed by 'information obtained from physicians, patients and the published literature'. Drafted vignettes were validated by patients.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Health states were evaluated by 100 members of the UK general public. The study states that these data were aligned with the census, but the method used to achieve this is not described and data are not presented to show that the sample is representative of the UK general population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the people having the health benefit, except in specific circumstances	In line with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

Abbreviations: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; SLR, systematic literature review; STS, soft tissue sarcoma; TA: technology appraisal

4.2.2. Model structure

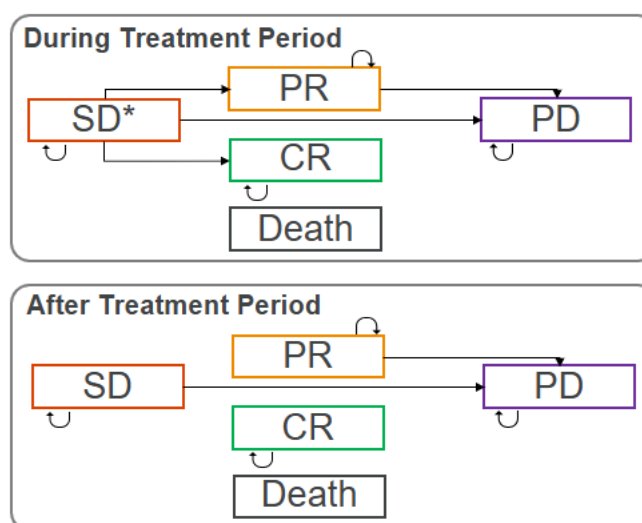
The company submission stated that the modelled time horizon was 62.8 years (which would imply a cut off at age 100). There are 28-day cycles, with half cycle correction applied in the base case. The company applied half cycle correction to drug costs which was not appropriate given the pack size is equal to the model cycle length. However, the EAG did not consider this to be an important area of uncertainty.

The company defined health states based on the RECIST classification system, with the following health states.

- Stable disease
- Partial response
- Complete response
- Progressed disease
- Death

Clinical experts interviewed by the EAG said that these health states were reflective of clinical practice. Progressed disease in the trial was defined as image-based progression (using RECIST) or clinical progression (onset or worsening of symptoms causing discontinuation of study treatment and initiation of subsequent treatment).

The company made a number of assumptions regarding the way in which patients could transition between the health states, which are discussed in Section 4.2.5. The company confirmed at clarification stage that they are recommending a 2-year stopping rule (Clarification Question B2a). The EAG believed this represented a key area of uncertainty, and this is discussed further in Section 4.2.5.2.

Figure 9 Model structure (taken from the company submission Figure 3.1)

Note: “during treatment period” and “after treatment period” correspond to the “on tx” and “off tx” health states in the model, respectively. The treatment period will be either up to 1 year or 2 years. Patients can transition to “death” from any health state. Progression to PD ‘after tx’ can be modified by treatment and it is assumed in the reference case that there is no progression from PR to PD for patients treated with nirogacestat. Responses were measured by CT or MRI and were evaluated by Central Imaging Review for all participants using RECIST v1.1.

*All patients start here.

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; tx, treatment; v, version.

Source: Gounder et al (2023)²⁶

4.2.3. Population

The target population was adult patients with progressing DT; this aligns with the De-Fi trial.²⁶ In places this was also described as ‘patients requiring systemic treatment’. The company cites evidence that this would represent 40% of DT patients.

4.2.4. Intervention

The intervention was nirogacestat, taken in the form of three 50mg pills ingested twice daily.

The company only included best supportive care as a comparator. The EAG considered whether tyrosine kinase inhibitors (TKIs) should have been included as a comparator. The EAG determined that these treatments are only currently available as part of compassionate use programmes, so are not considered a relevant comparator at this point in time.

The company stated that ‘Chemotherapy treatment is used more frequently than TKIs and is included in the current clinical practice guidelines (Kasper et al. 2024⁹) as an option for patients;

however, it is not considered the SoC and is associated with significant toxicity issues'. The EAG did not agree that this provided sufficient grounds to exclude chemotherapy as a comparator. The EAG also noted that the company modelled chemotherapy (in the form of doxorubicin) as a potential subsequent treatment, suggesting that the company acknowledged that these patients regularly received chemotherapy. Clinicians told the EAG that vinorelbine was the chemotherapy drug most commonly prescribed to these patients. They said that these patients primarily received three 90mg doses during 28 days of treatment, doxorubicin is also used but rarely.

The EAG included chemotherapy as a comparator. Chemotherapy was considered at the same point in the treatment pathway as nirogacestat. The effectiveness of chemotherapy was modelled as a class. The costs of chemotherapy were informed by the costs of vinorelbine as clinicians advised that this was the chemotherapy treatment used most in clinical practice for these patients. The effectiveness of chemotherapy was informed by evidence for methotrexate with vinblastine, as this was the only robust evidence available (more detail in Section 3.4.1). Some evidence suggests that vinorelbine has a more favourable safety profile than methotrexate.¹ No evidence was identified as to whether there is a difference in efficacy.

The company model assumed that 100% of patients who receive subsequent treatment receive doxorubicin. Clinicians advised that these patients would be more likely to receive vinorelbine. Costs were updated to reflect this, but no data were available on the impact this would have on other outcomes.

There were 51 out of 142 patients (36%) who had received chemotherapy at baseline in the De-Fi trial.²⁶ These patients will have received a mixture of different chemotherapy treatments, based on clinician input it is likely that a substantial portion of them received vinorelbine.

There was no clear evidence from the De-Fi trial to suggest that prior chemotherapy is an effect modifier for nirogacestat in the De-Fi trial (Appendix C of the company submission). Clinical experts suggested that patients who have previously failed systemic therapy are less likely to respond to other systemic therapies. There were no data available on the effectiveness of subsequent chemotherapy in a chemotherapy experienced population. So, whilst it was generally considered that chemotherapy was likely to be less effective in a chemotherapy experienced population, there were no data to demonstrate the extent of this effect. Likewise, patients also go on to experience chemotherapy after treatment with nirogacestat, but there

were no data on whether this subsequent treatment would be more or less effective in patients who had experienced one or more courses of chemotherapy, compared with patients who had experienced nirogacestat.

4.2.5. Treatment effectiveness and extrapolation

4.2.5.1. Source of evidence

The Phase 3 De-Fi trial was used to inform the efficacy of nirogacestat. The trial was summarised in Table 3.4 of the company submission. It included a randomised phase up to two years of treatment, then an open-label extension. Patients stayed in the open-label extension up to four years from the start of the trial.

The company stated in response to clarification question B10 that ‘the model included data from the double-blind and OLE phases for the nirogacestat treatment arm’. But it’s not clear how as the model only included patients receiving nirogacestat to Year 2 and this is not clearly labelled in the model file or described in the company submission or response to clarification questions.

The EAG conducted three network meta-analyses, these analysed progression-free survival, objective response rate and adverse events (Grade 3+). The network was used to inform the effectiveness and safety of chemotherapy within the model. Chemotherapy was informed by the Toulmonde et al. (2019) randomised open label study,¹⁷ which included pazopanib (a TKI) and methotrexate-vinblastine (a chemotherapy treatment). The De-Fi trial²⁶ and Gounder 2018¹² were also included in the network.

4.2.5.2. Stopping rule

The company assumed that patients received up to two years of treatment in the base case and up to one year of treatment in a scenario. This was justified as representing the median treatment time of 20.6 months observed in the nirogacestat arm of the De-Fi trial. This is not an appropriate assumption or justification. Patients continued to receive treatment for up to 4 years in the open-label extension.³⁰ At the clarification stage the company stated that they are recommending a 2-year stopping rule (Clarification Question B2a response). The company said that their clinical experts advised that most patients would likely cease treatment before 2 years, with the decision informed by ‘symptomatic improvements’. They stated that:

'It is expected that response to treatment would be assessed initially at 1 year, where the majority of patients would be expected to discontinue, then re-assessed every 2-3 months thereafter.' (Clarification Question B2a response)

A clinician told the EAG that they would be open to a 2-year stopping rule with some conditions. The conditions they proposed were that patients should be able to continue to treatment past 2 years if their tumour size is shrinking and has not plateaued, and that patients should be able to restart treatment after they stop at 2 years, if their tumour starts growing again or if they take a break from treatment due to toxicity issues.

The company presented some data at clarification stage on the proportion of patients whose tumour plateaued at the end of 2 years, to indicate what proportion of patients would stop treatment at 2 years (Clarification Question B2b). The company did not state how they defined tumour size plateauing, and the data were presented in the wrong format (the proportion of patients with tumours that plateaued that were in each health state, rather than the probability of patients' in each health states' tumour plateauing). In Figure 2.13 of the company submission, a reasonable proportion of patients continue to experience reductions in tumour size after year 2. One of the EAG's clinical experts suggested that based on the information provided by the company on patients' tumour sizes during the De-Fi trial, they would choose to keep approximately ■■■ patients on treatment after 2 years, and approximately ■■■ patients after 3 years. The other clinician said that they would expect to keep roughly 10% of patients on treatment to 2 years, 5% to 3 years and 3% to 5 years.

Both experts consulted by the EAG agreed that the decision to stop treatment can be made earlier (in line with the above estimates) when it is possible to restart treatment, if the person subsequently progresses.

The EAG therefore assumed a 3-year stopping rule in the base case, with 2 years, 4 years and 5 years tested in sensitivity analysis.

4.2.5.3. Premature discontinuation

In the base case, the company assumed that the only patients who discontinued treatment before 2 years, were those whose disease progressed. This is not a realistic assumption as in the trial, there were patients who discontinued treatment prematurely, for reasons other than progression. The reasons included adverse events, non-compliance, patient decision making or clinician decision making. The company provided Kaplan Meier curves for discontinuation at the

CQ response stage (Figure 10). Table 28 presents annual discontinuation for reasons other than discontinuation or study termination.

Figure 10: Kaplan-Meier curve of treatment discontinuation (CQ B8a)

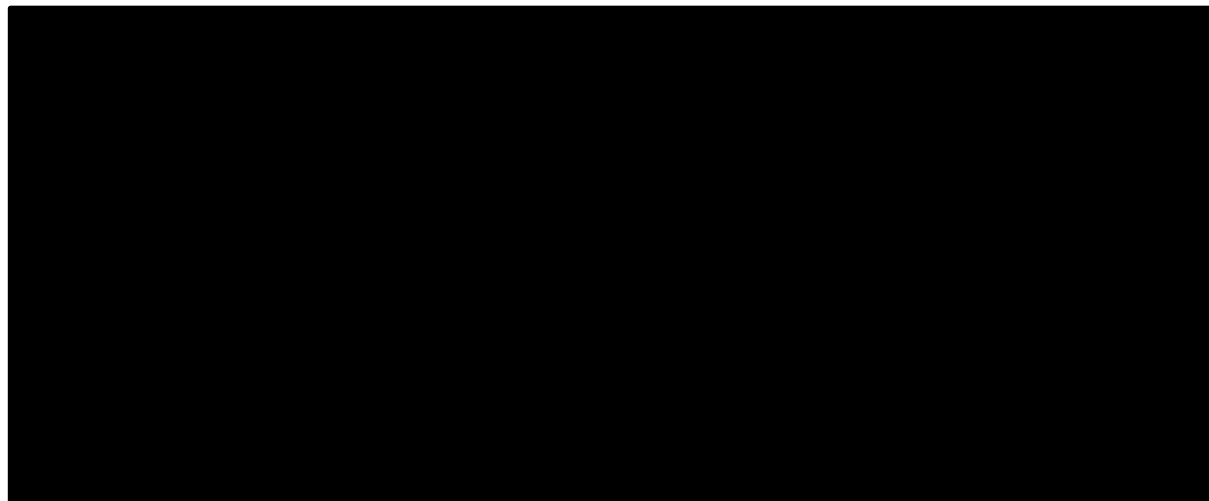


Table 28: Nirogacestat premature discontinuation for reasons other than progression calculated from the OLE phase of De-Fi

Year	Premature discontinuation not due to progression (n=70)		
	Cumulative	Annual number	Probability
Year 1 (n=██)	██	██	██
Year 2 (n=██)	██	██	██
Year 3 (n=██)	██	██	██
Year 4 (n=██)	██	██	██
Average (Year 1-4)			██

Discontinuation for reasons other than progression appeared fairly constant at █ % , so the EAG implemented this as a constant rate. The EAG assumed that discontinuation for reasons other than progression was evenly distributed across health states. Data were not available to validate this assumption.

A standard course of vinorelbine is 6 x 4 weekly cycles. Treatment can continue if people have not experienced serious toxicity for up to 12 treatments total. The EAG therefore assumed that

patients in the chemotherapy arm would only accrue the costs of chemotherapy for a maximum of one year. This was not assumed to impact the effectiveness of chemotherapy as this was modelled separately. Chemotherapy treatments were low cost, so changes to the length of time for which patients accrued chemotherapy costs had a minor impact.

4.2.5.4. Transition probabilities

Natural history

The company said that there were no external data on natural history for a relevant patient population. The company discussed only potential source, Colombo et al. (2025)⁴⁰, they did not provide any information on how this study was identified or whether there were other potential alternatives. The submission states that the data on natural history from the Colombo et al. (2025)⁴⁰ study were too optimistic. The study was a prospective observation study including patients from Italy, the Netherlands and France evaluating active surveillance as an approach to managing patients with desmoid tumours. The company's assessment is somewhat reasonable as the patients in the paper were on active surveillance, with one third receiving active treatment. They would therefore be a milder population than the population for the decision problem, whose tumours were all progressing at baseline and all considered to require systemic treatment.

Nevertheless, the study does demonstrate that the rate of progression flattened after around two years. There were 43% patients who had progressed at Year 3 and 45% who had progressed at Year 5. This suggests that if patients have not progressed by two or three years, they are unlikely to experience progression, regardless of treatment. Also, in the study there were approximately 30% of patients who experienced spontaneous regression (24% by year 3 and 32% by year 5). This demonstrates the possibility of patients achieving a response at later time points, which means that patients may not achieve maximal benefit over a 2-year period.

Whilst these findings are from a study that is not wholly representative of the decision problem, they do provide some contextual information as to the natural history of the condition.

Transition probabilities: overarching issues

Definition of progression and response

In the De-Fi trial, progression was defined as image-based progression (using RECIST) or clinical progression (discontinuation). The wording of the company submission suggested that progression in the model was defined as image-based progression only. The company clarified at the clarification stage that this was a typo and that the broader trial definition of clinical or image-based progression was used throughout.

Response was defined using the RECIST criteria. Clinicians advised that these criteria are clinically relevant. They raised one limitation that sometimes treatment can lead to tumours hollowing out, meaning that they are less symptomatic and will not grow in future, but their size has not changed. This means RECIST may not fully capture all treatment benefits, so classifying response using RECIST can be considered conservative.

Use of best overall response rather than actual response

Patients' response was informed by their best overall responses, such that if a patient achieved a complete response at any timepoint during the two-year trial, they would be classified as a complete responder at the end of 2 years. Clinicians advised the EAG that while measurement error is a consideration, that tumour size does not substantially fluctuate so it is reasonable to assume that patient's best confirmed response will be representative of the underlying level of response they will maintain. The EAG believes that this still represents a somewhat optimistic assumption as if measurements are subject to error, a patient's best overall response may be more favourable than their response at other time points as a result of measurement error. So, using best overall response has the potential to compound the impact of measurement error in a way that yields favourably biased results. The EAG requested data on actual response, which the company provided as clarification stage. However, these data appear to contain errors, as discussed later in the section.

The company calculated the progression risk for each progression free state (stable, partial response, complete response), by calculating the probability of maintaining progression free survival for one year, conditional on that progression free state being their 'best response' and on them receiving one year, or two years, of treatment without early discontinuation (Table 3.8 and Table 3.9). **This approach has a number of issues.**

Failure to account for patients whose disease did not stabilise or respond

The approach appears not to account for the fact that some patients never achieved disease control (progression free survival) within the clinical trial (■ patients in the placebo arm and ■

in the nirogacestat arm Table 14 of the clinical study report for De-Fi²¹). It is not appropriate to exclude these patients from the analysis. The EAG preferred to include patients who did not achieve disease control, when calculating the transition probabilities. There were also 4 patients who were non evaluable in the nirogacestat arm and 1 patient who was non evaluable in the BSC arm. It is not clear how these patients were handled in the analyses. One clinical expert stated that these are usually patients who have not had a scan, so should be considered to be similar to observed patients the other considered that it was likely that these patients are different but that it was not easy to determine in what way. The EAG's approach to developing the model reflected this.

Failure to account for patients who discontinued treatment early prior to progression

The company's approach of restricting the analysis to patients who did not prematurely discontinue for reasons other than discontinuation, effectively disregarded patients who discontinued treatment for other reasons. It was inappropriate to disregard patients who prematurely discontinued treatment in this way: these patients were observed in the trial, premature discontinuation happens in clinical practice, and these patients should have been accounted for in the model. The EAG preferred to incorporate the possibility of premature discontinuation.

Numbers of patients responding was not consistent across data provided by the company

The clinical study report²¹ suggests that six patients achieved a partial response on best supportive care (Table 14), but the company's response to clarification question B9b suggests there were only ■ patients who achieved a partial response. This does not affect the results of the economic model provided.

Use of calibration to "fix" issues with trial data not matching modelled results

The company implemented a **calibration approach**, in order to match the modelled proportion of progressed patients to the proportion observed in the trial. This created further issues, as the company did not compare like with like, when following this process. Implementing calibration reduced the company's ICER from ■ to ■.

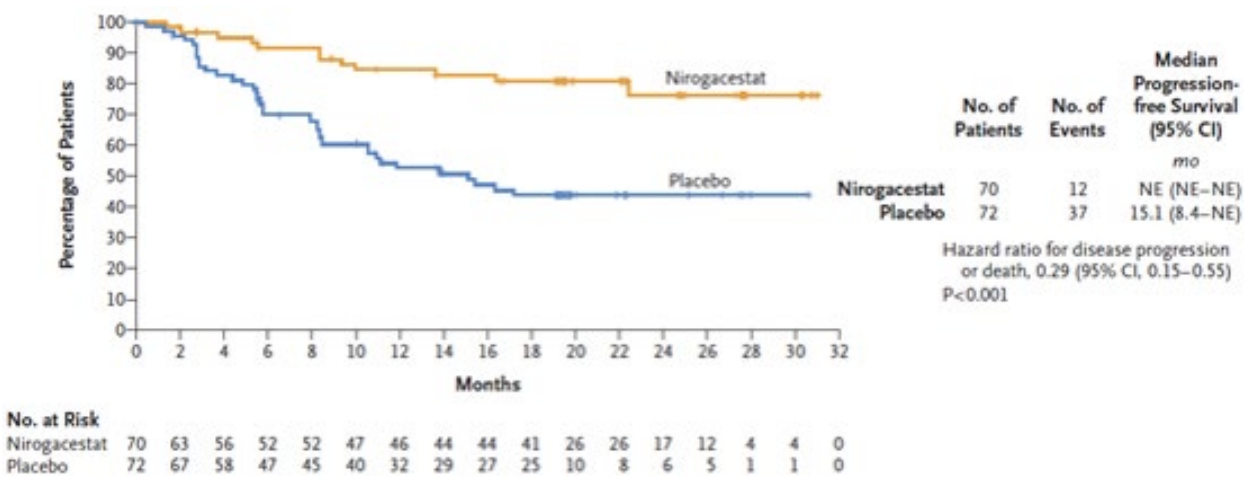
The company stated the following in relation to nirogacestat:

'The extrapolated values were compared with the De-Fi trial, which reported 12 out of 70 (17%) events of disease progression within the first 2 years of treatment with

nirogacestat.’ And, [REDACTED]
[REDACTED]
[REDACTED]

This fails to account for the role of censoring. Whilst it was true that there were 12 progression events observed over 2 years in the nirogacestat arm, there were not 70 patients at risk of progression throughout this time period; some of those patients were censored, mostly due to discontinuation or lack of follow up (See Table 10). The Kaplan-Meier curve demonstrated that there was around 25% progression by 2 years in the nirogacestat arm (Figure 11).

Figure 11: Kaplan Meier curve for progression free survival



The residual discrepancy was likely a result of the fact that the company used the proportion of progressed patients at one year to calculate a monthly transition probability and assumed that this transition probability was constant through time. They then compared modelled progression with observed progression at Year 2. In reality, the Kaplan-Meier curve demonstrated that the proportion of progressed patients plateaued in both arms in the second year of the trial (Figure 11).

Fundamentally, a ‘calibration approach’ should not be necessary if a valid approach was taken to using the trial data to inform transition probabilities within the model. It should have been possible to use trial data to calculate transition probabilities such that state membership in the model aligned with the trial, without the need for post-hoc adjustment.

The company stated the below in relation to the progression risk for BSC patients:

'While median PFS (mPFS) was not reached for nirogacestat, the mPFS for placebo was 15.1 months; therefore, it was expected that the proportion of BSC/placebo participants in PD by 15 months should be approximately 50%. Data was available for the BSC participants at 24 months, which showed that 50% of participants (36/72) had progressed.'

The first part of this statement was correct, as can be seen in the Kaplan-Meier curve (Figure 11). The second part of this statement was incorrect, again, this was due to censoring. It was true that there were 36 progression events by month 24, but there were not 72 patients at risk, for the entire time period. Some of these patients had been censored, so it was unknown whether they would have progressed, had they continued to be observed. The percentage of BSC patients who experienced progression in the trial by month 15 was 50% and by month 24 it was around 56% (Figure 11). The company compared this to the [REDACTED] of patients in Table 3.8 who achieved progression free survival of 12 months, conditional on having achieved stable disease and received BSC treatment for one year ([REDACTED] for those who received treatment for two years). This suffered from the same issue as in the nirogacestat arm, that patients who never achieved a stable disease, and patients who discontinued treatment prematurely, were erroneously excluded from the analysis. The choice to calibrate at month 24 in the nirogacestat arm and month 15 in the BSC arm was inconsistent and added further uncertainty and potential for bias.

The issue can be further understood by examining the company's scenario which was restricted to patients who received one year of treatment. In that scenario, the transition probabilities were calculated based upon transitions observed in the first year, so the modelled number of progressed patients at the end of one year should have matched the trial. Table 29 shows that in the nirogacestat arm, the proportion of patients modelled to reach progression using the uncalibrated transition probabilities, matched the proportion of progressed patients in the trial (using the Kaplan-Meier curves) hence there is no need for calibration. In the BSC arm, this was not the case. This was likely because of the 10 patients in the BSC arm who progressed immediately. There was only one patient in the nirogacestat arm who immediately progressed, so the fact that the company excluded these patients likely did not have a meaningful impact on the nirogacestat arm. Focusing on this scenario removed the impact of progression risk varying through time and isolated the impact of excluding patients that immediately progressed. When these patients were placed in the progressed state from the start of the model, the modelled

number of progressed patients in the nirogacestat arm at Year 1 was ■■■ (compared with ■■■ in the trial) and the modelled number of progressed patients in the BSC arm at Year 1 was ■■■ (compared with ■■■ in the trial).

Table 29: Modelled progression rates in the one year of treatment scenario

	Uncalibrated model		Uncalibrated model (immediately progressed patients accounted for)		Calibrated model		Trial
	Annual transition from stable disease to progressed disease	Progressed patients at Year 1	Patients starting in progressed	Progressed patients at Year 1	Annual transition from stable disease to progressed disease	Progressed patients at Year 1	Progressed patients at Year 1
Nirogacestat	■■■	■■■	■■■	■■■	■■■	■■■	■■■
BSC	■■■	■■■	■■■	■■■	■■■	■■■	■■■

Notes: ^a Taken from the company model, in the uncalibrated transition probability scenario ^b Taken from the company model, in the uncalibrated transition probability scenario, with immediately progressed patients added to progressed in the first cycle ^c Taken from the company base case, ^d Table 2.8 of the company submission.

The above analysis focused on the company scenario for patients receiving 1 year of treatment, because the company said that the transition probabilities in both the one year of treatment scenario and the base case (two years of treatment) were calculated using state membership at 1 year, so these data were subject to less noise. Similar issues were observed in the base case analysis, presented in Table 30.

Table 30: modelled progression rates in the base case (two years of treatment)

	Uncalibrated model		Uncalibrated model (immediately progressed patients accounted for)		Calibrated model		Trial
	Annual transition from stable disease to progressed disease	Progressed patients at Year 2	Patients starting in progressed	Progressed patients at Year 2	Annual transition from stable disease to progressed disease	Progressed patients at Year 2	Progressed patients at Year 2
Nirogacestat	■■■	■■■	■■■	■■■	■■■	■■■	■■■
BSC	■■■	■■■	■■■	■■■	■■■	■■■	■■■

Notes: ^a Taken from the company model, in the uncalibrated transition probability scenario ^b Taken from the company model, in the uncalibrated transition probability scenario, with immediately progressed patients added to progressed in the first cycle ^c Taken from the company base case, ^d Table 2.8 of company submission.

Transition probability calculation issues

There was a further issue identified with the way that the probability that patients achieved a response was implemented. The company applied a constant risk of response to stable patients

in each monthly cycle, based on the proportion of patients who had a response at the end of one or two years of treatment. But the approach taken did not account for the fact that the number of stable patients reduced each cycle as some of them progressed. This caused the proportion of responders to be under-estimated and the proportion of progressed patients to be overestimated.

Assumption that long-term transitions will match the probabilities observed in the randomised phase of the trial

The company assumed that the transition probabilities observed in two-year randomised control period of the De-Fi trial would be constant over time. The Kaplan Meier curve suggested that this was not the case, with no progression events occurring after Month 18 in the BSC arm and one in the nirogacestat arm (Figure 11). Clinicians input also suggested that transition probabilities would be expected to flatten over time.

The next sections discuss the transition probabilities in detail for each health state, before outlining the EAG preferred approach to tackling the issues described and finally outlining the desired approach for calculating the transition probabilities.

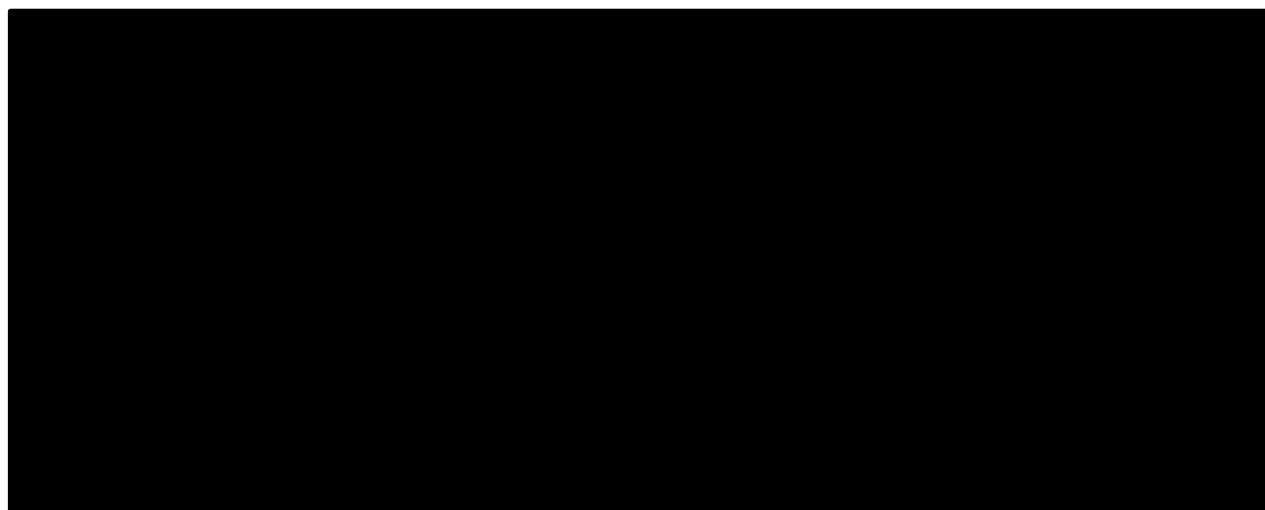
Progression risks by health state

No **complete responders** experienced progression during the trial, so the company assumed that it was not possible transition from complete response to progressed disease. This includes patients who responded and then stopped treatment. The EAG broadly supports this assumption as it is in line with input from clinicians who said that it is rare for patients who achieve a full response to experience regression. One clinician said they would expect this in 5% of patients, but did not have data to support this.

For **partial responders**, the company calculated the proportion of patients who achieved a partial response, then went on to experience progression. Figure 7 in the clinical study report²¹ showed that out of the ■ placebo patients who achieved a partial response, ■ went on to experience progression. Out of the ■ nirogacestat patients who experienced a partial response, ■ went on to experience progression. ■. This did not align with the values reported in Table 3.6 and Table 3.7 of the company submission. These values were likely a result of restricting the analysis only to patients who did not prematurely discontinue treatment. This was inappropriate. Table 3.7 states that the annual rate of progression from PR to PD, for patients

with 2 years of treatment was ■ (implying ■) but for patients with 1 year of treatment the rate is ■. This was confusing, as presumably all patients with up to 2 years of treatment, also had up to 1 year of treatment. It's also unclear why the Kaplan-Meier curve the company shared (Figure 12) suggested that there were ■ patients who achieved a partial response in the BSC arm, when Table 2.8 of the company submission shows that there were ■.

Figure 12: Progression free survival among partial responders (CSR Figure 7)



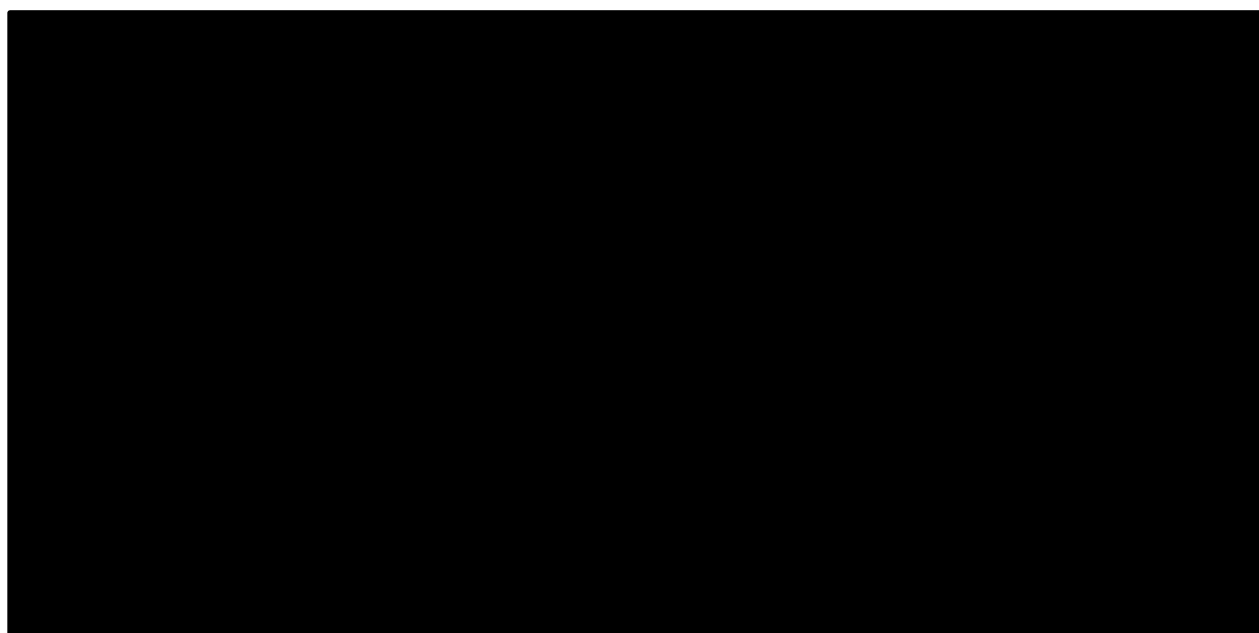
For patients with **stable disease**, the company appeared to have used data similar to that presented in Figure 8 from the CSR (except restricted to patients who achieved stable disease as their best overall response only) to calculate the probability of maintaining progression free survival for one year, conditional on them having achieved a response of stable disease only and on them receiving one year, or two years, of treatment without early discontinuation (Table 3.8 and Table 3.9). The issues with the approach taken are discussed in the previous section and the EAG's preferred solution is described in Section 4.2.5.4.

For **patients who stopped receiving nirogacestat** at two years (or one year in a scenario), the company assumed their progression risk was unchanged. The company argued that nirogacestat has a disease modifying effect, that alters the course of the disease. Clinical experts who advised the EAG broadly supported this assumption, but said that some patients would be continuing to receive benefits at two years, so should not come off treatment. The EAG assumed that no additional progression occurs in either arm after two years and that patients stay on treatment until year 3, with a two year and four year stopping rule tested in sensitivity analysis. Unlike the company model, the EAG's model included the possibility of

patients discontinuing treatment prematurely for reasons other than progression. The EAG assumed that these patients would experience the same progression risks as BSC patients, given that they had not received nirogacestat for long enough to benefit from its disease modifying effects.

The company assumed constant progression risks over **the long term**. This was not a plausible assumption because the Kaplan-Meier curve clearly shows that the proportion of patients entering the progressed disease state plateaus (Figure 11). The EAG preferred to assume that no patients progress on both arms after Year 2. This was supported by the fact that only one patient experienced progression after Month 18 in the nirogacestat arm in the randomised phase of the trial, and no patients experienced progression after Month 18 in the placebo arm. Ratan 2025 states that no patients progressed after two years of treatment in the open label extension.³⁰ Clinicians also advised that if patients did not experience progression after 2 years, they were unlikely to experience it in subsequent years. Figure 11 shows that the rate of progression plateaus in the second year with around 45% progressed patients and there are no progression events from Month 18 in the placebo arm. In the company model, over 90% of patients have progressed in the placebo arm by Year 5. This is in sharp contrast to advice the EAG received from clinicians that a substantial portion of all DT patients experience spontaneous regression or stabilisation regardless of treatment.

Figure 13: Modelled state membership in the BSC arm of the company model



Notes: BSC, best supportive care; SD, Stable disease; PR, Partial response; CR, Complete response; PD, Progressed disease.

Response probabilities for each health state

The company calculated the probability of progressing separately for patients in each health state, which were defined using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. All patients started in the stable response health state, then their chance of achieving a partial response, or complete response, was informed by their best overall response during one or 2 years of treatment (Table 3.5 of the company submission).

The company made a number of assumptions about the way in which patients could transition through progression-free health states.

The company assumed that ‘those in CR (i.e., those patients who experience full disappearance of all target lesions) cannot transition to PR, stable disease, or PD, and would therefore remain in their current health state.’ Clinicians told the EAG that they supported this assumption and that once patients achieved response, they rarely go on to experience progression.

The company assumed that patients who achieved a partial response could not go on to achieve a complete response. This is not an unreasonable assumption as response was defined as best overall response over a two-year period, so by definition no patients were observed to transition from partial response to complete response within 2 years.

The company assumed that no additional patients achieved a partial response or complete response after two years. Clinical experts advised that most patients who experience a treatment benefit, do so in the first two years. The limited data available on patients’ response after two years suggest that response is maintained. Data from the OLE provided in response to Clarification Question B5, shows that some patients receiving nirogacestat gained a complete response after two years of treatment (Table 31 and Table 32).

Table 31 Response data for nirogacestat patients in Year 2 to 3 (N=) (CQ A16)

From/To ^a	CR	PR	SD	PD
CR				
PR				
SD				

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

Table 32 Response data for nirogacestat patients in Year 3 to 4 (N=) (CQ A16)

From/To ^a	CR	PR	SD	PD
CR				
PR				
SD				

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

It was possible that some additional BSC patients who achieved a partial response within the two-year trial would go on to achieve a complete response over a longer period, but there were no data to support this and it would have a limited impact on the results given that only six patients achieved a partial response in the BSC arm. The EAG implemented the response probabilities observed for nirogacestat patients in Year 3 (and Year 4 in a scenario).

The overall company approach to defining transition probabilities between the health states is summarised in Figure 14 and Figure 15.

Figure 14: Health states and transition probabilities in the company base case for nirogacestat

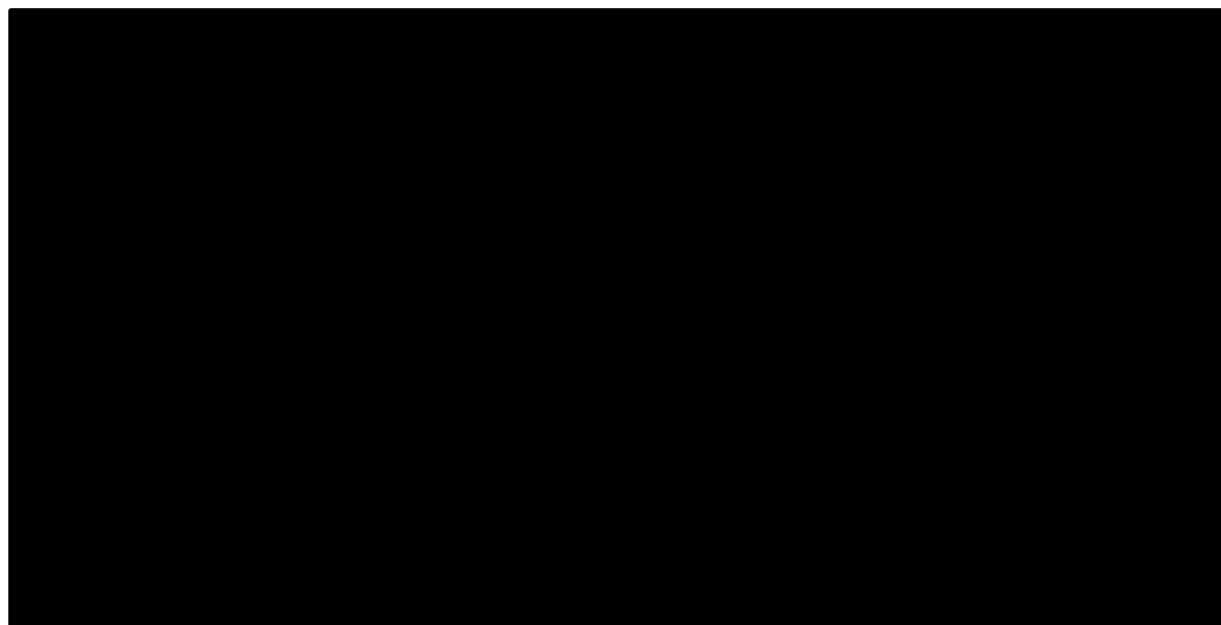
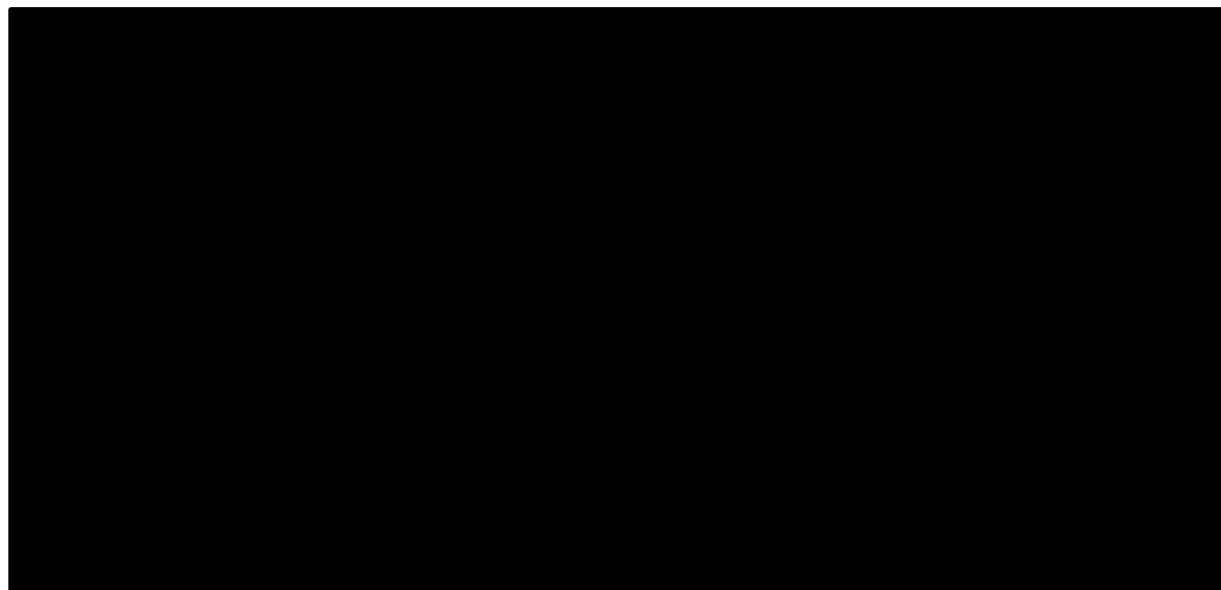


Figure 15: Health states and transition probabilities in the company base case for BSC



At clarification, the company shared data on patients' actual response, as well as their best overall response. At all timepoints, the data appear to be more favourable for actual response than best overall response, which was counterintuitive. By definition the best overall response by the end of year 1 should be as favourable or more favourable than the actual response at the end of year one because either the response at the end of year was the best overall response,

or the best overall response was a timepoint during year 1, in which case it will be better than the actual response at the end of the year. This suggested there may have been a calculation error or the definition of the endpoints is unclear. When looking at the table provided in response to B5, the percentages in the actual response column do not sum to 100%, demonstrating calculation errors.

Table 33: Transition probabilities from company base case (best overall response) and scenario analysis (actual response)

Endpoint definition	Health state	Nirogacestat		BSC/placebo	
		1 year	2 years	1 year	2 years
Best overall response (base case)	Complete response	■	■	■	■
	Partial response	■	■	■	■
Actual response (scenario)*	Complete response	■	■	■	■
	Partial response	■	■	■	■

Notes:* these data are thought to contain errors

The EAG prefer to use the data on best overall response in the base case as this is the more conservative of the two options available, with the actual response data not used (as the EAG believe these to be erroneous).

The company assumed that no further patients experience a response after Year 2. This is at odds with the trial data, which show that ■ (■) of patients in partial response at the end of, went on to achieve a complete response by the end of Year 2 and ■ of patients (■) in stable response went on to achieve a partial response (Clarification Question A16)(Table 34). The EAG preferred to take this into account by assuming that patients could continue to respond to treatment up until the end of Year 3, in the nirogacestat arm. The possibility of further patients achieving a response in Year 4 (Table 35) was included in a scenario with a four-year stopping rule. These data were not available for the BSC arm and rates of response in the BSC arm were lower, so disregarding the possibility of late response in the BSC arm is not considered a key area of uncertainty.

Table 34: Patient response observed in Year 3 of the De-Fi trial (n=■) (CQ A16)

From/To ^a	CR	PR	SD	PD
CR	■	■	■	■
PR	■	■	■	■
SD	■	■	■	■

a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

Table 35: Patient response observed in Year 4 of the De-Fi trial (n=■) (CQ A16)

From/To ^a	CR	PR	SD	PD
CR	■	■	■	■
PR	■	■	■	■
SD	■	■	■	■

^a Percentages calculated using the denominator for each response category (each row) as the total number of patients in each response category at the end of the previous year and have response data in the follow year.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressed disease.

Transition probabilities for patients off treatment

In the company model, the only patients off treatment before two years, were those who progressed. For patients who discontinued nirogacestat after two years, it was assumed that patients with stable disease, progression risks were unchanged, and no more patients responded. Patients who had achieved a response were assumed to maintain their level of response, with no progression risk.

The EAG introduced the possibility of patients discontinuing treatment before the stopping rule, for reasons other than progression. The EAG assumed that these patients experienced the transition probabilities associated with patients who remained on treatment. This was necessitated by the broader approach the EAG used to calculate transition probabilities, where monthly transition probabilities were calculated based on the proportion of patients in each health state at the end of the two year period. Data were not available to the EAG to calculate transition probabilities separately for patients who were on and off treatment.

The EAG accepted the assumption that patients who achieved a response by the end of a full course of treatment, would not experience progression. Clinicians supported the rationale that these patient's will have had the course of their disease altered by treatment. But the EAG believed that those who discontinue treatment early, would not experience these benefits.

EAG's preferred approach

In light of all of the issues with the company's approach, the EAG decided to take a different approach. The approach taken by the EAG was not optimal but was the best approach available given that the company did not provide data that the EAG requested. The EAG assumed constant transition probabilities in the first 2 years of the model and that patients could only

progress from the stable health state. The EAG used the proportion of patients in the following categories at the end of two years (one year in a scenario) as a starting point:

- **Progressed disease:** Patients who progressed
- **Complete Response:** Patients who achieved a best response of complete response, and didn't progress
- **Partial response:** Patients who achieved a best response of partial response, and didn't progress
- **Stable disease:** Patients who achieved a best response of stable disease, and didn't progress

The EAG then used this to calculate monthly transition probabilities from the stable state to the four health states described above. The EAG assume no further progression or response after Year 2. This is detailed in Table 36. Non evaluable patients were excluded from the analysis, as clinicians stated that these are likely patients who missed a scan, so would be representative.

Taking this approach required the assumption that patients can only reach complete response, partial response or progressed disease, from the stable disease health state (this state is assumed to include patients who immediately responded, without ever achieving stable disease). This was mostly in line with the assumptions made by the company, except that the company included the possibility of progressing from the partial response health state. The EAG were not able to model this explicitly, as sufficiently granular data were not provided by the company. There was only one patient who progressed from the partial response health state in each arm. This was not therefore considered to be an important area of uncertainty.

Table 36: Transition probabilities in the EAG base case in years 0 - 2

		Nirogacestat	Placebo
State membership	Complete Response		
	Partial Response		
	Progressed Disease		
	Stable		
Cycle transition probabilities from stable disease to...	Complete response		
	Partial response		
	Progressed disease		
	Stable disease		

The EAG preferred to assume no further progression after Year 2 for reasons given in Section 4.2.5.4. The EAG also preferred to assume that it was possible for patients to achieve a response in the third year of treatment, for reasons given in Section 4.2.5.4.

The EAG approach is summarised in **Figure 16** and **Figure 17**.

Figure 16: Health states and transition probabilities in the EAG base case for nirogacestat

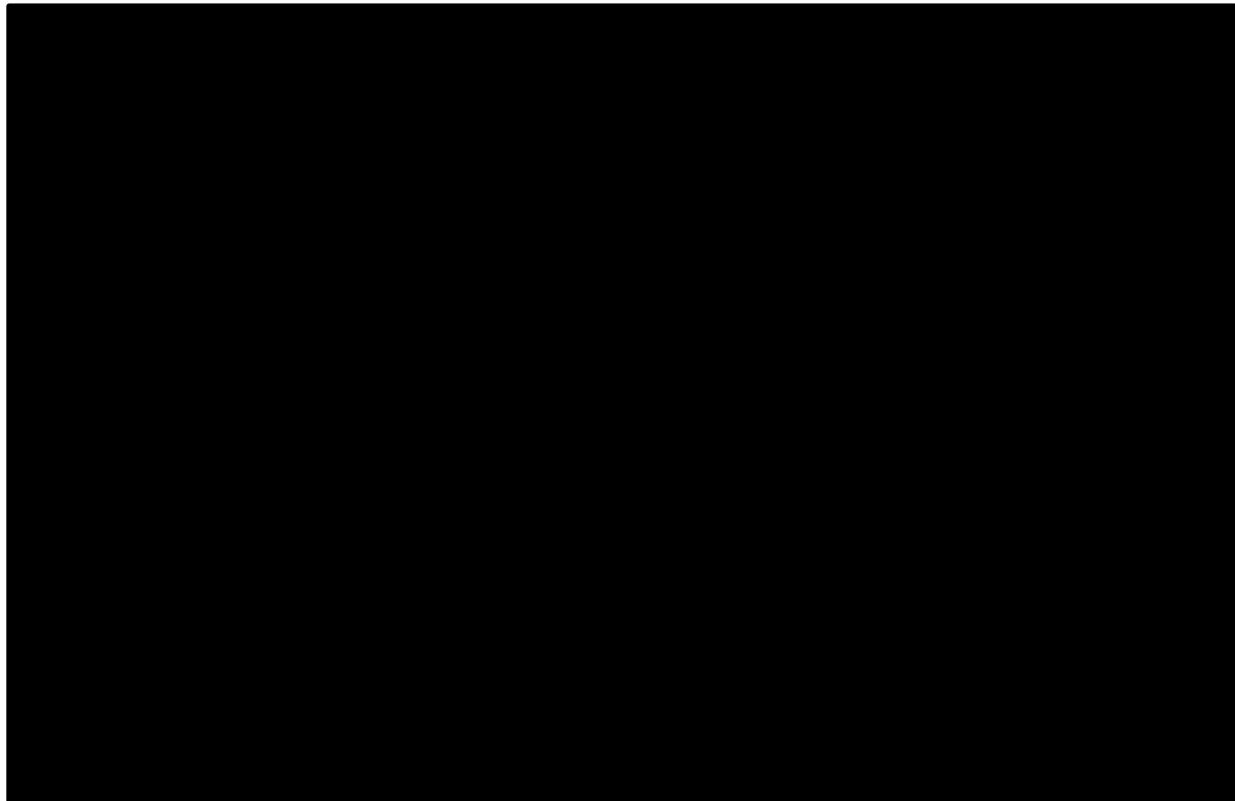


Figure 17: Health states and transition probabilities in the EAG base case for BSC

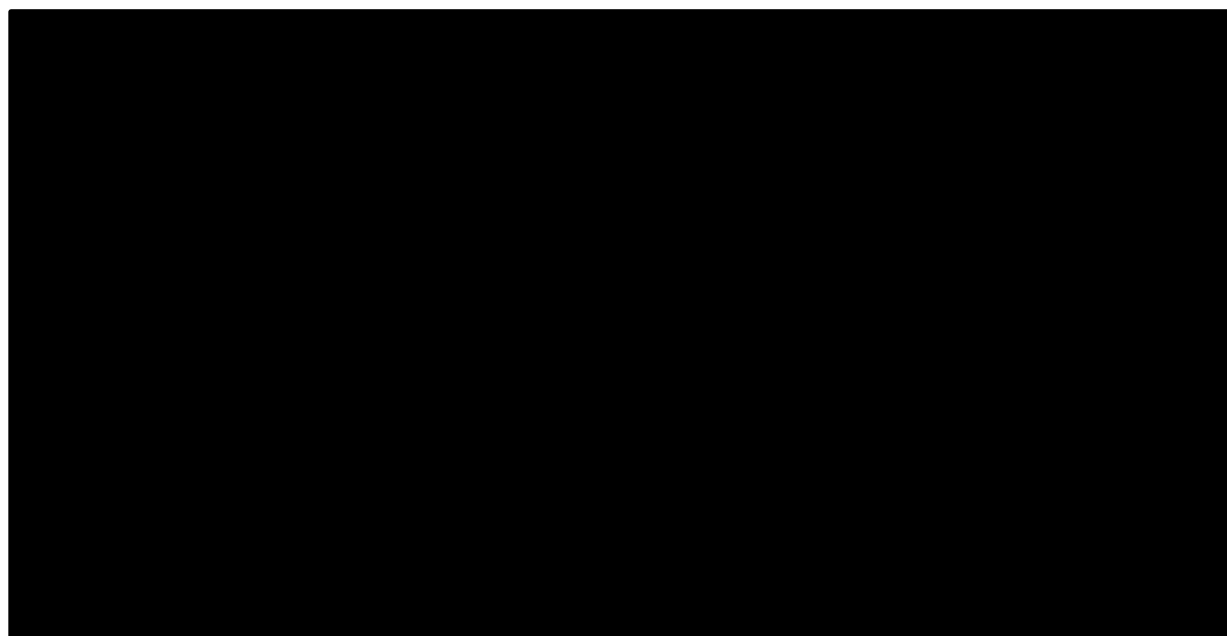


Table 37 demonstrates reasonably close alignment between the modelled state membership in the EAG base case, and the state membership observed in the De-Fi trial, validating the EAG's approach. The match is closer at Year 2, but this was acceptable as misalignment between Year 0 and Year 2 was expected to have a modest impact. Misalignment in response at Year 2 would have a major impact as this was then extrapolated into later years.

Table 37: State membership in the EAG base case and De-Fi trial

		EAG base case		Trial	
		Year 1	Year 2	Year 1	Year 2
Nirogacestat	Stable disease	■	■	■	■
	Partial responders	■	■	■	■
	Complete responders	■	■	■	■
	Progressed	■	■	■	■
BSC	Stable disease	■	■	■	■
	Partial responders	■	■	■	■
	Complete responders	■	■	■	■
	Progressed	■	■	■	■

Transition probabilities for chemotherapy

The EAG conducted a network meta-analysis, in order to include chemotherapy as a comparator (Section 3.4.1). The NMA yielded a hazard ratio of 0.37 (CI: 0.07, 1.80) for progression-free survival for chemotherapy, compared with nirogacestat. The EAG also conducted a network meta-analysis for the Objective Response Rate (ORR). It found that the odds ratio for an objective response for chemotherapy compared with nirogacestat was 0.14 (CI 0.02, 0.88). The results for progression-free survival are very uncertain, with the confidence interval crossing one (equivalence) by a substantial margin. The clinical experts advising the EAG considered that it did not make sense to have such divergent results for PFS and objective response rate. The heterogeneity between the studies included in the network, and small number of patients in the trials, contribute to the uncertainty in the results. The objective response rate NMA was considered to be more reliable than the PFS NMA as it did not require the same level of statistical power and follow up to achieve a robust result and the differences in trial design and inclusion criteria were considered likely to have a greater impact on PFS.

In light of this, the EAG asked clinicians to advise as to how effective chemotherapy would be, relative to the comparators. The clinicians stressed the uncertainty associated with network meta-analysis results. Both clinicians said they would expect nirogacestat to have more favourable response rates and progression free survival than chemotherapy and that they would expect chemotherapy to have more favourable response rates than BSC. The clinical experts were more uncertain about the impact of chemotherapy on progression free survival; they considered that it was unlikely there would be much improvement over BSC.

The EAG used the NMA results to inform the objective response rate for chemotherapy. The EAG used this to calculate an overall response rate for chemotherapy of ■ at Year 2, it assumed that these were all partial responders given that this response rate is close to that of placebo and there were not complete responders in the placebo arm.

In the base case, the EAG assumed progression-free survival for chemotherapy was equivalent to best supportive care. In a scenario, it assumed that progression free survival was equivalent to nirogacestat.

4.2.5.5. Mortality

A mortality hazard ratio of 1.3 for patients with desmoid tumour patients with progressive disease compared to the general population was calculated by the company based on the

Anneberg et al (2022)⁴¹ study. This was a retrospective study in Denmark that ran from 2009 to 2018. Clinicians advised that this level of increased mortality was higher than what they observe in clinical practice. They stated that this was likely due to the fact that the study is outdated and will include patients who died as a result of inappropriate surgical interventions. One clinician also discussed the possibility that the increased mortality was specifically associated with FAP desmoid tumours.

In the Anneberg study, of patients with first contact between 2009 and 2014, 76.2% received surgery. For patients with first contact between 2015 and 2018, this fell to 23.8% of patients, which is expected as clinicians advised that use of surgery to treat desmoid tumours has fallen over time. There were 75 out of 142 patients who experienced surgery prior to enrolment in the De-Fi study (53%).²⁶ There were 7.2% of patients in the Anneberg study who had FAP. Table 2.5 of the CS shows that there were 25/142 patients who had a family history of FAP (17%).

There were 55.9% of patients who had received medication 3 years prior to their first contact with the data base and 67% who received systemic medication 3 years later. This could imply that this was a less severe population than the De-Fi trial, as the trial was restricted to patients requiring systemic therapy. On the other hand, this could reflect the limited availability of systemic therapy options at the time of the study.

In the Anneberg study, most deaths occurred in FAP patients despite only representing 7% of identified DT patients.

The EAG was willing to accept the use of the Anneberg study to inform mortality in the absence of an alternate data source. Whilst it was an old study with an over representation of patients who received surgery, it also appeared to be in a milder population with fewer patients who have FAP. It was thought that these two considerations will balance out to some degree. The EAG tested a hazard ratio of 1 for mortality compared with the general population in a scenario analysis. Mortality was not found to be a key driver of the cost-effectiveness results.

General population mortality was informed by sex and age weighted UK life tables. This approach was appropriate.

4.2.5.6. Adverse events

The company stated that adverse events were included if they were Grade 3+ and occurred in more than 5% of patients. This included diarrhoea, folliculitis and rash or skin disorders. Ovarian

dysfunction was also included, as a Grade 1-2 event that impacted a substantial portion of nirogacestat patients.

The company did not model non-melanoma skin malignancies because they did not meet the 5% threshold. The data suggested they were more likely on treatment, and the company provided a clinical rationale for why this would be expected. Clinical experts advised the EAG they have also observed these events with similar treatments and that the usual treatment is cryoablation which is effective. The cryoablation national average unit cost is £266 (currency code AB15Z, outpatient procedure).⁴² Given the small numbers and low cost of treatment the EAG also excluded non-melanoma skin malignancies from the analysis.

There appeared to be some inconsistency in the rates of ovarian dysfunction reported, which likely relate to different definitions being used. The CSR reported that in the nirogacestat arm there were ■ patients who experienced investigator identified reproductive system and breast disorders, 27 patients who experience ovarian dysfunction based on a 'narrow search' and ■ patients in the nirogacestat arm who experienced reproductive system and breast disorders overall (■■■■■■■■■■). Data from Ratan 2025³⁰ suggests that these events predominately took place in the first year of treatment, and rates were substantially lower in subsequent years (38 events in the first year, compared with 9, 3, 6 and 0 in the 2nd to 4th year respectively). The company submission and clarification question response reported the 27 out of 36 women figure. The EAG were happy to accept this estimate, given that the variation is modest. In the model, the company also appeared to have assumed ■ of patients experienced ovarian dysfunction, which was the proportion with 'unresolved' ovarian dysfunction (which appeared to mean those still experiencing it at the end of the trial period), not the total proportion that experienced it at any point during treatment.

At clarification stage the company said that they switched from modelling ovarian dysfunction as an intermittent short-term event, to a one-off event that occurred at the start of the model for ■ days. There were ■ events, which impacted 27 patients (or 39% of patients), each patient experienced ovarian dysfunction for an average of ■ days. It was unclear why these values are lower than those reported in Ratan 2025. The company reported that OD was resolved in 79% of women of childbearing potential during treatment (Company submission). This implied that the ■-day average duration may slightly underestimate the total duration as some women will have had unresolved OD at the end of the study, but the EAG did not believe this to be a key area of uncertainty as many patients would stop treatment after 3 years. The EAG believed

modelling ovarian dysfunction as a long-lasting one-off event to be more appropriate, however the company did not appropriately implement this change in the version of the model provided. The EAG have therefore implemented this change.

The EAG believed the approach to inclusion of other adverse events was appropriate.

The EAG conducted a network meta-analysis of the risk of Grade 3+ adverse events. It yielded an odds ratio of 6.34 for nirogacestat compared with placebo. The EAG believes this is adequately handled by implementing adverse events based on the De-Fi trial data. It yielded an odds ratio of 1.23 (CI: 0.39, 3.87) for chemotherapy compared with nirogacestat. This was a small difference. Clinical experts advised the EAG that they would expect single agent vinorelbine to be less toxic than the double-agent chemotherapy in the NMA. Given adverse events are not a key driver of cost-effectiveness, the EAG believes it is appropriate to assume the side effect profile was the same for nirogacestat and chemotherapy. This approach was supported by Ou 2024,¹ where the adverse events listed were similar, with constipation being the main adverse event that is more prevalent for chemotherapy than for nirogacestat and diarrhoea the main event that is more common for nirogacestat than chemotherapy. Whether these differences are significant, was not known.

4.2.6. Health-related quality of life

4.2.6.1. Health state utility values

The De-Fi trial did not collect EQ-5D data. The trial did collect a number of other quality-of-life measures. The most suitable candidate for mapping was the EORTC QLQ-C30 data. The company attempted to map the EORTC QLQ-C30 data to EQ-5D. The company used the mapping algorithm from Young et al. (2015)⁴³. The company stated the importance of the mapping algorithm being informed by a relevant patient population and that whilst this mapping algorithm was the best available match, the patients used were of limited relevance as they had lung cancer and breast cancer which are substantially more severe conditions. The mapping study also had a mean age of 68 years, compared to 37 years in De-Fi. Based on a pragmatic search the EAG accepted that this was likely the most suitable mapping algorithm available.

The company also highlighted issues with the sample size, particularly for the complete response, partial response and progressed disease health states. The company did not provide these data (only that there were 134 patients with some EORTC-QLQ-C30 data), so the EAG were not able to validate this claim. In response, the company stated that they attempted to map

utility values using only health states for patients with, and without, progressed disease. Again, data were not provided regarding this analysis. The company also highlighted that PRO data collection and disease assessment did not necessarily occur at the same time point. They claimed that this means that the impacts of progression may not have been reflected in the quality-of-life data collected. In the EAG's view, the key consideration was whether there were health-related quality-of-life data available for later timepoints post progression, as these would provide a clearer picture on the utility of progressed patients and similarly whether data existed post observation of best overall response for responders. The company did not provide sufficient information on this. Finally, partly as a result of these issues, the company noted that there were large standard errors associated with the calculated health state utility values, when mapping EORTC QLQ-C30 to EQ-5D. Again, these were not reported by the company.

The EAG accepted these limitations, but all analyses were subject to limitations, and this did not mean that the trial data should be entirely disregarded. This was particularly important in this instance as there are no health state utility values available for desmoid tumour patients from other sources. The EAG requested that the company provide the results of their utility mapping exercise. The company refused, which added to the uncertainty as to how health state utility values should be modelled and means that the companies claims regarding the limitations of their attempted mapping exercise cannot be verified.

The company did not identify any quality-of-life studies for patients with desmoid tumours in their quality-of-life SLR. They then searched for studies in chronic neuropathic pain but did not use any of the identified studies. They then reviewed the economic evaluations SLR for soft-tissue sarcoma SLR, and identified a cost-effectiveness study which had used quality-of-life data from Shingler et al (2013).³⁵

This was a time trade off (TTO) study that used vignettes. This did not comply with the NICE reference case and is not appropriate unless other options are not available. Vignettes for patients with advanced soft-tissue sarcoma were informed by 'information obtained from physicians, patients and the published literature'. Advanced soft tissue sarcoma was defined as stage IV/unresectable soft tissue sarcoma, meaning that the tumour cannot be removed or has metastasised. Typical overall survival for a soft tissue sarcoma patient whose tumour has metastasised was 2 years.⁴⁴ The definition of progressed disease in the study included a number of statements that were not reflective of desmoid tumours. It included the line: 'You experience pain which means you need to take regular pain medication to control it. You

frequently become short of breath and sometimes cough up blood' As stated previously, only a minority of patients in the De-Fi study experienced uncontrolled pain at baseline. It stated, 'You have a life-threatening illness and your condition is getting worse despite undergoing rounds of treatment.' The mortality associated with desmoid tumours was fairly modest and is not life threatening for most patients. It stated that 'You are depressed and often think about dying. You worry about how your loved ones will manage without you.' Whilst this may apply to some patients, insufficient evidence has been presented to justify that this statement is a typical reflection of the experiences of the majority of patients with a progressing desmoid tumour.

There were only four patients involved in reviewing the vignettes, which represents a key risk of bias. Health states were evaluated by 100 members of the UK general public. The study states that these data were aligned with the census, but the method used to achieve this are not described and data were not presented to show that the sample was representative of the UK general population.

The company's utility value for patients with progressed disease, modelled using this source, was 0.2630. This would be in line with patients who have cancer and are receiving terminal care. Amdahl 2014,³⁴ the study that utilised the Shingler 2013³⁵ utility data identified by the company stated:

'The latter [an estimate of utility in the terminal phase of the disease] was based on the estimated utility value for progressive disease from a vignettes study by Shingler and colleagues' Amdahl 2014,³⁴ page 5.

This highlights that the Shingler 2013³⁵ utility values used by the company were based on the terminal phase of soft tissue sarcoma.

Clinicians confirmed that this value is unrealistically low, they stated that desmoid tumours were rarely as serious as soft tissue sarcoma. They suggested that a suitable proxy would be patients who experience painful surgical complications, such as a hip replacement that becomes infected, or an unsuccessful shoulder operation, when the EAG asked whether neuropathic pain would be a suitable analogue, they said it would. They stated that desmoid tumours are rarely as serious as soft tissue sarcoma. Table 2.5 of the company submission indicates that 58/142 (41%) patients had uncontrolled pain at baseline. This was defined as:

'Brief Pain Inventory–Short Form average worst pain intensity score of more than 4 (range 0-10 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.' (company submission)

Table 2.5 of the company submission shows that there were 31/169 target tumours that were abdominal (22%). Of the extra abdominal tumours, it is difficult to determine based on the categories provided which tumours would be on joint areas that would be likely to cause pain and mobility issues. A clinical expert stated that 'it could be 20-30% of the desmoid population with progressive tumours that have pain.'

Overall, the use of the Shingler 2013 paper was not considered to be appropriate.

The EAG preferred to use utility values from Reichardt et al, 2012.² The only other studies identified with potential utility values: Eldabe et al 2020 and Eldabe et al 2023 were identified in the company HRQoL SLR for CNP and collected EQ-5D directly from patients at baseline, 3 months, 6 months and at 36 month follow up. The studies analysed the impact of screening patients who were undergoing spinal cord stimulation implantation. The EAG considered patients undergoing chemotherapy for STS as a more appropriate source of utility estimates given the patient experience of receiving pharmacological treatment and symptom profile of STS is likely to be more similar to HRQoL for patients with DT than patients undertaking spinal cord stimulation in chronic neuropathic pain but note considerable limitations in the use of progressed disease utilities from STS for desmoid tumours. The Reichardt 2012 utility values were detailed within Tikhonova 2018². Tikhonova 2018 is a published EAG report for olaratumab in STS, the utility data used was from Reichardt et al 2012,³ a publication on the quality-of-life of patients with metastatic soft tissue and bone sarcoma in the SABINE study.

Table 38 Utility values sourced from Reichardt 2012

Health state	Mean EQ-5D (SD)
1 st line chemotherapy	0.72 (0.31)
2 nd line chemotherapy	0.64 (0.33)
3 rd line chemotherapy	0.77 (0.14)
Progressed disease	0.56 (0.27)
Off treatment pre-progression	0.77 (0.14)

Abbreviations: EQ-5D, Euroqol 5 Dimension; SD, standard deviation

The EAG accepted there may be selection bias in that the study selected patients with a favourable response to chemotherapy, despite this factor the EAG still consider the utility values from this source to be more appropriate than the source used in the company base case (Shingler et al, 2013³⁵) as they are estimated from patients with STS in a clinical trial setting using the EQ-5D as opposed to using vignettes.

Given that the Reichardt 2012³ utility values are reported by line of therapy rather than by disease severity (which is how the company model is structured), the EAG applied the first-line chemotherapy utility value to the stable disease health state. The incremental difference between the company's base-case utilities for partial response and stable disease was applied to the EAG base case stable disease utility to reflect the improvement in health-related quality of life associated with a partial response. The same approach was followed for the complete response health state. The progressed disease utility value from Reichardt 2012 was applied directly to the progressed disease health state in the EAG base case. The EAG base case utility values are presented in Table 40.

In the company's base case (Table 39), patients who achieved a complete response were assumed to accrue utility values equivalent to UK population norms. Clinical experts consulted by the company considered this assumption reasonable. However, the EAG believed that a complete response may not equate to the absence of symptoms or functional impairment, particularly where residual tumour mass or pain persists. The EAG considered that applying general population utility values to patients with a complete response may overestimate health-related quality of life in complete responders. This was tested in sensitivity analysis.

In response to clarification questions, the company conducted a scenario analysis with the Reichardt 2012³ 1st line chemotherapy utility value (0.72) applied to the stable disease, partial response and complete response health states and the progressed disease utility value (0.56) to the progressed disease health state.

Table 39 Company base case utility values

Health state	Utility value	Data source	Incremental vs SD
SD (on or off treatment)	0.736	Shingler, 2013 (mean utility value for 'SD') (Shingler et al. 2013 ³⁵)	0
PR (on or off treatment)	0.792	Shingler, 2013 (mean utility value for	0.056

Health state	Utility value	Data source	Incremental vs SD
		'treatment response') (Shingler et al. 2013 ³⁵)	
CR (on or off treatment)	0.860	UK population norms for EQ-5D (Kind et al. 1999 ⁴⁵)	0.124
PD	0.263	Shingler, 2013 (mean utility value for 'PD') (Shingler et al. 2013 ³⁵)	-0.473

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease.

Table 40 EAG base case utility values

Health state	Utility value (Base case)	Utility value (scenario)	Data source
SD (on or off treatment)	0.720	0.720	Reichardt 2012 ³
PR (on or off treatment)	0.775	0.775	Company base case incremental utility PR vs SD relative to EAG base case SD utility
CR (on or off treatment)	0.841	0.841	Company base case incremental utility CR vs SD relative to EAG base case SD utility
PD	0.560	0.720*	Reichardt 2012 ³

Abbreviations: CR, complete response; EAG, external assessment group; EQ-5D, Euroqol 5 dimension, PD, progressed disease; PR, partial response; SD, stable disease. Notes: PD utility assumed to be the same as stable disease in a scenario.

Additionally, the company's HRQoL SLR identified Liedgens et al. (2016),⁴⁶ a burden-of-illness study in patients with neuropathic pain. The company highlighted a substantial overlap in symptom burden and functional impairment between DT and CNP, particularly regarding chronic pain, mobility limitations, and psychological distress. Liedgens 2016 reported that UK patients with a mean BPI pain score of 5 had an associated EQ-5D utility value of 0.57. Given that the De-Fi trial defined uncontrolled pain as a BPI score greater than 4, and 41% of patients in De-Fi reported uncontrolled pain at baseline, the EAG considered these findings to support a progressed-disease utility value closer to (and likely greater than) 0.57, rather than the substantially lower value of 0.263 used in the company's base case.

The EAG included a scenario in which the utility value accrued by progressed patients was assumed to be the same as the utility value accrued by stable patients (Table 40). The

progressed disease estimates from Reichardt 2012 may overstate the impact of a progressing desmoid tumour, as they are from metastatic soft tissue and bone sarcoma. The EAG believes the truth likely lies somewhere between this scenario and the base case assumption.

Overall, the EAG includes that the company's approach of using Shingler 2013 is inadequate. The EAG believes that using mapped data from the trial would have been the most appropriate option and it is a key limitation that the company has refused to present these data which introduces substantial uncertainty. The EAG's approach represents the best available option given the data provided.

4.2.6.2. Adverse events

Explicit utility decrements were modelled, using a mixture of different published sources (Table 3.17 of the company submission). The decrement associated with diarrhoea was taken from Shingler et al. (2013).³⁵ The decrement associated with rash or skin disorders was taken from Nafees et al. (2008).⁴⁷ Folliculitis was assumed to have the same impact as rashes or skin disorders. The utility decrements associated with these events were assumed to last for 7 days. Figure 2.17 in the company submission showed that the rate and severity of adverse events substantially diminished after the first year.

The EAG broadly accepted the approach taken to modelling the utility impact of these adverse events.

The company modelled ovarian dysfunction as an event, which lasted for ■ days. The utility decrement (-0.095) was taken from van Stein et al. 2023.⁴⁸ It was assumed that a fixed proportion of patients experienced this event each cycle. This is an inappropriate approach to modelling ovarian dysfunction. In the trial, a proportion of patients experienced ovarian dysfunction once they started treatment. There were ■ patients in the nirogacestat arm who experienced ovarian dysfunction (■), they experienced it for an average of ■ days, or approximately ■ cycles. This yields a total decrement of ■ per patient.

The company stated that they amended the model at the clarification stage, so that ■ of patients experienced ovarian dysfunction for ■ days, to align with the trial. However, the model file did not contain this change, so the EAG implemented it instead. More detail on this is provided in Section 4.2.5.6.

This utility decrement does not capture any impact of ovarian dysfunction on the patients' fertility. The appropriate method for modelling the health impacts of lack of fertility is an area for future research within health economics. Excluding this consideration means that application of the utility decrement for ovarian dysfunction can be thought of as potentially understating their overall impact on the patient.

4.2.6.3. Carer utilities

The company included carer disutilities in a scenario analysis. A utility decrement of -0.07 was taken from a previous NICE submission (HST20). This was applied to all patients with progressive disease. This decrement came from a source which relates to carers of children with activity limitations as a result of non-ambulatory Duchenne Muscular Dystrophy (DMD). This includes children who have lost the ability to walk independently and are wheelchair dependent. It may therefore overstate the utility impact of caring for an adult with activity limitations.

The NICE Reference Case⁴⁹ states that carer disutilities should be included in the base case analysis, where relevant but the evidence provided to support inclusion of carer disutilities in this case was not particularly strong.

Clinicians stated that the patients with active caregivers would be those with progressed disease, whose tumour is causing them pain and generally those where the tumour is on a limb joint. There were 42% with uncontrolled pain at baseline in the De-Fi trial. This was in line with feedback from one clinician who said that around 30-40% of patients who are progressing would have a carer supporting them with daily activities. Another said that: 'It could be 20-30% of the desmoid population with progressive tumours that have pain.'

The EAG applied the carer utility decrement to 40% of patients with progressive disease, in a scenario.

The EAG preferred to apply the method recommended in Pennington et al. (2025),⁵⁰ where a multiplier of 0.12 is applied to the difference between the patients' utility in a state that requires caring and a state that does not. This would be applied to the difference between the stable disease and progressed disease utility (0.16 in the EAG base case) to give a carer decrement of 0.0192 per patient year in the progressed health state.

4.2.7. Resources and costs

4.2.7.1. Treatment costs

Nirogacestat was assumed to be taken in the form of three 50mg pills taken twice daily. The list price per pack of 56 nirogacestat pills was £15,189.04. The PAS price for nirogacestat was [REDACTED]. The relative dose intensity (RDI) of nirogacestat was [REDACTED] based on the De-Fi trial.

Chemotherapy was modelled as a class, with the cost of vinorelbine used in the base case, with the costs of doxorubicin and methotrexate with vinblastine used in sensitivity analysis.

Vinorelbine is taken as three 90mg doses per 28-day cycle. The price for vinorelbine is £29.50 per 30mg tablet. Doxorubicin is taken as one 10mg/5ml IV infusion, with 1.25 doses per cycle. The price for doxorubicin was £4.20 per 10mg/5ml infusion. Methotrexate is taken as 30mg/m² with vinblastine taken as 5mg/m², each taken every 6 weeks. The cost of methotrexate was £21.93 for five 50mg/2ml vials. The price of vinblastine was £82.65 for five 10mg/10ml vials. Patient's average body surface area in the De-Fi trial was 1.9m². The maximum lifetime dose for doxorubicin of 550mg p/m² which equates to [REDACTED], which means approximately 6 months of treatment. The cost of chemotherapy was assumed to apply for one year based on clinician advice about the maximum course of vinorelbine they would prescribe clinical practice. A scenario was implemented where it was assumed to be used for 6 months. No data were available for relative disease intensity (RDI) for chemotherapy, so this was assumed to be the same as for nirogacestat.

A cPAS appendix is not required, as there are no comparators with confidential prices.

A drug administration cost of £152 was assumed for IV treatments, which was based on the National Schedule of NHS Costs (2023/2024).⁴² This assumes that all IV treatments would be administered in an outpatient setting. This was a reasonable assumption given the patient population. No drug administration cost was assumed for oral treatments.

The company amended the model at clarification stage to account for wastage by assuming that each patient throws away half a pack of each oral medication on average. The EAG supports this approach. They assumed that vial sharing was carried out for IV treatments which the EAG agrees with given that the comparator is a low cost, common chemotherapy treatment.

Table 41 Treatment cost per 28-day cycle

Subsequent treatment	Unit ^a strength	Cost per unit ^a	Dose per admin	Admin cost	Cost per 28-day cycle
Doxorubicin	10 mg	£4.20	130 mg	£152.00 ^b	■
Vinorelbine DHA338	30 mg	£29.50	90 mg	£0	■
Methotrexate	50mg	£4.39	30mg/ m ²	£152.00 ^b	
Vinblastine	10mg	£16.53	5mg/m2	£0	
Methotrexate with vinblastine	-	-	-	£152.00 ^b	■
Nirogacestat	150mg	£230.55 ^c	150mg	£0	■ ^d

Abbreviations: admin, administration; IV, intravenous.

^a A unit refers to a tablet, capsule, or vial.

^b A drug administration cost of £152.00 per IV administration was assumed.

^c List price

^d RDI for nirogacestat from the De-Fi trial was ■. This adjusted cost per 28-day cycle is used in the analyses. Chemotherapy was assumed to have the same RDI due to lack of alternative data.

4.2.7.2. Subsequent treatments

The submission stated that a 'mixed basket' of subsequent treatments was used. In the model, all patients in the progressed disease state were assumed to receive doxorubicin. Clinical experts stated that DT patients who receive chemotherapy generally receive vinorelbine, rather than doxorubicin. This is with the exception of patients who have already received vinorelbine, who would go on to receive doxorubicin. The EAG base case reflected this, with vinorelbine used as subsequent therapy in the nirogacestat and BSC arms, and doxorubicin used as subsequent therapy in the chemotherapy arm. The costs of doxorubicin and vinorelbine using eMIT are presented in Table 41.

4.2.7.3. Concomitant treatments

The company has not included any modelling of concomitant treatments. Table 2.5 in the company submission indicates that the majority of patients were receiving concomitant treatments. The company state that these medicines were excluded as they were mostly low cost and were well balanced across the arms. The EAG accepted this response, as the CSR indicates that these medications were predominantly low-cost pain killers, anti-virals and medications to prevent vomiting.

4.2.7.4. Healthcare resource use

Medical resource use was not evaluated in the De-Fi trial, so disease management costs were informed by published literature. They were summarized in Table 3.23 of the company submission.

A study was identified in the SLR that included healthcare resource use rates from the QUALIFIED observations study (Schut et al, 2013).³⁸ The study included DT patients from the UK and the Netherlands. The study grouped patients according to whether they had high, intermediate or low severity symptoms, and according to pain. These were mapped onto the PD, stable and partial response states, respectively.

The company noted that in the De-Fi trial, patients receiving nirogacestat with stable disease experienced better PROs, including in relation to pain, physical functioning, role functioning and quality of life, compared with patients with stable disease receiving the placebo. The company argued that patients who are on treatment with stable disease should be assumed to accrue the GP and specialist visits associated with 'intermediate symptoms – low pain', whereas stable patients not receiving treatment should accrue the GP and specialist visits associated with 'intermediate symptoms – high pain'. They stated that clinicians supported this assumption.

Given the percentage of patients in the De-Fi trial with controlled pain at baseline (when patients were progressing), defined as a BPI score less than 4 was 39% in the nirogacestat arm and 43% in the placebo arm, the EAG considered it more appropriate to set GP and specialist visit frequency equal between treatment arms in the SD health state (aligned with intermediate symptoms – low pain), as presented in Table 42.

The EAG validated the company estimates of specialist visits with clinical experts. They stated that two specialist visits in stable disease and partial response was not a realistic reflection of clinical reality. They estimated that four specialist visits per year would be a more accurate reflection of the volume of visits for a patient with DT seeing their specialist while in stable disease or partial response. The EAG clinical experts also considered the number of specialist visits for patients in progressed disease to be underestimated in the company base case. They considered six specialist visits per year to be more accurate. The EAG used these assumptions to model specialist visits in its base case presented in Table 42

Schute 2013 did not include all relevant healthcare resources, so the company sourced additional data from Verboom et al. (2019),³⁹ to inform the frequency of laboratory tests, MRI

and CTI scans and hospitalisations. This study was conducted in soft tissue sarcoma patients. The company acknowledged the misalignment and stated that the estimates were validated by clinicians.

The company assumed that patients who achieved a complete response would accrue no healthcare-related resource use. Following consultation with clinical experts, the EAG did not consider it appropriate to assume that patients who achieved a complete response would immediately cease all healthcare-related contacts. Clinical experts stated that patients would be monitored twice per year for five years post treatment. The EAG in its base case assumed two visits per annum for the whole time horizon for patients in complete response. The EAG tested limiting complete response visits to five years post treatment initiation and found it had a negligible impact on the results.

The company calculated the cost of hospitalisations by weighting the mean cost of non-elective inpatient long and short stays. The hospitalisation rate was sourced from Verboom 2019., which reports hospitalisation days; however, the company's base case applied these data as hospitalisation visits.

Upon clarification, the company revised their model to align the hospitalisation frequency inputs. In the revised base case, the per-visit cost of hospitalisation (£2,597) was maintained from the original submission, while the frequency inputs were updated to reflect the number of visits per year rather than the number of days. The updated frequency inputs were 2.6 visits per year for patients in stable disease or partial response, as reported in the UK-specific study by Mytelka 2018 (Mytelka et al, 2018), and 3.9 visits per year for patients in progressed disease, assuming that patients in the PD health state experience 1.5 times the frequency of hospitalisations compared with those in stable disease or partial response. The EAG considered this an appropriate method of modelling hospitalisations related to patients with DT.

The validity of this mapping, and whether these sources represent the best available evidence, is uncertain but healthcare resource use has a minor impact on the incremental results, so this is not considered to be a key area of uncertainty.

The unit costs for physician visits were obtained from the Unit Costs of Health and Social Care 2023 Manual and the National Schedule of NHS Costs 2023/24.⁴² The EAG considers this to be appropriate. The cost of hospitalisations was informed by the weighted mean cost for non-elective inpatient long stay and short stays.

Table 42 Annual healthcare resource utilisation frequency

	SD nirogacestat		SD placebo		PR		CR		PD	
	Company	EAG	Company	EAG	Company	EAG	Company	EAG	Company	EAG
GP (per visit) ^b	2.55	2.55	1.61	2.55	1.18	1.18	0.00	0.00	3.68	3.68
GP DT (per visit) ^b	0.40	0.40	0.21	0.40	0.18	0.18	0.00	0.00	1.02	1.02
Specialist (per visit) ^a	1.96	4.00	2.24	4.00	1.14	2.00	0.00	2.00	2.38	6.00
Full lab test (per test)	12.24	12.24	12.24	12.24	12.24	12.24	0.00	0.00	14.88	14.88
MRI (per test)	0.12	0.12	0.12	0.12	0.12	0.12	0.00	0.00	0.00	0.00
CT scan (per test)	3.72	3.72	3.72	3.72	3.72	3.72	0.00	0.00	4.44	4.44
Hospitalisation visits	2.60	2.60	2.60	2.60	2.60	2.60	0.00	0.00	3.90	3.90

Abbreviations: CR, complete response; CT, computed tomography; DT, desmoid tumour; EAG, external assessment group; MRI, magnetic resonance image; PD, progressed disease; PR, partial response; SD, stable disease

^a. CR specialist visit for the first year post CR only

^b. Data were digitised from Figure 3 from the Schut et al. 2023 publication for healthcare resource use by physical symptom burden clusters. The assumption that high symptom burden could inform PD, intermediate symptoms could inform stable disease (low pain for nirogacestat, high pain for BSC/placebo), and low symptom burden could inform PR was validated with clinical experts.

The terminal care cost was £1,117.42 based on the Unit Costs of Health and Social Care 2024 Manual was applied to all patients who die in each model cycle.⁵¹ The EAG notes that most patients will die of causes unrelated to their desmoid tumour, but inclusion of these costs is unlikely to substantially impact results.

4.2.7.5. Adverse event costs

To reflect the safety profile of treatments in the model, TEAE data from the De-Fi trial was used, where AEs were modelled as either severe/serious (i.e., Grade ≥ 3) one-off events or mild-to-moderate (i.e., Grade 1 or 2) recurring events.

One-off adverse event costs

It was assumed that patients who experienced a one-off adverse event, only accrued the associated resource use once, in the first cycle. Figure 2.17 in the submission shows that the rate and severity of adverse events substantially diminished after the first year. The EAG therefore considered this assumption appropriate.

Costs for managing each AE episode were obtained from the National Schedule of NHS Costs 2023/24.⁴²

The cost of managing diarrhoea was informed by the NHS Reference cost for gastrointestinal infections (weighted average of codes FD01A:FD01J, non-elective setting). The cost of managing folliculitis, and rash or skin disorders, was informed by the NHS Reference costs for skin disorders (weighted average of codes JD07A–JD07K, non-elective setting).

Clinicians advised the EAG that this was likely to overstate the resource use associated with these adverse events as some patients who experienced these adverse events may not have required additional medical care. They suggested that these patients' symptoms would likely improve if they received low-cost medicines to treatment the symptoms.

Removing these adverse event costs has a limited impact on the incremental results, and the approach is conservative, so the EAG did not consider this to be a key area of uncertainty.

Recurring/long term adverse event costs

A proportion of patients in the clinical trial experienced ovarian dysfunction. The way that this was modelled was problematic, as described in Section 4.2.5.6. The company assumed that these patients accrued the costs associated with two hospital visits (WF01A and WF01B) and a

diagnostic ultrasound (FD40Z). The total cost was £485. This was quite a high estimate given that clinical experts suggested some of these patients would merely cease receiving the treatment. Given that this event only occurred in the nirogacestat arm, this made the analysis conservative. This cost was described as a 'recurring adverse event unit cost', and was applied as such, but it was actually a one-off cost. The company should have applied these one-off costs to all patients who experienced ovarian dysfunction in the first cycle. The EAG amended this.

4.2.7.6. Societal costs

Patient and caregiver costs were included in scenario analysis. Productivity loss costs were calculated by multiplying the number of working hours lost per week by health state by the hourly wage and employment rate in the UK. These costs were only applied to the proportion of patients who were employed and only up to the retirement age of 66.

The number of workdays lost was informed by a study of Spanish older adults with post-herpes zoster pain,⁵² which was identified in the systematic literature review. The company stated that 'It was assumed that productivity loss for employed patients would only occur in the PD health state, since it is the most "severe" state (i.e., stable disease, PR, and CR do not have productivity loss).' This approach is not robust as clinicians advised that the impact of desmoid tumours on patients' daily activities is determined by the pain they experience, which in turn is impacted by the location and size of tumour, not its rate of growth over time.

Patients in the PD health state were assumed to lose 6.16 working hours per week, as the study reported a mean of 9.9 workdays was lost over a period of 90 days.⁵²

The company assumed that "0.81 hours of informal caregiver time per week was needed for patients in the PD health state based on the study by Díez-Domingo et al. (2021)⁵² that reported caregivers lost an average of 1.3 paid workdays over a period of 90 days."

Given this scenario is not included in the base case, it has a small incremental impact and it is not in line with the NICE Reference Case, the EAG does not consider this to be an important area of uncertainty.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Company's base case

The company presented base case results pre-clarification questions and an updated base case post clarification questions. The company made a number of changes at the clarification stage, including amending hospitalization rate, implementing drug wastage, changing the modelling of ovarian dysfunction and amending the approach to including ordered parameters in the PSA. These changes were at the request of the EAG and the EAG considered most of the changes to be improvements, except the changes to the modelling of ovarian dysfunction, which were not correct. The company also implemented a PAS discount of [REDACTED] which the EAG used for its analysis.

The company base case results, post clarification-questions, are presented in Table 43. The deterministic incremental cost-effectiveness ratio (ICER) was [REDACTED] per QALY gained including a x1.2 severity weighting.

Table 43: Company's deterministic base-case cost-effectiveness results with severity weighting (PAS price)

-	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Nirogacestat	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: BSC, best supported care; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year;

Note: A severity modifier of x1.2 has been applied to the QALYs in line with the company submission

Table 44: Company's probabilistic base case cost-effectiveness results with severity weighting (PAS price)

-	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	■	■	■	■	■
Nirogacestat	■	■	■	■	■

Abbreviations: BSC, best supported care; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year;

Note: A severity modifier of x1.2 has been applied to the QALYs in line with the company submission

5.1.2. Company's sensitivity and scenario analyses

The company presented scenario analysis in Section 3.10.3 of the company submission. These were run with the old base case, which was then updated at the clarification stage and a cPAS price discount was applied, so these results have been superseded.

The company's probabilistic ICER and deterministic ICER did not differ materially. The relative dose intensity of nirogacestat, the health state utility value for partial responders, the hospitalisation rate and the proportion of patients who responded were all key drivers of cost-effectiveness.

Key scenario analyses that increased the ICER included changing the utility value for patients with progressive disease (from 0.26 to 0.51) and increasing the hospitalisation rate. The key scenario that reduced the ICER included assuming no patients progress from stable disease after they cease nirogacestat treatment. Adopting a societal perspective led a minor reduction in the ICER.

The influence of the hospitalisation rate was likely the result of an error in implementing hospitalisation rates. This was one of the key changes the company made at clarification stage at the request of the EAG, alongside the implementation of drug wastage, changes to the modelling of ovarian dysfunction and amendments to including ordered parameters in the PSA. The company also implemented a PAS discount at clarification.

5.2. EAG's additional analyses

5.2.1. Model validation and face validity check

The EAG identified a few fairly modest errors that are described in the previous section. Overall, the company model had an appropriate lay out and formatting, and the model functionality was fit for purpose.

5.2.1.1. Chemotherapy

The company refused to include chemotherapy as a comparator, even though this was requested and supported by evidence from clinical experts that vinorelbine is in regular use for this patient group. The EAG prefers to include chemotherapy as a comparator. Chemotherapy was modelled as class, using a network meta-analysis. The network meta-analysis was informed by a study of methotrexate with vinblastine.

When the EAG modelled chemotherapy, costs were aligned with vinorelbine in the base case as this is the chemotherapy treatment in most regular use. The costs of doxorubicin and methotrexate with vinblastine were used in scenario analysis. This affects chemotherapy as a comparator and as a subsequent treatment. The assumed effectiveness was unchanged.

5.2.1.2. Error in applying response rates

There was an error in the way the company has applied the transition probabilities for response and partial response. This is described in Section 4.2.5.4. The company started with the proportion of responders at the end of the first year. They used this to calculate a monthly probability of gaining a response, assuming constant transition probabilities. They then applied this to the stable disease health state only. But these transition probabilities were relevant for the whole cohort of patients, whereas the proportion of patients in stable disease reduced each cycle. This caused the model to substantially underestimate the proportion of responding patients in the nirogacestat arm. This meant that there were ■ responders at Year 2 in the model compared with ■ when using the proportions observed in the trial.

This error was addressed as part of broader changes implemented by the EAG to the way in which transition probabilities were calculated within the model, that are described in the next section.

5.2.1.3. Ovarian dysfunction

The company modelled ovarian dysfunction as an intermittent event, when in fact patients predominately experienced it as a single long-lasting event that started on treatment initiation. The company stated that they amended this in the model at clarification stage, but their implementation was not correct. The company continued to model ovarian dysfunction as an intermittent event with a constant risk, they merely assumed that risk turned to zero after [REDACTED] days (the average length of time patients with ovarian dysfunction experienced it for). The company also appear to have assumed [REDACTED] of patients experienced ovarian dysfunction, which was the proportion with 'unresolved' ovarian dysfunction (which appears to mean those still experiencing ovarian dysfunction at the end of the trial period), not the total proportion that experienced it during treatment. The EAG have addressed this, so that ovarian dysfunction matches the trial. A more detailed description is provided in Section 4.2.5.6.

5.2.1.4. Uncertainty for mortality

The company applied an arbitrary log normal distribution to health states where they state that they are assuming mortality is the same as the general population. The EAG has amended this.

5.2.1.5. eMIT error for doxorubicin

The company implemented the cost of doxorubicin incorrectly at £4.08 per unit. The correct price is £4.20 per unit. The EAG amended this.

5.2.1.6. Company corrected base case results

The EAG made several corrections to the company base case. EAG results have been produced using deterministic analyses.

In respect of the severity modifier the EAG calculated the relevant severity modifier for the BSC and chemotherapy comparisons separately and has applied the lowest severity modifier of the two in fully incremental analysis. This was considered appropriate as it is not possible to calculate a different modifier in each comparison within fully incremental analysis and where the severity modifier differed in the two comparisons the lower modifier related to chemotherapy which was understood to be the primary comparator for this patient population (defined in the draft SmPC as eligible for systemic treatment).

The EAG corrections increased the ICER for nirogacestat compared with BSC from [REDACTED] to [REDACTED]. The ICER for nirogacestat increased from [REDACTED] to [REDACTED] in fully incremental analysis,

where chemotherapy became the primary comparator. This means nirogacestat [REDACTED] [REDACTED] at willingness to pay thresholds of £20,000 to £30,000. This increase was because corrections to the transition probabilities and the inclusion of chemotherapy as a comparator meant that the severity modifier no longer applied. Without this change, the impact on the ICER would have been minimal.

None of the individual changes led to substantial changes in the ICER, other than the inclusion of chemotherapy as a comparator and corrections to the transition probabilities.

Table 45: Company corrected base case result

Report section	EAG corrections	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs co.
	Company base case*									
5.2	EAG correction to doxorubicin price*									
5.2	Correction to mortality probabilistic values*									
5.2	Ovarian dysfunction applied as a one-off event, instead of intermittent*									
4.2.4.4	Transition probabilities calculated based on									

	best overall response at 2 Years*	■	■	■	■	■	■	■	■	■
	EAG corrected company base case	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■

Abbreviations: BSC, best supported care; EAG, external assessment group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Note: *A severity modifier of x1.2 has been applied to the QALYs in these scenarios, in all other scenarios no severity modifier was applied

5.2.2. EAG's exploratory analyses using company's base case

5.2.2.1. Calculation of progression and response transition probabilities in the first two years

The company calculated progression risks based on the trial data, then used an erroneous calibration approach to adjust them. The EAG preferred to calculate transition probabilities themselves, based on state membership observed at Year 2 in the De-Fi trial, assuming constant hazards. A detailed description is provided in Section 4.2.5.4.

5.2.2.2. Extrapolation of progression after Year 2

The company assumed that the rate of progression observed within the 2-year randomised period in the De-Fi trial would continue for the rest of the patient's life. This resulted in over 90% of patients having progressed in the BSC arm by Year 5. This was in contrast with the trend observed in the trial in which one patient progressed after month 18 in the nirogacestat arm and no patients progressed after month 18 in the BSC arm. Clinicians also advised the EAG that a substantial portion of patients experience spontaneous regression or stabilisation of disease. The EAG assumed that no additional progression occurred after Year 2.

5.2.2.3. Premature discontinuation

The trial data shows that some patients discontinued treatment before Year 2 for reasons other than progression. The EAG preferred to assume that a proportion of nirogacestat patients discontinue treatment prematurely for reasons other than progression, to align with the clinical trial and expectations in practice. These patients accrued the transition probabilities associated with nirogacestat patients. This was a necessary consequence of the approach taken by the EAG, which in turn was the best available option given the data provided.

Further detail is provided in Section 4.2.5.2.

5.2.2.4. Stopping rule

The company assumed that a two-year stopping rule applied for all patients and that the only patients who discontinued before this were those who progressed. Clinicians informed the EAG that, given the choice, they would not discontinue all patients at Year 2. They would only take patients off treatment if their tumour size had plateaued. The company did not provide clear data on the proportion of patients this would apply to. The EAG showed clinicians data on the

evolution of patients tumour size over the course of the trial. Based on these data, clinicians indicated that they would keep a reasonable proportion of patients on treatment past two years.

The EAG preferred to assume a three-year stopping rule in the base case, based on clinician input, with a two-year and four-year stopping rule tested in scenario analysis. The EAG also modelled the possibility of patients responding after 2 years.

5.2.2.5. Response after year 2

The EAG modelled the possibility of nirogacestat patients responding to treatment in Year 3 (Year 4 in a scenario with a four-year stopping rule). This was based on information provided by the company on the proportion of patients who achieved a response in Year 3 and Year 4 in the De-Fi trial. The model assumed that BSC patients could not achieve a response in Year 3 or Year 4, as no data were available, but this was not considered to be an important area of uncertainty given the low response rates in the BSC arm.

5.2.2.6. Health state utility values

The company used health state utility values from Shingler 2013.³⁵ This included a progressed disease utility value that was implausibly low for this patient group. The EAG prefers to use utility values from Tikhonova 2018² for stable disease and progressed disease, then apply the relative difference between stable disease and partial response and complete response, to model these health state utility values. The EAG, however, notes that considerable uncertainty remains around the utility values used within the model and would prefer the company to present the results of their mapping of the trial data to inform the analysis.

5.2.2.7. Health care resource use

The EAG have made a number of minor amendments to align the modelling of healthcare resource use with input from clinical experts:

The company did not estimate any resource use for patients in complete response. After validation with clinical experts the EAG considered this assumption not to be appropriate, clinical experts stated that bi-annual monitoring would occur for five years post treatment.

EAG clinical experts estimated that six specialist visits per annum was a more accurate reflection of clinical reality compared to the 2.38 visits per annum estimated by the company.

EAG clinical experts estimated that four specialist visits per year would be a more accurate reflection of the volume of visits for a patient with DT seeing their specialist while in stable disease or partial response. The company estimated 1.96 and 2.24 visits for patients in stable disease receiving nirogacestat or BSC respectively and 1.14 for patients in partial response.

5.2.2.8. Summary of EAG base case

Table 46: Summary of EAG's exploratory analyses included within the EAG base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Did not model premature discontinuation	Modelled the possibility of premature discontinuation, using data from De-Fi	Premature discontinuation for reasons other than progression would be expected in clinical practice	4.2.5.2
2	The company assumed a two-year stopping rule	The EAG assumed a three-year stopping rule	This reflects uncertainty about the proportion of people who would continue treatment past Year 2	4.2.5.2
3	Assumed progression rate was constant over time	Assumed no further progression after Year 2.	This reflects the trends observed in the trial and clinical expert opinion	4.2.5.4
4	Assumed not further response after Year 2	Assumed some patients respond after Year 2	Data from the trial suggested that some patients responded after Year 2.	4.2.5.4
5	Used Health State Utility Values from Shingler 2013	Used health state utility values from Reichardt 2012 for SD and PD health states. Used company base case PR and CR incremental utility applied to EAG base case SD for PR and CR utility	This ensured that the health state utility value for PD patients in particular had face validity and reflects input from clinical experts	4.2.6
6	Resource used was informed by	Made minor changes to	This more accurately reflects clinical	4.2.7.4

	Verboom 2019 and Schute 2023.	resource use, based on clinical opinion: Four specialist visits in SD, two specialist visits in PR/CR and six specialist visits in PD	reality in DT patients regarding healthcare resource use	
7	Doxorubicin used as subsequent therapy	Vinorelbine used as subsequent therapy, except for chemotherapy as a comparator, where doxorubicin was used as subsequent treatment.	This was in line with clinician input as to current clinical practice.	4.2.7.2

Abbreviations: CR, complete response; DT, desmoid tumour; EAG, evidence assessment group; GP, general practitioner; PD, progressed disease; SD, stable disease;

5.2.2.9. EAG base case results

Table 47 presents the EAG's base case using the EAG's preferred assumptions. In the fully incremental analysis, vinorelbine was [REDACTED] and nirogacestat was associated with an ICER of [REDACTED], compared with BSC. Nirogacestat was associated with [REDACTED] QALYs and total costs of £[REDACTED], compared with [REDACTED] QALYs and £[REDACTED] costs for BSC and [REDACTED] QALYs and £[REDACTED] total costs for chemotherapy.

The EAG assumption that had the largest impact within the EAG base case was the alternative utility source (Reichardt 2012) with an ICER of [REDACTED]. The ICER for nirogacestat compared with BSC was also substantially increased by implementing a three-year stopping rule.

Assuming no progression after Year 2 meant that [REDACTED] (as the small increase in response was outweighed by increased adverse events), instead of [REDACTED]. This change also increased the ICER for nirogacestat to [REDACTED] in the fully incremental analysis.

Implementing premature discontinuation reduced the ICER for nirogacestat compared with BSC. This was partly due to the assumption made by the EAG that patients off treatment have the same outcomes as those receiving treatment, this was necessitated by the fact that the EAG did not have access to separate data on the outcomes of patients who discontinued treatment. This is not expected to lead to bias in the EAG base case results overall but does potentially skew the results for premature discontinuation when implemented in isolation. Implementing the possibility of patients responding in Year 3 and Year 4 also led to a reduction in the ICER for nirogacestat compared with BSC.

Introducing alternative assumptions for healthcare resource use and assuming vinorelbine was the subsequent therapy used in the nirogacestat and BSC arms, had small impacts on the results.



Figure 18 presents the results of the probabilistic sensitivity analysis. BSC was the most cost-effective comparator in 100% of samples of the PSA. Nirogacestat was associated with an ICER of [REDACTED] compared to BSC in the fully incremental analysis. The cost-effectiveness plane demonstrated that there was substantial uncertainty in incremental quality-adjusted life years between nirogacestat and best supportive care. This is probably largely driven by the fact that the company assumed each health state was independently associated with a standard error of 10% of the mean. This method was used by the company in the absence of information on the uncertainty surrounding each health state utility value. Health state utility values within this model are highly uncertain, so this result is not unrepresentative. Figure 19 also shows that health state utility values were key drivers of the cost-effectiveness results, again likely for similar reasons as those stated above.

Table 47: Results of EAG's base case using EAG's preferred assumptions

Section	EAG base case	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	Fully incremental ICER (cumulative)	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs
	EAG Corrected	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
4.2.4.3	Premature discontinuation included (to match De-Fi)	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
4.2.4.2	3-Year stopping rule	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
4.2.4.4	No progression after Year 2 (matches De-Fi)	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
4.2.4.4	Patients can achieve a response after Year 2 (matches De-Fi)	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
5.2	Utilities taken from Reichardt 2012	■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■
		■	■	■	■	■	■	■	■	■	■

Section	EAG base case	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	Fully incremental ICER (cumulative)	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs
5.2	Alternative HCRU assumptions (monitoring complete responders and more specialist visits)										
5.2	Vinorelbine as subsequent therapy										
	EAG base case										

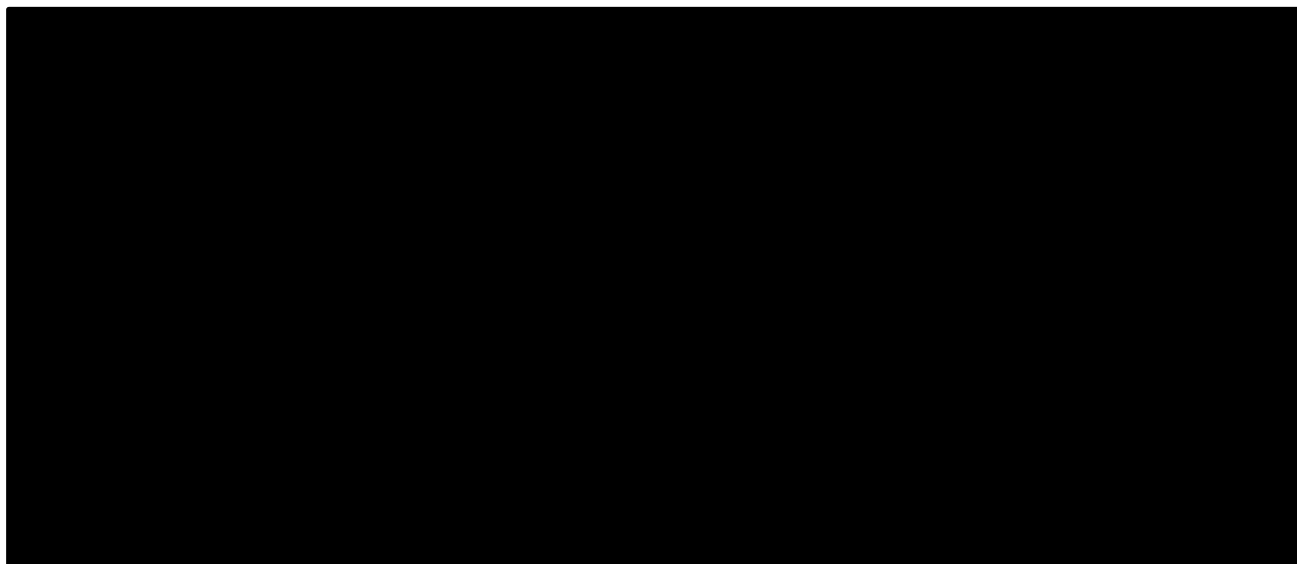
Abbreviations: BSC, best supported care; EAG, external assessment group; HCRU, healthcare costs and resource use; ICER, incremental cost effectiveness ratio; Inc, incremental; NHB, net health benefit; QALY, quality adjusted life year; WTP, willingness to pay

Note: *A severity modifier of x1.2 has been applied to the QALYs in these scenarios, in all other scenarios no severity modifier was applied

Table 48: Results of probabilistic analysis using EAG base case

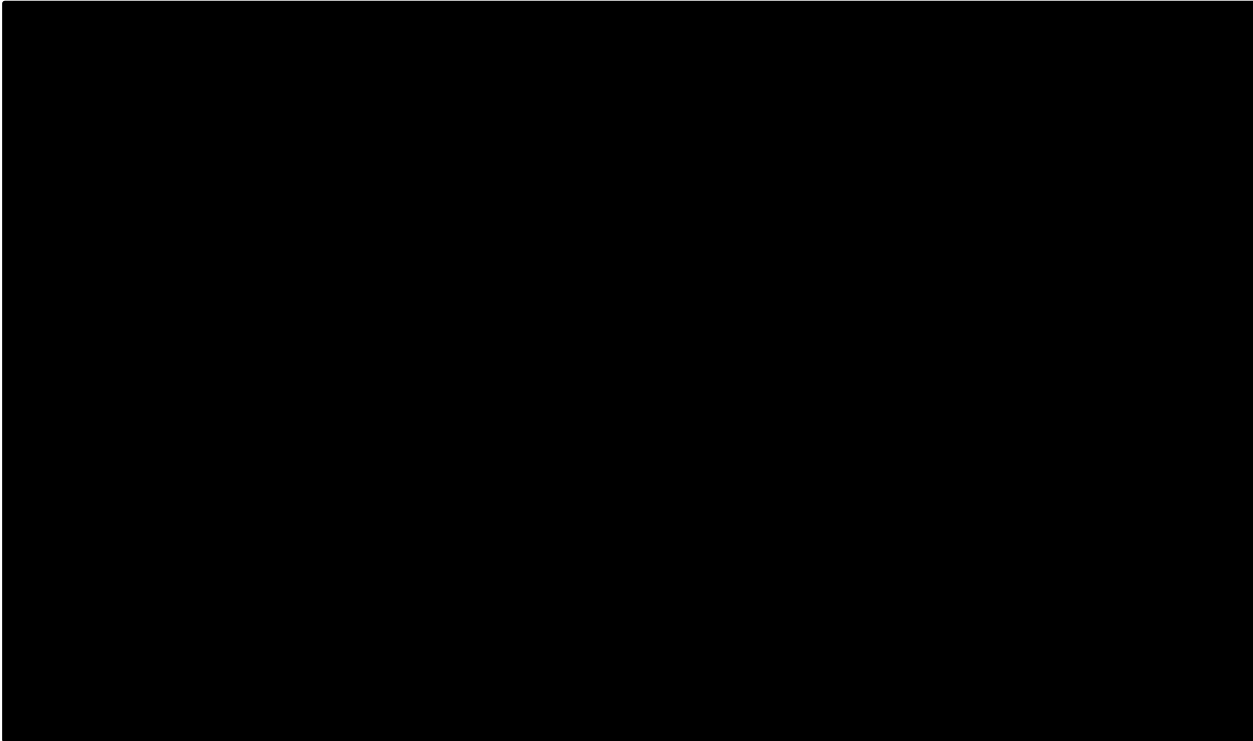
EAG base case	Intervention	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY	% cost effective at £30k threshold
EAG base case							

Abbreviations: BSC, best supported care; EAG, external assessment group; ICER, incremental cost effectiveness ratio; Inc, incremental; QALY, quality adjusted life year

Figure 18: Cost-effectiveness plane in the EAG base case for nirogacestat compared with best supportive care

Abbreviations: EAG, external assessment group; QALY, quality adjusted life year

Figure 19: Cost-effectiveness acceptability curve in the EAG base case



Abbreviations: EAG, external assessment group; QALY, quality adjusted life year

Figure 20: One-way sensitivity analysis in the EAG base case



Abbreviations: BSC, best supportive care; EAG, external assessment group; ICUR, incremental cost-utility ratio; PD, progressive disease; PR, partial response; RDI, relative dosing intensity; SD, stable disease

5.2.3. Scenario analyses using EAG's preferred assumptions

5.2.3.1. Chemotherapy costs

In the base case, patients in the chemotherapy arm were assumed to take vinorelbine. Scenarios were implemented where they received doxorubicin or methotrexate with vinblastine. These scenarios only impacted the costs of treatment, not the health effects. In the base case, chemotherapy costs were assumed to apply for one year, based on clinician feedback. They were assumed to apply for 6 months in a scenario.

5.2.3.2. Stopping rule

The EAG assumed a three-year stopping rule in the base case. The EAG assumed a two, four-year and five-year stopping rules in scenario analysis to test model sensitivity. This is described in Section 4.2.5.2.

5.2.3.3. Mortality

The company assumed a hazard ratio of 1.3 for mortality of desmoid tumour patients, compared with the general population, in the base case (taken from Anneberg et al. 2022⁴¹). The EAG accepted this approach in the base case due to lack of alternative data sources. It tested a mortality hazard ratio of 1 in a scenario, to account for the fact that Anneberg 2022 study is somewhat outdated and clinicians advised that it may overstate mortality risks for desmoid tumour patients in the current English NHS.

5.2.3.4. Extrapolation of progression

In the base case, it was assumed that no progression takes place after Year 2. Scenarios were implemented in which progression continued to Year 2 or Year 3. See Section 4.2.5.4.

5.2.3.5. Carer disutilities

The company included carer disutilities in a scenario analysis. In this scenario, they assumed that all progressed disease patients would require an active carer. The proportion of patients experiencing pain in the trial, and feedback from clinicians, suggested that only a fraction of progressed disease patients would require an active carer (See Section 4.2.6.3). The EAG included a scenario in which 40% of progressed disease patients required an active carer.

5.2.3.6. Health state utility value for patients with progressed disease

The EAG included a scenario in which the utility value accrued by progressed patients was assumed to be the same as the utility value accrued by stable patients (Table 40). The progressed disease estimates from Reichardt 2012 may overstate the impact of a progressing desmoid tumour, as they are from metastatic soft tissue and bone sarcoma. The EAG believed the truth likely lies somewhere between this scenario and the base case assumption.

5.2.3.7. Progression-free survival for chemotherapy

In the base case, the effectiveness of chemotherapy for PFS was assumed to be the same as BSC. A scenario was implemented in which the effectiveness of chemotherapy was assumed to align with nirogacestat. See Section 4.2.5.4.

Table 49: Summary of EAG's scenario analyses using EAG's preferred assumptions

	EAG's base-case assumption	EAG's scenario
1	Chemotherapy cost assumed as vinorelbine cost	Chemotherapy cost assumed as methotrexate with vinblastine cost
2	Chemotherapy cost assumed as vinorelbine cost	Chemotherapy cost assumed as doxorubicin cost
3,4,5	Stopping rule = 3 years	Stopping rule or 2 years, 4 years or 5 years
6	Mortality HR = 1.3 (Anneberg 2022 ⁴¹)	Mortality HR = 1
7	No additional progression occurs after Year 2	Progression risk is constant after Year 2
8	Cost of chemotherapy applies for one year	Cost of chemotherapy applies for two years
9	Excluded carer disutilities	Included carer disutilities, for 40% of PD patients
10	HSUV PD was 0.57, taken from Reichardt et al. 2012	A scenario where the HSUV for PD was equal to the HSUV for SD
11	PFS for chemotherapy assumed to align with BSC	PFS for chemotherapy assumed to align with nirogacestat
12	Monitoring for complete responders for whole lifetime	No resource use for complete responders 5 years from treatment initiation

Abbreviations: BSC, best supportive care; EAG; evidence assessment group; HR, hazard ratio; PFS, progression

5.2.3.8. EAG scenario analysis

Table 50 presents the EAG's scenario analyses. Several scenarios increased the ICER for nirogacestat. These included increasing the time before applying the stopping rule. There was

an ICER of [REDACTED] for nirogacestat vs BSC with a 4-year stopping rule and [REDACTED] with a five-year stopping rule, in the fully incremental analysis. Increasing the utility value accrued by progressed patients to align with stable patients, yielded an ICER of [REDACTED] for nirogacestat vs BSC. In a scenario where PFS for chemotherapy was aligned to nirogacestat instead of BSC, chemotherapy dominated BSC and the ICER for nirogacestat compared with chemotherapy was [REDACTED] in the fully incremental analysis.

Several scenarios reduced the ICER for nirogacestat. These included implementing a 2-year stopping rule, which was associated with an ICER of [REDACTED] for nirogacestat vs BSC. Assuming constant extrapolation of progression to Year 3 was associated with an ICER of [REDACTED]

Altering the cost of chemotherapy, implementing a mortality hazard ratio of 1, including carer disutilities and assuming no healthcare resource use for complete responders after Year 5, all had modest impacts on the results.

Table 50: Results of EAG's scenario analyses

Section	EAG base case	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs
	EAG base case									
										
										
5.2	Methotrexate with vinblastine chemo cost									
										
										
5.2	Doxorubicin chemo cost									
										
										
4.2.4.2	2-year stopping rule									
										
										
4.2.4.2	4-year stopping rule									
										
										
4.2.4.2	5-year stopping rule									
										
										
4.2.4.5										

Section	EAG base case	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs
	Mortality HR of 1									
4.2.5.4	Constant extrapolation of progression to Year 3									
4.2.7.1	Cost of chemotherapy applies for 6 months									
4.2.6.3	Carer disutilities calculated using Pennington 2025 (assume 40% of PD patients have a carer)									
4.2.6.1	HSUV for PD = SD									
4.2.5.4	Chemotherapy PFS equal to nirogacestat									
4.2.7.4	No resource use for complete									

Section	EAG base case	Intervention	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Fully incremental ICER	ICER niro vs comparator	NHB (£30k WTP)	+/- EAG corrected vs
	responders 5 years from treatment initiation									

Abbreviations: BSC, best supported care; chemo, chemotherapy; EAG, external assessment group; HCRU, healthcare costs and resource use; ICER, incremental cost effectiveness ratio; inc, incremental; QALY, quality adjusted life year; WTP, willingness to pay

5.3. Decision modifiers

5.3.1. QALY weighting for severity

The company calculated the severity weight using the Schneider 2021 QALY shortfall calculator. Data informing the QALY shortfall calculation for the reference case were based on:

- Life tables: England, 2017-2019 (pooled) (Office for National Statistics 2024b);
- Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study (MVH Group 1995);
- Health state profiles: EQ-5D-3L from the Health Survey for England 2014 (University College London 2014), Model: ALDVMM by Hernández Alava et al. (2022).

Table 51: Summary of company's and EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)	Reference to section in submission or rationale
Sex distribution	64.8% female	De-Fi trial
Starting age	37.20	De-Fi trial
Discount rate	3.5%	NICE Reference Case

The key parameters used are provided in Table 51: Summary of company's and EAG's preferred assumptions for general population QALY shortfall estimates. This gave total life-time QALYs for this population of 19.39, which yielded an absolute shortfall of [REDACTED] and a proportional shortfall of [REDACTED] %. This implied that a QALY weighting of 1.2x would be acceptable in the company base case. The company's approach to calculating the severity weighting itself was appropriate.

When chemotherapy is introduced as a comparator in the company base case with no other changes a severity modifier of 1.2 remains applicable, however, in the EAG corrected base case the relevant severity modifier drops to 1 versus chemotherapy (1.2 versus BSC).

In the EAG base case, the absolute shortfall fell to [REDACTED] and the proportional shortfall fell to [REDACTED] versus BSC. This was primarily impacted by differences in progression rates and the health state utility value accrued by progressed patients. This meant that a weight of 1x is acceptable for nirogacestat and chemotherapy compared with both BSC and chemotherapy in the EAG base case.

5.3.2. Uncaptured benefits

The company stated the following in the submission:

'Nirogacestat may offer some benefit to QALYs through increasing the capacity for patients and caregivers to work and allowing patients to have a long-term positive outlook on life; however, it was not possible to capture this in the model design and economic analysis because there were no published data'

The company included a scenario with a societal perspective. The EAG believed that these benefits would be modest given that only a subset of patients enter the progressed disease state and clinicians advised the EAG that only a subset of the patients in the progressed disease state would experience pain and mobility issues substantial enough to impact their activities of daily living. Nonetheless, these impacts would be important to that patient group. Scenario testing around the impact of including carer utilities showed a limited impact on the ICER.

5.3.3. Health inequalities

The company submission did not discuss health inequalities. These are not thought to be a key consideration in relation to this submission.

5.4. Confidential comparator and subsequent treatment prices

There were no comparators or subsequent treatments included in this report with confidential prices and therefore no cPAS appendix is presented.

5.5. Conclusions of the cost-effectiveness section

The company did not include chemotherapy in their analysis, even though it is a relevant comparator and they were requested to do so.

The EAG corrections increased the ICER for nirogacestat compared with BSC from [REDACTED] to [REDACTED]. The ICER for nirogacestat increased from [REDACTED] to [REDACTED] in fully incremental analysis, where chemotherapy became the primary comparator. This meant nirogacestat [REDACTED] at willingness to pay thresholds of £20,000 to £30,000. This increase was because corrections to the transition probabilities and the inclusion of chemotherapy as a comparator meant that the severity modifier no longer applied. Without this change, the impact on the ICER would have been minimal.

The EAG base case included more substantial changes, which increased the ICER for nirogacestat compared with BSC from to [REDACTED], [REDACTED] the NICE cost-effectiveness threshold of £20,000 - £30,000 per QALY. Chemotherapy was [REDACTED] in the EAG base case. The implementation of the EAG base case assumptions mean that the technology was no longer eligible for a severity modifier.

The key drivers of cost-effectiveness included:

- The health state utility values used, particularly for patients with progressing disease.
- The progression free survival associated with chemotherapy.
- The choice of stopping rule.
- The extrapolation of progression after Year 2.

The company conducted an analysis of healthcare utility data from the De-Fi trial but refused to present their results as they claimed they were not robust. The EAG requested that the company should present the results and did not agree with their justification for not presenting the results. The company used an inappropriate source to model health state utility values. In particular, the health state utility value applied to progressed patients (0.26) was implausibly low as it was in line with utility values observed for patients receiving terminal care. The EAG preferred to use a more appropriate source, in which the health state utility value for progressed patients was 0.56. The EAG believes that even this may overstate the healthcare burden of desmoid tumour patients, as clinicians informed the EAG that some but not all patients with progressing desmoid tumours experience pain and mobility issues. Also, the De-Fi trial did not demonstrate a clear relationship between progressing disease and high pain scores. Health related quality of life studies among desmoid tumour patients could help to reduce uncertainty in this area.

The progression free survival associated with chemotherapy remains an important area of uncertainty. The indirect treatment comparison conducted by the EAG is subject to substantial uncertainty, particularly because the only randomised control study that was included in the NMA was a study in the wrong chemotherapy treatment (methotrexate with vinblastine instead of vinorelbine) and was not designed to be comparative. The results in relation to overall response are thought to be somewhat reliable, but the results in relation to progression free survival lack credibility as they conflict with the overall response results and clinicians suggested

that they suggested the baseline populations were too different between the studies to draw firm conclusions. This is an area in which further evidence collection could substantially reduce decision uncertainty.

The stopping rule again remains an area of uncertainty; the company indicated at clarification stage that they propose a 2-Year stopping rule. Clinicians indicated to the EAG that they would support this, if there were some caveats, including the option for patients to cease treatment early then restart treatment if needed, and the option to keep patients on treatment past two years of treatment, if their tumour size had not yet plateaued. The company did not provide adequate data to confirm what proportion of patients would remain on treatment after two years. Clinicians advised that it would be a minority of patients, based on data from the De-Fi trial on the evolution of patients' tumour sizes. The EAG assumed a three-year stopping rule in the base case, with two year, four-year and five-year stopping rules tested in scenario analysis. This is an area in which further evidence collection, and a clearer definition of the stopping rule in line with clinical expert guidance, could substantially reduce decision uncertainty.

The company model assumed that patients' progression risk would remain fixed indefinitely. This was in contrast to the trend observed in the De-Fi trial and clinical expert opinion. The EAG assumed no further progression after two years. The EAG was fairly confident that this was an appropriate assumption given the evidence available, though studies with larger sample sizes over longer periods, including for best supportive care patients, would provide further evidence to ensure a robust approach to modelling progression over the long term.

There remain a number of key uncertainties that are unresolved. Firstly, relative efficacy of chemotherapy remains highly uncertain. The indirect treatment comparison did not provide reliable information on the progression free survival associated with chemotherapy and clinicians advised that they were unsure of this. They suggested that they would not expect chemotherapy to substantially impact progression free survival, but it would be likely to reduce pain. Comparative evidence was not available for the extent to which the treatments reduced pain and the model structure did not explicitly accommodate the possibility of pain being reduced, other than as a consequence of a response using the RECIST criteria.

Secondly, the long-term outcomes experienced by desmoid tumour patients remain uncertain. Limited data were available for nirogacestat patients over the long term. Data were not available for BSC and chemotherapy patients over the long term. The EAG implemented a number of

scenarios to explore this uncertainty, informed by the trends observed in the trial and clinician input. Data on patient outcomes over the long term would help to reduce this uncertainty.

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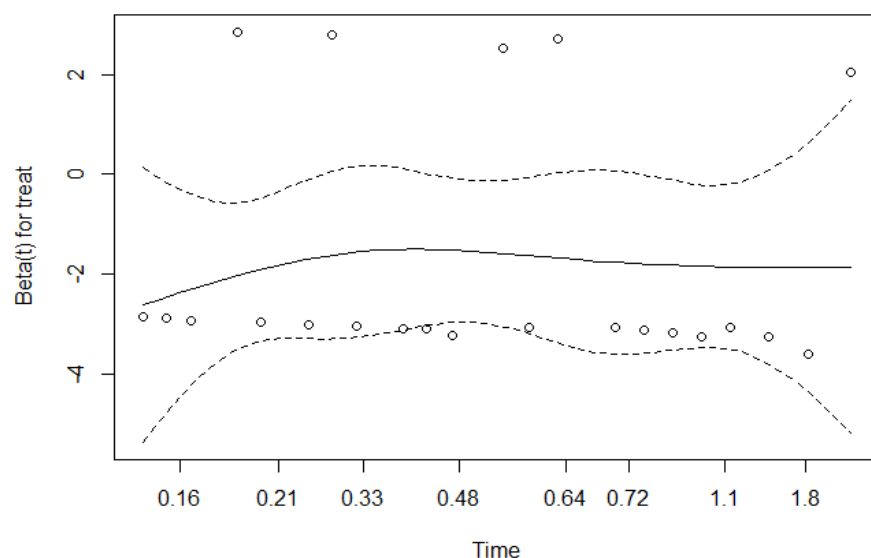
Appendix A: Testing the proportional hazards assumption

This appendix presents the results that were used to determine whether the assumption that hazard functions were proportional between treatment groups was appropriate for the outcome of PFS in each of the studies included in the NMA conducted by the EAG.

Gounder et al. 2018

Results based on digitising the KM curves that appear in Figure 2 of Gounder et al. (2018).

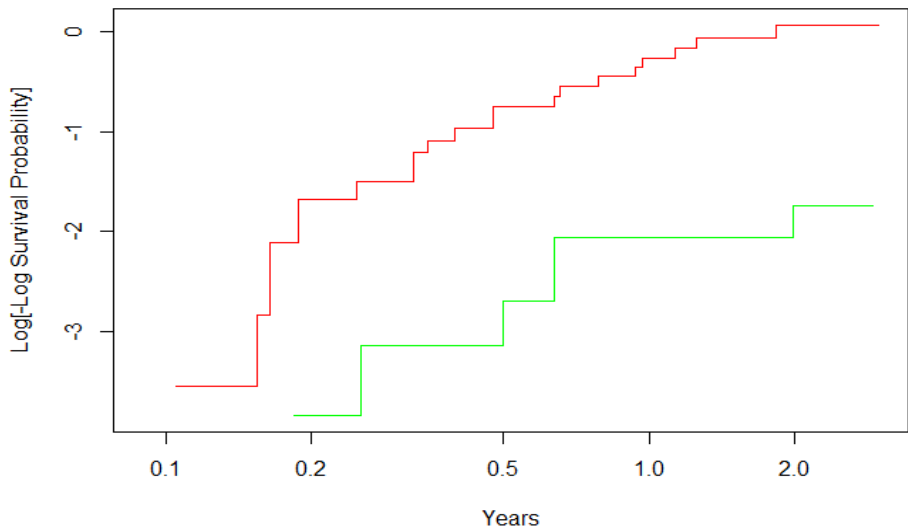
Table 52: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for Gounder et al. (2018)



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

0.0639 (p=0.8)

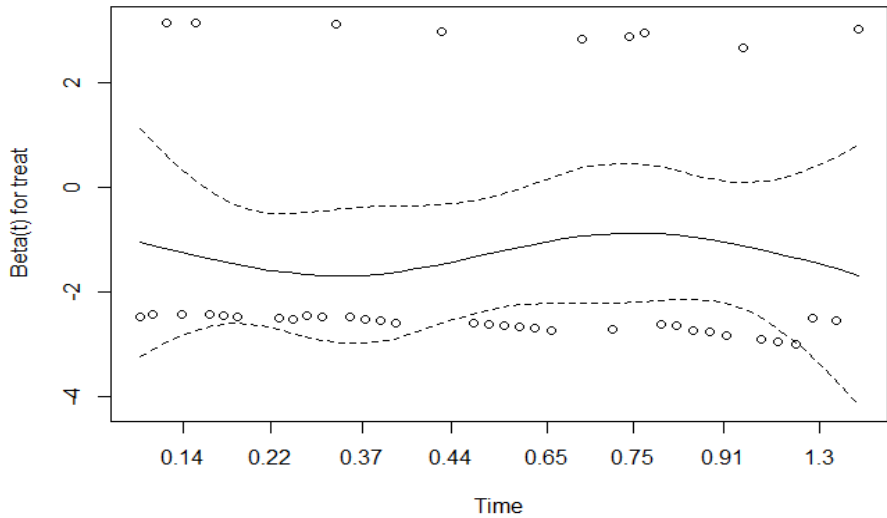
Table 53: Log cumulative hazard plots for the TKI arm (green line) and the placebo arm (red line) of Gounder et al. (2018)



De-Fi (Gounder et al. 2023)

Results based on digitising the KM curves that appear in Figure 1A of Gounder et al. (2023).

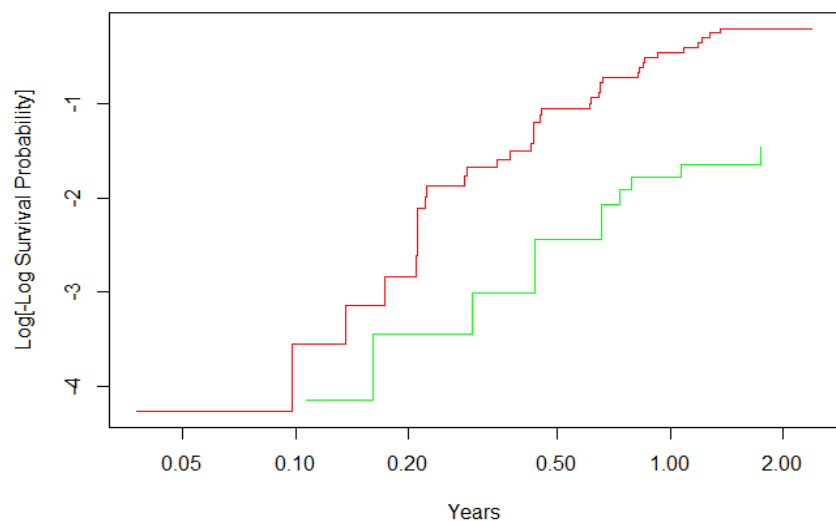
Table 54: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for the De-Fi trial



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

0.0844 (p=0.77)

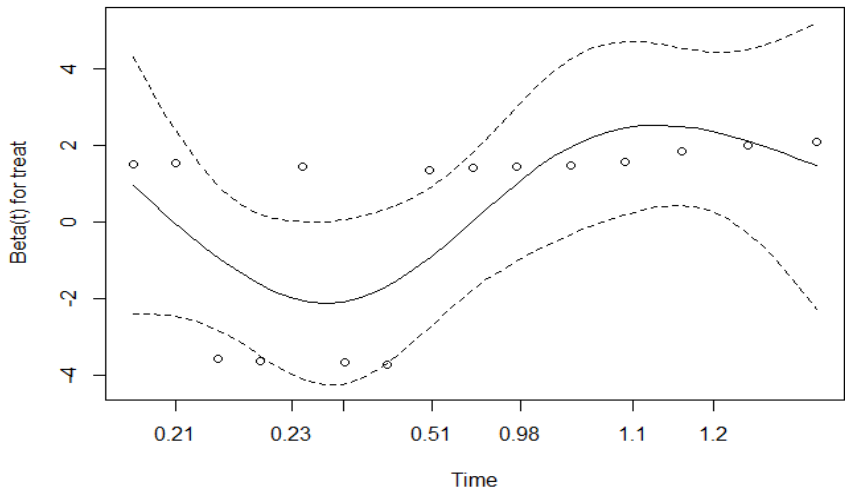
Table 55: Log cumulative hazard plots for the Nirogacestat arm (green line) and the placebo arm (red line) of the De-Fi trial



DESMOPAZ (Toulmonde et al. 2019)

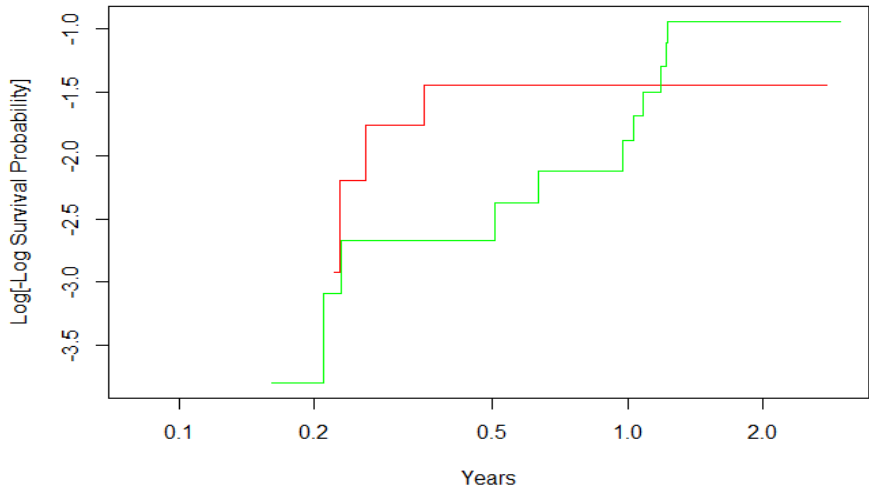
Results based on digitising the KM curves that appear in Figure 2 of Toulmonde et al. (2019).

Table 56: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for DESMOPAZ



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:
3.3 (p=0.069)

Table 57: Log cumulative hazard plots for the TKI arm (green line) and the chemotherapy arm (red line) of DESMOPAZ



Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 10 December 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Frequency of imaging scans for active surveillance

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The frequency of imaging scans for people on active surveillance is not accurately captured per DTWG 2020 guidelines. It is unclear where this statement is from due to the lack of reference. “People on active surveillance are given imaging scans and an assessment every six week or three months depending on their history.” (Section 2.1.1, page 36 of EAG report).	Based on DTWG 2020 guidelines, active surveillance requires continuous monitoring (using MRI or CT), with first imaging completed within 1-2 months, then in 3-6 month intervals (Desmoid Tumor Working Group 2020). The company requests that the language be revised in this section to align with the guidance outlined by DTWG.	This correction will provide an accurate representation of the monitoring required for active surveillance of DT, which is a critical piece of the treatment pathway for DT.	The EAG does not consider this to be a factual inaccuracy. The timings of scans was based on expert feedback received by the EAG. However, the EAG have edited the report to make it clear that this was based on expert feedback.

Issue 2 Inaccurate course of treatment for vinorelbine (chemotherapy)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 4 of the EAG report (pages 38-39) report state that the standard course of treatment is 18 weeks for vinorelbine (chemotherapy). However, this does not align with the number of cycles reported by the NHS (i.e., 12 cycles, with each cycle being 28 days) (National Health Service (NHS) 2025). It is unclear where the 18 weeks is sourced from without a supporting reference.	The company requests that the standard course of treatment be revised to 12 cycles.	12 cycles (with each being 28 days) is much longer than 18 weeks and would therefore have an impact on drug costs.	The EAG does not consider this to be a factual inaccuracy. The course of treatment was based on expert feedback received by the EAG. However, the EAG have edited the report to make it clear that this was based on expert feedback.

Issue 3 Patient-reported outcomes (“double-phase”)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.7 of the EAG report (page 57), it is unclear why only EORTC QLQ-C30 Physical Functioning and EORTC	The company proposes to specify “in the double-blind phase” in the leading sentence of this section, to indicate all PROs are measured in the double-blind phase, removing the specific	This amendment will mitigate possible confusion that only EORTC QLQ-C30 Physical Functioning and EORTC QLQ-C30 Role Functioning	Thank you for pointing this out. The EAG have removed the mention of the double-blind phase. It was not necessary as the

QLQ-C30 Role Functioning specify “during the double-phase period”. The company assumes the “double-phase” is referring to the double-blind phase, in which all of the mentioned PROs in this section are measured during the double-blind phase.	mention for EORTC QLQ-C30 Physical Functioning and EORTC QLQ-C30 Role Functioning.	were measured in the double-blind phase of the study.	timing (baseline to Cycle 10) was stated.

Issue 4 Objective response rate data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The objective response rate 95% confidence interval reported for the nirogacestat arm is not reported correctly in Table 11 on page 63 of the EAG report.	Data based on the DeFi CSR was used to inform the submission, which reported the objective response rate, n (%) [95% CI] for the nirogacestat arm to be 29 (41) [29.8, 53.8].	This update will correctly report the objective response rate data per the DeFi CSR.	Thank you for pointing this out. It has been updated in line with the company’s suggestion.

Issue 5 Incorrect patient-reported outcomes section number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.3.4 of the EAG report (page 63), the section referencing the results of the PROs in the company submitted template is not reported correctly.	The EAG report states that the results of PROs in the DeFi trial were reported in Section 2.6.6.4. However, this section of the company submitted document reports the OLE results, whereas the data presented is from the double-blind phase of the study. Please revise the section number on page 63 of the EAG report to Section 2.6.5 of the company submitted document, which reports PRO data from the double-blind phase of the study.	This amendment will clearly reference where the double-blind PRO data is housed within the company submitted document. Presenting data from the double-blind phase, while linking to the OLE section may source confusion.	Thank you for pointing this out. It has been updated in line with the company's suggestion.

Issue 6 Incorrect hazard ratio reported for PFS subgroup (participants whose DT was relapsed or refractory to treatment)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.3.8.1 of the EAG report (page 71), the hazard ratio reported for the PFS subgroup for participants whose DT was	Please revise the hazard ratio to be 0.30 (currently 0.20), to align with the data in Figure 3 of the EAG report.	This amendment will ensure the correct data is presented and is aligned with Figure 3 of the report.	Thank you for pointing this out. It has been updated in line with the company's suggestion.

relapsed or refractory to treatment is incorrect.			

Issue 7 Incorrect extent of exposure section number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.3.9 of the EAG report (page 73), the section referencing the extent of exposure in the company submitted template is not reported correctly.	The EAG report states that the extent of exposure data is presented in section 2.22.1 of the company submitted document. However, this data is presented in section 2.11.1. Please revise this to section 2.11.1.	This amendment will ensure that the correct section in the company submitted document is referenced.	Thank you for pointing this out. It has been updated in line with the company's suggestion.

Issue 8 Incorrect table title on Table 15 of EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Table 15 title on page 76 of the EAG report states "Grade ≥ 3 TEAEs occurring in $\geq 4\%$ of participants in either arm (safety population)". Per the DeFi CSR and the company submitted document, this should report Grade ≥ 3	Please revise the table title of Table 15 to "Grade ≥ 3 TEAEs occurring in ≥ 2 participants in either arm (safety population)."	This correction will ensure that the data presented in Table 15 of the EAG are accurately described and aligned with the data presented in the DeFi CSR.	The EAG reported Grade ≥ 3 TEAEs occurring in $\geq 4\%$ of participants in either arm in Table 15 rather than reproducing the company's table in the CS / CSR. No

TEAEs occurring in ≥ 2 participants.			changes have been made to the report.

Issue 9 Incorrect reference to clarification response number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4.1.2 on page 80 of the EAG report, there is reference to a clarification response submitted by the company related to the feasibility of indirect comparisons. Clarification response A4 is cited, however, this should indicate clarification response A14.	Please correct “A4” to “A14” in the following statement: “However, as noted by the company in their clarification response (A4), there were limited relevant studies in the DT population, and it would not have been possible to form a network without including this trial.”	This amendment will refer to the appropriate clarification response (A14), for ease of reference.	Thank you for pointing this out. It has been updated in line with the company’s suggestion.

Issue 10 EAG correction to timing of progression in trace

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The problem relates to the correction noted on page 30 and 150 of the EAG report (“EAG correction to timing of progression in trace”) and	The company requests that this EAG correction be removed.	This correction is not required for the company submitted base case and incorrectly suggests that the	The EAG identified a minor issue with the labelling of this change in the model which has been corrected, though

described more fully in cells B30:M30 of the 'EAG sheet' in the EAG model. In the model, the EAG claimed that the "company linked progression column to incorrect cycle row". The company wishes to clarify that this was not an error but an intentional programming choice. The below explanation is provided for column U in the 'Trace – Nirogacestat' sheet; similar explanations apply to the other columns/sheets wherein this EAG correction was implemented. This programming choice was made intentionally to satisfy the assumption that after 2 years, patients on tx will move to off tx. U13 is set up to use the prior cycle row (G12) when checking treatment duration to make sure that at the first cycle after 2 years (cycle 27), patients from SD on tx move		company made an error in their analysis.	this is not believed to impact the results. The EAG accepts the company's explanation. The EAG agrees the change is not correct when applied to the company base case. The change is a necessary part of the EAG base case. If this change were not implemented in the EAG base case, progression would be extrapolated for an additional cycle, which would be incorrect. The EAG has therefore altered this change, so that it only applies in the EAG base case (specifically when the scenarios related to early discontinuation and extrapolation of progression both apply).

to SD off tx and PD. If U13 does not use G12 and uses G13 as other columns, at cycle 27, all patients from SD on tx will move to SD off tx and no patients will go to PD, which is not correct. So overall, the programming is done to allow patients to move to PD at the first cycle after treatment duration. Furthermore, this rationale can be visualized by adding a plot of how patients in each health state move. If the programming is not done as described herein, there will be a gap at the cycle 27.			Removing this change from the EAG corrected company base case had a minor impact, reducing the ICER for nirogacestat compared with BSC from [REDACTED] to [REDACTED].

Issue 11 Vinorelbine Dosing Schedule

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
A vinorelbine dosing schedule of three 90 mg doses per 28-day cycle aligns with that reported for patients with DT in the	The company requests that the inconsistency in vinorelbine dosing schedule on page 106 of the EAG report ("three 30 mg pulls during 28 days of treatment") be corrected to	The requested amendment is required to ensure a consistent description of the vinorelbine dosing schedule throughout the EAG report.	Thank you for highlighting this typo, it has now been corrected.

published literature (Gennatas, Chamberlain et al. 2020). Thus, the company believes that the correct vinorelbine dosing schedule has been noted on page 138 of the EAG report ("Vinorelbine is taken as three 90mg doses per 28-day cycle") and applied in the EAG model. However, there is an inconsistency in how this dosing schedule is described on page 106 of the EAG report ("three 30mg pills during 28 days of treatment").	align with that described in the published literature and reported on page 138 and used in the EAG model ("three 90 mg doses per 28-day cycle").		<i>'They said that these patients primarily received three 90mg doses during 28 days of treatment, doxorubicin is also used but rarely.'</i> Page 105

Issue 12 Section 5.2.1.6 Heading

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Section 5.2.1.6 heading on page 148 of the EAG report is currently a duplicate of the 5.2.1.5 heading ('eMIT error for doxorubicin').	The Section 5.2.1.6 heading should be amended to "Varying of drug costs in PSA"	The requested amendment is required to accurately communicate the content within Section 5.2.1.6.	Thank you for highlighting this issue, this heading has now been removed in response to Issue 13.

Issue 13 Varying of drug costs in PSA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG reports that the “company treated drug costs as probabilistic in the base case when it is convention to treat these as fixed”. The EAG implemented a correction to fix this (Section 5.2.1.6 on page 148 of EAG report and Table 45 on page 151 of EAG report [Drug costs fixed in PSA (not variable)]). The company wishes to clarify that, although the submitted model includes an option to vary drug costs in the probabilistic analysis, this option was set to “No” in the submitted model (L370 of Parameters sheet). Thus, no correction is required.	The company requests that this EAG correction be removed.	This correction is not required for the company submitted base case, nor does it impact the results of the probabilistic analysis. Thus, this correction incorrectly implies the presence of an error in the company’s submitted model.	Thank you for highlighting this issue. The EAG accepts the company’s explanation and has removed this amendment from the report and model file.

Issue 14 Table 46, Exploratory Analysis 6, EAG Scenario Inputs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company is aligned with the updated healthcare resource use inputs used in the EAG model and reported in Table 42 on page 142 of the EAG report (2.55 GP visits [SD] and 1.18 GP visits [PR]; 4 specialist visits [SD] and 2.0 specialist visits [PR]), as these reflect variable use of resources across health states, similar to what was assumed in the company submission. However, there is an inconsistency in how these inputs are described in Table 46 on page 155 of the EAG report (“Four GP and specialist visits per year in SD/PR”).	The company requests that the inconsistency in healthcare resource use inputs on page 155 of the EAG report (“Four GP and specialist visits per year in SD/PR”) be corrected to align with that reported on page 142 and used in the EAG model (2.55 GP visits [SD] and 1.18 GP visits [PR]; 4 specialist visits [SD] and 2.0 specialist visits [PR]).	The requested amendment is required to ensure a consistent description of the updated healthcare resource use inputs throughout the EAG report	EAG has edited table 46 to reflect table 42. “Minor changes to resource use Four specialist visits in SD, two specialist visits in PR/CR and six specialist visits in PD”

Issue 15 Uncertainty for Mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG assumed no uncertainty for mortality hazard ratios versus the general population (Section 5.2.1.4, page 148 of EAG report); however, this assumption may not accurately incorporate potential uncertainty in mortality risk among the population of interest. Furthermore, the company's decision to assess the impact of this uncertainty in a probabilistic analysis should be interpreted as an intentional modelling decision, rather than an error.	The company requests that EAG keep the mortality hazard ratios varied in the probabilistic analysis to account for potential uncertainty, or, at minimum, the company requests that the EAG does not describe this decision as an error in the company submitted model.	The requested amendment will more accurately reflect potential uncertainty in the mortality hazard ratios and, moreover, will avoid suggesting that the company made an error.	The EAG does not believe that applying the log normal distribution to a mortality hazard ratio of 1 was appropriate in this instance. It is an assumption that the hazard ratio is one and there are no data to inform a credible interval around this value. Also, as currently implemented, these hazard ratios are varied independently, which means that in some runs of the PSA, complete response patients face a higher mortality risk than partial response patients, for example. This means that overall, the EAG believes the company's approach to including these variables in the

			PSA introduced more uncertainty than it addressed. Nevertheless, the EAG does not believe this to be a key area of uncertainty and it is unlikely to substantially impact the results, given that mortality overall has a small impact on the results of this model.

Issue 16 HR used in PD Health State for Probabilistic Analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In cell S65 of the 'Parameters' sheet of the EAG model, the formula assigns a HR of 1.00 to the probabilistic analysis for the PD health state, irrespective of whether the variable EAGsw_mortality is toggled between 1.00 and 1.30. For example, in the current model, please notice that F65 of the Parameter sheet	The company requests that EAG correct the programming in cell S65 of the 'Parameters' sheet to align with whichever input is being used for the deterministic analysis (i.e., 1.0 or 1.3, depending on the input selected for EAGsw_mortality) rather than being hardcoded as 1.0.	The amendment is required for accuracy of the probabilistic analysis.	Thank you for highlighting this. This has now been corrected in the EAG model file. This change does not impact the results presented by the EAG as the EAG only presented probabilistic results in the EAG base case (as a result of the PSA run time and small

uses a value of 1.30 in the deterministic analysis, whereas S65 is set to 1.00 for the probabilistic analysis.			difference between deterministic and probabilistic results). In the EAG base case, the correct value is 1, which is the value that this cell is hard coded to.

Issue 17 Time Horizon

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report claims that the model time horizon was 82 years and extended to age 120 (Section 4.2.2, page 104 of EAG report, and Table 27, page 102 of EAG report). The company believes that the EAG has made this claim because the trace sheets in the model extend for 82 years. However, the company wishes to clarify that the total results (costs, LYs, and QALYs) taken from the trace sheets only sum rows that fall within the	The company requests that the EAG remove claims that the time horizon of the model was 82 years.	The amendment is required to adequately reflect the model time horizon.	Thank you for this correction. We have removed the relevant line from the EAG report. This does not impact the results of the EAG analysis.

specified time horizon (e.g., CI11:CV11, CX11:DE11, DI11:DT11, DW11:EJ11, EM11:ET11, and EW11:FH11 on the 'Trace – Nirogacestat' sheet, and analogous cells on the other trace sheets). The time horizon specified in the model is defined as 62.8 years (and is the named variable set_timehorizon).			

Issue 18 Body Surface Area

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 138 of the EAG report states that "Patient's average body surface area in the De-Fi trial was [REDACTED]". However, the company submitted documents and model specified a body surface area of 1.90m ² .	The company requests that the EAG correct this text on Page 138 and implement any downstream calculations, if applicable (note: the correct body surface area of 1.90m ² appears to be used in the EAG model).	The requested amendment is required to accurately reflect the De-Fi trial population characteristics.	Thank you for this correction, this has now been amended. This does not impact the results because the number of required doses is rounded, so this small change in BSA does not impact the

			required number of doses. <i>'Patient's average body surface area in the De-Fi trial was 1.9m²'</i> Page 137

Issue 19 Utility Value Source Description

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 133, the EAG explains that "Tikhonova 2018 is a published EAG report for olaratumab in STS, the utility data used was from Reichardt et al 2012". (Reichardt, Leahy et al. 2012, Tikhonova, Jones-Hughes et al. 2018). However, the relationship between Reichardt 2012 and Tikhonova et al 2018 is not always made clear. For example, when describing	When noting that the EAG prefers to use utility values from Tikhonova, the relationship between Tikhonova and Reichardt should be made clear, so that the reader can reconcile this preference for Tikhonova with the Reichardt reference cited in the EAG base case.	This correction will provide the reader with more clarity about the EAG's base case source for utility values and how it relates to the Tikhonova source identified by the company.	Edited Key Issue 9 to "The EAG prefers to use estimates from Reichardt et al 2012" Edited page 99 "the EAG considered the utility data source in Tikhonova et al (2018), which was Reichardt et al. (2012)³, to be more appropriate. No justification for the exclusion of the

the EAG base case utility values, Reichardt 2012 is reported as the source (e.g., Table 40 on page 135; Table 47 on page 157, etc.). Conversely, in other instances, the report notes that the EAG prefers to use utility values from Tikhonova 2018 (e.g., Key Issue 9, page 24; Section 5.2.2.6 on page 153, etc.), without explaining the connection between the two sources.			Reichardt 2012 utility data was provided by the company nor any scenario analyses using the Reichardt 2012 utility data was performed in the company submission“ Edited page 133 “The EAG preferred to use utility values from Reichardt et al, 2012” Edited page 133 “The Reichard 2012 utility values were detailed within Tikhonova 2018².Tikhonova 2018 is a published EAG report for olaratumab in STS, the utility data used was from Riechardt et al 2012,³ a publication on the quality-of-life of patients with metastatic soft tissue and bone sarcoma in the SABINE study” The EAG has made corrections on page 133, page 99 and to Key Issue 9.

Issue 20 ORR median follow-up time

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19 of the EAG Report (page 90) reports the median follow-up time as 15.9 months for ORR in the DeFi trial. Please note that this follow-up time is for PFS in the DeFi trial (Gounder, Ratan et al. 2023).	The company is requesting that a footnote be added to Table 19 of the EAG Report (page 90), indicating that the 15.9-month value is estimated using the median follow-up time for PFS, and does not represent calculated clinical data for ORR.	This amendment will provide clarity for the source of this value being used.	Thank you for pointing this out. As suggested by the company, a clarification has been added as a footnote to the table.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
External Assessment Group (EAG) Report, Key Issue 6, page 21.	The patient progression in the trial should be marked as confidential, aligned with rates of progression being marked as confidential in the	This was in contrast with the trend observed in the trial in which [REDACTED] patient progressed after month 18 in the Nirogacestat Arm and [REDACTED] patients progressed after month 18 in the placebo arm.	Thank you, this has been corrected

	company submitted document.		
External Assessment Group (EAG) Report, Section 3.3.8.2, page 72.	The number of events in the participants with a family history of FAP subgroup should be marked as confidential, as the data in Figure 4 of the EAG report is marked as confidential.	However, they were based on only [REDACTED] events in the participants with a family history of FAP subgroup, and as such, were not considered robust estimates by the EAG.	Thank you, this has been corrected
External Assessment Group (EAG) Report, Section 3.3.8.3, page 73.	The reasons for uncertainty in the differences between subgroups should be marked as confidential, aligned with the company submitted document.	Where there did appear to be differences between the subgroups it was too uncertain given the [REDACTED] or [REDACTED].	Thank you, this has been corrected
External Assessment Group (EAG) Report, Section	The following statement should be marked as confidential, aligned with the	In the double-blind phase of the De-Fi study, bone fractures were reported in 6% of participants receiving nirogacestat compared with no participants receiving placebo. All reports of bone fracture were non-serious and Grade 1 or Grade 2. [REDACTED]	Thank you, this has been corrected

3.3.10.4, "Bone Fracture" page 78.	company submitted document: "All of the participants who reported a bone fracture were women 50 years of age or older."	██████████ Bone fracture events did not lead to dose reduction or treatment discontinuation in any participants receiving nirogacestat.	
External Assessment Group (EAG) Report, Table 28, page 109.	The number of patients with premature discontinuation not due to progression should be marked as confidential for consistency with rest of Table 28 in the EAG report.	Premature discontinuation not due to progression (██████████)	This does not need to be marked up as it's publicly reported in Table 1 of Ratan 2025 .
External Assessment Group (EAG) Report, Section 4.2.5.4, "Failure to account for patients whose disease did not stabilise or	The number of patients who did not achieve disease control should be marked as confidential.	The approach appears not to account for the fact that some patients never achieved disease control (progression free survival) within the clinical trial (██████ patients in the placebo arm and ██████ in the nirogacestat arm Table 14 of the clinical study report for De-Fi.	Thank you for highlighting this, this marking has now been corrected.

respond", page 111.			
External Assessment Group (EAG) Report, Section 4.2.5.4, "Numbers of patients responding was not consistent across data provided by the company", page 112.	The number of patients achieving a partial response submitted in response to clarification question B9b should be marked as confidential, aligned with the company submitted document.	The clinical study report suggests that six patients achieved a partial response on best supportive care (Table 14), but the company's response to clarification question B9b suggests there were only [REDACTED] patients who achieved a partial response.	Thank you for highlighting this, this marking has now been corrected.
External Assessment Group (EAG) Report, Section 4.2.5.4, "Use of calibration to "fix" issues with trial data	The text describing the numbers of patients from Table 3.8 of the original submission should be marked as confidential, aligned with the	The company compared this to the [REDACTED] of patients in Table 3.8 who achieved progression free survival of 12 months, conditional on having achieved stable disease and received BSC treatment for one year ([REDACTED] for those who received treatment for two years).	Thank you for highlighting this, this marking has now been corrected.

not matching modelled results”, page 114.	company submitted document.		
External Assessment Group (EAG) Report, Section 4.2.5.4, “Use of calibration to “fix” issues with trial data not matching modelled results”, page 114-115.	The number of progressed patients in the model and the trial at Year 1 should be marked as confidential, aligned with the company submitted document and the EAG report Table 29.	When these patients were placed in the progressed state from the start of the model, the modelled number of progressed patients in the nirogacestat arm at Year 1 was [REDACTED] (compared with [REDACTED] in the trial) and the modelled number of progressed patients in the BSC arm at Year 1 [REDACTED] (compared with [REDACTED] in the trial).	Thank you for highlighting this, this marking has now been corrected.
External Assessment Group (EAG) Report, Section 4.2.5.4, “Response probabilities for	The number of patients moving between health states should be marked as confidential, aligned with the company submitted	This is at odds with the trial data, which show that [REDACTED] of patients in partial response at the end of, went on to achieve a complete response by the end of Year 2 and [REDACTED] of patients [REDACTED] in stable response went on to achieve a partial response	Thank you for highlighting this, this marking has now been corrected.

each health state”, page 122.	document and the EAG report Table 34.		
External Assessment Group (EAG) Report, Section 4.2.5.7, “Adverse events”, page 129.	The number of reproductive system and breast disorders overall events should be marked as confidential.	...patients in the nirogacestat arm who experienced reproductive system and breast disorders overall (██████)	Thank you for highlighting this, this marking has now been corrected.
External Assessment Group (EAG) Report, Section 1.3, Key Issue 6, page 22.	Cost-effectiveness results for chemotherapy should be marked as confidential, for consistency with the rest of the EAG report.	Chemotherapy remained ██████ in the fully incremental analysis.	Thank you for highlighting this, this marking has now been corrected.
External Assessment Group (EAG) Report,	Cost-effectiveness results for chemotherapy should be marked	In the fully incremental analysis, vinorelbine was ██████	Thank you for highlighting this, this marking has now been corrected.

Section 5.2.2.9, page 155	as confidential, for consistency with the rest of the EAG report.		
External Assessment Group (EAG) Report, Section 5.5, page 170	Cost-effectiveness results should be marked as confidential, for consistency with the rest of the EAG report.	... [REDACTED] the NICE cost-effectiveness threshold of £20,000 - £30,000 per QALY. Chemotherapy was [REDACTED] in the EAG base case.	Thank you for highlighting this, this marking has now been corrected.

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- Desmoid Tumor Working Group (2020) The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. *Eur J Cancer* 127 96-107
- Gennatas S, Chamberlain F, Smrke A et al. (2020) A Timely Oral Option: Single-Agent Vinorelbine in Desmoid Tumors. *Oncologist* 25 (12): e2013-e2016
- Gounder M, Ratan R, Alcindor T et al. (2023) Nirogacestat, a γ -Secretase Inhibitor for Desmoid Tumors. *New England Journal of Medicine* 388 (10): 898-912
- National Health Service (NHS) (2025) Oral Vinorelbine (Fibromatosis). Accessed on: 09 December 2025. Available online at: <https://www.swagcanceralliance.nhs.uk/wp-content/uploads/2022/12/Vinorelbine-fibromatosis-v1.pdf>.
- Ratan R, Kasper B, Alcindor T, et al. (2025) Efficacy and Safety of Long-Term Continuous Nirogacestat Treatment in Adults With Desmoid Tumors: Results From the DeFi Trial. *J Clin Oncol*. 43(34):3646-3651.
- Reichardt P, Leahy M, Garcia Del Muro X et al. (2012) Quality of Life and Utility in Patients with Metastatic Soft Tissue and Bone Sarcoma: The Sarcoma Treatment and Burden of Illness in North America and Europe (SABINE) Study. *Sarcoma* 2012 740279
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Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

Nirogacestat for treating desmoid tumours [ID6453]

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on 3 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Merck Serono Ltd / SpringWorks Therapeutics Inc.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Exclusion of chemotherapy as a comparator	Yes	As noted in the company submission (p. 22-23), there are no approved therapies for desmoid tumours (DT) in the UK. Despite its off-label use, chemotherapy was not included as a comparator because it is not clearly established as UK standard practice and lacks high-quality evidence of efficacy (with available data limited to retrospective or single-arm studies). Furthermore, as outlined in response to NICE clarification questions (A14 and B1), a robust indirect treatment comparison (ITC) between nirogacestat and chemotherapy is limited due to the lack of a common comparator, limited and inconsistent baseline reporting, small sample sizes, and differences in study design. The EAG conducted a pragmatic network meta-analyses (NMA) to compare nirogacestat versus chemotherapy, as they considered chemotherapy a relevant comparator. However, consistent with the arguments provided by the company, the EAG acknowledged that this NMA, and the trial data informing it, was subject to a number of limitations and considerable uncertainty (Key Issue 2). Still, the EAG added chemotherapy as a comparator in their economic model, with efficacy informed by results of the NMA. The EAG acknowledged that the resultant estimates of cost-effectiveness for nirogacestat versus chemotherapy were highly uncertain. Although the company maintains its original concerns related to the inclusion of chemotherapy as a comparator, it has addressed the EAG's request to conduct an ITC which may be more comprehensive than the pragmatic NMA (although still subject to extensive limitations). Thus, the

Technical engagement response form

		company has conducted a matching adjusted indirect comparison (MAIC) (described in response to Key Issue 2 below) and used this to inform the addition of chemotherapy as a comparator in the cost-effectiveness model. The new company base case (which also includes revisions described in Response to Key Issue 4) produced an ICER of [REDACTED] for nirogacestat versus chemotherapy. <i>Please note: In the company's new version of the EAG model (provided with this TE response form with new scenarios programmed in), the company has added chemotherapy as an "additional" comparator versus adding this onto the EAG's existing chemotherapy comparator option, as several inputs differed between the EAG assumption(s) and the company's internal assumption(s), and the programming would have required significantly more work to allow the functionality to switch between the two.</i>
Key Issue 2: Uncertainty related to the network meta-analysis	Yes	As described in response to Key Issue 1 above, the EAG noted that the company may be able to conduct a more comprehensive ITC given the extensive SLR that was conducted by the company (in contrast to the pragmatic NMA conducted by the EAG). As described by the company in the response to NICE clarification question A14, the systematic literature review (SLR) identified two full text publications, Palassini et al. (2017) and Toulmonde et al. (2019) (DESMOPAZ trial) as evidence for the efficacy of chemotherapy in DT. In addition, there were two conference abstracts (Costa et al 2022 and Woods et al 2022) that were also identified in the SLR; however, these studies present significant limitations that make an ITC with nirogacestat not feasible. Specifically, these two abstracts reported small sample sizes, included very different patient populations and follow-up duration, had outdated treatment periods (especially for Costa et al 2022), lacked baseline characteristic data by treatment arm, had missing outcome information, and was a retrospective study design which undermines the validity of any ITC between DeFi versus Costa et al 2022 or DeFi versus Woods et al 2022 (for more details, please refer to response to NICE clarification question A14). In contrast, full text publications offer additional trial details (i.e., eligibility criteria, attrition, outcome definitions) and more complete outcome data. As a result, this allows for a more thorough assessment of risk of bias and confounding prior to conducting an ITC. Evidence from the DESMOPAZ trial was used to inform an ITC. Due to extensive limitations in study design, study population and outcome assessment, a robust ITC was not feasible using the Palassini et al. (2017) study.

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		DESMOPAZ is a randomised controlled trial (RCT), similar to DeFi, with a prespecified assessment timepoint which allows for a fairer comparison as both trials allowed a similar timepoint for which events are captured. In contrast, Palassini et al. (2017) was a retrospective study spanning a longer follow-up period. This increases the risk of confounding factors that are difficult to adjust for in an ITC as the study has significantly longer median follow-up periods than the DeFi trial, which is likely to bias progression free survival (PFS) estimates by potentially underestimating PFS in DeFi. Moreover, it is likely that the older timeframe of the observational period (1989–2014) for Palassini et al. (2017) does not reflect current clinical practice, while the DESMOPAZ trial contains more recent data (2012–2017) on patients with DT and is likely more reflective of current clinical practice for DT. The DESMOPAZ trial had a single, clearly defined chemotherapy arm as all control arm patients received an intravenous regimen combining vinblastine (5 mg/m² per dose) with methotrexate (30 mg/m² per dose), administered weekly for 6 months and then every other week for 6 months. In contrast, Palassini et al. (2017) included three different treatment groups: vinorelbine alone, methotrexate with vinorelbine, or methotrexate with vinblastine. Baseline characteristics in Palassini et al. were not reported by treatment group, and not all outcomes were reported for each treatment group. This further limits any conclusions made from an ITC between DeFi and Palassini et al. (2017) as the differences in the baseline characteristics within the three treatment groups cannot be adjusted for due to lack of reporting and time-to-event outcomes missing for treatment arms. Overall, compared to Palassini et al. (2017), DESMOPAZ offers higher quality evidence for chemotherapy and results in a more robust ITC against DeFi. To inform the present response, the company has conducted a post-hoc ITC (i.e., matching adjusted indirect comparison [MAIC]) between DeFi and DESMOPAZ to assess the relative treatment effect between nirogacestat and methotrexate combining vinblastine (chemotherapy). Although DESMOPAZ offers more robust evidence for chemotherapy compared to Palassini et al (2017), there were still limitations with using this study. There were cross-trial differences that were important to align on such as ECOG score eligibility for study entry and outcome assessment periods between DeFi and DESMOPAZ. Since the company has individual patient data (IPD) from DeFi, population adjusted ITCs were feasible and an MAIC can account for these differences more effectively than a network meta-analysis (NMA). Although NMAs are typically used to synthesise evidence across multiple comparisons, nirogacestat (DeFi, vs. placebo) and chemotherapy (DESMOPAZ, vs. pazopanib) were only indirectly connected through a study comparing sorafenib (another tyrosine kinase inhibitor [TKI])

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		like pazopanib) vs. placebo (Gounder et al. 2018), which could introduce additional uncertainty into the analysis (Figure 5 of the EAG NMA). Hence, an unanchored MAIC was considered a more appropriate statistical method in the absence of a shared comparator and within a sparse network. More importantly, MAICs are able to adjust for treatment effect modifiers, improving internal validity compared to an NMA where the analysis relies on aggregate level study characteristics (which are less credible). For example, the standardised mean difference (SMD) for prior systemic therapy was 0.306, signifying a substantial difference between DeFi and DESMOPAZ for this important variable. As such, the company believes that results from an MAIC are more defensible as it also offers interpretable diagnostics (e.g., ESS, SMDs, weight distribution) to show how differences were addressed whereas NMAs rely on unadjusted aggregate-level differences. Finally, as noted in the EAG report, one limitation with using the DESMOPAZ study is that the chemotherapy evaluated (methotrexate plus vinblastine) was not the chemotherapy most commonly used in the NHS (i.e., vinorelbine or doxorubicin). Given that there is no high-quality evidence for vinorelbine or doxorubicin in people with DT, there is no evidence comparing the efficacy of vinorelbine to methotrexate with vinblastine, and advice from the EAG clinical experts suggest that vinorelbine may be less effective than methotrexate, the results of any analyses resulting from the comparison of DeFi to DESMOPAZ should be interpreted with caution when informing decision-making in the UK. Based on the feasibility assessment, objective response rate (including complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) and PFS were available for comparison. DESMOPAZ enrolled patients with ECOG of 0 or 1. Matching was performed by removing the one patient with ECOG > 1 from DeFi prior to adjustment. Covariates selected for adjustment were chosen based on their clinical relevance as prognostic factors for DT outcomes, as identified through an SLR specifically conducted to identify potential prognostic factors and/or effect modifiers. The top six ranked factors included age, tumour location, number of prior lines of therapy (LOTs), type of prior therapy, presence of Gardner syndrome, and presence of multifocal disease. Given that not all covariates were reported consistently in the comparator trial, adjustment was based on data availability. Univariate analyses were also conducted to assess the impact of each covariate. Factors were ranked based on strength of the prognostic factors and degree of imbalance between studies. Factors with largest differences from the matched ITC were determined to have the greatest impact and thus ranked higher. To avoid over-adjustment (i.e., including excessive or weakly relevant covariates that could reduce the ESS and increase variance), additional covariates were planned to be incorporated using a stepwise approach, conditional on maintaining a minimum ESS threshold

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(e.g., ≥50% of the matched nirogacestat cohort). Based on data availability and the univariate analysis in consideration of clinical importance, the following factors were adjusted for in the ITC: intra-abdominal tumour location, age, prior systemic therapy, prior radiation therapy, prior surgery, prior TKI exposure, CTNNB1 mutation, ECOG score, and sex.

The base case as determined by ESS adjusted for ECOG, tumour location, age, and prior systemic therapy (■■■■■). After adjusting for differences in baseline characteristics, base case results for response outcomes showed that nirogacestat was associated with ■■■■■ of ORR, CR, and PR, and ■■■■■ of SD compared to chemotherapy. In addition, a ■■■■■ rate of PD was observed. In the PFS analysis, median PFS was not reached in either study, with 95% CI not estimable (NE). The hazard ratio (HR) for PFS comparing nirogacestat to chemotherapy was ■■■■■. Results were either comparable or numerically favourable towards nirogacestat across all scenarios. A summary of results of each comparison is presented in Table 1 below.

Table 1: Summary of company ITC results for nirogacestat vs. chemotherapy

Comparison (nirogacestat vs. chemotherapy)	
ORR, OR (95%CI), p-value	■■■■■
CR, OR (95% CI), p-value	■■■■■
PR, OR (95% CI), p-value	■■■■■
SD, OR (95% CI), p-value	■■■■■
PD, OR (95% CI), p-value	■■■■■
PFS, HR (95% CI), p-value	■■■■■

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; OR = odds ratio; ORR = objective response rate; PFS = progression-free survival; PR = partial response.

Overall, the MAIC of efficacy outcomes showed that compared to chemotherapy, nirogacestat was associated with a statistically significant reduction in PD, while other comparisons showed either numerical trends favouring nirogacestat (ORR, CR, PR) or comparable efficacy (SD).

		Feedback on EAG NMA The company wishes to emphasise that both the EAG NMA and the company's post-hoc MAIC are subject to a high degree of uncertainty. When consulted about the EAG's NMA, the EAG's clinical experts "stressed the uncertainty associated with network meta-analysis results", particularly citing concerns related to the PFS results, given its wide confidence intervals and divergence from the ORR NMA results. Of note, although both the EAG's NMA and the company's MAIC showed the same directionality of ORR results (i.e., [REDACTED]), there is a substantial range in the values and uncertainty margins (see below). - Company MAIC (nirogacestat versus chemotherapy): - ORR OR (95%CI): [REDACTED] - EAG NMA (nirogacestat versus chemotherapy, p89, Table 20): - ORR OR (95% Credible interval [CrI]): [REDACTED] As a result, the company wishes to re-iterate our original position that including available evidence on chemotherapy in an ITC would introduce significant heterogeneity, and be subject to significant methodological limitations, and is therefore not recommended. With regards to PFS, both ITCs showed [REDACTED], with the company's analysis showing [REDACTED] and the EAG's analysis [REDACTED] (see below). - Company MAIC (nirogacestat versus chemotherapy): - PFS HR (95%CI): [REDACTED] - EAG NMA (nirogacestat versus chemotherapy, p92, Table 22): - PFS HR (95%CrI): [REDACTED] As a result, the company is aligned with the EAG's clinical experts who stressed the uncertainty in the NMA results, with PFS results considered the most uncertain. As such, the company agrees with the EAG's decision that PFS results from their NMA should not be used to inform transition probabilities within the model (per p126 of EAG report).

		Overall, the high degree of variability in the results further underscores the uncertainty in the evidence for the efficacy of nirogacestat versus chemotherapy, and the need for caution when interpreting cost-effectiveness results generated using these ITC inputs in the context of decision making.																																																												
Key Issue 3: Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Yes	As requested by the EAG, the company has conducted post-hoc subgroup analyses in participants with uncontrolled pain at baseline to establish whether nirogacestat offers a clinically meaningful benefit over placebo. Results from these subgroup analyses are presented below. Table 2: Sub-group analysis of DeFi trial endpoints by controlled pain at baseline (BPI-SF API ≤4) vs. uncontrolled pain at baseline (BPI-SF API >4) <table><tr><th></th><th colspan="2">Controlled Pain at Baseline (BPI-SF API ≤4)</th><th colspan="2">Uncontrolled Pain at Baseline (BPI-SF API >4)</th></tr><tr><th></th><th>Nirogacestat (████)</th><th>BSC (████)</th><th>Nirogacestat (████)</th><th>BSC (████)</th></tr><tr><td>PFS</td><td></td><td></td><td></td><td></td></tr><tr><td>Median (Months, 95% CI)</td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td>HR (95% CI)</td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td>One-sided p-value</td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td>ORR up to Year 1</td><td></td><td></td><td></td><td></td></tr><tr><td><u>N (%), 95% CI</u></td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td><u>RR (95% CI)</u></td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td>ORR up to Year 2</td><td></td><td></td><td></td><td></td></tr><tr><td><u>N (%), 95% CI</u></td><td>████</td><td>████</td><td>████</td><td>████</td></tr><tr><td><u>Relative Risk (95% CI)</u></td><td>████</td><td>████</td><td>████</td><td>████</td></tr></table> Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤4 or BPI-SF API >4, respectively (SpringWorks Therapeutics 2022). Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ORR =objective response rate; PFS = progression-free survival; RR = relative risk. Table 3: Sub-group analysis of per cycle change from baseline in BPI-SF score by controlled pain at baseline (BPI-SF API ≤4) vs. uncontrolled pain at baseline (BPI-SF API >4)		Controlled Pain at Baseline (BPI-SF API ≤4)		Uncontrolled Pain at Baseline (BPI-SF API >4)			Nirogacestat (████)	BSC (████)	Nirogacestat (████)	BSC (████)	PFS					Median (Months, 95% CI)	████	████	████	████	HR (95% CI)	████	████	████	████	One-sided p-value	████	████	████	████	ORR up to Year 1					<u>N (%), 95% CI</u>	████	████	████	████	<u>RR (95% CI)</u>	████	████	████	████	ORR up to Year 2					<u>N (%), 95% CI</u>	████	████	████	████	<u>Relative Risk (95% CI)</u>	████	████	████	████
	Controlled Pain at Baseline (BPI-SF API ≤4)		Uncontrolled Pain at Baseline (BPI-SF API >4)																																																											
	Nirogacestat (████)	BSC (████)	Nirogacestat (████)	BSC (████)																																																										
PFS																																																														
Median (Months, 95% CI)	████	████	████	████																																																										
HR (95% CI)	████	████	████	████																																																										
One-sided p-value	████	████	████	████																																																										
ORR up to Year 1																																																														
<u>N (%), 95% CI</u>	████	████	████	████																																																										
<u>RR (95% CI)</u>	████	████	████	████																																																										
ORR up to Year 2																																																														
<u>N (%), 95% CI</u>	████	████	████	████																																																										
<u>Relative Risk (95% CI)</u>	████	████	████	████																																																										

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Time point	Change from Baseline	Controlled Pain at Baseline (BPI-SF API ≤4)		Uncontrolled Pain at Baseline (BPI-SF API >4)	
		Nirogacestat ()	BSC ()	Nirogacestat ()	BSC ()
Cycle 2	n				
	Mean				
	SD				
	Median				
	Min, Max				
	LS Mean				
	LS SE				
	95% CI				
	LS Mean Diff. to Placebo*				
	LS SE Diff. to Placebo*				
	95% CI*				
	One-sided p-value*				
Cycle 3	n				
	Mean				
	SD				
	Median				
	Min, Max				
	LS Mean				
	LS SE				
	95% CI				
	LS Mean Diff. to Placebo*				
	LS SE Diff. to Placebo*				
	95% CI*				
	One-sided p-value*				
Cycle 4	n				
	Mean				
	SD				
	Median				
	Min, Max				
	LS Mean				
	LS SE				
	95% CI				
	LS Mean Diff. to Placebo*				
	LS SE Diff. to Placebo*				
	95% CI*				
	One-sided p-value*				

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			LS SE																	
			95% CI																	
			LS Mean Diff. to Placebo*																	
			LS SE Diff. to Placebo*																	
			95% CI*																	
			One-sided p-value*																	
		Cycle 24	n																	
			Mean																	
			SD																	
			Median																	
		Cycle 25	Min, Max																	
			n																	
			Mean																	
			SD																	
		Cycle 26	Median																	
			Min, Max																	
			n																	
			Mean																	
		Cycle 27	SD																	
			Median																	
			Min, Max																	
			n																	
		Cycle 28	Mean																	
			SD																	
			Median																	
			Min, Max																	
		Cycle 29	n																	
			Mean																	
			SD																	
			Median																	
		Cycle 30	Min, Max																	
			n																	
			Mean																	
			SD																	
		Cycle 31	Median																	
			Min, Max																	
			n																	

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		* LS mean and SE were from a mixed model with repeated measures (MMRM) with treatment and visits as factors. Baseline BPI SF score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, and included Baseline by visit and treatment by visit interactions. A heterogenous autoregressive 1 covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation. Only participants with a Baseline and at least one post-Baseline score were included in the analysis. Scheduled visits with less than 10 participants in the arm and unscheduled visits were not included in the model. Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; LS = least squares; NA = not available; SE = standard error. Figure 1: Kaplan-Meier plot of progression-free survival in subgroup with controlled pain at baseline (BPI-SF API ≤ 4)  Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤ 4 or BPI-SF API > 4, respectively (SpringWorks Therapeutics 2022). Abbreviations: : BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; CI = confidence interval; NE = not evaluable.

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		Figure 2: Kaplan-Meier plot of progression-free survival in sub-group with uncontrolled pain at baseline (BPI-SF API >4)  Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤ 4 or BPI-SF API > 4, respectively (SpringWorks Therapeutics 2022). Abbreviations: : BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; CI = confidence interval; NE = not evaluable. <i>Note: The EAG requested a post-hoc analysis of patients' change from baseline in BPI-SF pain score according to best overall response status and treatment arm. The company has now provided this data.</i> Table 4: Sub-group analysis of per cycle change from baseline in BPI-SF score by controlled pain at baseline (BPI-SF API ≤ 4) vs. uncontrolled pain at baseline (BPI-SF API > 4) among patients with CR as best overall response

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		Time point	Change from Baseline	Controlled Pain at Baseline (BPI-SF API ≤4)		Uncontrolled Pain at Baseline (BPI-SF API >4)	
				Nirogacestat	BSC	Nirogacestat	BSC
		Cycle 2	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 3	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 4	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 5	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 6	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 7	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 8	n				
			Mean				
			SD				
			Median				
			Min, Max				
		Cycle 9	n				
			Mean				
			SD				
			Median				

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Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤ 4 or BPI-SF API >4 , respectively (SpringWorks Therapeutics 2022).
Note: A positive change from Baseline value indicated worsening of API and a negative change from Baseline value indicates improvement of API. A negative LS mean difference (between Nirogacestat and placebo) favoured Nirogacestat over placebo.
Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; CR = complete response; NA = not available ;SD = standard deviation.

Table 5: Sub-group analysis of per cycle change from baseline in BPI-SF score by controlled pain at baseline (BPI-SF API ≤ 4) vs. uncontrolled pain at baseline (BPI-SF API >4) among patients with PR as best overall response

Time point	Change from Baseline	Controlled Pain at Baseline (BPI-SF API ≤ 4)		Uncontrolled Pain at Baseline (BPI-SF API >4)	
		Nirogacestat	BSC	Nirogacestat	BSC
Cycle 2	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 3	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 4	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 5	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 6	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 7	n				
	Mean				
	SD				
	Median				
	Min, Max				

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Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤ 4 or BPI-SF API >4 , respectively (SpringWorks Therapeutics 2022).

Note: A positive change from Baseline value indicated worsening of API and a negative change from Baseline value indicates improvement of API. A negative LS mean difference (between Nirogacestat and placebo) favoured Nirogacestat over placebo.

* LS mean and SE were from a mixed model with repeated measures (MMRM) with treatment and visits as factors, Baseline BPI SF score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, and included Baseline by visit and treatment by visit interactions. A heterogeneous autoregressive 1 covariance structure was used and degrees of freedom were estimated using the Kenward-

Roger approximation. Only participants with a Baseline and at least one post-Baseline score were included in the analysis.

Scheduled visits with less than 10 participants in the arm and unscheduled visits were not included in the model

Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; LS = least squares; NA = not available; SD = standard deviation; SE = standard error.

Table 7: Sub-group analysis of per cycle change from baseline in BPI-SF score by controlled pain at baseline (BPI-SF API ≤ 4) vs. uncontrolled pain at baseline (BPI-SF API >4) among patients with PD as best overall response

Time point	Change from Baseline	Controlled Pain at Baseline (BPI-SF API ≤ 4)		Uncontrolled Pain at Baseline (BPI-SF API >4)	
		Nirogacestat	BSC	Nirogacestat	BSC
Cycle 2	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 3	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 4	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 5	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 6	n				
	Mean				
	SD				
	Median				
	Min, Max				
Cycle 8	n				

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			Mean					
			SD					
			Median					
			Min, Max					
			Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤4 or BPI-SF API >4, respectively (SpringWorks Therapeutics 2022). Note: A positive change from Baseline value indicated worsening of API and a negative change from Baseline value indicates improvement of API. A negative LS mean difference (between Nirogacestat and placebo) favoured Nirogacestat over placebo. Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; NA = not available; PD progressed disease; SD = standard deviation.					
Table 8: Sub-group analysis of per cycle change from baseline in BPI-SF score by controlled pain at baseline (BPI-SF API ≤4) vs. uncontrolled pain at baseline (BPI-SF API >4) among patients with best overall response as not evaluable								
Time point	Change from Baseline	Controlled Pain at Baseline (BPI-SF API ≤4)		Uncontrolled Pain at Baseline (BPI-SF API >4)				
		Nirogacestat	BSC	Nirogacestat	BSC			
Cycle 2	n							
	Mean							
	SD							
	Median							
	Min, Max							
Cycle 3	n							
	Mean							
	SD							
	Median							
	Min, Max							
Follow-up	n							
	Mean							
	SD							
	Median							
	Min, Max							
Note: Controlled or uncontrolled pain at baseline is defined in accordance with the DeFi trial's statistical analysis plan (SAP) for patient reported outcomes (PROs) as BPI-SF API ≤4 or BPI-SF API >4, respectively (SpringWorks Therapeutics 2022). Note: A positive change from Baseline value indicated worsening of API and a negative change from Baseline value indicates improvement of API. A negative LS mean difference (between Nirogacestat and placebo) favoured Nirogacestat over placebo. Abbreviations: BPI-SF API = Brief Pain Inventory Short Form Average Pain Index; BSC = best supportive care; CI = confidence interval; NA = not available; PD progressed disease; SD = standard deviation.								
Overall, subgroup results show that a benefit of nirogacestat over placebo with respect to PFS and ORR was seen in both patients with controlled and uncontrolled pain at baseline. Moreover, an								

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		improvement in pain was generally observed across both subgroups. The subgroup analyses (Table 3) demonstrate that the LS mean difference in BPI-SF API from cycles 2-16 was consistently greater among patients with uncontrolled pain at baseline than those with controlled pain. In the majority of cycles, the difference in the uncontrolled group represented a clinically meaningful benefit when judged against an MID of 2 points. At Cycle 10, a statistically significant benefit with nirogacestat versus placebo was present in both subgroups, although the LS mean difference in BPI-SF API was greater among patients with uncontrolled pain at baseline than those with controlled pain (■■■■ vs ■■■■), with the difference in the controlled group approximating a clinically meaningful benefit when judged against an MID of 2 points. Lastly, the subgroup analyses by health state (Tables 4-8) demonstrate that improvements in pain generally persisted across health states, although analyses were often limited by small sample sizes. In addition, the company has conducted an ITC comparing nirogacestat to chemotherapy for reduction in pain related to DT. Comparisons of patient reported outcomes (PROs) were determined to be feasible for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30), specifically global health status and physical functioning, and Brief Pain Inventory (BPI). DESMOPAZ (the trial described in response to Key Issue 2 reported median and interquartile range at baseline and cycle 6 for PROs. Mean and standard deviation (SD) used in the ITCs were estimated using quintile estimation method (McGrath et al. 2020). The assessment frequency for PROs and cycle length varied slightly between trials; as a result, differences were aligned by matching an equivalent follow up time between the two trials. DeFi collected PROs at baseline and every 28 days (i.e., 4 weeks) while DESMOPAZ collected PROs at baseline, every 4 weeks in the first 3 months, and then every 12 weeks starting at cycle 5. Month 9 was determined to be the time period where there was equal follow up between DeFi and DESMOPAZ; hence, mean change in EORTC and BPI were compared from month 9 (i.e., cycle 10 in DeFi and cycle 6 in DESMOPAZ) to baseline. To address missing data at key follow-up cycles (i.e., cycle 10 in DeFi IPD), values from the nearest available adjacent cycle (± 1 cycle) were used to maximise sample size. Besides prioritising the top 6 covariates similar to the comparison of efficacy outcome (see response for Key Issue 2), baseline PRO was adjusted prior to any other covariates. Prior to matching and adjustment, there were 50 patients with quality of life (QoL) measurements at baseline and cycle 10 (± 1 cycle) in DeFi. Only one patient was removed after matching on ECOG (N = 49). The base case as determined by ESS was adjusted for baseline global health status, tumour

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		location, and age (ESS = 25). Similarly, for EORTC physical functioning, the base case as determined by ESS was adjusted for baseline physical function (ESS = 27). For BPI, ESS were too low after adjusting for baseline BPI (ESS = 2), hence the matched estimates were summarised below. After adjusting for differences in baseline characteristics, nirogacestat was associated with larger mean change from baseline for global health status ([REDACTED]) in base case and results were statistically significant. Nirogacestat was associated with numerically larger mean change from baseline for physical functioning compared to chemotherapy ([REDACTED]). In the BPI pain comparisons with the DESMOPAZ trial, due to the large difference on baseline BPI pain between nirogacestat ([REDACTED]) and chemotherapy ([REDACTED]), ESS dropped to 2 after adjusting for baseline BPI pain. Therefore, no factors were adjusted in the analysis. The results demonstrated that nirogacestat was associated with numerically smaller change from baseline for BPI pain ([REDACTED]) after matching, however, these results were not significantly different. Overall, MAIC results showed comparable or better improvements in QoL and comparable reduction in pain between nirogacestat and chemotherapy. While the matched and unadjusted results presented show that reduction in pain may be comparable between nirogacestat and chemotherapy, significant limitations in the available analyses likely influence the results. Most notably, adjusted results could not be presented due to the magnitude of difference in baseline BPI score between trials, which caused a significant reduction in the ESS after adjustment; thus, the presented results do not adjust for any important differences between trials. Moreover, the confidence interval for the comparison of BPI is very wide, further indicating a large degree of uncertainty in the results of the analysis. As a result, while the company conducted an ITC comparing nirogacestat to chemotherapy for reduction in pain related to DT in response to the EAG's requested analysis, it is recommended that results be interpreted with caution.
Key Issue 4: Calculation of progression risks during trial randomised period/first 2 years	No	Upon review of the EAG report, the company agrees that the EAG's revised modelled state membership reported in Table 37 of the EAG report provides a closer fit to the trial data than that derived using the company submitted model. However, while the EAGs approach to calculating transition probabilities did produce a close match to trial data in Year 2 (per Table 37 of the EAG report), the company would like to emphasise that this approach is still subject to limitations; as for

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	nirogacestat, the rates of SD and PR are underestimated at Year 1, and for BSC, rates of SD are overestimated and rates of PD are underestimated at Year 1. Nonetheless, the company has adjusted its base case to use the same transition probabilities as implemented in the EAG model for nirogacestat and BSC. Furthermore, to fully align with how transition probabilities were implemented in the EAG model, the company implemented the assumption that patients do not progress after 2 years (for more information, see Response to Key Issue 6). Please note that the company model was adjusted to use the EAG’s transition probabilities for nirogacestat and BSC as reported in G66, G70:73, I66, I70:72 of the ‘Scenario data’ sheet of the EAG model; however, the company would like to flag that the values contained within the model differed slightly from the transition probabilities reported in Table 36 of the EAG report. Please also note that for the base case, the company recalculated the chemotherapy transition probabilities using the company conducted post-hoc MAIC (described in response to Key Issue 2). To calculate the transition probabilities for chemotherapy, the state membership at the end of the 2-year period for nirogacestat for CR (█%), PR (█%), SD (█%), and PD (█%) were converted into odds according to $\left[\frac{prob}{(1-prob)}\right]$. Then, the ORs from the company’s MAIC as reported in Key Issue 2 (with results adjusted to chemotherapy vs. nirogacestat) for CR (█), PR (█), SD (█) and PD (█) were applied to the respective health state values, and then the odds were converted back to probabilities (█). Given that the 2-year MAIC-adjusted health state memberships for chemotherapy did not sum to 100%, values were then normalised, to result in the following: █. Then, the same approach as nirogacestat and chemotherapy was applied, wherein the SD membership at month 26 was converted to the hazard of staying in SD each month (█), and then the remaining █ of patients who leave SD each month were distributed amongst the transition probabilities of █. A summary of the monthly transition probabilities used in the revised company base case during the 2-year treatment period is presented in Table 9 below. Table 9: Monthly health state transition probabilities over 2-year treatment period from revised company base case <table><tr><th></th><th></th><th>Nirogacestat</th><th>BSC</th><th>Chemotherapy</th></tr><tr><td>Cycle transition probabilities from SD to...</td><td>CR</td><td>█</td><td>█</td><td>█</td></tr></table>			Nirogacestat	BSC	Chemotherapy	Cycle transition probabilities from SD to...	CR	█	█	█
		Nirogacestat	BSC	Chemotherapy							
Cycle transition probabilities from SD to...	CR	█	█	█							

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		While the company agrees that longer term data on patients’ progression rates would reduce uncertainty, such data were not feasible nor available to attain within the current appraisal time frame.																																		
Key Issue 5: Calculation of response	Yes	The company wishes to address the EAG’s concerns regarding the accuracy of the actual response data provided during the clarification stage. On p121 of the EAG report, the below concern was raised with Table 33 of the EAG report displaying the data in question. <i>“At clarification, the company shared data on patients’ actual response, as well as their best overall response. At all timepoints, the data appear to be more favourable for actual response than best overall response, which was counterintuitive. By definition the best overall response by the end of year 1 should be as favourable or more favourable than the actual response at the end of year one because either the response at the end of year was the best overall response, or the best overall response was a timepoint during year 1, in which case it will be better than the actual response at the end of the year. This suggested there may have been a calculation error or the definition of the endpoints is unclear.” - per p121 of EAG report</i> Regarding the data reported in Table 33 of the EAG report, the company wishes to clarify that the actual response data provided during the clarification stage included only patients who reached the one- or two-year landmark in the denominator, whereas best overall response rates from the originally submitted model consider entire population in denominator. This discrepancy can be readily addressed, and thus the company has reanalysed the actual response data to consider the entire population in the denominator. This reanalysed data is provided in Table 11 below: Table 11: Reanalysed actual response vs. best overall response data from DeFi trial for year 1 and year 2 <table><tr><th></th><th></th><th colspan="2">Nirogacestat</th><th colspan="2">BSC/Placebo</th></tr><tr><th>Endpoint</th><th>Health State</th><th>1 year</th><th>2 years</th><th>1 year</th><th>2 years</th></tr><tr><td rowspan="2">Best overall response</td><td>CR</td><td>■</td><td>■</td><td>■</td><td>■</td></tr><tr><td>PR</td><td>■</td><td>■</td><td>■</td><td>■</td></tr><tr><td rowspan="2">Actual response</td><td>CR</td><td>■</td><td>■</td><td>■</td><td>■</td></tr><tr><td>PR</td><td>■</td><td>■</td><td>■</td><td>■</td></tr></table>			Nirogacestat		BSC/Placebo		Endpoint	Health State	1 year	2 years	1 year	2 years	Best overall response	CR	■	■	■	■	PR	■	■	■	■	Actual response	CR	■	■	■	■	PR	■	■	■	■
		Nirogacestat		BSC/Placebo																																
Endpoint	Health State	1 year	2 years	1 year	2 years																															
Best overall response	CR	■	■	■	■																															
	PR	■	■	■	■																															
Actual response	CR	■	■	■	■																															
	PR	■	■	■	■																															

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		Note: Best overall response data aligns with that used in the original company submission and NICE clarification stage; actual response data has been reanalysed for the present TE response. Both sets of data use the entire study population as the denominator. Abbreviations: BSC = best supportive care; CR = complete response; PR = partial response. Importantly, the company acknowledges that even in this reanalysed data, the actual response data (PR with nirogacestat at 1 and 2 years and with BSC/placebo at 1 year) still exceeds the corresponding best overall response data. The reason for this discrepancy relates to the difference in definition between the two outcomes. A <u>best overall response</u> of CR or PR requires <u>confirmation by a subsequent scan</u> at least four weeks later. As a result, the proportion of patients with a given actual response at fixed timepoints (e.g., 1 or 2 years) is not necessarily capped by the reported best overall response. For example, a patient may have an actual response of CR at the end of Year 1, but if confirmation criteria have not yet been met, that patient would not have a best overall response of CR. Given the actual response data provided during the NICE clarification stage has been reanalysed per the data shown in the table above, the company has rerun the deterministic scenario in which transition probabilities are informed by patients' actual responses at year 1 and year 2 (conducted in response to B4 during the clarification stage). The scenario with revised actual response data produced ICERs of █████ per QALY versus BSC and █████ per QALY versus chemotherapy, in contrast to the ICER of █████ per QALY versus BSC from the original scenario submitted during the NICE clarification stage. To further address concerns related to the accuracy of the actual response data provided during the clarification stage, the company wishes to clarify the issue raised on p121 of the EAG report: <i>"When looking at the table provided in response to B5, the percentages in the actual response column do not sum to 100%, demonstrating calculation errors."</i> The company would like to flag that this was not a calculation error: the denominator included the full study population but not all patients had a recorded response at each timepoint (i.e., some patients did not have scheduled visit data, meaning they may be collected on unscheduled visits or totally missing, and some patients dropped out early). An updated dataset has been provided that displays categories for patients with missing data or early dropout as additional rows, while maintaining the total population as denominator. Please see below: Table 12: Observed response for nirogacestat and BSC according to health state at various trial time points

		Time point	Health State	Observed Response	
				Nirogacestat (N=70)	BSC (N=72)
				Trial (DB+OLE)	Trial
		Cycle 4 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 7 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 10 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 13 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 16 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 19 Day 1	CR		
			PR		
			SD		
			PD		
		Cycle 22 Day 1	CR		

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[illegible]

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[illegible]

Finally, to further clarify this issue, the company is providing a summary of shifts between actual response and best overall response at Years 1 and 2 (from trial). Please see below:

Table 13: Summary of shifts between actual response and best overall response at Year 1 from DeFi trial

		Best Overall Response by End of Year 1*									
		Nirogacestat (N=70)					BSC (N=72)				
		CR	PR	SD	PD	NE	CR	PR	SD	PD	NE
Last response by end of Year 1	CR	■	■	■	■	■	■	■	■	■	■
	PR	■	■	■	■	■	■	■	■	■	■
	SD	■	■	■	■	■	■	■	■	■	■
	PD	■	■	■	■	■	■	■	■	■	■
	NE	■	■	■	■	■	■	■	■	■	■

* Confirmed best response is defined as the best response obtained across all assessments considered. PR and CR require confirmation by subsequent scans.
Note: 1 patient in the nirogacestat arm had missing data and has been excluded from the table.

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease.

Table 14: Summary of shifts between actual response and best overall response at Year 2 from DeFi trial

		Best Overall Response by End of Year 2									
		Nirogacestat (N=70)					BSC (N=72)				
		CR	PR	SD	PD	NE	CR	PR	SD	PD	NE
Last response by end of Year 2	CR	■	■	■	■	■	■	■	■	■	■
	PR	■	■	■	■	■	■	■	■	■	■
	SD	■	■	■	■	■	■	■	■	■	■
	PD	■	■	■	■	■	■	■	■	■	■
	NE	■	■	■	■	■	■	■	■	■	■

* Confirmed best response is defined as the best response obtained across all assessments considered. PR and CR require confirmation by subsequent scans.
Note: 1 patient in the nirogacestat arm had missing data and has been excluded from the table.

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease.

Note: The company has now provided a summary of shifts between actual response and best overall response at Years 3 and 4 (from OLE).

Table 15: Summary of shifts between actual response and best overall response at Year 3 from DeFi trial

		Best Overall Response by End of Year 3									
		Nirogacestat (N=70)					BSC (N=72)				
		CR	PR	SD	PD	NE	CR	PR	SD	PD	NE
Last response by end of Year 3	CR	■	■	■	■	■	■	■	■	■	■
	PR	■	■	■	■	■	■	■	■	■	■
	SD	■	■	■	■	■	■	■	■	■	■
	PD	■	■	■	■	■	■	■	■	■	■
	NE	■	■	■	■	■	■	■	■	■	■

* Confirmed best response is defined as the best response obtained across all assessments considered. PR and CR require confirmation by subsequent scans.
Note: 1 patient in the nirogacestat arm had missing data and has been excluded from the table.

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease.

Table 16: Summary of shifts between actual response and best overall response at Year 4 from DeFi trial

		Best Overall Response by End of Year 4									
		Nirogacestat (N=70)					BSC (N=72)				
		CR	PR	SD	PD	NE	CR	PR	SD	PD	NE
Last response by end of Year 4	CR	■	■	■	■	■	■	■	■	■	■
	PR	■	■	■	■	■	■	■	■	■	■
	SD	■	■	■	■	■	■	■	■	■	■
	PD	■	■	■	■	■	■	■	■	■	■
	NE	■	■	■	■	■	■	■	■	■	■

* Confirmed best response is defined as the best response obtained across all assessments considered. PR and CR require confirmation by subsequent scans.
Note: 1 patient in the nirogacestat arm had missing data and has been excluded from the table.

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease.

Key Issue 6: Extrapolation of progression	Yes	Upon consideration of the points raised by the EAG, the company acknowledges that over 90% of patients having progressed in the BSC arm by Year 5 may be overly pessimistic. Furthermore, a clinical expert consulted by the company in response to the EAG Report confirmed that the EAG's assumption of no progression after two years is indeed clinically reasonable. These considerations further support the company's revised base case described in response to Key Issue 4, wherein the revised transition probabilities are consistent with the EAG's assumption of no progression after two years.
Key Issue 7: Assumed stopping rule	Yes	The company maintains that their originally proposed 2-year stopping rule reflects the anticipated usage of nirogacestat in UK practice, based on feedback from clinical experts. As noted by the EAG, clinicians broadly agreed to a 2-year stopping rule as long as patients whose tumours have not plateaued would be allowed to continue treatment past 2 years and patients who had discontinued due to adverse events would be allowed to re-start treatment if their tumour begins to grow again. The EAG's clinicians specifically estimated that they would expect to keep only 10-15% of patients on treatment to 2 years and only 3-5% on treatment to 3 years, based on patients' tumour size during the DeFi trial. A clinical expert consulted by the company also strongly supported a two-year stopping rule, noting that a large proportion of patients would in fact stop treatment prior to 2 years. In addition, the clinical expert further indicated that they would expect <5% of patients to continue treatment beyond two years and that the proportion of patients expected to be re-challenged with nirogacestat would be extremely low. Furthermore, most clinical benefits of treatment in the DeFi trial were observed prior to the 2-year cap (31/32 [96.9%] of nirogacestat-treated patients who achieved ORR did so by 24.4 months) (Ratan et al. 2025), further justifying the current rationale for ceasing the accumulation of treatment costs after 2 years. Per the EAG's request, the company wishes to clarify that tumour size plateau was defined as reaching the following response at two consecutive visits: CR to CR, PR to PR, PR to CR, SD to SD, or PD to PD. Furthermore, the company has reanalysed the data to show the probability of patients in each health state experiencing a tumour plateauing (rather than the proportion of patients with tumours that plateaued that were in each health state, as was provided in the response to clarification questions). Please see Tables 17 and 18 below: Table 17: Probability of patients in each health state according to best overall response at any time up to Year 1 achieving a tumour plateau for nirogacestat and BSC

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		Best Overall Response At Any Time Up to Year 1							
		Nirogacestat (N=70)				BSC (N=72)			
		CR	PR	SD	PD	CR	PR	SD	PD
	Tumour size plateau								
Abbreviations: BSC = best supportive care; CR = complete response; PD = progressed disease; PR = partial response; SD = stable disease.									
Table 18: Probability of patients in each health state according to best overall response at any time up to Year 2 achieving a tumour plateau for nirogacestat and BSC									
		Best Overall Response At Any Time Up to Year 2							
		Nirogacestat (N=70)				BSC (N=72)			
		CR	PR	SD	PD	CR	PR	SD	PD
	Tumour size plateau								
Abbreviations: BSC = best supportive care; CR = complete response; PD = progressed disease; PR = partial response; SD = stable disease.									
The above data demonstrate that tumour size plateau was achieved by 100% of patients in CR and PR, and more than three-quarters of patients in SD, by two years. Therefore, based on the above data on tumour plateau and feedback from multiple clinical experts supporting a two-year stopping rule, the company considers a three-year stopping rule to overestimate the number of patients that would continue on treatment after two years. Nonetheless, to explore potential uncertainty in patients who may receive treatment past two years, the company has conducted a scenario analysis to assess the impact of a small number of patients continuing on treatment after two years. Based on input from the clinical experts consulted by both the EAG (stating only 3-5% on treatment to 3 years) and the company (estimating <5% of patients to continue treatment beyond two years), the current scenario applies the higher end of the estimate and assumes that 5% of patients would remain on treatment for an additional one year beyond the initial 2 year treatment duration. This scenario produced ICERs of per QALY for nirogacestat versus BSC and per QALY for nirogacestat versus chemotherapy.									
Key Issue 8: Approach to early discontinuation	Yes	The company base case excluded patients who discontinued treatment prematurely as routine follow-up data was not available from the DeFi trial after participants discontinued treatment. The company would like to clarify that although patients in the DeFi trial were not scheduled for routine follow up							

visits after treatment discontinuation, an EOT visit was planned if a scan had not been conducted within the last three months of treatment. Therefore, while it was possible that a progression event may have been detected at the EOT visit after a patient has discontinued treatment, progression status was not routinely assessed post-discontinuation. The company would also like to note that in the DeFi trial, only one placebo subject experienced progression following premature treatment discontinuation (after a treatment duration of 283 days, this patient experienced radiographic progression documented at the EOT visit which occurred █ days after treatment discontinuation); no other subjects in either treatment arm progressed after discontinuation. Thus, having discontinued treatment prematurely is not anticipated to have meaningfully impacted the clinical outcomes in the model, which is further demonstrated by the data presented below.

As requested by the EAG, the company is providing separate data on the response and progression outcomes of patients who stopped treatment prematurely and patients who remained on treatment (see below). Data is reported for (i) best overall response at end of years 1 and 2 by treatment status at the end of each year; (ii) actual response at end of years 1 and 2 by treatment status at end of each year; (iii) the response achieved at the last assessment prior to discontinuation (actual response at discontinuation) among patients who discontinued treatment early; and (iv) the response at the first post-discontinuation assessment among patients who discontinued treatment early; and (v) PFS by treatment status.

Table 19: Best overall response at the end of Year 1 according to treatment status at the end of Year 1

	Tx Status at End of Yr 1					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
Best Overall Response at End of Year 1	█	█	█	█	█	█
CR	█	█	█	█	█	█
PR	█	█	█	█	█	█
SD	█	█	█	█	█	█
PD	█	█	█	█	█	█
NE	█	█	█	█	█	█
Missing	█	█	█	█	█	█

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 1, including one subject who was never treated.

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**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Table 20: Best overall response at the end of Year 2 according to treatment status at the end of Year 2

Best Overall Response at End of Year 2	Tx Status at End of Yr 2					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 2, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Note: The company has now provided a summary best overall response at the end of Years 3 and 4 according to treatment status at the end of Years 3 and 4.

Table 21: Best overall response at the end of Year 3 according to treatment status at the end of Year 3

Best Overall Response at End of Year 3	Tx Status at End of Yr 3					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 3, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Table 22: Best overall response at the end of Year 4 according to treatment status at the end of Year 4

Best Overall Response at End of Year 4	Tx Status at End of Yr 4					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 4, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Table 23: Actual response at the end of Year 1 according to treatment status at the end of Year 1

Actual Response at End of Year 1	Tx Status at End of Yr 1					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 1, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

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Table 24: Actual response at the end of Year 2 according to treatment status at the end of Year 2

Actual Response at End of Year 2	Tx Status at End of Yr 2					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 2, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Note: The company has now provided a summary actual response at the end of Years 3 and 4 according to treatment status at the end of Years 3 and 4.

Table 25: Actual response at the end of Year 3 according to treatment status at the end of Year 3

Actual Response at End of Year 3	Tx Status at End of Yr 3					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 1, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

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Nirogacestat for treating desmoid tumours [ID6453]

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Table 26: Actual response at the end of Year 4 according to treatment status at the end of Year 4

Actual Response at End of Year 4	Tx Status at End of Yr 4					
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**	
	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC
CR						
PR						
SD						
PD						
NE						
Missing						

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 4, including one subject who was never treated.

**Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death

Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.

Table 27: Actual response achieved at last assessment prior to discontinuation according to treatment status at the end of Year 1 among patients who discontinued treatment early

Actual Response Achieved at Last Assessment Prior to Discontinuation	Tx Status at End of Yr 1	
	Premature Off Tx*	
	Nirogacestat	BSC
CR		
PR		
SD		
PD		
NE		
Missing		

*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 1, including one subject who was never treated.

Abbreviations: BSC = best supportive care; CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment; Yr = year.

Table 28: Actual response achieved at last assessment prior to discontinuation according to treatment status at the end of Year 2 among patients who discontinued treatment early

	Tx Status at End of Yr 2	
	Premature Off Tx*	

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		Actual Response Achieved at Last Assessment Prior to Discontinuation	Nirogacestat	BSC																						
		CR																								
		PR																								
		SD																								
		PD																								
		NE																								
		Missing																								
		*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 2, including one subject who was never treated. Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment; Yr = year.																								
		Table 29: Actual response achieved at first post-discontinuation assessment according to treatment status at the end of Year 1 among patients who discontinued treatment early																								
		<table><tr><td></td><td colspan="2">Tx Status at End of Yr 1</td></tr><tr><td></td><td colspan="2">Premature Off Tx*</td></tr><tr><td>Actual Response Achieved at First Post-Discontinuation Assessment</td><td>Nirogacestat</td><td>BSC</td></tr><tr><td>CR</td><td></td><td></td></tr><tr><td>PR</td><td></td><td></td></tr><tr><td>SD</td><td></td><td></td></tr><tr><td>PD</td><td></td><td></td></tr><tr><td>Discontinued</td><td></td><td></td></tr></table>				Tx Status at End of Yr 1			Premature Off Tx*		Actual Response Achieved at First Post-Discontinuation Assessment	Nirogacestat	BSC	CR			PR			SD			PD			Discontinued
	Tx Status at End of Yr 1																									
	Premature Off Tx*																									
Actual Response Achieved at First Post-Discontinuation Assessment	Nirogacestat	BSC																								
CR																										
PR																										
SD																										
PD																										
Discontinued																										
* Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 1, including one subject who was never treated. Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.																										
Table 30: Actual response achieved at first post-discontinuation assessment according to treatment status at the end of Year 2 among patients who discontinued treatment early																										
<table><tr><td></td><td colspan="2">Tx Status at End of Yr 2</td></tr><tr><td></td><td colspan="2">Premature Off Tx*</td></tr><tr><td>Actual Response Achieved at First Post-Discontinuation Assessment</td><td>Nirogacestat</td><td>BSC</td></tr><tr><td>CR</td><td></td><td></td></tr><tr><td>PR</td><td></td><td></td></tr><tr><td>SD</td><td></td><td></td></tr></table>				Tx Status at End of Yr 2			Premature Off Tx*		Actual Response Achieved at First Post-Discontinuation Assessment	Nirogacestat	BSC	CR			PR			SD								
	Tx Status at End of Yr 2																									
	Premature Off Tx*																									
Actual Response Achieved at First Post-Discontinuation Assessment	Nirogacestat	BSC																								
CR																										
PR																										
SD																										

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		PD																																															
		Discontinued																																															
		*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death by the end of year 2, including one subject who was never treated. Abbreviations: BSC = best supportive care; CR = complete response; NE = not evaluable; PD = progressed disease; PR = partial response; SD = stable disease; Tx = treatment.																																															
		Table 31: Summary of PFS in the DB phase according to treatment status																																															
		<table><tr><td></td><td colspan="6">Tx Status</td></tr><tr><td></td><td colspan="2">On Tx</td><td colspan="2">Premature Off Tx*</td><td colspan="2">Off Tx due to PD/Death**</td></tr><tr><td>PFS in DB Phase</td><td>Nirogacestat</td><td>BSC</td><td>Nirogacestat</td><td>BSC</td><td>Nirogacestat</td><td>BSC</td></tr><tr><td>Median PFS (95% CI)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>HR (95% CI)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>One-sided p-value</td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							Tx Status							On Tx		Premature Off Tx*		Off Tx due to PD/Death**		PFS in DB Phase	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC	Median PFS (95% CI)							HR (95% CI)							One-sided p-value						
	Tx Status																																																
	On Tx		Premature Off Tx*		Off Tx due to PD/Death**																																												
PFS in DB Phase	Nirogacestat	BSC	Nirogacestat	BSC	Nirogacestat	BSC																																											
Median PFS (95% CI)																																																	
HR (95% CI)																																																	
One-sided p-value																																																	
		*Subjects who stopped treatment prematurely due to any reason rather than radiographic/DB phase qualified clinical progression/death in DB phase, including one subject who was never treated. **Subjects who reached Radiographic/DB Phase Qualified Clinical Progression/Death Abbreviations: BSC = best supportive care; CI = confidence interval; DB = double blind; HR = hazard ratio; NE = not evaluable; PFS = progression-free survival; Tx = treatment.																																															

Figure 3: Kaplan-Meier plot of progression-free survival from randomisation by treatment status (subjects on treatment) in DB phase (ITT population)

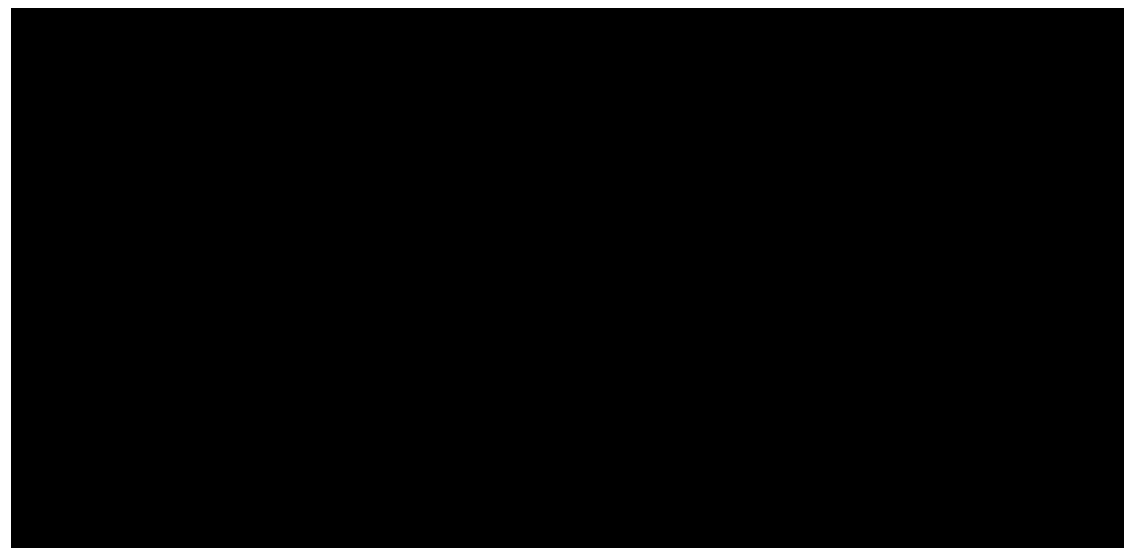


Figure 4: Kaplan-Meier plot of progression-free survival from randomisation by treatment status (subjects prematurely off treatment) in DB phase (ITT population)

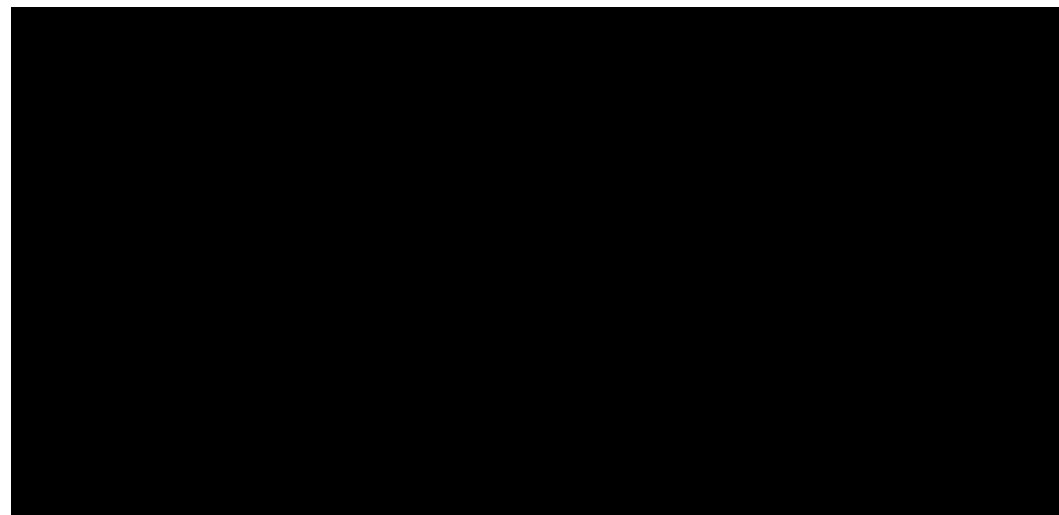
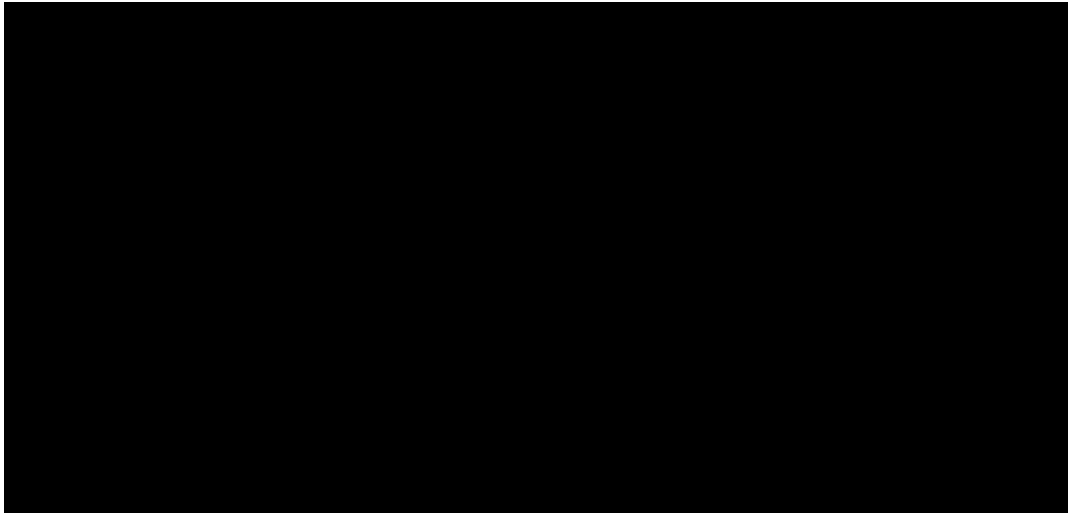


Figure 5: Kaplan-Meier plot of progression-free survival from randomisation by treatment status (subjects who reached radiographic/DB phase qualified clinical progression/death) in DB phase (ITT population)



Finally, to further clarify this issue, the company is providing a summary of shifts between overall response at Year 1 to overall response at Year 2 for subjects who were ongoing at the end of Year 1 and discontinued treatment at the end of Year 2 (from trial).

Table 32: Summary of shifts between overall response at Year 1 to overall response at Year 2 for subjects who were ongoing at the end of Year 1 and discontinued treatment at the end of Year 2 from DeFi trial

		Overall Response by End of Year 2							
		Nirogacestat				BSC			
		CR	PR	SD	PD	CR	PR	SD	PD
Overall Response	CR								
	PR								

by End of Year 1	SD								
	PD								

Abbreviations: BSC = best supportive care; CR = complete response; PD = progressed disease; PR = partial response; SD = stable disease.

Note: The company has now provided a summary of shifts from Years 2 to 3 and Years 3 to 4 (from OLE).

Table 33: Summary of shifts between overall response at Year 2 to overall response at Year 3 for subjects who were ongoing at the end of Year 2 and discontinued treatment at the end of Year 3 from DeFi trial

		Overall Response by End of Year 3							
		Nirogacestat [REDACTED]				BSC [REDACTED]			
		CR	PR	SD	PD	CR	PR	SD	PD
Overall Response by End of Year 2	CR	█	█	█	█	█	█	█	█
	PR	█	█	█	█	█	█	█	█
	SD	█	█	█	█	█	█	█	█
	PD	█	█	█	█	█	█	█	█

Abbreviations: BSC = best supportive care; CR = complete response; PD = progressed disease; PR = partial response; SD = stable disease.

Table 34: Summary of shifts between overall response at Year 3 to overall response at Year 4 for subjects who were ongoing at the end of Year 3 and discontinued treatment at the end of Year 4 from DeFi trial

		Overall Response by End of Year 4							
		Nirogacestat ■				BSC ■			
		CR	PR	SD	PD	CR	PR	SD	PD
Overall Response by End of Year 3	CR	■	■	■	■	■	■	■	■
	PR	■	■	■	■	■	■	■	■
	SD	■	■	■	■	■	■	■	■
	PD	■	■	■	■	■	■	■	■

Abbreviations: BSC = best supportive care; CR = complete response; PD = progressed disease; PR = partial response; SD = stable disease.

		Collectively, the data suggest premature discontinuation is not anticipated to impact progression/ORR data nor have a large impact on results. For example, the best overall response and actual response observed at the end of each year of treatment is similar for patients who remained on treatment to those who discontinued prematurely. Therefore, efficacy outcomes in the model are not expected to be impacted by excluding patients who discontinued treatment. As such, the company respectfully disagrees with the EAG's assumption (in relation to the inclusion of premature discontinuation into the model) "that these patients would experience the same progression risks as BSC patients, given that they had not received nirogacestat for long enough to benefit from its disease modifying effects" (p117 of EAG report).
Key Issue 9: Health state utility values	No	The company maintains their original position that data from the EORTC QLQ-C30 could not to be robustly mapped to the EQ-5D-3L based on published algorithms due to significant methodological limitations. Due to these limitations, the company considers the results of the analysis to lack face validity and therefore not interpretable or applicable for consideration in this appraisal. As described by the company in the response to NICE clarification questions, one of the main limitations of the attempt to map the EORTC QLQ-C30 from DeFi to EQ-5D was the lack of a suitable mapping algorithm to represent patients in the DeFi trial. The mapping algorithm used to explore the feasibility of mapping, and identified as the most suitable mapping algorithm available by the EAG, included oncology patients with multiple myeloma, breast cancer, and lung cancer, whose tumour types are considered to be distinctly different than patients with DT. The patients in this sample were also notably older than patients in the DeFi trial (mean age of 68 years versus 37 years, respectively) and had a higher proportion of men (44% versus 35%, respectively). Therefore, the mapping algorithm was determined to be non-generalisable to the DeFi population, as important differences in the patient populations could affect health state utility values and severely limit the suitability of the mapping algorithm. Additionally, methodological limitations further limit the mapping of EORTC QLQ-C30 from DeFi to EQ-5D, including a small effective sample size available to inform mapping from the DeFi trial leading to few observations in the DeFi dataset for the CR, PR and PD health states, a temporal mismatch between PRO and progression assessments in DeFi leading to high variability in predicted utility values for the PD health state, and a lack of data for patients after they progress. As mapped utilities could not be reliably produced from the DeFi trial, and there is no evidence in the published literature to inform health state utilities in patients with DT, the company acknowledges that

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		the health state utilities for this patient population remain uncertain. In the absence of available data to inform health state utility values for patients with DT, both the company and the EAG considered STS to be the most appropriate analogue with available data suitable to inform health state utility values in the economic model; however, there still remains limitations in data availability for patients with STS. Shingler et al. (2013) reported utility values that could inform different levels of response/health states considered in the economic model design (i.e., PR, SD, PD) which is why utilities from this study were considered by the company to be the most suitable for the base case analysis. However, the company acknowledges that Shingler et al. (2013) was a time trade off (TTO) study using vignettes, which is not NICE's preferred method of measuring health-related utility. The utility data source preferred by the EAG, Reichardt et al. (2012), used EQ-5D to measure health-related utility, in line with NICE's preferred methods. However, as the utility values in Reichardt et al. (2012) are reported by line of therapy rather than by health states considered in the economic model, they could not be applied directly to the economic model for several health states, and instead the incremental difference between health states in the company's base-case utilities was applied to estimates that could be informed by Reichardt et al. (2012). Therefore, the company considers that due to the absence of robust data to inform health state utility values for patients with DT, leading to inherent limitations in the estimation of health state utility values in both the company's base case and the EAG base case, the true health state utility values for this patient population may fall between the utilities proposed in the company base case and the EAG's preferred estimates. To explore potential uncertainty in the health state utility values, the company has conducted a scenario analysis to assess the impact of implementing the EAG's base case utility values. This scenario produced ICERs of [REDACTED] versus BSC and [REDACTED] versus chemotherapy.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Conduct of the De-Fi trial	Section 1.4 (p25) and Section 3.2.9	Yes	Regarding differences in baseline characteristics between treatment arms of the DeFi trial, the company wishes to reiterate that the clinical experts consulted by the EAG “did not suggest these imbalances would overtly bias the trial results in any specific direction” (Section 3.2.2.2 of EAG Report). In addition, according to Section 3.2.9, the EAG mentioned that the company had “noted an imbalance in the dropouts between treatment arms” in the assessment. The EAG further clarified to the company that their concerns around missing outcome data were linked to the censoring in Table 12 of the CSR. More people were censored due to no adequate disease status assessment in the nirogacestat arm. The EAG noted that if all these people had progressed, but were not reported as such, then this would favour the nirogacestat arm. The company would like to note that Table 12 of the CSR shows that 4 participants were censored due to no adequate disease status assessment in the nirogacestat arm. Among these participants, 3 patients only had baseline tumor assessment and 1 had no baseline tumor assessment. Therefore, there is no data available to decide whether these participants had disease progression or not.

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			Finally, regarding the different way PFS was measured in the DeFi trial in comparison to other trials, section 3.2.9 mentioned the comparison was with the sorafenib trial. The EAG further clarified that the difference between De-Fi and the sorafenib trial was the addition of "investigator-determined clinical progression" in addition to the standard imaging-based progression according to RECIST. The EAG did not offer a judgement of whether combining imaging-based progression with clinical progression was more or less appropriate than imaging-based progression alone, but more that it was different than the other relevant trials. Also, the EAG noted that including clinical progression favoured nirgacestat. The company would like to clarify that only qualified clinical progression was considered as an event for PFS. According to the protocol, events of clinical progression would be adjudicated by an independent blinded central clinical review committee which would qualify events of clinical progression for inclusion in the primary analysis of PFS prior to study unblinding according to a Central Clinical Review Charter.
Additional issue 2: The company did not present any details of the studies included in the clinical SLR outside of the title each paper and the study it reported on	Section 1.4 (p26) and Section 3.1	Yes	Per the alternative approach suggested by the EAG, the company has generated and provided an included studies table that summarises the key characteristics of each study identified in the clinical SLR (see below).

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			 SpringWorks_Nirog acestat_DT Clinical_5
Additional issue 3: Assumed health related resource use	Section 1.4 (p27) and Section 4.2.7.4	Yes	Upon reviewing the EAG Report, the company consulted a clinical expert to further understand the most appropriate health-related resource use inputs for the model. In general, the expert acknowledged that some resource use, such as specialist visits, can vary widely depending on the specific patient and severity of their disease. Therefore, although the company maintains their originally submitted model inputs as these were carefully selected based on the best available data and discussions with clinical experts, the company acknowledges the potential for uncertainty in these inputs (and variability based on practicing clinician and patient needs). Thus, the company has conducted a scenario using the health-related resource use inputs proposed by the EAG. This scenario produced ICERs of [REDACTED] per QALY for nirugacestat versus BSC and [REDACTED] per QALY for nirugacestat versus chemotherapy.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

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Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 1 (Exclusion of chemotherapy as a comparator) and Key Issue 2 (Uncertainty related to the network meta-analysis)	The company excluded comparator from the model due to chemotherapy's limited relevance in the current treatment landscape and due to feasibility limitations related to the conduct of a robust indirect treatment comparison (ITC).	Chemotherapy has been added as a comparator, using hazard/odds ratios obtained from the company's ITC (MAIC). <i>Please note: in the company's new version of the EAG model (provided with this TE response form with new scenarios programmed in), the company has added chemotherapy as an "additional" comparator versus adding this onto the EAG's existing chemotherapy comparator option, as several inputs differed between the EAG assumption(s) and the company's internal assumption(s), and the programming would have required significantly more work to allow the functionality to flip between the two.</i>	<u>Nirogacestat versus chemotherapy:</u> New ICER: █████ per QALY Change from company's base case ICER: N/A <u>Note: This ICER also incorporates edits made in response to Key Issue 4 and Key Issue 6</u>
Key Issue 4 (Calculation of progression risks during trial randomised period/first 2 years) and Key Issue 6	Transition probabilities derived using the company's calibration approach, as described and reported in Section 3.3.3 and	The company has adjusted its base case to use the same transition probabilities as implemented in the EAG model for nirogacestat and BSC and	<u>Nirogacestat versus BSC:</u> New ICER: █████ per QALY Change from company's base case ICER: increase of 41% (versus

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(Extrapolation of progression)	3.3.4 of the company's submission dossier.	assume no progression after two years	company's original base case ICER of [REDACTED] <u>Nirogacestat versus chemotherapy:</u> New ICER: [REDACTED] per QALY Change from company's base case ICER: N/A
Company's base case following technical engagement (or revised base case)	Versus BSC: Incremental QALYs: [REDACTED] Versus Chemo: [REDACTED]	Versus BSC: Incremental costs: [REDACTED] Versus Chemo: [REDACTED]	Versus BSC: [REDACTED] per QALY Versus Chemo: [REDACTED] per QALY

Sensitivity analyses around revised base case

As described in Table 2 above, several new scenario analyses around the company's revised base case were conducted in response to specific Key Issues and Additional Issues. These scenarios and their corresponding ICERs are reported below:

Key Issue 4: Scenario analysis wherein EAG's base case transition probabilities for chemotherapy were maintained: ICUR = [REDACTED] per QALY for nirogacestat versus BSC; ICER = [REDACTED] per QALY for nirogacestat versus chemotherapy

Key Issue 5: Scenario analysis wherein transition probabilities are informed using reanalysed actual response data: ICER = [REDACTED] per QALY for nirogacestat versus BSC; ICER = [REDACTED] per QALY for nirogacestat versus chemotherapy

Key Issue 7: Scenario analysis wherein 5% of patients were assumed to continue treatment for an additional 1 year: ICER = [REDACTED] per QALY for nirogacestat versus BSC; ICER = [REDACTED] per QALY for nirogacestat versus chemotherapy

Key Issue 9: Scenario analysis wherein the health state utilities were aligned to the EAG's preferred values: ICER = [REDACTED] per QALY for nirogacestat versus BSC and [REDACTED] per QALY for nirogacestat versus chemotherapy

Additional Issue 3: Scenario analysis wherein healthcare resource use frequency inputs were aligned with those suggested by EAG: ICER = [REDACTED] per QALY for nirogacestat versus BSC; ICER = [REDACTED] per QALY for nirogacestat versus chemotherapy

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References Cited

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- SpringWorks Therapeutics (2022). Statistical Analysis Plan for Patient Reported Outcomes - An Addendum to NIR-DT-301 Statistical Analysis Plan (PRO Addendum) - Protocol NIR-DT-301. Final Version 2. Unpublished
- Toulmonde M, Pulido M, Ray-Coquard I et al. (2019) Pazopanib or methotrexate-vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study. *Lancet Oncol* 20 (9): 1263-1272

Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm on 3 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating desmoid tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Sue Clark
2. Name of organisation	Association of Coloproctology of Great Britain and Ireland; St Mark's Hospital, LNWUH NHS Trust; Imperial College, London; NHS(E) Hereditary Gastrointestinal Polyposis Syndromes Rare Disease Collaborative Network; International Society for Gastrointestinal Hereditary Tumours
3. Job title or position	Consultant colorectal surgeon Chair of RDCN
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with desmoid tumours? ☐ A specialist in the clinical evidence base for desmoid tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for desmoid tumours? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1. To prevent death/life-threatening complications due to relentlessly progressive desmoid. 2. To treat significant complications (eg ureteric and bowel obstruction due to intra-abdominal desmoid) and pain/mechanical limitations due to abdominal wall and extra-abdominal desmoid. 3. To prevent the above by treating progressive desmoid disease before significant symptoms/complications arise.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This is a very difficult question to answer as desmoid disease is heterogenous, and symptoms/complications are related to both site and extent/size. The use of RECIST is applicable in situations (predominantly but not exclusively abdominal wall and extra-abdominal sites) where desmoid forms a mass with resulting compression of neighbouring structure – however the reduction in size required to produce improvement in symptoms will depend a great deal on the actual site and size of the lesion. Intra-abdominal desmoid in patients with familial adenomatous polyposis (FAP) are often plaque-like sheets of cicatrisation leading to puckering and obstruction of ureters and bowel. In these circumstance really only symptom improvement (eg resolution of bowel obstruction allowing a patient to obtain adequate nutrition orally rather than being on intravenous nutrition) or avoidance/reduction in interventions (ureteric stenting, radiological/surgical drainage of sepsis, surgical bowel diversion, bowel resection) are meaningful endpoints.
10. In your view, is there an unmet need for patients and healthcare professionals in desmoid tumours?	Yes 90% of desmoids are sporadic, and 10% associated with FAP. 20% of patients with FAP develop desmoid, and of those about 50% cause significant symptoms and 10% result in death. There is very little good quality evidence to support treatment decisions, in particular in FAP (the subgroup analysis in DeFi did not reach statistical significance).

Clinical expert statement

	There is an unmet need in terms of desmoid overall, but particularly in FAP patients in whom it remains a major contributor to disease-related morbidity and mortality. There are important differences between sporadic and FAP related desmoids in terms of diagnosis, site, clinical manifestations and treatment. These are often overlooked by units treating desmoids, whose predominant experience is with sporadic disease.
11. How is desmoid tumours currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current guidelines on the management of FAP are used, but have very little on desmoid as a result of the poor evidence base. Monahan KJ, et al. Gut 2019;0:1–34. doi:10.1136/gutjnl-2019-319915 Kasper et al. JAMA Oncol. doi:10.1001/jamaoncol.2024.1805 is labelled as a review, but includes guidelines; these overlook some of the specific issues n FAP-associated desmoid. Sommovilla J et al. Clin Colon Rectal Surg 2024;37:185–190 is the most up to date review of specifically FAP associated desmoid. The pathway is not well defined. Most patients with FAP are looked after by colorectal surgeons and gastroenterologists in centres that are part of the Hereditary GI Polyposis RDCN, where the approach is consistent (watch and wait, referral to sarcoma oncology if systemic treatment might be considered, to sarcoma surgery for extra-abdominal desmoids requiring surgery, and occasionally to transplant units for enterectomy and small bowel/multivisceral transplant). However FAP patients cared for outside the RDCN are often managed inappropriately by clinicians with limited or no experience of FAP associated desmoid. When systemic therapy is indicated, what is actually offered varies considerably (different chemotherapy regimens, sorafenib). The availability of nirogacestat would offer a systemic therapy with better side effect profile and subject to fewer contra-indications than current chemotherapy.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes- it will be used in the same way as current systemic therapy – given by sarcoma oncology teams in a specialist setting. No additional investment is required to introduce it.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The DeFi trial shows promising outcomes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is very difficult to comment on the FAP group as they formed such a small subgroup in DeFi – but FAP associated desmoid occurs predominantly intra-abdominally (in contrast to sporadic desmoids which mostly are extra-abdominal). They are also more diffuse (ie less a well defined mass) and more often multi-focal. Thus systemic therapy is indicated in a higher proportion in this subgroup, who are therefore likely to benefit more from the availability nirogacestat.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	No change

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acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Given the heterogeneity of desmoid disease it is very difficult to provide appropriate rules but: 1. Diagnosis – desmoid is very rare. Sporadic desmoid appears as a growing mass in an otherwise healthy individual; alternative diagnoses such as sarcoma are much more likely than desmoid, and biopsy is essential to make the diagnosis (and more importantly exclude other diagnoses). Most of these desmoids are extra-abdominal or in the abdominal wall, and accessible and relatively safe to biopsy. In FAP 20% of patients will develop desmoid, usually in the 5 years following risk-reducing colectomy. There is genotype-phenotype correlation, such that some FAP-causing constitutional pathogenic variants in the APC gene (3' of codon 1400) are associated with increased risk, as is (independently) a family history of desmoid. Thus the prior probability of a typical mass being a desmoid is several orders of magnitude higher than in the sporadic situation. Most FAP-associated desmoids (and the majority of those that cause significant clinical problems) are within the small bowel mesentery, wrapped in small bowel and teathered to it, in patients who have undergone colectomy and are likely to have significant adhesions. Biopsy in this setting is technically challenging, sometimes impossible, and carries a significant risk of bowel perforation. I have personally cared for 2 patients in the last year who have had to undergo emergency laparotomy to deal with complications of attempted biopsy, and a third who was scheduled for laparotomy to biopsy (radiological needle biopsy had failed) a stable desmoid that did not even need treatment. It is not necessary or appropriate to confirm a diagnosis of desmoid with biopsy in a patient with FAP who has a clinically and radiologically typical presentation, and in whom there is no concern about peritoneal metastases (ie no history of abdominopelvic cancer in the last 5 years) and this needs to be clarified to avoid harming these patients. 2. Should only be used for progressive desmoid, and in situations when surgery is not first line.

Clinical expert statement

	3. There should be a stopping rule – 2 years is reasonable, but it should be possible to re-start treatment if the desmoid progresses again in the future.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The potential avoidance of the need for intravenous nutrition (used in patients with chronic small bowel obstruction), repeated ureteric stenting/nephrostomy (for ureteric obstruction), radiological or surgical drainage of intra-abdominal sepsis, surgical bowel defunctioning and enterectomy and small bowel/multivisceral transplantation (occasionally used for advanced intra-abdominal desmoid when chemotherapy has failed or is contra-indicated) have not been considered. Treatment of complex desmoid tumors in familial adenomatous polyposis syndrome by intestinal transplantation E Canovai, et al. .Transplantation Direct 2024; 10 (2): e1571. DOI: 10.1097/TXD.0000000000001571
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes It provides an orally administered treatment in a situation where the only currently available systemic treatment is intravenous cytotoxic chemotherapy with a worse adverse effect profile.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This treatment will only be given for progressive desmoid; the adverse effects are minimal compared to the effect of untreated disease or systemic cytotoxic chemotherapy.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	Only DeFi is relevant. It is very difficult to be sure exactly what the indications were for systemic treatment given the wide variety of anatomical sites. Patient reported outcomes (pain and QoL) are the most important and were measured. Progression free survival is also helpful (given the caveat that RECIST is not always appropriate, particularly in the setting of cicatrising intra-abdominal lesions).

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There are none
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	-

- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of chemotherapy as a comparator	I think it is reasonable to exclude chemotherapy. There are no randomised trial data, various different regimens are used, with different aims (eg pain relief vs tumour shrinkage). In some patients chemotherapy is contra-indicated but they might be able to take nirogacestat.
Uncertainty related to the network meta-analysis	Not in my area of expertise
Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Pain is a major issue in sporadic desmoids, due to the predominantly extra-abdominal location (nerve compression, mechanical issues etc). It is much less of an issue in FAP-associated desmoids, which are predominantly intra-abdominal (resulting in ureteric and bowel obstruction, sepsis and distention).
Calculation of progression risks during trial	Not in my area of expertise

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randomised period/first 2 years	
Calculation of response	Not in my area of expertise
Extrapolation of progression	Not in my area of expertise
Assumed stopping rule	This is desirable from a clinical perspective
Approach to early discontinuation	Not in my area of expertise
Health state utility values	Not in my area of expertise
Are there any important issues that have been missed in EAR?	My area of expertise is in FAP-associated desmoid. 90% of desmoids are sporadic, and 10% associated with FAP. 20% of patients with FAP develop desmoid, and of those about 50% cause significant symptoms and 10% result in death. Desmoid is one of the two commonest causes of disease-related mortality in FAP, the other being upper GI cancer. The EAR states: 'In the CS, the company noted that in some cases, people with DT experience more severe symptoms such as bowel obstruction and perforation, organ dysfunction, and sepsis. Both of the EAG's clinical experts stressed that these are rare complications, one noting that in four years he had seen three or four cases of bowel obstruction and perforation'. These experts clearly do not look after patients with FAP. We admit this number of patients annually with intra-abdominal sepsis and/or bowel obstruction, and on average two per year have gone on to enterectomy and small bowel/multivisceral transplant. Patients with abdominal sepsis are often not referred to oncologists as chemotherapy is contra-indicated – so they will not see this group where the management is primarily supportive and sometimes surgical. The potential avoidance of the need for intravenous nutrition (used in patients with chronic small bowel obstruction), repeated ureteric stenting/nephrostomy (for ureteric obstruction), radiological or surgical drainage of intra-

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	abdominal sepsis, surgical bowel defunctioning and enterectomy and small bowel/multivisceral transplantation (occasionally used for advanced intra-abdominal desmoid when chemotherapy has failed or is contra-indicated) have not been considered in the modelling. Trials of systemic treatment for desmoid will of course, include many more sporadic than FAP-associated desmoids, but distinction of the FAP subgroup is essential. Recruitment through polyposis specialist centres is likely to be fruitful. The group needs to be properly defined – in DeFi they are defined by ‘family history of FAP’ – which is meaningless as 20% of FAP cases arise de novo and do not have a family history, and 50% of people with a first degree relative with FAP with not have it themselves. In DESMOPAZ they are labelled as ‘Gardner’s syndrome’, a term which should no longer be used as it is not a distinct entity. Neither study is sufficiently clear about the distinction between constitutional and somatic variants. These issues could be avoided by involving experts in FAP in trial design.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There are important differences between sporadic and FAP associated desmoid and how it is managed; patients having systemic therapy should be managed jointly by sarcoma and polyposis specialist teams.

Desmoid is common in FAP, and usually intra-abdominal in patients who have had extensive abdominal surgery; as long as the clinical and radiological features are typical, and there is no recent history of cancer, histological confirmation is hazardous and should not be mandated before systemic therapy.

Intra-abdominal desmoid in patients with familial adenomatous polyposis (FAP) are often plaque-like sheets of cicatrisation leading to puckering and obstruction of ureters and bowel; in these circumstance symptom improvement and reduction in interventions (eg ureteric stenting, radiological or surgical drainage of sepsis, stoma formation, parenteral nutritional support or need for enterectomy and transplantation) are the only meaningful endpoints.

The use of RECIST is applicable in situations (predominantly but not exclusively abdominal wall and extra-abdominal sites) where desmoid forms a mass with resulting compression of neighbouring structure – however the reduction in size required to produce improvement in symptoms will depend a great deal on the actual site and size of the lesion.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

Thank you for your time.

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Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm on 3 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating desmoid tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Robin Jones
2. Name of organisation	Royal Marsden
3. Job title or position	Professor
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with desmoid tumours? ☒ A specialist in the clinical evidence base for desmoid tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for desmoid tumours? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for Desmoid tumours is to improve patient symptoms, particularly pain and limited mobility.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant response would consist of improvement in pain and mobility.
10. In your view, is there an unmet need for patients and healthcare professionals in desmoid tumours?	There is an unmet need for patients + clinicians in Desmoid tumours. There are no approved systemic therapies.
11. How is desmoid tumours currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Desmoid tumours are usually treated with active surveillance or chemotherapy. Please note that none of the chemotherapy drugs used are approved for Desmoid tumour. The only reason they are used is because there are currently no approved treatments. In addition, chemotherapy can cause significant acute and long-term toxicities. The long-term complications are very important in view of the fact that most patients with Desmoid tumour are young and patients very, very rarely die from Desmoid tumour. The new technology would give patients and clinicians access to the first ever approved treatment for Desmoid tumour. It would help us manage patients' symptoms, specifically pain, increase mobility and potentially control disease progression. It would give patients a chance of improving their quality of life.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes, the technology will be used in the same way as current (unlicensed) care in the NHS. Access to unlicensed drugs varies across the United Kingdom. The technology is administered orally, which means there is no need for any equipment or facilities.

Clinical expert statement

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Yes, the technology will provide clinically meaningful benefits compared to current unlicensed therapy. The treatment is very well tolerated. Desmoid tumour is very rarely fatal. The technology will increase health-related quality of life as reported in the prospective Phase 3 trial.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the Phase 3 trial efficacy was demonstrated across all subgroups.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology will be easier to use compared to currently used unlicensed therapy as it is administered orally and is very well tolerated.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing is required. Starting and stopping treatment will be based on an individual case basis.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	The technology is an oral medication is easier to administer than unlicensed chemotherapy. Some of the chemotherapy schedules are administered intravenously weekly.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	The technology is innovative and will have a significant impact on health-related benefits. In addition to drastically reducing pain levels, it can help with improving range of motion and controlling disease progression. As a result, patients will have a chance to increase their physical activity, improve their emotional state and overall health. The fact that it is well tolerated means that patients can continue working and engage in socio-economic activities while on treatment. The technology addresses the unmet need for approved therapy in managing Desmoid tumours.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are manageable.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trial reflects current UK practice. UK sites were among the top recruiters to the trial. The most important outcomes are improvement in pain and mobility, i.e. quality of life improvement. There are no adverse events that have become apparent subsequent to the clinical trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Currently, there are limited real world data with nirogacestat.

Clinical expert statement

Nirogacestat for treating desmoid tumours [ID6453]

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23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Desmoid tumour is rare disease and access to unlicensed therapy varies across the UK.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of chemotherapy as a comparator	There are a number of different (unlicensed) chemotherapy schedules that are used to treat Desmoid tumours. Most chemotherapy studies are retrospective. Chemotherapy is used only because there is currently no approved treatment for desmoids.
Uncertainty related to the network meta-analysis	It is important to note that most of the evidence base for using unlicensed chemotherapy in Desmoid tumours consists of retrospective studies. I support the use of best overall response rate.
Uncertainty related to the efficacy of nirugacestat and chemotherapy in reducing pain	The prospective Phase 3 trial has shown that nirugacestat improves quality of life compared to placebo with significant improvement in pain and mobility.

Clinical expert statement

Nirugacestat for treating desmoid tumours [ID6453]

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Calculation of progression risks during trial randomised period/first 2 years	In the clinical trial at the time of analysis, 29 (97%) patients on nirogacestat with a radiological response were still on treatment.
Calculation of response	The benefit of treatment to patients with Desmoid tumour is improvement in pain and mobility. Radiological response is less important. There can be a lack of correlation between symptoms and radiological changes in Desmoid tumours.
Extrapolation of progression	In my opinion, following 2 years of treatment with nirogacestat, the number of patients with disease progression beyond 2 years will be very low.
Assumed stopping rule	There will be a very small number of patients continuing nirogacestat after 2 years.
Approach to early discontinuation	The number of patients stopping nirogacestat early is also very low. With time and greater use oncologists also get better at managing side effects, so that patients can continue on treatment for longer.
Health state utility values	It is important to note that Desmoid tumour can have a dramatic effect on health state utility. The disease can stop patients from working and cause severe life changing pain, poor mobility and physical disfigurement .
Are there any important issues that have been missed in EAR?	Most patients with Desmoid tumours are young. The disease can stop them from working, creating families and contributing to society.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Desmoid tumours are incurable and very challenging to manage.

Desmoids can cause life-changing effects on quality of patients' lives.

There are no approved treatments for desmoids.

Current treatments on the NHS aren't effective enough in managing disease progression or symptoms, and none of them are licenced.

Desmoid tumour patients, as well as oncologists, are in need of innovative, approved and effective treatments.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking you about living with desmoid tumours or caring for a patient with desmoid tumours. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

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The deadline for your response is **5pm on 3 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with desmoid tumours

Table 1 About you, desmoid tumours, current treatments and equality

1. Your name	Inga Abramian
2. Are you (please tick all that apply)	☒ A patient with desmoid tumours? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with desmoid tumours? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Sarcoma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Desmoid community Facebook groups in the UK and the US (Desmoid UK and Desmoidian) ☒ I have completed part 2 of the statement after attending the expert

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	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with desmoid tumours? If you are a carer (for someone with desmoid tumours) please share your experience of caring for them	I was diagnosed with a desmoid tumour at the age of 27. Ever since the diagnosis, I lost my freedom. Every area of my life has been affected - from simple everyday tasks to family life and work. The only way to describe life with this disease is it's constant physical and emotional torture and suppression of all aspects of life. The size of the tumour (25cm) caused severe disfigurement that I have to live with and hide every single day and have done so for the past eleven years. When I was diagnosed, I was the only one who could see it, but due to failed treatments the desmoid grew rapidly. With agonising despair, I had to admit to myself that I could no longer wear the clothes I wanted to wear as I didn't want anyone to stare at me, so I started wearing baggy clothes in order to hide the disfigurement. The extent of this disfigurement is so horrifying that some medical professionals were left startled. I forgot what it's like to live pain free. I am so used to being in pain that it's become normal to me. Since it's on my hip, leg and glute muscles, even sitting down or standing up for too long can trigger pain which can be felt throughout my leg and the rest of my body. Simple daily activities like tying up my shoes, changing or staying active are very challenging. I struggle to stay physically active and can't do what other people of my age enjoy doing. Trying to live your life with pain every day without a break is challenging, but it's even worse when rest is affected too. Sleeping through the night without waking up in pain feels like a luxury. My sleep has been severally disrupted for years due to the symptoms and the size of the tumour which is now at 25cm after multiple failed treatments. In a state of constant physical and mental exhaustion, I start my day by going to work. Having to support myself and my dependants, I don't have a choice but to work so I can pay my bills. I must do well at work too, otherwise I will be replaced with someone else. No one wants to invest in the development of a person who is

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	unwell every day while tolerating their consistently requested time off due to medical appointments. If I decide to leave for a better role, it's going to be much harder for me to do so compared to others as I have to always consider the timing of potential treatments, scans and the severity of symptoms. I had to take time off work in the past when starting treatments, which left me questioning how I was going to afford to pay my rent and support myself during those months. Having to think about this whilst going through serious treatment is unfair. It adds a whole other layer of complexity to the situation. I am now, once again, in a similar place where I might need to start treatment and a new job at the same time, and I don't know how I am going to manage that. Pursuing my dreams isn't an option any longer either. I am not free to choose where I live as I need to be close enough to a treatment centre with consultants who know and understand this disease, otherwise it will be mismanaged. This fact on its own adds another financial burden on top of everything else. Life with this disease is just existence and survival. When it comes to family life, I am in my late thirties, and I've been single for a long time. I had to complete a cycle of IVF all by myself just to give myself a small chance of having a child in the future, but with time I gave up on the idea that I might create a family one day as this condition would inevitably affect my partner and children too. This realisation comes at a cost, affecting the state of my mental health and adding a strain to everything, from living without spousal emotional support to having to manage finances on my own. Hardly anyone can understand this rare condition, which often leads to isolation and depressive feelings. I've started avoiding seeing my friends. It seems like everyone is planning something interesting – a trip, a weekend away, or something even bigger – a wedding. Somehow it feels impossible to experience any of this. Frankly, I am having trouble contributing to conversations as I can hardly plan anything beyond my 3-month medical appointments. It feels like I run out of good memories at this point in my life. While everyone else is planning life milestones, I am having to come up with a plan on how to manage the next treatment.

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	As a result of having to manage life with desmoid fibromatosis, I feel like I am living in a constant physical and emotional strain. I am in a never-ending intense state of stress, and, as a result, I am in therapy, which only acts as an outlet to communicate my feelings and only slightly contributes to managing my emotions in this ongoing battle.
7a. What do you think of the current treatments and care available for desmoid tumours on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	a) My case is one of the many examples that prove the ineffectiveness of current treatments available on the NHS. When I was diagnosed, the condition was at 7cm, which is large but also small enough for others to not notice. Within two years of diagnosis and after the first line of treatment, which was Tamoxifen and Naproxen, the tumours grew to 25cm. I had to start wearing baggy clothes in order to hide the affected area. It grew rapidly and steadily while on Tamoxifen. I was then told that Tamoxifen only works in 20% of cases. Vinorelbine was the second line of treatment, which slowed the progression down slightly, but it didn't improve any of the symptoms and it didn't put the tumour into remission. As a result, it started growing again the day I stopped taking Vinorelbine. After that I got Sorafenib via the compassionate use programme. It put most of the affected site into remission and shrunk it slightly on one side, but there are still active areas remaining even today. Sorafenib currently isn't available on the NHS. Cryoablation works for some people but the success of the treatment very much depends on the size and location of the disease. In many cases it can only be used to treat a part of the affected area, which was also the case for me. While I'm grateful for the treatments I had access to, it's clear that none of them truly work. Some people had a little more luck with them, but none of those treatments are considered to be a cure or even an approved treatment for this specific condition, nor do they have lasting positive effects. I know there are so many patients like me, who struggle with the fact that nothing seems to work,

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	especially patients with extra-abdominal disease. Current treatments have proven to be outdated and with no real proven efficacy. Managing the side effects of current treatments comes at a cost for the NHS too. It's also very tough for medical professionals, who are trying to find an answer, but hardly have any real treatment options available. I lost count of how many times I heard "we don't know" from medical consultants, and how many times we had tough conversations because there wasn't much they could do as there wasn't anything effective enough to treat with. b) Other patients feel the same way. Frustration and despair is very common in the community, and most patients have had similar outcomes with current treatments, which is a very minimal improvement in size, if any, and no symptomatic relief.
8. If there are disadvantages for patients of current NHS treatments for desmoid tumours (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Current treatments available on the NHS have significant side effects that are a huge challenge on their own, both physical and emotional. Imagine losing your hair and having to manage gastro-intestinal disturbances, fatigue and a number of other side effects just to then be told that it did little to improve the condition, and then trying something else and going through the exact same experience again and again. I often feel like I have no choice but to go for yet another treatment at a significant cost to my health, knowing that the treatment will likely do nothing to the disease. Disadvantages of current treatments available on the NHS are: • None of them are approved to specifically treat desmoid tumours • None of them really work in shrinking tumours or have lasting effects • None of them provide short-term or lasting symptomatic relief • All of them have high toxicity, including significant side effects such as hair loss, fertility issues, various internal organ issues. • Having current treatments feels like an experiment rather than a real treatment

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9a. If there are advantages of nirogacestat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does nirogacestat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a) Having Nirogacestat available on the NHS could bring us hope and a better solution to this devastating disease. It would be the first ever treatment specifically designed for desmoid tumour patients. I believe we finally deserve to have one so we can better manage this condition. Advantages of Nirogacestat over current NHS treatments include: • The first approved treatment specifically designed to target desmoid tumours • High potential in shrinkage of tumours which would bring both symptomatic relief and positively affect mobility • Symptomatic (specifically pain) relief • Potential positive lasting effects in terms of symptom relief and tumour control As a result of symptomatic relief and a potential reduction in tumours' sizes, patients would have a drastically improved quality of life as they would potentially be able to work/ stay in education. They would be able to look after their dependants or create a family. Patients could lead a more active lifestyle, resulting in better overall physical and mental health, which would in turn positively influence their life, contribution to society whilst reducing healthcare costs. No current treatments offer similar benefits. b) The important advantages are: potential shrinkage; symptomatic relief, including pain relief and improved mobility; ability to work c) Nirogacestat addresses a number of mentioned disadvantages of current NHS treatments. Since the medication has been designed to specifically target desmoid tumours, taking it would feel like an actual treatment rather than an experiment. It has proven to work in ~70% of cases, and no current treatment offers this level of efficacy. Nirogacestat provides symptomatic relief, including pain reduction. It was referred to as a 'miracle drug' by many patients within the community. Even though this medication still has a

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	number of side effects, it also has a much higher probability of modifying the disease, which makes it worth the risk.
10. If there are disadvantages of nirogacestat over current treatments on the NHS please describe these. For example, are there any risks with nirogacestat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Disadvantages could include skin toxicity and fertility issues, but those are also possible on current treatments available on the NHS.
11. Are there any groups of patients who might benefit more from nirogacestat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None that I am aware of.
12. Are there any potential equality issues that should be taken into account when considering desmoid tumours and nirogacestat? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	None that I am aware of.

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Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	It feels like other chronic incurable conditions have better treatment options. The desmoid community has nothing.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in [table 2](#). We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of chemotherapy as a comparator – is chemotherapy a relevant comparator? (we consider patient perspectives may particularly help to address this issue)	I think chemotherapy isn't a relevant comparator. Even though chemotherapy medications, such as Vinorelbine, are used in desmoid tumour treatment, the only reason they are used is because there is currently no approved treatment for the condition. There is nothing else that can be used, therefore, oncologists have no choice but to prescribe chemotherapy. Based on my own experience, and the experience within the desmoid tumour community, chemotherapy has very little benefit on management of the disease. In my case, it slowed the growth down for the duration of the treatment, but it did not stop the growth completely, and the tumours started growing quicker as soon as I stopped treatment. While on chemotherapy, I did not benefit from pain reduction, the size or tumour activity reduction. I am not aware of any individuals in the community who have greatly benefitted from any type of chemotherapy, and most patients needed further treatment within a very short period of time after completing chemotherapy course. In addition, chemotherapy has significant side effects with potential long-term issues.

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Uncertainty related to the network meta-analysis	
Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Chemotherapy does not have a positive impact on pain reduction. Based on my experience, chemotherapy provided very little symptomatic relief, and I have never heard any patients mention that it helped them with pain reduction. In terms of Nirogacestat, patients call it 'a miracle drug' as it eliminated pain within 1-2 weeks of taking it regardless of impact on tumour size. Reducing pain can significantly impact the quality of life, allowing patients to work and engage in more social activities and contribute to society.
Calculation of progression risks during trial randomised period/first 2 years	
Calculation of response	
Extrapolation of progression – would additional progression occur beyond 2 years? (we consider patient perspectives may particularly help to address this issue)	It's difficult to say as this disease is often unpredictable, and patients have different experiences.
Assumed stopping rule – is a 2 year stopping rule for all people appropriate? (we consider patient	I don't think a 2-year stopping rule for everyone is appropriate. Some patients might stop taking Nirogacestat before the 2-year mark, based on their individual cases, and some might need treatment beyond the 2-year mark. Some patients might need to stop and then go back on it after some time. It would be unfair and devastating to have to come off the medication that helps simply because of the 2-year stopping rule. As mentioned, there are no other treatment options for desmoid tumour patients,

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perspectives may particularly help to address this issue)	therefore, what would treatment options look like for patients after they've completed their 2 years on Nirogacestat? I think flexibility in treatment availability is important based on the evidence of how unpredictable desmoid fibromatosis is.
Approach to early discontinuation – what proportion of people would stop nirogacestat before 2 years of treatment due to adverse events? (we consider patient perspectives may particularly help to address this issue)	It's impossible to predict as everyone reacts to medication differently, including any other medication than Nirogacestat. Based on conversations within the community, Nirogacestat is well tolerated with manageable side effects. In addition, patients might have to stop taking it due to their personal circumstances, such as expanding their family, rather than side effects.
Health state utility values – what is an appropriate health state utility value for people with progressive disease? (we consider patient perspectives may particularly help to address this issue)	While I am unable to give a specific number in this case, I have previously had debates with other patients and health care professionals that desmoid tumour diagnosis might have a worse impact on the state of health than cancer. The reason for this is the fact that cancer treatment has a time limit, and patients face a certain outcome, whether that's a positive one or a negative one. Desmoid Fibromatosis is a chronic, incurable condition, and patients live their whole life with it. Some patients spend their lives in a wheelchair because of it. Many face treatment after treatment for years. Many patients can't complete basic, every day activities because of the limit of range of motion, and all of us live in pain. It's truly never ending, and there is no break from suffering.
Are there any important issues that have been missed in EAR?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Desmoid Fibromatosis is a devastating life-long disease which brings physical and emotional pain and despair to patients' lives.
- Desmoid tumours cause severe disfigurements, restricted mobility, and are extremely difficult to treat.
- Desmoid tumours interrupt patients' ability to work, have a family, they cause depression, anxiety and other mental health issues.
- There is no approved treatment that specifically targets the disease, and all current treatments available on the NHS are outdated and do not work.
- The desmoid tumour community is currently very much underrepresented within the world of rare diseases. We desperately need new, effective treatments. If approved, Nirogacestat would be the first EVER treatment to specifically target desmoid tumours.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Single Technology Appraisal

Nirogacestat for treating desmoid tumours [ID6453]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

Nirogacestat for treating desmoid tumours [ID6453]

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on 3 February 2026**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	This is being submitted as a joint Sarcoma UK and Desmoid Aid UK response.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	- On 16/05/25, Merck awarded Sarcoma UK the value of £3,000. The sum was put towards hosting our Sarcoma Community Day event in June 2025. - In September/ October 2025, Sarcoma UK were in discussion with Springworks (which was acquired by Merck in July 2025) regarding potential funding for our 2025 Shining Stars Awards Ceremony, but we did not receive any eventual sum. - Desmoid Aid UK have not received any funding from the company bringing the treatment to NICE for evaluation or any comparator treatment companies in the last 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	We do not have any direct or indirect links with, or funding from, the tobacco industry.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Exclusion of chemotherapy as a comparator	Yes/No	• Chemotherapy should not be included as a comparator, since it is not a treatment designed or effective for the treatment of desmoid-type fibromatosis (DF). • However, exclusion of chemotherapy as a comparator does not fully reflect the reality of treatment received by DF patients in England. While there is no documentation of chemotherapy use as a treatment for DF, in practice it does occur. Vinorelbine is generally first line of call if resorting to chemotherapy, since its side effects are less extreme than doxorubicin. • Despite its present use, we do not recommend chemotherapy should be included as comparator since its use is due to the current absence of any effective targeted treatment, meaning chemotherapy is sometimes used as an alternative to providing no treatment at all, or undergoing potentially harmful surgery or cryotherapy. It can lead to some small improvement in patient condition, but overall, treatment of DF with chemotherapy is not effective, hence the need for nirogacestat as a targeted treatment. • It is important that the committee understand the inadequacies of chemotherapy for treating DF in order to understand how necessary, effective and tolerable nirogacestat is.

Technical engagement response form

		○ Nirogacestat is proven to be effective in controlling growth or causing regression, whereas chemotherapy is not. Chemotherapy can be considered as 'experiment over treatment'. Not only is this significant clinically, but should be understood in terms of the emotional impact on the patient. We know that for patients, deciding to begin and undergoing a treatment with such a huge physical, mental and social impact, with hope that the condition will improve, to find no or little improvement can be emotionally devastating. ○ Nirogacestat reduces symptoms, whereas chemotherapy does not. Please see below for expansion. ○ Nirogacestat has a long-term impact, whereas any positive effects of chemotherapy, where they occur at all, do not remain long-term. ○ Nirogacestat has limited side effects, whereas the effects of chemotherapy are highly disruptive for a patient. Patients have told us that receiving chemotherapy leads them to experience both life-inhibiting pain and nausea, in addition to their existing DF symptoms. ○ In addition, nirogacestat does not present additional side effects that do not also occur with chemotherapy. For example, potential negative effects on fertility exist for both treatments. • Please also note that the treatment of patients with sporadic desmoid tumours and the treatment of patients with FAP (familial adenomatous polyposis) related DF tumours. For those with FAP, chemotherapy is not often used in practice, and surgery is preferred. Regarding the exclusion of 'other relevant treatments in the NHS' (EAG Report p.16): • Cryoablation: the feasibility of cryotherapy is dependent on the tumour placement, location and size. • TKIs: sorafenib was previously available via compassionate access, but is no longer offered on compassionate access schemes from December

Technical engagement response form

		2025. As page p.16 notes, it should have been a comparator treatment if routinely available. Please note that for patients with, FAP related DF, treatment differs. Chemotherapy is very rarely used. Surgery is often necessary due to the location of the DF in the abdomen. DF tumours in this location make the patient at risk of bowel perforation and must be removed to save the life of the patient. However, these surgeries can be dangerous, have negative impacts on the patient's quality of life, and cause further clinical harm. Nirogacestat would reduce the need for these surgeries.
Uncertainty related to the network meta-analysis	Yes/No	While we will not comment on the validity of evidence for the efficacy of chemotherapy, we can offer support to the clinicians' expectations that they would 'not expect to see substantial improvements in PFS associated with chemotherapy'.
Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Yes/No	- The importance of pain reduction for sporadic DF patients should not be underestimated. As a chronic condition in need of ongoing management, treatment is not just about tumour response but symptom management. - As the EAG report suggests, for patients, reduction in pain is often the outcome of treatment more desired than a reduction or stabilisation of tumour size. Patients are aware that DF will not be cured and often undertake treatment with the primary goal of symptom management. - Patients have consistently told us that nirogacestat is effective at reducing pain, typically reporting reduced pain within 1-2 weeks. Patients have described this effect to us as life changing in terms of quality of life. - Sporadic DF patients report significant pain, with little effective treatment. The chronic pain impacts their ability to work, their social life and their caring responsibilities. - In addition, reduction of pain through effective treatment reduces the need for strong pain management medication (often morphine) that can impact patients' quality of life through reduced mental capacity, fatigue, constipation and limitations on ability to drive.

Technical engagement response form

		- Patients do not report to us that chemotherapy has the same effectiveness in pain reduction. - The importance of pain reduction in treatment of DF differs for patients with FAP related tumours. For these patients, pain does not originate from the tumours themselves, but from the impacts of the tumour on the abdominal region.
Calculation of progression risks during trial randomised period/first 2 years	Yes/No	- Calculation is difficult as progression is unpredictable. Patients may experience slower or faster periods of growth unrelated to external factors, including treatments. - Patients may also experience spontaneous regression. Complete regression is highly unusual.
Calculation of response	Yes/No	No comment.
Extrapolation of progression	Yes/No	No comment.
Assumed stopping rule	Yes/No	- It is not possible to make an assumption about the point at which 'all' patients should stop treatment. Point at which treatment ends is a clinical decision based on the condition of the individual patient. - A set 'cut-off point' is also likely to be emotionally challenging for patients given the effectiveness of the treatment. From a patient experience perspective, the prospect of an arbitrary point at which treatment ends, thus the possibility of disease progression and symptom resumption may be very challenging. - Some clinicians may suggest that a two year mark is an appropriate mark to pause treatment with nirogacestat. DF is non-cancerous process, and some clinicians would argue that most patients should at some point come off the drug to assess how the tumour(s) act without it. The tumour(s) may remain dormant. However, it is highly important that the option to restart the

Technical engagement response form

		treatment is available for patient who begin to experience symptoms again when they pause or stop treatment with nirogacestat.
Approach to early discontinuation	Yes/No	- Ultimately, the proportion of patients stopping treatment prior to the end of a two year period is unknown. There is no longitudinal data to call upon. - From a patient perspective, some may choose to stop treatment due to adverse effects, practical difficulties in accessing treatment or personal circumstances. - Please note, treatment for FAP related DF patients differs due to the nature of their disease. Bowel specialists rather than sarcoma specialist teams will lead on their care.
Health state utility values	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses - It is our understanding that the ERG committee doubts that the use of a quality of life score for soft tissue sarcoma (STS) is not an appropriate substitute for quality of life score for DF, considering it 'not credible as it was in line with the utility values experienced by patients receiving terminal care for cancer' and STS is a 'more severe condition' than DF (EAG report, p. 23). - Questions over the methodology of data from the Shingler study is not for patient representatives to comment on. However, from the perspective of a patient representative organisation, we suggest that the quality of life of sarcoma patients is not universally worse than that of DF patients. On comparison of the two conditions, an argument can be made that DF patients face a poorer quality of life than STS patients. - The quality of life of STS patients is undoubtably poor. Yet while sarcoma patients experience the emotional and mental impacts of fear of death and

		isolation of a rare disease, and aggressive symptoms, they can expect treatment and an outcome. Treatments often help to control symptoms. • DF patients, conversely, face the prospect of a lifelong disease with no possibility of a positive outcomes, thus an end to their symptoms. DF often develops early in life, affecting patients from early adulthood. The mental and emotional impact of the knowledge that their condition is incurable and lifelong should not be underestimated. They also experience the sense of isolation felt by sarcoma patients in experiencing a rare disease with little public awareness. In addition, DF patients often feel invalidated by the inability to call their condition cancer and the tumour being benign. DF patients face extreme side effects (including pain and mobility restrictions) effecting ability to work, form relationships, socialise and care for themselves independently. • To provide a sense check for quality of life scores from the perspective of a patient representative organisation (where 1 represents perfect health and 0 represents death), both 0.263 or 0.69 are possible scores for an individual with DF. Given that the impact can range from noticeable but manageable limitations on daily life, to severe pain and near total reliance on a carer, we would suggest that a very approximate average would sit in the range of 0.30 to 0.60.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Technical engagement response form

Nirogacestat for treating desmoid tumours [ID6453]

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Conduct of the De-Fi trial	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: The company did not present any details of the studies included in the clinical SLR outside of the title each paper and the study it reported on	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 3: Assumed health related resource use	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue :			[INSERT / DELETE ROWS AS REQUIRED]

Difference in treatment of sporadic desmoid tumours and FAP related desmoid tumours.	p. 36 - 'The EAG's experts also noted that the treatment pathway was the same whether or not a person has FAP.'	Yes	Due to the differences in location between the tumours of a patient with FAP associated DF and a patient with sporadic DF, differences in treatment and specialist care exist. For FAP associated DF patients, 80% desmoid tumours are intraabdominal, compared to just 5% of sporadic desmoid tumours (Maria Laura de Marchis et. al., <i>Desmoid Tumors in Familial Adenomatous Polyposis</i> , Anticancer Research, 2017). The rest appear as extra abdominal tumours, such as limbs. Due to the majority of tumours occurring in the abdominal regions, there is a risk of bowel obstruction and perforation, so a FAP patient is far more likely to be operated on due to the need to remove tumours to save the life of the patient where possible. A FAP patient is therefore less likely to undergo chemotherapy due its limited effectiveness at the point of need of treatment.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form



Nirogacestat for treating desmoid tumours [ID6453]

A Single Technology Appraisal

EAG Response to Technical Engagement

March, 2026

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

<i>Alex Allen</i>	Project manager. Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
<i>Frank Grimsey Jones</i>	Led on critical appraisal of the company's economic evidence and analysis and drafted sections of the report
<i>Saul Stevens</i>	Critical appraisal of the company's economic evidence and analysis and drafted sections of the report
<i>Alan Lovell</i>	Critical appraisal of the company's literature search and editorial input.
<i>Jamie Bowater</i>	Reviewed the company's ITC and contributed to the report
<i>Dan Stark</i>	Expert clinical advice to the EAG about desmoid tumours and their treatment
<i>Andrea Napolitano</i>	Expert clinical advice to the EAG about desmoid tumours and their treatment
<i>Dawn Lee</i>	Project director and guarantor. Critical appraisal of the company submission, writing and editorial input.

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1. INTRODUCTION

The purpose of this addendum is to present the EAG's review of new evidence presented by the company and stakeholders at the technical engagement stage.

2. EAG RESPONSE TO COMPANY'S TECHNICAL ENGAGEMENT RESPONSE FORM

2.1. Key issue 1: Exclusion of chemotherapy as a comparator

The company states that 'Despite its off-label use, chemotherapy was not included as a comparator because it is not clearly established as UK standard practice and lacks high-quality evidence of efficacy (with available data limited to retrospective or single-arm studies).' This is somewhat contradictory as if a treatment receives substantial use within the English NHS, it is considered to be part of the 'established UK standard practice' for the purpose of NICE decision making, even if its use is 'off-label'.

Nevertheless, the company did submit evidence in the form of an indirect treatment comparison (ITC) with chemotherapy and added chemotherapy as an "additional" comparator in the economic model. Therefore, the EAG considers this key issue has been resolved.

The company applied dosing for vinorelbine in line with the vinorelbine 30mg SmPC,¹ 60mg p/m² once weekly for the first three administrations then 80mg p/m² once weekly for the subsequent administrations. When rounded to the nearest pill using the body surface area of 1.9m² in the model, this equates to a 120mg weekly dose in cycle one and a 150mg weekly dose in cycle two onwards. This has a large impact on the cost of the vinorelbine comparator, at £542.42 in cycle one and £638.14 per cycle from cycle two onwards. The EAGs original dosing assumption was based on clinical expert feedback that in the DT indication he would expect a weekly dose of 90mg of vinorelbine. This equates to £232.03 per model cycle.

Further clinical expert consultation during the technical engagement process yielded two retrospective observational studies on the use of vinorelbine in desmoid tumours (DT) in adult patients. In Mir et al (2020),² a flat weekly dose of 90mg was given due to hematological toxicities being observed in doses of 120mg and above. Similarly, in Gennatas et al (2020),³ a flat weekly dose of 90mg was observed in all patients from 2004 - 2019. These studies further highlight that a 90mg weekly dose of vinorelbine was in line with clinical practice in the DT indication.

2.1.1. Stakeholders

Sarcoma UK and Desmoid Aid UK submitted a joint response to technical engagement. They accepted that chemotherapy, principally vinorelbine, was used as a treatment for people with

desmoid tumours. However, they argued that it was used in absence of effective treatment and was an alternative to undergoing potentially harmful surgery or cryotherapy. They explained the inadequacies of chemotherapy in relation to its efficacy and in relation to its safety. The clinicians and patient member also considered that chemotherapy was not an appropriate comparator, mainly due to lack of evidence, and lack of efficacy. The patient member commented that he had tried chemotherapy and found it slowed tumour growth, but only for the duration of treatment, and he did not find it reduced pain. The clinician experts did not remark on the efficacy based on their experience of prescribing chemotherapy to people but did highlight the lack of high-quality evidence (RCTs).

The EAG recognised the limitations in the evidence for chemotherapy and concerns related to its efficacy and safety. This was explored in Section 3.4.1.2 of the EAG report and is further explored in Section 2.2.2 of this report. However, in a NICE STA a comparator is a technology that is currently used in the NHS and could be replaced by the intervention, if NICE recommends the new technology. At the time of this appraisal, chemotherapy was the primary systemic therapy used for desmoid tumours in the NHS. Indeed, the company noted that it was recommended in the 2024 guideline update⁴: “Medical therapy (including TKIs and chemotherapy) is recommended as one of the first-line treatment options for patients who require treatment for a DT in the abdominal wall, mesentery, retroperitoneum, pelvis, extremities, girdles, or chest wall”. Therefore, the EAG considered it to be the most relevant comparator in the population addressed in this appraisal, i.e. people with desmoid tumours who require systemic treatment.

2.2. Key issue 2: Uncertainty related to the network meta-analysis

In Key issue 2, the EAG noted uncertainties relating to the pragmatic nature of the network meta-analysis (NMA) that they conducted to compare nirogacestat with chemotherapy. The EAG suggested that the company may be able to conduct a more appropriate ITC given the extensive SLR they conducted. This could have entailed the company using this SLR to determine whether all relevant trial data had been included in the NMA that the EAG had conducted or whether nirogacestat and chemotherapy could have been connected through a more extensive treatment network graph, which could have opened up the possibility of the company choosing to present another NMA on the basis of a more appropriate or extensive set of trial data. Also, the company could have conducted structured expert elicitation with clinicians

to determine appropriate estimates for the effect size of treating DTs with chemotherapy in the UK or supplemented trial data with secondary data sets, e.g. patient registry data. Finally, another possible option for the company was to utilise individual data (IPD) from its own De-Fi trial to conduct a matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) of nirogacestat versus chemotherapy. Faced with the options just mentioned, the company chose the latter option and, in particular, chose to conduct an unanchored MAIC of nirogacestat versus chemotherapy.

2.2.1. An NMA versus an unanchored MAIC

It is often not easy to decide which ITC methodology should be regarded as producing the most trustworthy results and there are various factors that should influence this decision. The EAG chose to conduct an NMA to compare nirogacestat with chemotherapy in its report, while the company chose to conduct an unanchored MAIC of these two treatments in its response to technical engagement. The company provided little justification for its decision to conduct an unanchored MAIC given the other available options that are discussed in TSD18,⁵ e.g. an STC.

The main advantage of an NMA over an unanchored MAIC is that we do not need to assume that prognostic variables are constant over the treatment network graph as effect estimates in an NMA are constructed on the basis of relative rather than absolute treatment effects. An NMA does, however, depend on assuming that effect modifiers are constant over the treatment network graph. On the other hand, the main advantage of an unanchored MAIC over an NMA is that by using individual patient data (IPD) for the study of the intervention of interest, some adjustment (albeit usually only partial adjustment) can be made for differences in both prognostic variables and effect modifiers between the studies of the treatments being compared. Another advantage of an unanchored MAIC over an NMA is that since unanchored MAICs are constructed from single-arm trials and individual treatment groups taken from multi-arm studies, there may be substantially more data available that can be incorporated into an unanchored MAIC rather than an NMA.

Furthermore, the NMA presented by the EAG in its original report relied on a treatment network graph that connected nirogacestat to chemotherapy via three studies, one of which had neither treatment with nirogacestat nor chemotherapy as one of its treatment arms (namely a trial of sorafenib versus placebo) rather than two studies that each evaluated one of these two treatments. This potentially represents another disadvantage of the NMA conducted by the EAG in comparison to an unanchored MAIC of nirogacestat versus chemotherapy. Therefore, the

benefits obtained from conducting an unanchored MAIC of nirogacestat versus chemotherapy as had been done by the company in their response to technical engagement was definitely worthy of consideration.

2.2.2. Studies included in the company's unanchored MAIC

The company conducted an unanchored MAIC of nirogacestat versus chemotherapy on the basis of trial data from the De-Fi trial of nirogacestat versus placebo and the DESMOPAZ trial of methotrexate with vinblastine versus pazopanib. Data from both of these trials were included in the NMA conducted by the EAG and so the company's decision to conduct an unanchored MAIC did not lead to data from additional trials being incorporated into the estimation of the efficacy and safety of nirogacestat compared to chemotherapy. Furthermore, the EAG was of the opinion that the exclusion of data from additional studies from this unanchored MAIC was highly questionable.

In particular, the EAG was concerned that the company used subjective reasons and arbitrary criteria to exclude three studies from their unanchored MAIC, namely Costa et al. (2022),⁶ Palassini et al. (2017)⁷ and Wood et al. (2022).⁸ These studies are summarised in Table 1 along with the included DESMOPAZ trial.

Table 1: Studies of chemotherapy considered for inclusion in the MAIC

Study identifier	DESMOPAZ	Costa et al. (2022) ⁶	Palassini et al. (2017) ⁷	Wood et al. (2022) ⁸
Company's inclusion decision	INCLUDE	EXCLUDE	EXCLUDE	EXCLUDE
Patient group	Adults with desmoid tumours	Teenagers and adults with desmoid tumours	Adults with desmoid tumours	Adults with desmoid tumours
Age of patients	Median: 42 years	Median: 37 years	Median: 36.6 years	Median: 33 years
Line of treatment	First-line and second-line	First-line only	First-line and second-line	First-line and second-line
Intervention	Methotrexate with vinblastine (n=22)	Sorafenib (n=32), doxorubicin with dacarbazine (n=13), liposomal doxorubicin (n=11), methotrexate with vinblastine (n=11),	Methotrexate with vinblastine (n=30), methotrexate with vinorelbine (n=43), vinorelbine monotherapy (n=2)	Oral vinorelbine (n=37)

		methotrexate with vinorelbine (n=8) and methotrexate monotherapy (n=1)		
Comparator	Pazopanib	None	None	None
Baseline characteristics reported	Age, sex, ECOG performance status, tumour site, mutational status, Gardner syndrome, previous treatment, number of previous lines of systemic treatment	Age, sex race/ethnicity, tumour site, prior surgery	Age, sex, tumour site, pain/discomfort, year of diagnosis, previous surgery, previous radiation, previous medical treatment.	Age, sex
Scoped outcomes that were reported	Objective response rate, progression-free survival, overall survival, HRQoL, pain intensity, adverse events	Progression-free survival, adverse events, treatment-related deaths	Treatment duration, objective response rate progression-free survival, overall survival, adverse events	Duration of treatment, objective response rate, adverse events
Results for ORR and PFS	ORR: 26.3% One-year and two-year PFS: 79% [95% CI: 53.2, 91.5]	Two-year PFS: 80%	ORR: 48% Two-year PFS: 83%	ORR: 16%
Study design	RCT (but only the chemotherapy arm was used)	Retrospective	Retrospective	Retrospective
Study time period	2012 to 2020	2000 to 2021	1989 to 2014	2020 to 2022
Time on treatment	12 months	Not stated	Median: 13.9 months	Median: 7 months
Follow-up period	3 years	Median: 5.6 years	Median: 6.6 years	Not stated
Country	France	USA	Italy	UK (London)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, Progression-free survival.

As mentioned in the EAG report, the primary chemotherapy agent used to treat desmoid tumours in the UK is vinorelbine though low dose doxorubicin can also be used. The classic chemotherapy option for treating desmoid tumours was methotrexate with vinblastine but methotrexate with vinorelbine or vinorelbine monotherapy have gained favour in recent years due to their tolerability and ease of administration. From Table 1, it can be seen that substantial

numbers of participants in DESMOPAZ, Costa et al. (2022),⁶ Palassini et al. (2017)⁷ and Wood et al. (2022)⁸ received methotrexate with vinblastine, methotrexate with vinorelbine or vinorelbine monotherapy. Therefore, the EAG considered that the exclusion of Costa et al. (2022), Palassini et al. (2017) or Wood et al. (2022) was not justified on the grounds of the type of chemotherapy administered in these studies.

Also, the reporting of patient characteristics in the studies presented in Table 1 could be described as adequate except for Wood et al. (2022)⁸ which only reported the age and sex of people included in their study. Therefore, the case could be made to exclude Wood et al. (2022) from the MAIC for this reason, but the EAG felt that this decision would still have been somewhat arbitrary, especially since the type of chemotherapy considered in this study was oral vinorelbine which has become the chemotherapy of preference for desmoid tumours in UK clinical practice. In terms of outcomes reported, all these studies reported results for more than one outcome included in the NICE scope for this appraisal. It could be pointed out that Costa et al. (2022)⁶ does not report objective response rate and Wood et al. (2022) does not report progression-free survival, but these would not usually be sufficient reasons for excluding studies from an ITC for other outcomes of interest.

Other reasons cited by the company for excluding Costa et al. (2022),⁶ Palassini et al. (2017)⁷ and Wood et al. (2022)⁸ from their ITC relate to follow-up period, the timeframe of the studies, time on treatment, inclusion of adolescent peoples, previous treatment, treatment subgroup reporting of baseline characteristics and outcomes and study design (retrospective rather than prospective). Details about these study characteristics are given in Table 1 for the studies of interest. The EAG was of the opinion that none of these reasons was particularly strong and the decision to exclude any of these studies for one or a collection of these reasons would be too arbitrary for the results of the corresponding ITC to be regarded as being objective.

With regard to efficacy outcomes from Costa et al. (2022),⁷ Palassini et al. (2017)⁷ and Wood et al. (2022)⁸ that can be compared to the included DESMOPAZ trial, ORR was 48% in Palassini et al. (2017), 16% in Wood et al. (2022) and not reported in Costa et al. (2022)⁶ which compares to 26.3% in the DESMOPAZ trial and two-year PFS was 83% in Palassini et al. (2017), 80% in Costa et al. (2022) and not reported in Wood et al. (2022) which compares to 79% in the DESMOPAZ trial. These summary statistics do not give a clear indication that the company's decision to exclude Costa et al. (2022), Palassini et al. (2017) and Wood et al. (2022) led to

their unanchored MAIC being heavily biased, however, this decision certainly led to a decrease in corroborative evidence and probably led to a decrease in the precision of efficacy estimates.

2.2.3. Statistical procedures used in the company's unanchored MAIC

The company applied standard methodology to perform an unanchored MAIC of nirogacestat versus chemotherapy. However, the EAG considered that the lack of transparency and methodological details with regard to how this MAIC was carried out raised substantial doubts about the objectivity of the choices that were made by company in performing this analysis. In particular, although some general criteria were presented by the company for how the matching variables in this MAIC analysis were chosen, it is unclear how these criteria were applied to choose the matching variables for the MAIC that was used in the company's base case. Also, the company did not present a statistical analysis to justify the proportional hazards assumption on which its MAIC analysis was based and did not provide a justification for conducting MAICs rather than simulated treatment comparisons (STCs).

To be more specific, it would appear that the company identified the six prognostic variables that were the most likely to cause bias in the results of an ITC if no adjustment for imbalances in these variables between trials was made and then ranked these six variables in order of importance. The company reported in Table 4.1 of MAIC technical report that these six factors in order of importance were tumour site, age, prior systemic therapy, prior radiation therapy, prior surgery and prior TKI exposure. However, conflicting information provided by the company in its report means that it is unclear whether these variables were chosen purely on the basis of subjective clinical knowledge or also on the basis of their degree of imbalance between studies. Also, no detailed explanation or statistical analyses, e.g. subgroup analysis, are presented by the company to justify or validate the subjective clinical judgements that were made.

The company stated in its report that after applying its criteria for choosing matching variables, the matching variables for the MAIC that were used in the company's base case were: intra-abdominal (or tumour site), age and prior systemic therapy. The effective sample size of the De-Fi trial after reweighting the participants in this trial according to these three matching variables was ■ compared to its actual sample size of 69 which represents quite a substantial fall in the evidential weight given to this trial. Therefore, the decision by the company to limit the number of matching variables to only three is to some extent laudable. Nevertheless, the potential bias in the results of this MAIC caused by the somewhat arbitrary selection of a limited number of matching variables is an important consideration.

In this respect, the company presented in Table 5.1. of MAIC technical report the baseline characteristics of the De-Fi study before and after the participants in this study were reweighted according to the three matching variables in question. It can be seen from this table that there were large discrepancies between the DESMOPAZ trial and De-Fi trial for the baseline characteristics of prior radiation and prior TKI exposure after the matching criteria were applied (4.2% vs. ■■■% and 8.3% vs ■■■%, respectively) and notable differences between these two trials after matching for the baseline characteristics of prior surgery and sex (33.3% vs. ■■■% and 62.5% vs. ■■■%, respectively). All of these variables, except sex, were ranked by the company in the top six most important prognostic variables for this MAIC and so even using the company's own ranking system of prognostic variables, these discrepancies raise justifiable concerns that the results of the MAIC conducted by the company may be substantially biased.

For the patient reported outcomes of global health status and physical functioning, the baseline values of these outcomes were also used as matching variables in the MAIC along with the prognostic factors of tumour site, age and prior systemic therapy that were used as matching variables in the other MAICs. This is generally regarded as a better way of adjusting for heterogeneity in the baseline values of outcomes rather than transforming the raw outcomes into difference from baseline outcomes.

However, for the patient-reported outcome of BPI pain, the company chose to conduct a naive unadjusted ITC of nirogacestat versus chemotherapy rather an unanchored MAIC with adjustments for the baseline patient characteristics of baseline BPI pain, tumour site, age and prior systemic therapy. The reason that the company provided for doing this was that, due to large differences in baseline BPI pain between the De-Fi and DESMOPAZ trials, when an attempt was made to reweight participants in the De-Fi trial according to baseline BPI pain, the effective sample size in the De-Fi trial fell from 44 to just 2 people. The EAG was very concerned that not only was this ITC not adjusted on the basis of any baseline patient characteristics (except for the exclusion of one person with an ECOG greater than one) but also the comparison between the trials of nirogacestat and chemotherapy was conducted on the basis of raw values for BPI pain rather than change from baseline values for BPI pain. Furthermore, due to missing data, this ITC was based on reported BPI pain for only four patients in the DESMOPAZ trial. This means that the estimates of the mean difference of BPI pain between treatment groups that were produced by this ITC are likely to be heavily biased. Unfortunately, it was not possible for the EAG to determine the likely direction in which these

estimates were biased due to a summary of the baseline values of BPI pain for the De-Fi trial not being reported in the CS or in the company's response to technical engagement.

For the time-to-event outcome of progression-free survival, the MAIC presented by the company depended on the assumption of proportional hazard functions between the groups treated with nirogacestat and chemotherapy. The company acknowledges that this is the case and states that some visual assessment of this assumption was made from plots of the KM curves and log-cumulative hazard plots. Although the company did not present a formal assessment of this assumption or the log-cumulative hazard plots in question, it can be clearly seen from the KM curves for the treatment groups concerned that are presented in Figure 5.7 of MAIC technical report that this assumption is highly questionable. This raises concerns about additional bias in the results of the MAIC that would be caused by the failure of this assumption. It should be pointed out that the NMA that was conducted by the EAG for comparing nirogacestat with chemotherapy also relied on a proportional hazards assumption but the EAG presented a formal assessment of this assumption in its report and included that this assumption was adequate with respect to the study data that had been included in the NMA (which is different from the study data included in the company's MAIC).

2.2.4. Results of the company's unanchored MAIC

In the preceding two sections, the EAG raised concerns about the study inclusion criteria and the statistical procedures used by the company in conducting the unanchored MAIC of nirogacestat versus chemotherapy that was presented in its response to technical engagement. The EAG is of the opinion that the methodological deficiencies that have been identified may have led to the results produced by this MAIC being substantially biased. Nevertheless, some comments will now be made regarding the estimates of the relative efficacy of nirogacestat that were produced by the company's unanchored MAIC.

With regard to ORR, the odds ratio was estimated to be [REDACTED] but with a very wide 95% confidence interval of [REDACTED] to [REDACTED] (Table 2). As noted by the company, this estimate is quite different from the estimate of the odds ratio of ORR that was produced by the NMA conducted by the EAG of [REDACTED] [95% CI: [REDACTED], [REDACTED]]. Nevertheless, the two 95% CIs for this odds ratio derived from these two analyses substantially overlap which is indicative of the inherent uncertainty there is about the true value of this quantity.

The company also conducted unanchored MAICs of nirogacestat versus chemotherapy for other response rates namely complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The estimates of [REDACTED] and [REDACTED] for the odds ratio for CR and PR, respectively, [REDACTED], while the odds ratios of [REDACTED] for SD [REDACTED]

[REDACTED] (Table 2). By contrast, the estimate of [REDACTED] for the odds ratio of PD [REDACTED]

[REDACTED] of [REDACTED] to [REDACTED] for this odds ratio. The data on which this estimate of PD was based consisted of 4 out of 19 people being classed as having PD in the DESMOPAZ trial and one out of 70 people being classed as having PD in the De-Fi trial. These are very small patient numbers to assess an outcome such as PD which is open to some inter-study variability in the way it is evaluated. These additional response rates were not estimated in the NMA comparing nirogacestat versus chemotherapy that the EAG presented in its report.

With regard to PFS, the hazard ratio was estimated to be [REDACTED] (95% CI: [REDACTED], [REDACTED]) [REDACTED] by the company's MAIC which contrasts with the estimate of the hazard ratio of PFS that was produced by the NMA conducted by the EAG of [REDACTED] (95% CI: [REDACTED], [REDACTED]). However, again [REDACTED]

[REDACTED] which means that these odds ratio estimates are not inconsistent with each other. This provides further justification for treating the estimate of the odds ratio of PD produced by the company's MAIC as potentially being a statistical artefact.

With regard to the patient reported outcome of BPI pain, the mean difference of [REDACTED] estimated by the company's MAIC again favoured nirogacestat over chemotherapy but, as reported in Section 2.2.3, the EAG had grave concerns about the reliability of this estimate, and also, this result was nowhere near statistically significant as the hypothesis of no difference in effect was easily contained in the very wide 95% confidence interval of [REDACTED] to [REDACTED]. It was not possible to obtain an estimate of this mean difference using the NMA that the EAG presented in its report.

The company also conducted unanchored MAICs of nirogacestat versus chemotherapy for the patient reported outcomes of global health status and physical functioning. With regard to global health status, the mean difference of [REDACTED] again favoured nirogacestat over chemotherapy with this difference being statistically significant ($p=[REDACTED]$) as confirmed by the hypothesis of no difference falling outside the wide 95% confidence interval for this difference of [REDACTED] to [REDACTED]

which demonstrates a meaningful quality of life benefit for nirogacestat over chemotherapy. By contrast, with regard to physical functioning, the mean difference between the two treatments was very small with its value of [REDACTED] just tipping in favour of nirogacestat but with a very wide 95% confidence interval of [REDACTED] to [REDACTED]. Again, it was not possible to obtain estimates of these mean differences for global health status and physical functioning using the NMA that the EAG presented in its report.

It should be pointed out that the company did not conduct an ITC using MAIC methodology with regard to adverse events, e.g. Grade ≥ 3 adverse events, as the EAG had done using NMA methodology in its report. A reason was not provided by the company for not having done this even though the necessary data was available to the company for this analysis to be carried out. The EAG note, however, that adverse events were not a key driver of cost-effectiveness outcomes.

Table 2: Comparative results of the unanchored MAIC and NMA

	MAIC	NMA
PFS, HR (95%CI), p-value	[REDACTED]	2.23 (0.72, 6.86)
ORR, OR (95%CI), p-value	[REDACTED]	7.28 (1.14, 49.3)
CR, OR (95% CI), p-value	[REDACTED]	Not evaluated
PR, OR (95% CI), p-value	[REDACTED]	Not evaluated
SD, OR (95% CI), p-value	[REDACTED]	Not evaluated
PD, OR (95% CI), p-value	[REDACTED]	Not evaluated
Grade 3+ AEs, OR (95% CI)	Not evaluated	0.81 (0.14, 4.39)
BPI Pain, MD (95% CI) , p-value	[REDACTED]	Not evaluated
Global health status, MD (95% CI) , p-value	[REDACTED]	Not evaluated
Physical functioning, MD (95% CI) , p-value	[REDACTED]	Not evaluated

Abbreviations: CI, confidence interval; CR, Complete response; HR, hazard ratio; OR, odds ratio; MD, mean difference; PD, Progressed disease; PFS, Progression-free survival, PR, Partial response; SD, Stable disease

2.2.5. Modelling the relative effectiveness of chemotherapy within the economic model

The company have conducted four separate MAICs for the outcomes ‘complete response’, ‘partial response’, ‘stable disease’ and ‘progressed disease’. They have then implemented this in the model by applying these four separate treatment effects for chemotherapy vs nirogacestat, to state membership observed in the nirogacestat arm of the nirogacestat trial, in

order to model state membership for chemotherapy patients. The company discovered that this resulted in [REDACTED] of a patient in the chemotherapy arm of the model, which is not possible. The company addressed this by reducing membership of each state in order to ensure that only a single patient was modelled (“normalisation”).

Implementing four separate ITCs with four separate treatment effects in this way is not an appropriate approach and the need for ‘normalisation’ is evidence of this. It would not be possible to address this without re-running the ITCs and the direction of bias associated with the company’s approach is unclear.

We noted that the company model included the progressed disease MAIC, rather than the progression free survival MAIC. The EAG believes that the progressed disease MAIC is subject to greater uncertainty because it is based on progression assessed at specific timepoints, rather than using the Kaplan-Meier curves. The EAG also notes that the [REDACTED]. The former suggests [REDACTED], whereas the latter suggests [REDACTED]. Observing such large differences in such closely related measures is further evidence of the uncertainty associated with these MAICs.

Given the uncertainty in the company’s MAIC, the EAG prefers to keep with its original approach for incorporating chemotherapy within the model of using the network meta-analysis to inform objective response, and assuming that progression free survival for chemotherapy patients is the same as for best supportive care patients.

The EAG considered whether explicitly including pain within the model may be necessary to fully capture the benefits of all treatment, but the limited available evidence suggests the current health states are appropriate (Section 2.3.2).

2.3. Key issue 3: Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain

2.3.1. Pain reduction in people in pain at baseline

The company presented a range of analyses in relation to Key Issue 3. Key issue 3 primarily noted uncertainty that treatment with nirogacestat resulted in a clinically meaningful reduction in

pain. The EAG posited that the reason the benefit reported was not clinically meaningful was because the analysis included people who did not have uncontrolled pain at baseline. The EAG suggested that a subgroup analysis in people with uncontrolled pain at baseline would be appropriate to establish whether nirogacestat did offer a meaningful benefit in pain relief. In the CS, the company reported the least squares (LS) mean difference (SE) in worst pain intensity score at Cycle 10 (10 months) using the Brief Pain Inventory (Short Form; BPI-SF) was -1.34 (■■■■; $p < 0.001$). This was below the minimally important difference (MID) of two points.

In the technical engagement response, the company reported change from baseline in BPI-SF score from cycle 2 to cycle 40. Based on the results reported, this was not *worst pain intensity* as was reported in the CS and instead was potentially *average pain score* but this was not specified. It was reported in two subgroups, people with controlled pain at baseline (BPI-SF API ≤ 4) and people with uncontrolled pain at baseline (BPI-SF API > 4). The EAG considered the latter subgroup to be appropriate to address the concerns raised in Key issue 3.

To match what was the company reported in the CS, the EAG will critique the (average?) change in pain reported at cycle 10. Twenty-seven (38.6%) participants in the nirogacestat arm and 31 (43.1%) participants in the placebo arm had uncontrolled pain at baseline. The company reported on ■■■■ participants in the nirogacestat arm, and ■■■■ participants in the placebo arm with uncontrolled pain at baseline at cycle 10. The LS mean difference (95% CI) was ■■■■ (■■■■, ■■■■; p ■■■■). In people who did not have uncontrolled pain at baseline, the LS mean difference (95% CI) was ■■■■ (■■■■, ■■■■; p ■■■■). This confirmed the EAG's concern that nirogacestat's pain relief was underreported due to the population's pain at baseline. The updated LS mean difference (95% CI) at 10 cycles was ■■■■ (■■■■) and was still ■■■■ ■■■■ the MID of two points. However, the point estimate was ■■■■ (■■■■) at cycle 9 and cycle 11. Therefore, the EAG interpreted this as a clinically important reduction in pain in people in pain in baseline but cautioned that the 95% confidence interval stretched well below the MID.

2.3.2. Chemotherapy pain reduction

Clinicians advised the EAG that the principle benefit of chemotherapy was reducing pain and it was not effective at reducing tumour size. The EAG were concerned that this benefit of chemotherapy was not represented in the economic model because the economic model did not utilise change in pain as an input. The EAG used a two-pronged approach to addressing this. Firstly, the EAG requested a post-hoc analysis of patients' change from baseline in BPI-SF pain

score according to best overall response status and treatment arm. This was to assess whether a person's response to treatment was correlated with their change in pain. Secondly, the EAG requested the company complete an ITC comparing nirogacestat to chemotherapy for change in pain.

2.3.2.1. Pain and best overall response status

The company presented a post-hoc analysis of peoples' change from baseline in BPI-SF pain score according to best overall response status and treatment arm (Table 3, Table 4 and Table 5 of their response). These data are summarised in Table 3. People with a best-overall response of partial or complete response had a greater reduction in pain than people with a best-overall response of stable disease. The EAG has grouped these data for ease of interpretation. For example, there was a reduction of [REDACTED] for partial responders by Year 2, compared to a reduction of [REDACTED] for patients with a best-overall response of stable disease by Year 2. This was consistent across time points. This provided some evidence that objective response rate was a reasonably good proxy for pain and the two measures of patient outcomes are reasonably well correlated.

These data should be interpreted with caution as they have a wide confidence interval, for example, whilst at Year 2 there was a mean change in pain (BPI) from baseline of [REDACTED] among partial responders to nirogacestat, there were only [REDACTED] patients in this group, with a confidence interval of [REDACTED].

Table 3: Mean change in pain (BPI) from baseline, sample size (n) in brackets

Best overall response	Timepoint	Controlled		Uncontrolled		Grouped change in pain
		Nirogacestat (n)	BSC (n)	Nirogacestat (n)	BSC (n)	
Complete response	Cycle 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 12	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 24	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Partial response	Cycle 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 12	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 24	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Stable disease	Cycle 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 12	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 24	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Progressed disease	Cycle 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 12	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Cycle 24	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Notes: This table is informed by Table 3, Table 4 and Table 5 of the company submission. The right hand side column has been calculated by the EAG by calculating a weighted average of the other columns. **Abbreviations:** BPI, Brief Pain Inventory; BSC, best supportive care; n, number

2.3.2.2. Pain ITC

The EAG requested that the company conduct an ITC in relation to pain. Clinicians advised the EAG that chemotherapy may be relatively more effective at reducing pain than enabling patients to achieve an overall response. This would mean that only incorporating response, and progression, in the model would understate the benefits of chemotherapy.

Also, a clinical expert informed us that 'The benefit of treatment to patients with Desmoid tumour is improvement in pain and mobility. Radiological response is less important. There can be a lack of correlation between symptoms and radiological changes in Desmoid tumours.'

The company conducted a naive unadjusted ITC of nirogacestat versus chemotherapy, rather an unanchored MAIC with adjustments for the baseline patient characteristics of baseline BPI pain, tumour site, age and prior systemic therapy. As reported in Section 2.2.3, the results of this ITC suggested that the efficacy of nirogacestat was perhaps marginally better than chemotherapy in terms of BPI pain. However, as discussed in Section 2.2.3, the EAG had grave concerns about the reliability of the estimate of the mean difference in BPI pain between the nirogacestat and chemotherapy treatment groups that was produced by this ITC.

2.3.2.3. Chemotherapy pain summary

As noted in Section 2.3.2.1, it appeared from the data provided by the company that response rate was a reasonably good proxy for pain and the two measures of patient outcomes were reasonably well correlated. Also, as noted in the EAG report the EAG was unable to connect nirogacestat to chemotherapy in a NMA for pain, and at technical engagement the company presented a naïve unadjusted ITC and the EAG had grave concerns about the reliability of the estimate. Given the apparent correlation of pain and response, and the uncertainty of the ITC reported, the EAG concluded the limited available evidence suggested the current health states were appropriate.

2.4. Key issue 4: Calculation of progression risks

We welcome the company's acknowledgement that 'the EAG's revised modelled state membership reported in Table 37 of the EAG report provides a closer fit to the trial data than that derived using the company submitted model'.

The company states that 'while the EAGs approach to calculating transition probabilities did produce a close match to trial data in Year 2 (per Table 37 of the EAG report), the company would like to emphasise that this approach is still subject to limitations; as for nirogacestat, the rates of SD and PR are underestimated at Year 1, and for BSC, rates of SD are overestimated and rates of PD are underestimated at Year 1.'

We acknowledge this. However, we believe this deviation would largely cancel out by Year 2, so we do not consider this to be a key area of uncertainty. Also, the company had the opportunity to model transition probabilities separately for Year 1 and Year 2 and chose not to do so. It would have been highly challenging, if not impossible, for the EAG to model transition probabilities separately for Year 1 and Year 2 using only the data provided by the company.

We welcome the fact that 'the company has adjusted its base case to use the same transition probabilities as implemented in the EAG model for nirogacestat and BSC. Furthermore, to fully align with how transition probabilities were implemented in the EAG model, the company implemented the assumption that patients do not progress after 2 years (for more information, see Response to Key Issue 6).

The EAG previously conducted a network meta-analysis comparing nirogacestat with chemotherapy for both Objective Response Rate and Progression Free Survival. The EAG report explained why the network meta-analysis was not reliable for progression free survival:

'The results for progression-free survival are very uncertain, with the confidence interval crossing one (equivalence) by a substantial margin. The clinical experts advising the EAG considered that it did not make sense to have such divergent results for PFS and objective response rate. The heterogeneity between the studies included in the network, and small number of patients in the trials, contribute to the uncertainty in the results. The objective response rate NMA was considered to be more reliable than the PFS NMA as it did not require the same level of statistical power and follow up to achieve a robust result and the differences in trial design and inclusion criteria were considered likely to have a greater impact on PFS.' (EAG report)

The EAG have determined that the company's unanchored MAICs for progression and progression free survival are also unreliable (See Key Issue 2). The EAG therefore continued to assume that chemotherapy was associated with the same progression rate as BSC in the base case, with a scenario in which chemotherapy has the same progression rate as nirogacestat.

2.5. Key issue 5: Calculation of response

We thank the company for clarifying that 'the actual response data provided during the clarification stage included only patients who reached the one- or two-year landmark in the denominator, whereas best overall response rates from the originally submitted model consider entire population in denominator.'

We also thank the company for clarifying that 'even in this reanalysed data, the actual response data (PR with nirogacestat at 1 and 2 years and with BSC/placebo at 1 year) still exceeds the corresponding best overall response data. **The reason for this discrepancy relates to the difference in definition between the two outcomes.** A best overall response of CR or PR requires confirmation by a subsequent scan at least four weeks later. As a result, the proportion of patients with a given actual response at fixed timepoints (e.g., 1 or 2 years) is not necessarily capped by the reported best overall response.'

We would also like to thank the company for clarifying that 'the denominator included the full study population but not all patients had a recorded response at each timepoint (i.e., some patients did not have scheduled visit data, meaning they may be collected on unscheduled visits or totally missing, and some patients dropped out early).' and for updating the data provided to include patients whose data was missing or who had a tumour that was not evaluable. This does not have a bearing on the cost-effectiveness results but does help to ensure confidence in the accuracy of the data.

The new data presented by the company in Table 6 of their technical engagement submission suggest that the results are similar using both definitions of response (actual response or best overall response), the actual response data appear slightly more favourable to nirogacestat. As the company has chosen to continue to use 'best overall response' in their best case, we are willing to align with this assumption.

2.6. Key issue 6: Extrapolation of progression

We welcome the company's acceptance of the EAG's assumption of no progression after Year 2 in any of the treatment arms.

2.7. Key issue 7: Assumed stopping rule

The original company model implicitly assumed a two-year stopping rule, without providing sufficient justification or detail as to how it would be implemented. When the EAG consulted clinicians, they suggested they would keep some patients on treatment past two years if their tumour size had not plateaued, and it was difficult to state with confidence what proportion of patients this would apply to given the available data. Clinicians also said that they would like to be able to reinitiate treatment in patients where necessary. They said that:

'I don't think a 2-year stopping rule for everyone is appropriate. Some patients might stop taking Nirogacestat before the 2-year mark, based on their individual cases, and some might need treatment beyond the 2-year mark. Some patients might need to stop and then go back on it after some time.' (Clinical expert)

This was also highlighted as a priority by the patient expert as part of technical engagement. The model does not currently allow for the possibility of reinitiation, reinitiation would effectively add to the proportion of patients on treatment past Year 2 and the associated treatment costs. The EAG therefore assumed a three-year stopping rule as a conservative assumption.

Clinical experts indicated to the EAG that they would keep 10-15% of patients on treatment past two years. The company mischaracterised this by saying that 'The EAG's clinicians specifically estimated that they would expect to keep only 10-15% of patients on treatment to 2 years and only 3-5% on treatment to 3 years, based on patients' tumour size during the De-Fi trial.' The company also consulted with a clinical expert who said they would keep '<5% of patients' on treatment past two years.

The company presented data in Table 10 and Table 11 that attempts to establish what proportion of patients' tumours plateau by the end of the first and second year. The company defined tumour plateau as 'reaching the following response at two consecutive visits: CR to CR, PR to PR, PR to CR, SD to SD, or PD to PD'. The EAG does not consider this a reasonable

definition of tumour plateau, for example, if a patient experiences stable disease at two consecutive points within two years, then goes on to achieve a response or to experience progression by the end of two years, their tumour had not plateaued at Year 2. Table 12 in the EAG report shows that 3 patients achieved a response after Year 2, it is very likely that those patients had stable disease for at least two consecutive time points prior to Year 2. Section 2.6.6.3 of the original company submission suggests there would be at least some patients for whom this would be true, but it would be difficult to determine how many from the data provided. Further, the data are misleading because of the way patients who progress are accounted for. Table 11 reports that [REDACTED] patients with best-overall response of stable disease by two years, did not achieve tumour plateau. But the remaining [REDACTED] patients were all patients who had progressed before Year 2, so these patients would have discontinued treatment anyway.

The question of interest is actually what proportion of the [REDACTED] patients with a best-overall response of stable disease at Year 2 and the [REDACTED] patients with a best-overall response of partial response, whose tumour had not progressed, had a tumour that was still shrinking in size at the two-year time point and could therefore continue to benefit from treatment. These are the patients who clinicians would consider keeping on treatment past the Year 2 timepoint. The data provided by the company at technical engagement did not answer this question. The only data provided that does help to answer this question is Figure 2.13 in the original company submission. Based on these data, clinician experts informed the EAG that 10-15% of patients would remain on treatment after 2 years.

In the current EAG base case with a 3 Year stopping rule, when progression and discontinuation are factored in, [REDACTED] of patients are still on treatment at Year 2. The EAG have therefore updated their base case to assume that [REDACTED] of patients who remain on treatment at Year 2 discontinue treatment, so that only 15% of patients continue treatment into Year 3. We have assumed that this only affects drug costs and not treatment benefits, as the patients who remain on treatment would be those most likely to respond. This assumption favours nirogacestat, as does excluding the possibility of patients reinitiating treatment.

2.8. Key issue 8: Approach to discontinuation

The company stated that: The company base case excluded patients who discontinued treatment prematurely as routine follow-up data was not available from the De-Fi trial after

participants discontinued treatment. The EAG would like to reiterate that even if data were limited on the outcomes achieved by these patients, the fact remains that patients did discontinue treatment within the trial and this needs to be accounted for in the model.' (EAG Report).

The company have helpfully clarified that patients who discontinued treatment were not regularly monitored, but they did receive a single end of trial assessment. They provide some helpful data on the outcomes achieved by patients on treatment and patients off treatment (presumably including their End of Trial visit).

The company presented a range of data on the outcomes achieved by patients who discontinue treatment. The company states that they only have data on patient outcomes for one end of trial time point post discontinuation, so the long-term outcomes achieved by patients who discontinue treatment are unknown. These data provide helpful context

The company state that 'Collectively, the data suggest premature discontinuation is not anticipated to impact progression/ORR data nor have a large impact on results.'

The EAG would like to reiterate that the exclusion of discontinuation had only a minor impact on the ICER, increasing the ICER for nirogacestat vs BSC from [REDACTED] to [REDACTED] in a head-to-head comparison.

The company states that 'As such, the company respectfully disagrees with the EAG's assumption (in relation to the inclusion of premature discontinuation into the model) "that these patients would experience the same progression risks as BSC patients, given that they had not received nirogacestat for long enough to benefit from its disease modifying effects" (p117 of EAG report).'

The EAG would like to clarify its approach. Whilst the company has presented substantial data on the outcomes achieved by patients who discontinue, the company acknowledges that patients who discontinue nirogacestat were not regularly monitored, so it is uncertain whether their progression risk would be the same as nirogacestat patients or BSC patients following progression. The EAG believes that for patients who discontinue treatment very early (after one month for example), it is unlikely that they will achieve the same treatment benefits as patients who receive two years of treatment. If the company believes that patients who receive 2 months of treatment will accrue the same treatment benefit as patients who receive 2 years of treatment, then why provide patients with two years of treatment?

Within the model, the EAG's approach was constrained by the data available. Due to issues discussed in relation to Key Issue 4 and Key Issue 5, the EAG were forced to use state membership in each arm at the end of two years, to calculate transition probabilities in each cycle up to two years. The EAG applied the same treatment probabilities for patients on and off treatment, because the EAG used an approach that started with whether patients had progressed or responded by Year 2, then worked backwards to calculate transition probabilities. This was the best available approach given the data available. The only difference was that patients who discontinued treatment before Year 2 were not eligible for a late response in Year 3 or Year 4.

In summary, whilst the EAG stands by the logic of the quote on page 117, it is not reflective of the approach taken in the model, as a result of the constraints of the data provided. The EAG continues to believe that is appropriate to model the possibility of early discontinuation, as this is reflective of the trial and clinical practice, though agrees that this has a minor impact in the context of this model.

2.9. Key Issue 9: Health state utility values

The EAG acknowledges the company's stated concerns regarding the face validity of mapping EORTC QLQ-C30 data to EQ-5D-3L using published algorithms.

The company elected to use utility values derived from a time trade-off (TTO) study in soft tissue sarcoma patients rather than mapping their own trial data. The TTO methodology does not align with the NICE reference case.

Clinical experts advised that the company's progressed disease utility value of 0.26 lacks clinical plausibility. This value is lower than utilities reported for patients with terminal cancer, yet the condition being evaluated is not terminal.

The EAG selected alternative utility values from a different study⁹ in soft tissue sarcoma, with adjustments made to align with the health states defined in the company model. Specifically, the source data were presented by treatment line, necessitating adaptation. While we acknowledge these values are also uncertain, they do not exhibit the face validity concerns present in the company's estimates.

The company possesses EORTC QLQ-C30 data collected directly from the patient population enrolled in their clinical trial. Despite the EAG's recommendation of a mapping algorithm at clarification and subsequent requests for the company to provide mapped utility values, the company has declined to present these data although they do state they have undertaken the analysis.

The company suggests that mapping would lack face validity due to the algorithm being derived from populations including multiple myeloma, breast cancer, and lung cancer patients, rather than specifically from patients with DT. However, this objection is inconsistent with the company's own approach. The company was content to use utility values from a TTO study in soft tissue sarcoma patients, a population that also does not comprise DT patients specifically. The company cannot reasonably reject the mapping algorithm on the grounds of population mismatch while simultaneously accepting utility values from an equally non-specific population.

Had the company provided their trial-based utility estimates, this would have directly addressed both parties' concerns regarding the validity of externally sourced utilities. Furthermore, it would have enabled the EAG to present a range of utility scenarios derived from multiple sources.

The EAG has therefore opted to use the same base case assumptions as in the EAG report but note that the continued lack of provision of the trial data is concerning and may suggest that the EAG has over-estimated the benefit of nirogacestat compared to what has been observed.

2.10. Additional issue 1: Conduct of the De-Fi trial

2.10.1. Differences between the treatment arms in baseline characteristics

The EAG was concerned specifically about a higher proportion of participants in the placebo arm (76.4%) who were refractory to treatment compared to 61.4% in the nirogacestat arm. The company did not address this concern in their response but instead relayed a statement in the EAG report related to differences in ethnic background, BMI, and age quartile. However, as stated in Section 3.2.2.2. of the EAG report, "The EAG's experts explained that people who are refractory to treatment are less likely to respond to a new treatment and this imbalance favoured the nirogacestat arm." The EAG remained concerned that this difference favoured nirogacestat.

2.10.2. Imbalance in dropouts between treatment arms in De-Fi

The EAG stated a risk of bias associated with De-Fi was the censoring of four people in the nirogacestat arm and one person in the placebo arm due to no adequate disease status assessment. The company confirmed that of the four people in the nirogacestat arm who were censored, three only had baseline tumor assessment and one had no baseline tumor assessment. Therefore, there was no data available to decide whether these participants had disease progression or not and the concern related to missing data remained with a higher proportion missing in the nirogacestat arm.

2.10.3. Measuring PFS

The EAG also raised a concern regarding the different way PFS was measured in the De-Fi trial in comparison to the sorafenib trial. This was the addition of "investigator-determined clinical progression" in addition to the more standard radiological progression. The company highlighted that, despite the addition of clinical progression benefiting nirogacestat, it was adjudicated by an independent blinded central clinical review committee. The EAG accepted clinical progression was adequately measured but continue to note that it was measured differently to other trials in people with desmoid tumours.

2.11. Additional issue 2: Systematic literature review

In response to the EAG's Secondary issue 2, the company provided an included studies table for the SLR they conducted that summarised the key characteristics of each study. The company used this table to assess whether the company used the most appropriate chemotherapy trial in their MAIC. Their use of the SLR for this purpose is evaluated in Section 2.2 of this report.

2.12. Additional issue 3: Assumed health related resource use

The company acknowledged that there is potential uncertainty in their HCRU inputs and after consulting with a clinical expert conducted a scenario analysis using the EAGs HCRU inputs. The company did not provide the content of the clinical expert input or alter their base case.

The company base case assumed that patients who achieve complete response would accrue no HCRU. After consultation with clinical experts, the EAG concluded that patients who achieve a complete response would be monitored twice per year post treatment. The company also assumed in their base case that patients with progressed disease would only see a specialist

2.38 times per year. The EAG considered six specialist visits per year more appropriate after clinical expert feedback, as well as four visits per year in stable disease.

The differences in HCRU are not a major driver of the cost effectiveness of the intervention.

2.13. Stakeholder feedback on Familial Adenomatous Polyposis (FAP)

Ninety percent of desmoid tumours are sporadic, and ten percent associated with Familial Adenomatous Polyposis (FAP). People with FAP are around 20% likely to develop desmoid tumours, making them far more common in FAP than in the general population.¹⁰ There was stakeholder feedback on desmoid tumours in people with FAP from Professor Sue Clark, whose expertise is in FAP-associated desmoid tumours, and from Sarcoma UK and Desmoid Aid UK. They highlighted differences between the experience of people with sporadic desmoid tumours and desmoid tumours associated with FAP that were absent from the EAG report and company submission.

Professor Clark stated that 50% of people with FAP who develop a desmoid tumour have significant symptoms and 10% result in death. Desmoid is one of the two commonest causes of disease-related mortality in FAP. Sarcoma UK and Desmoid Aid UK stated that 80% desmoid tumours in people with FAP were intraabdominal, compared to just 5% of sporadic desmoid tumours. This leads to more severe symptoms such as bowel obstruction and perforation, organ dysfunction, and sepsis. Professor Clark explained that these severe symptoms lead to enterectomy and small bowel/multivisceral transplant (two per year in her Centre). She did not consider that the regularity of these events was adequately considered in the company's or EAG's economic model. She also raised concerns related to the reporting of outcomes of the FAP subgroups in De-Fi and DESMOPAZ.

The EAG thank the stakeholders for raising key differences in the severity of subgroup FAP-associated desmoid tumours and sporadic desmoid tumours. As noted above, 10 percent of desmoid tumours are associated with FAP and 24 (16.9%) participants in De-Fi with a family history of FAP. While the number of people with a family history of FAP is not the same as the number of people with FAP, it was still an indicator that the proportion of people with FAP-associated desmoid tumours in De-Fi was reasonably representative of the general population. Therefore, the results of De-Fi represented the efficacy and safety of a representative sample of the UK desmoid tumour population, at least in terms of the proportion of people with FAP-associated desmoid tumours. However, there may have been too few participants with FAP-

associated desmoid tumours, and the trial may have been too short, to offer a comprehensive assessment of the more severe events associated with intraabdominal desmoid tumours.

3. EAG RESPONSE TO CHANGES TO THE COMPANY COST-EFFECTIVENESS ESTIMATES

3.1. Company base case assumptions at technical engagement

The company have accepted two of the changes that the EAG made within their original appraisal, as part of the Company Technical Engagement Base Case (See Table 4 of the Company TE Response form). The first was that there is no additional progression after Year 2 (see Section 4.2.44 of the EAG report and the 4th row of Table 47 in the EAG report). The second is to accept a set of amendments to the way that transition probabilities were calculated within the model (see Section 4.2.44 of the EAG report and the 6th row of Table 45 in the EAG report). This is good as it addresses two of the most important issues with the original company model, but it means that the company's base case still contains a number of assumptions that are incorrect or lack credibility. The company did not accept any of the other assumptions implemented as part of the EAG corrected case or EAG base case, in the original EAG report.

The company did not include chemotherapy as part of their original base case but have included chemotherapy as part of the analysis they have presented at technical engagement. The company have not used the chemotherapy arm added by the EAG as a starting point but have instead added a new chemotherapy arm. The EAG have incorporated the differences between the chemotherapy arm added by the company and the EAG's original chemotherapy arm, into the EAG's original chemotherapy arm, such that in the new Company Technical Engagement Base Case, both chemotherapy arms match.

The key differences between the way chemotherapy was modelled in the EAG Base Case and the Company TE Base case are listed below. The second change also impacts the cost effectiveness of nirogacestat and best supportive care.

1. The company have made different assumptions about the dose that chemotherapy patients receive and how long they receive it for. The alternative dosage for chemotherapy is the use of 60mg/m² of vinorelbine in cycle one and 80mg/m² in subsequent cycles of the treatment duration, described in Key Issue One. The EAG assumed that the dose was 90mg for all patients, based on clinical expert advice. This also aligned with the protocols of relevant trials. The company assumed that chemotherapy patients remain on treatment for two years. The EAG have assumed

patients receive 6 months of chemotherapy treatment in the base case, based on clinical expert opinion and the protocols of relevant trials.

2. The company have added additional adverse events that are relevant to chemotherapy. The company also added these to the nirogacestat and best supportive care arms. The company's alternative adverse event assumptions for chemotherapy are the adverse events described in the SmPC for 30mg vinorelbine capsules.¹
3. The company have used effectiveness inputs from their MAIC, instead of the assumptions used by the EAG (NMA conducted by the EAG to inform response, and progression assumed to be equivalent to BSC). This is described in Key Issue Two (See Section 2.2).

Using the company's technical engagement assumptions gave an ICER of £[REDACTED] for nirogacestat versus BSC. [REDACTED].

The company presented a scenario where they adopted the utility values used by the EAG (Utilities taken from Reichardt 2012). They said:

'the company considers that due to the absence of robust data to inform health state utility values for patients with DT, leading to inherent limitations in the estimation of health state utility values in both the company's base case and the EAG base case, the true health state utility values for this patient population may fall between the utilities proposed in the company base case and the EAG's preferred estimates.' (TE Response Form).

The results of this scenario are presented at the bottom of Table 4 below. The ICER increased to £[REDACTED] for nirogacestat vs BSC. [REDACTED]

Table 4: Company technical engagement base case

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB	+/- EAG base case vs
Original EAG base case	BSC/placebo	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Vinorelbine	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB	+/- EAG base case vs
	Nirogacestat	██████	████	██████	████	██████	████	████
New adverse events included that are relevant to chemotherapy	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Ovarian dysfunction applied as intermittent	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Company treatment effect for chemotherapy (unanchored MAIC)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Company dosage for chemotherapy (60mg/m2 in cycle one then 80mg/m2 per cycle, for 2 years)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
No EAG correction to timing of progression in trace	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
No premature discontinuation included	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
2-Year stopping rule	BSC/placebo	██████	████	█	█	█	████	████

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB	+/- EAG base case vs
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██
Patients can't achieve a response after Year 2	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██
Utilities taken from Shingler 2013	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██
Company HCRU assumptions (no monitoring of complete responders and fewer specialist visits)	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██
Doxorubicin as subsequent therapy	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██

Company states that the ICER is expected to fall between the two below scenarios due to uncertainty in the data for utilities

1. Company base case TE	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██
	Nirogacestat	██████	████	██████	████	██████	██	██
2. Scenario on Company Base case (Utilities from	BSC/placebo	██████	████	█	█	█	██	██
	Vinorelbine	██████	████	█	█	██████	██	██

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NHB	+/- EAG base case vs
Reichardt 2012).	Nirogacestat	██████	████	██████	████	██████	████	████

Abbreviations: AE, adverse event; BSC, best supported care; EAG, external assessment group; ICER, incremental cost effectiveness ratio; NHS, net health benefit; QALY, quality adjusted life year; TE, technical engagement

3.2. EAG base case assumptions at technical engagement

The EAG sticks to its base case assumptions in all cases, for reasons detailed in this document and the EAG report, with two exceptions.

The EAG accepts that assuming a three-year stopping rule was a simplification that may overstate the average treatment duration. The EAG have therefore implemented an alternative stopping rule as part of their technical engagement base case, assuming that only 15% of patients continue treatment into Year 3 as described in Key Issue 7.

The EAG accepts the additional adverse events the company has added, as they are relevant to chemotherapy and the EAG has validated them with clinical experts.

Table 5 presents the EAG's technical engagement base case. Using the EAGs preferred assumptions, the ICER for nirogacestat versus BSC was £██████. The only assumption to have a meaningful impact on the ICER was the EAGs updated stopping rule.

Table 5 EAG technical engagement base case

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER	NHB	+/- Company TE base case vs
1. Company base case TE	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Ovarian dysfunction applied as a one-off event,	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████

Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER	NHB	+/- Company TE base case vs
instead of intermittent	Nirogacestat	██████	████	██████	████	██████	████	████
EAG treatment effect for chemotherapy (response informed by NMA)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
EAG dosage and duration for chemotherapy (90mg for 2 years)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
3-Year stopping rule, with 15% of patients on treatment past Year 2	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Premature discontinuation included (to match De-Fi)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Patients can achieve a response after Year 2 (matches De-Fi)	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Utilities taken from Reichardt 2012	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Alternative HCRU	BSC/placebo	██████	████	█	█	█	████	████

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Preferred Assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER	NHB	+/- Company TE base case vs
assumptions (monitoring of complete responders and more specialist visits)	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
Vinorelbine as subsequent therapy	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████
EAG base case TE	BSC/placebo	██████	████	█	█	█	████	████
	Vinorelbine	██████	████	█	█	██████	████	████
	Nirogacestat	██████	████	██████	████	██████	████	████

Abbreviations: AE, adverse event; BSC, best supported care; EAG, external assessment group; ICER, incremental cost effectiveness ratio; Inc., Incremental; NHS, net health benefit; QALY, quality adjusted life year; TE, technical engagement

Notes: * This correction has no impact when applied in isolation to the company base case, but is necessary when used in conjunction with other changes implemented by the EAG

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