Nirogacestat for treating desmoid tumours

For presenting – confidential information redacted.

Technology appraisal committee B [15 April 2026]

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Company: SpringWorks Therapeutics

Nirogacestat for treating desmoid tumours

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on desmoid tumours

Desmoid tumours are a rare type of intermediate, locally aggressive soft tissue tumour that can present in various parts of the body, with an unpredictable clinical course

Causes

- Exact cause uncertain: CTNNB1 gene associated mutations, also linked to trauma, surgery, hormonal changes, pregnancy.
- Linked to 2 molecular pathways: Wnt signalling pathway, Notch pathway.
- 5-10% of DTs are associated with familial adenomatous polyposis (FAP).

Epidemiology

- An estimated 3–6 cases per million population per year, corresponding to roughly 20,000–40,000 new cases annually worldwide (European and UK studies); higher incidence in women and increased risk in pregnancy and childbirth.

Symptoms and prognosis

- Symptoms and prognosis depends on the size and site of the tumour; some may be asymptomatic while others (such is within the abdominal cavity, in the head or neck) cause substantial pain, loss of function and mortality.
- Disease course is unpredictable, with periods of rapid progression, stable disease and spontaneous resolution

Abbreviations: DT, desmoid tumour.

Stakeholder feedback on Familial Adenomatous Polyposis

Patient and clinical expert comments (technical engagement)

- 90% of desmoids are sporadic, and 10% associated with Familial Adenomatous Polyposis (FAP). 20% of people with FAP develop desmoid, of those about 50% cause significant symptoms and 10% result in death
- Important differences between sporadic and FAP related desmoids in terms of diagnosis, site (80% desmoid tumours in people with FAP were intra-abdominal, compared to just 5% of sporadic desmoid tumours), clinical manifestations and treatment (chemotherapy rarely used in FAP cases, surgery often necessary). These are often overlooked by units treating desmoids, whose predominant experience is with sporadic disease
- Severe symptoms in people with FAP lead to enterectomy and small bowel/multivisceral transplant; stakeholders concerned these events is not adequately considered in company/EAG model
- Systemic therapy is indicated in a higher proportion in this subgroup, who are therefore likely to benefit more from the availability nirogacestat
- Unmet need in terms of desmoid overall, but particularly in people with FAP in whom it remains a major contributor to disease-related morbidity and mortality

EAG comments

- Results of De-Fi represented efficacy and safety of a representative sample of UK desmoid tumour population (16.9% in De-Fi had family history of FAP – acknowledge not same as proportion with FAP)
- 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

Abbreviations: FAP, familial adenomatous polyposis

Patient perspectives

Desmoid tumours significantly impact quality of life

Submissions from Desmoid Aid UK and Sarcoma UK

- Desmoid tumours are rare, locally aggressive soft tissue tumours. They do not metastasise but can recur around the site of the original tumour.
- The most debilitating effect of desmoid tumours is typically pain.
- Desmoid tumours can limit mobility because of size, location, or placement on a nerve.
- People with desmoid tumours frequently experience depression and anxiety
- Substantial impact on carers living with and caring for a loved one suffering with desmoid tumours
- Nirogacestat would be first ever treatment specifically designed for desmoid tumours
- Treatment may enable people to stay in work/education, engage in family life and be more active, resulting in better mental and physical health.

"The only way to describe life with this disease is it's [sic] constant physical and emotional torture and suppression of all aspects of life"

"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"

"It's brilliant having access to nirogacestat. 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"

Clinical perspectives

Current treatments are limited and target symptoms, not the underlying condition.

Submissions from clinical experts

- Main aim of treatment for Desmoid tumours is to improve symptoms, particularly pain and limited mobility
- As treatments aren't curative, symptom management may be achieved without eliminating the risk of recurrence
- There is an unmet need in Desmoid tumours, particularly FAP-related. There are no approved systemic therapies.
- Desmoid tumours are usually treated with active surveillance or chemotherapy. Chemotherapy only used because there are currently no approved treatments
- Chemotherapy can cause significant acute and long-term toxicities. The long-term complications are very important since most patients with Desmoid tumour are young
- Desmoid tumour is rare disease and access to unlicensed therapy varies across the UK.

Current treatments on the NHS aren't effective enough in managing disease progression or symptoms, and none of them are licenced.

Nirogacestat drastically reduces pain levels, it can help with improving range of motion and controlling disease progression.

Abbreviations: FAP, familial adenomatous polyposis

Equality considerations

Equalities considerations raised at scoping:

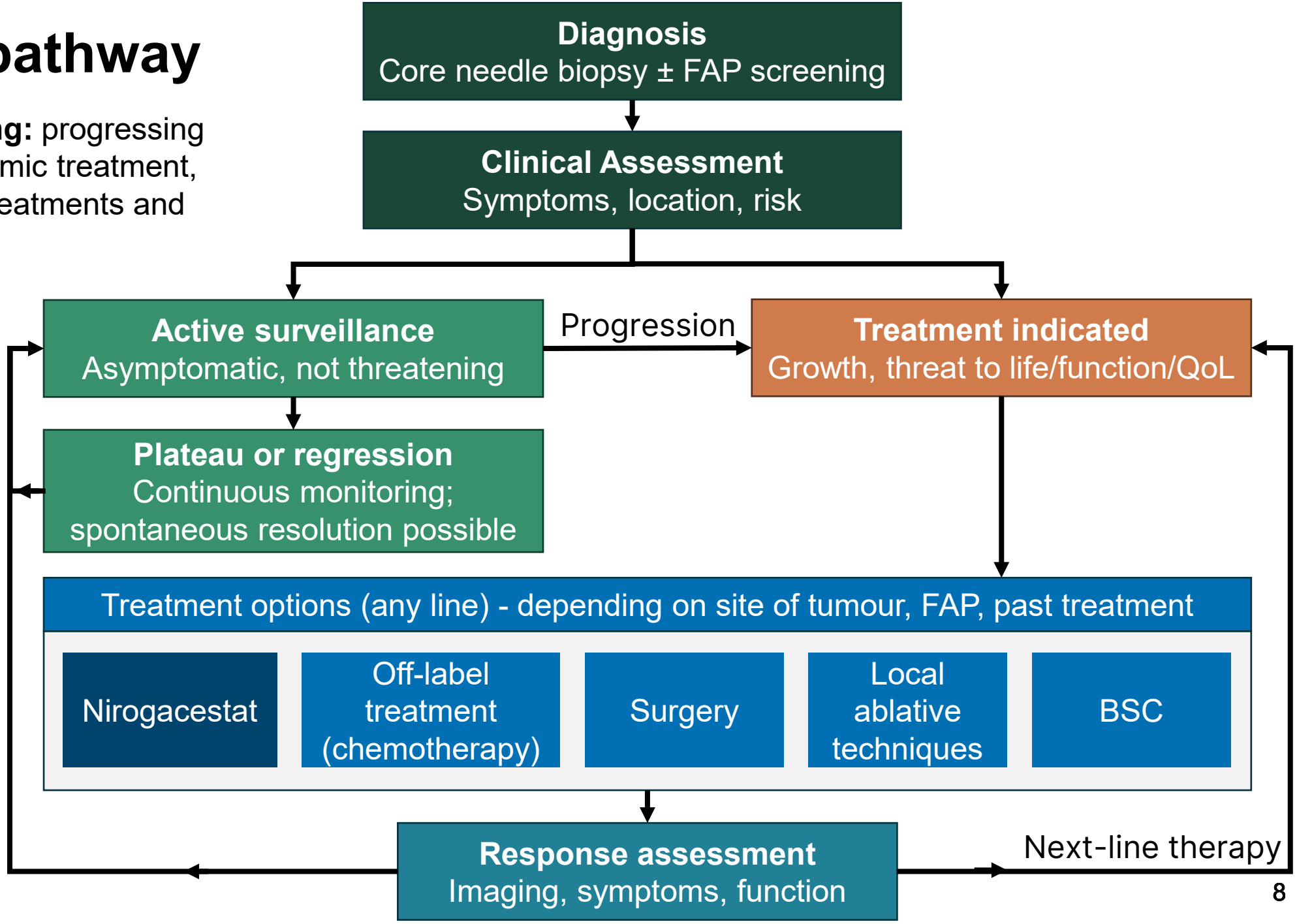
People who fall under the following protected characteristics under the Equality Act 2010—sex, pregnancy and maternity, and age—should be considered, because:

- there is a higher incidence of DTs amongst women (epidemiological studies report female cases 2.2-3.9 times higher than male cases)
- of the associated risk of DTs in pregnancy (One study observed a two-fold increase in risk of relapse or progression at 24 months after pregnancy [hazard ratio = 2.09, P = 0.018)
- of the relatively younger age profile of people who are diagnosed with DTs (frequently occur during adolescence, peak age around 30 years)

Abbreviations: DT, desmoid tumour

Treatment pathway

Company positioning: progressing DT that require systemic treatment, replacing off-label treatments and BSC



Is the treatment pathway reflective of NHS practice? What chemotherapy dose is used for DTs?

Abbreviations: BSC, best supportive care; DT, desmoid tumour; FAP, familial adenomatous polyposis; QoL, quality of life.

Nirogacestat (Ogsiveo, SpringWorks Therapeutics)

Marketing authorisation	• Nirogacestat as monotherapy is indicated for the treatment of adult patients with progressing DT who require systemic treatment. • Approval granted on 7th January 2026 by the MHRA under IRP (Reference regulator was the EMA who granted approval August 2025)
Mechanism of action	• Non-competitive GSI that blocks proteolytic activation of the Notch receptor, limiting DT growth and progression.
Administration	150 mg film-coated tablets twice daily (one in the morning and one in the evening, with or without food but avoiding grapefruit juice). 150 mg dose should not be exceeded. Can be continued until disease progression or unacceptable toxicity.
Price	• Anticipated list price: £15,189.04 per pack of 56, 150 mg tablets • A confidential patient access scheme is applicable.

Abbreviations: DT, desmoid tumour; EMA, European Medicines Agency; GSI, gamma secretase inhibitor; IRP, international recognition procedure; MHRA, Medicines and Healthcare products Regulatory Agency.

Key issues

EAR ID	Issue	ICER impact	Slide number
2	Uncertainty with the indirect treatment comparison	Unknown	Slides 17-18
3	Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Unknown	Slides 20-21
9	Health state utility values	Large	Slides 24-26
7	Assumed stopping rule	Small	Slides 27-28
8	Approach to discontinuation	Small	Slide 29

Abbreviations: EAR, evidence assessment report; ICER, incremental cost-effectiveness ratio.

Brief summary of issues resolved at technical engagement

EAR ID	Issue	Resolution at technical engagement
1	Exclusion of chemotherapy as a comparator.	Company included MAICs for nirogacestat versus chemotherapy.
4	Calculation of progression risks during trial randomised period/first 2 years	Company adjusted its base case to match EAG's approach (separate risks calculated for Y1, Y2, and Y3+; including premature discontinuation), but noted this was still subject to limitations with deviations at Y1. EAG acknowledges this but says the deviation largely cancels out by Y2. EAG continue to assume chemo associated with the same progression rate as BSC in base case (ISSUE 2)
5	Calculation of response	New data presented by the company (Table 6 technical engagement) suggests similar results for both actual response and BOR), with actual response appearing more favourable for nirogacestat. EAG notes the differences between the 2 responses are very small; it aligns with the company's assumption to use the (more conservative) BOR.
6	Extrapolation of progression	The company updated its base case to align with the EAG assumption no additional progression after Y2 in either arm (supported by its own clinical expert advice).

Abbreviations: BSC, best supportive care; BOR, best overall response; EAR, evidence assessment report; ITC, indirect treatment comparisons; MAIC, matching-adjusted indirect comparisons.

Chemotherapy as a comparator

Background

- After TE, company included chemotherapy as a comparator but stated chemotherapy is not clearly established as UK standard practice and lacks high quality evidence of efficacy
- Chemotherapy now included as a comparator. EAG consider issue now resolved (issues with ITC remain, see key issue 2)

Patient and clinical expert comments (technical engagement)

- Chemotherapy is used as 'experiment over treatment' for desmoid tumours, but only because there is currently no approved treatment for desmoids
- Important committee understand inadequacies of chemotherapy in order to understand how necessary, effective and tolerable nirogacestat is
- "Chemotherapy is not effective" in controlling growth or causing regression and "chemotherapy has very little benefit on management of the disease"; key treatment benefit of chemotherapy is pain reduction
- For those with FAP, chemotherapy is not often used in practice, and surgery is preferred
- Most experts believed chemotherapy should be excluded as a comparator, however 2 EAG clinical experts thought it should be included

Do people with DTs have chemotherapy? If yes: In which cases would chemotherapy be considered? What proportion receive chemotherapy? Is this different for FAP DTs vs non-FAP DTs? Should chemotherapy be included in the model as a comparator?

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Abbreviations: DT, desmoid tumour; FAP, familial adenomatous polyposis; ITC, indirect treatment comparison; TE, technical engagement

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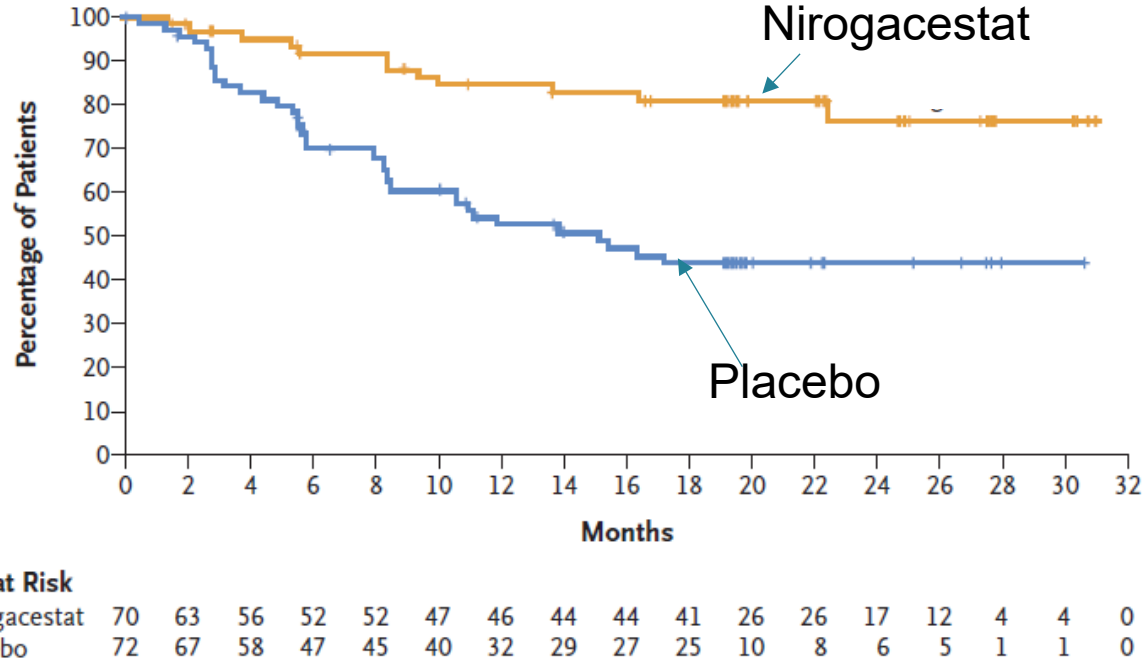
Phase 3 clinical trial (De-Fi) results – primary outcome

Nirogacestat improved PFS and reduced disease progression or death by 71%

De-Fi trial population: Adults with progressing desmoid tumours (≥20% within 12 months) according to the Response Evaluation Criteria in Solid Tumours, v1.1

Figure: Nirogacestat versus placebo – PFS



The double-blind period ≈ 20 months (August 2020 – April 2022), open-label extension continued to December 2024.

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table: baseline characteristics (see appendix for more)

	Nirogacestat (n=70)	Placebo (n=72)
Refractory/recurrent after previous treatment	52 (74%)	58 (80%)
Previous surgery	31 (44%)	44 (61%)
Previous chemo	24 (34%)	27 (38%)

Table: outcomes of interest

	Nirogacestat (n=70)	Placebo (n=72)
Overall median follow-up, months (range)	[redacted]	[redacted]
HR (95% CI), p-value	0.29 (0.15, 0.55), p<0.001	
Event free after 1 year (95% CI)	[redacted]	[redacted]
Event free after 2 years (95% CI)	[redacted]	[redacted]

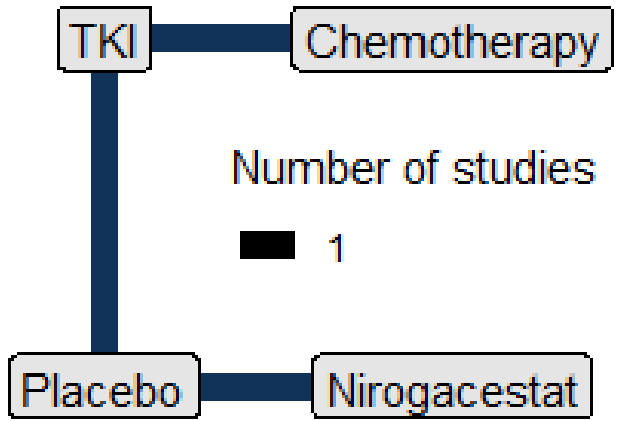
See appendix for: Trial characteristics, Patient characteristics, Summary of primary and secondary outcomes

ITC for nirogacestat versus chemotherapy - overview

- Original company submission did not include chemotherapy as comparator, so no indirect comparison of nirogacestat with chemotherapy. EAG conducted 'pragmatic' Bayesian NMA, requested ITC from company
- At technical engagement, company provided unanchored MAIC. Covariates identified through SLR based on clinical relevance as prognostic factors, adjusted based on data availability; incorporated in a stepwise approach to avoid overadjustment

Assumption	Company base case	EAG base case
ITC	Unanchored MAIC	Pragmatic NMA
Included studies	De-Fi (nirogacestat versus placebo) DESMOPAZ (pazopanib versus methotrexate plus vinblastine) (3 studies excluded due to limitations)	De-Fi (nirogacestat versus placebo) Gounder et al. 2018 (sorafenib versus placebo) DESMOPAZ (pazopanib versus methotrexate plus vinblastine)
Outcomes	ORR, PFS, CR, PR, SD, PD (identified through feasibility assessment)	ORR, PFS and Grade 3 or higher AEs (pain was also considered important but a network could not be established)
Proportional hazards?	Yes	Yes

Figure: Network diagram of treatment comparisons for the included studies in EAG NMA



See appendix for: EAG NMA methods, company MAIC methods and studies included/excluded in company MAIC

Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomised controlled trial; SLR, systematic literature review

Key issues: Uncertainty with the ITC (1/2)

ICER impact unknown

Company (at technical engagement)

- Maintains original concerns about chemotherapy as a comparator: A robust ITC comparing nirogacastat with chemotherapy limited due to lack of common comparator, limited/inconsistent baseline reporting, small sample sizes and study heterogeneity
- Provided unanchored MAIC using De-Fi and DESMOPAZ (methotrexate with vinblastine versus pazopanib)
- MAIC considered more appropriate than NMA for nirogacestat versus chemotherapy:
  - Differences/treatment effect modifiers can be adjusted for more effectively
  - NMA used sparse network with no shared comparator (studies indirectly connected by Gounder 2018)
- Used 4 separate MAICs for 'complete response', 'partial response', 'stable disease', and 'progressed disease' for the model; this resulted in ~160% of a patient in the chemo arm, so this was adjusted by normalising so that the model only contained a single patient.
- ITC results with DESMOPAZ should be interpreted with caution as methotrexate with vinblastine is not NHS standard of care

See appendix for: EAG NMA methods, company MAIC methods and studies included/excluded in company MAIC

Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomised controlled trial

Key issues: Uncertainty with the ITC (2/2)

ICER impact unknown

EAG comments

- The 2 trials included in the company MAIC were also included in the EAG NMA; Costa, Woods, and Pallassini were not included in the EAG analysis (no additional data were incorporated), because the EAG undertook a pragmatic adaptation of a previously published NMA, reflecting time and feasibility constraints, rather than as a result of selective exclusion based on treatment content.
- Company justifications to exclude Costa, Woods and Pallassini not strong enough and arbitrary; a substantial proportion of participants had methotrexate with vinblastine, methotrexate with vinorelbine or vinorelbine monotherapy.
- Unclear if excluding leads to the MAIC being biased, but reducing the corroborative evidence likely decreases the precision of the efficacy estimates.
- Lack of transparency and detail in how the MAIC was conducted, particularly how the matching variables were chosen; EAG cannot verify the objectivity of the company approach.
- Company did not provide MAIC results for adverse events (e.g. grade ≥3 adverse events); reason not given.
- Implementing 4 ITCs with 4 separate treatment effects not appropriate, evidenced by need to 'normalise'
- Company uses a progressed disease MAIC rather than progression-free survival MAIC; based on specific timepoints, not Kaplan-Meier, so subject to greater uncertainty and more favourable to nirogacestat.
- Given the uncertainty in the MAIC and based on clinical expert input, EAG prefers NMA approach to inform objective response, and that PFS for chemotherapy is the same as best supportive care.

See appendix for: EAG NMA methods, company MAIC methods and studies included/excluded in company MAIC

Abbreviations: ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PFS, progression-free survival; RCT, randomised controlled trial

ICER impact unknown

Results from nirogacestat vs. chemotherapy

	Company MAIC (ESS = 35)	EAG NMA
PFS, HR (95%CI), p-value	[redacted]	2.74 (0.56, 13.5)
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

See appendix: NMA results for chemo comparisons

*composite of CR and PR

** outcomes used in the model

Which studies are relevant to include?
What ITC approach should be used?
If chemo should be included in the model, how should this be done (implemented)? Using which outcomes?

Abbreviations: AE, adverse events; BPI, brief pain inventory; CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; MD, mean difference; NMA, network meta-analysis; OR, odds ratio; ORR, objective response rate; PD, progressed disease; PFS, progression-free survival; PR, partial response; RCT, randomised controlled trial; SD, stable disease.

Key Issue: Uncertainty related to the reduction in pain (1/2)

ICER impact unknown

Background

- EAG: efficacy of nirogacestat versus placebo (BSC) in reducing pain was unclear
  - De-Fi showed a statistically significant (LS mean difference with BPI-SF [redacted]) but not clinically meaningful benefit (minimally important difference: 2 points).
  - Unclear whether this reflected a lack of clinically meaningful benefit or the inclusion of participants without uncontrolled pain at baseline.
- EAG experts: key treatment benefit of chemotherapy is pain reduction rather than reducing tumour size. Pain can be reduced without the tumour shrinking.
- EAG unable to assess pain in its NMA; network could not be established. Concerned benefit of reducing pain was not represented in economic model, which may understate the benefits of chemotherapy

Company (technical engagement)

- 27 (38.6%) in the nirogacestat arm and 31 (43.1%) in the placebo arm had uncontrolled pain at baseline.
- Post-hoc analysis showed PFS and ORR improvements with nirogacestat versus placebo in subgroups with controlled and uncontrolled pain at baseline; general improvement in pain also seen.
- Clinically meaningful benefit with nirogacestat versus placebo in both subgroups, but a greater absolute difference in the uncontrolled pain at baseline group ([redacted] vs [redacted]).
- Unadjusted ITC: nirogacestat had statistically significant mean change from baseline for global health status versus placebo. Change in physical functioning and BPI pain were not statistically significant.

See appendix for secondary trial outcomes (PROs), BPI-SF over time, PFS in post-hoc subgroup analysis

Abbreviations: BPI-SF, brief pain index – short form; BSC, best supportive care; DT, desmoid tumour; ITC, indirect treatment comparison; LS, least squares; NMA, network meta-analysis; ORR, objective response rate; PFS, progression-free survival; PRO, patient-reported outcomes

Key Issue: Uncertainty related to the reduction in pain (2/2)

ICER impact unknown

Company (technical engagement) cont

- Significant limitations in ITC analyses likely influence the result and should be interpreted with caution

EAG comments

- Company TE included a different BPI-SF outcome (potentially average pain score, but not specified) to that in the CS (worst pain intensity) for nirogacestat versus placebo.
- LS mean difference change in pain at cycle 10 (to match what was reported in the original CS) confirms that pain relief with nirogacestat was underreported due to the population's baseline pain:
  - Uncontrolled pain at baseline: [redacted]
  - Controlled pain at baseline: [redacted]
- In subgroup with uncontrolled pain at baseline, treatment effect is slightly below the MID at cycle 10 but met the MID at cycles 9 and 11; EAG interpret this as clinically important reduction (note 95% CI goes below MID)
- Data from the company showed response rate and pain reasonably well correlated; given this and concerns on reliability of company's ITC, the EAG concludes the current health states are appropriate.

Patient and clinical expert comments (technical engagement)

- Pain major issue in sporadic DT (predominantly extra-abdominal); less issue in FAP-associated DT
- Chemotherapy does not have a positive impact on pain reduction and gives very little symptomatic relief; patients have reported that nirogacestat has improved pain, regardless of tumour size.

Is nirogacestat associated with a clinically important reduction in pain compared with BSC?
Does committee believe pain is sufficiently reflected in the model via tumour response rate? For nirogacestat? For BSC/placebo? For chemotherapy?

Abbreviations: BPI-SF, brief pain index – short form; BSC, best supportive care; DT, desmoid tumour; FAP, familial adenomatous polyposis; ITC, indirect treatment comparison; LS, least squares; NMA

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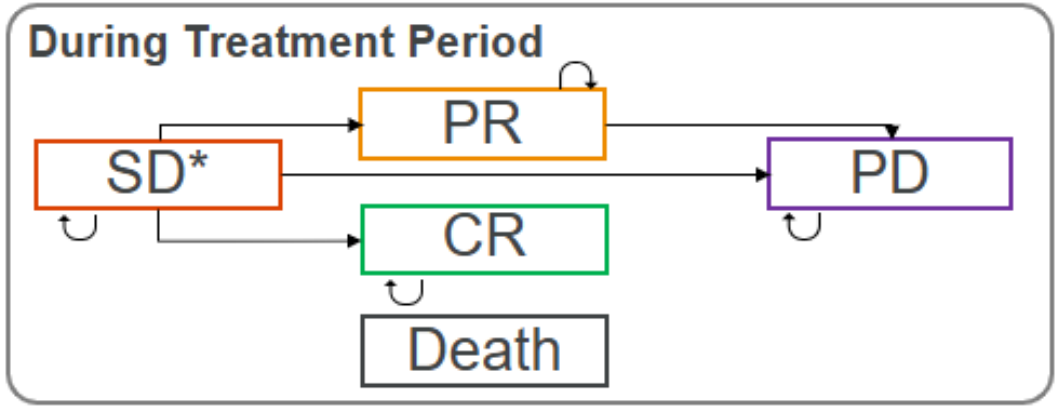
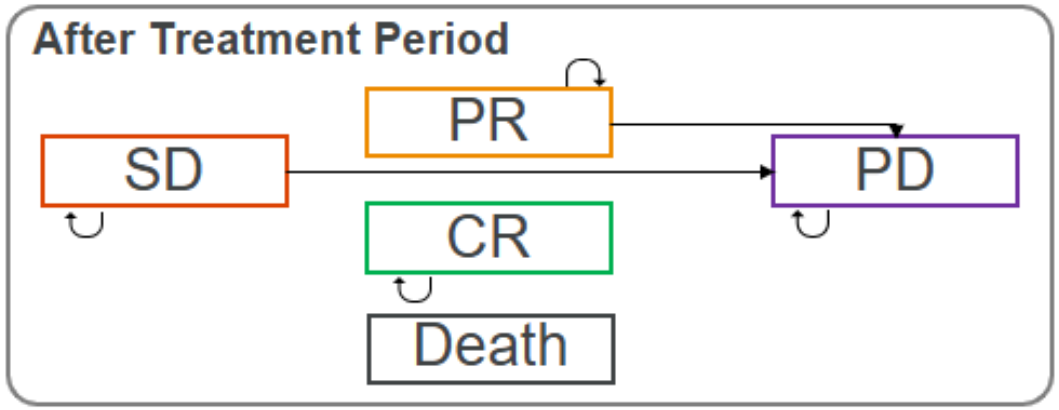
Company's model overview

Model structure: Semi-Markov model with 5 health states (stable disease, PR, CR, PD and death) across 2 different treatment phases

Model population: Adults with progressing DT who require systemic treatment (pooled population including both people with FAP and non-FAP DT)





- Technology affects **costs** by:
  - Increasing the drug costs associated with treatment
  - Reducing number of patients in PD reducing health-care resource use costs
  - Increasing number of patients in PR and CR reducing health-care resource use costs
  - Increasing cost of adverse events
- Technology affects **QALYs** by:
  - Increasing number of patients in PR and CR, and decreasing number of patients in PD, improving quality of life
  - Increasing frequency and duration of ovarian dysfunction, reducing quality of life
- Assumptions with greatest ICER effect:
  - Health state utility values
  - Assuming patients do not progress after year two, in line with data from the De-Fi trial
  - Stopping rule and allowing a response in year 3 (in line with De-Fi) had a moderate impact on the ICER

Is the model suitable for decision making? The population?

Abbreviations: CR, complete response; DT, desmoid tumour; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PR, partial response; QALY, quality-adjusted life-year; SD, stable disease

Key issue: Health state utility values (1/3)

ICER impact Large

Background

Company

- De-Fi trial collected EORTC QLQ-C30; EQ-5D not collected; EORTC data not provided because company state EORTC data could not be robustly mapped to EQ-5D.
- Company base case uses utility values from a soft-tissue sarcoma population (STS); Shingler 2013.

EAG

- Clinical experts advised that not all patients with progressing DT experience pain or mobility issues.
- PD utility value from Shingler (2013) would be 0.263 - not considered credible, reflects utilities associated with terminal cancer care, which is not an appropriate analogue for DT.
- Shingler (2013) was a TTO study, which is not aligned with the NICE reference case.
- EAG base case uses utility values from patients with STS in a clinical trial using EQ-5D (Reichardt 2012); noted that De-Fi trial-based utilities would have been preferable as they are the only QoL values in a DT population.

Technical Engagement - Company

- Maintains that data from De-Fi could not be robustly mapped to EQ-5D-3L due to methodological limitations; the resulting estimates were considered to lack face validity and be unsuitable for decision-making
- Mapping algorithm identified by EAG was based on non-DT oncology populations, that were older than the De-Fi population (mean 68 vs 37 years), with a greater proportion of men, and therefore not generalisable
- Acknowledges utilities remain uncertain and are likely to lie between the company and EAG estimates

Abbreviations: DT, desmoid tumour; EORTC, European Organisation for. Research and Treatment of Cancer; PD, progressive disease; STS, soft-tissue sarcoma; TTO, time trade off.

Key issue: Health state utility values (2/3)

ICER impact Large

Technical Engagement - EAG

- Inconsistent for the company to reject the mapping algorithm when Shingler (2013) also used a non-DT population; the EAG continued to prefer utilities from Reichardt (2012)
- Providing the trial-based utilities would have addressed concerns around non-DT populations, and enabled EAG to present a range of utility scenarios

Technical Engagement - Patient and clinical experts

- DTs may have a greater long-term impact on HRQoL than cancer, as cancer treatment is time-limited with a defined outcome, whereas DT are chronic and incurable.
- QoL for people with STS may not be universally worse than people with DT. An argument can be made that people with DT face a poorer QoL than people with STS
  - People with DT face the prospect of a lifelong disease with no possibility of a positive outcome or end to their symptoms
  - Desmoid tumours often develop early in adulthood, resulting in a prolonged lifetime burden of disease
- Utility values for an individual with desmoid tumours are considered highly variable; values of 0.263 or 0.69 may both be plausible for individual patients - given that the impact can range from noticeable but manageable limitations on daily life, to severe pain and near total reliance on a carer. An approximate average utility is suggested to lie between 0.30 and 0.60, reflecting the wide range of disease impact.

Abbreviations: DT, desmoid tumour; HRQoL, Health-related quality of life; QoL, quality of life; STS, soft tissue sarcoma

Key issue: Health state utility values (3/3)

ICER impact Large

Company and EAG utility values

Health state	Company base case		EAG base case	
	Utility value	Data source	Utility value	Data source
CR (on or off treatment)	0.860	UK population norms for EQ-5D (Kind et al. 1999)	0.841	Company base case incremental utility CR vs SD relative to EAG base case SD utility
PR (on or off treatment)	0.792	Shingler, 2013 (mean utility value for 'treatment response') (Shingler et al. 2013)	0.775	Company base case incremental utility PR vs SD relative to EAG base case SD utility
SD (on or off treatment)	0.736	Shingler, 2013 (mean utility value for 'SD') (Shingler et al. 2013)	0.720	Reichardt 2012
PD	0.263	Shingler, 2013 (mean utility value for 'PD') (Shingler et al. 2013)	0.560	Reichardt 2012

What utility values does committee consider to be most appropriate for each of the above health states?

Abbreviations: CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease

Key issue: Assumed stopping rule (1/2)

ICER impact
Small

Background

- The company assumed all nirogacestat patients stop treatment after 2 years of treatment.
- EAG clinical experts: broadly support 2-year stopping rule, if flexibility to continue beyond 2 years where tumour shrinking (had not plateaued), and restart treatment where AEs resolved or tumour growing again
- Proportion of patients who would discontinue after 2 years unclear from the evidence provided; data suggested people continue to respond in year 3 and 4

Company (technical engagement)

- Maintain 2-year stopping rule reflects anticipated usage of nirogacestat in UK practice
- Provided data on tumour size plateau, based on 2 consecutive visit in the same state or better (CR to CR, PR to PR, PR to CR, SD to SD, PD to PD)
- By year 2, tumour size plateau was achieved by 100% of patients in CR and PR and more than 75% for SD (see appendix); 3-year stopping rule overestimates number of people who continue treatment after 2-years
- Scenario analysis: 5% of people remain on treatment for an additional year beyond 2-year treatment

Patient and clinical expert comments (technical engagement)

- Not possible to make an assumption about point at which 'all' patients should stop treatment. Set 'cut-off point' is likely to be emotionally challenging
- Important option to restart treatment is available for people who begin to experience symptoms again
- **Clinical experts**: Will be a very small number of people continuing nirogacestat after 2 years.

Abbreviations: AE, adverse event; CR, complete response; PD, progressed disease; PR, partial response; SD, stable disease

ICER impact
Small

Key issue: Assumed stopping rule (2/2)

EAG comments

- EAG clinical expert input, and patient expert input at technical engagement, highlight need to be able to continue treatment beyond 2 years or restart treatment.
- Model does not currently allow for re-initiation; this would add to the proportion of patients on-treatment after year 2 and add to associated costs → 3-year stopping rule conservative
- Using 2 consecutive visits to determine tumour plateau not reasonable; people could experience stable disease at two timepoints then go on to have a response
- Data provided at technical engagement does not inform proportion of people who would benefit from treatment beyond 2 years because their tumour is still shrinking.
- Based on data from original CS (see appendix), clinical advice to EAG is that 10-15% of patients remain on treatment after 2 years. One expert expects ~10% on treatment to 2 years, 5% to 3 years, 3% to 5 years
- EAG base case uses 2-year stopping rule with criteria, with everyone off treatment at 3 years
  - updated [redacted] who remain on treatment at Year 2 discontinue, so only 15% continue treatment into Year 3; assumed to only affect drug costs and not treatment benefits which favours nirogacestat.

Is it appropriate to assume a stopping rule for nirogacestat? How should the stopping rule be implemented? What proportion of people would be expected to stay on treatment past 2 years?

For people who complete a full 2-year course of nirogacestat and stop treatment, would re-treatment with nirogacestat be allowed if disease later progresses? If so, in what proportion of people? How should this be reflected in the economic model?

Key issue: Approach to discontinuation

ICER impact Small

Background

- Company assumed nirogacestat arm continue treatment to 2 years, unless have disease progression
- EAG: not reflective of De-Fi in which [redacted] patients discontinued nirogacestat and [redacted] discontinued BSC before 2 years due to TAEs. Prefer to assume discontinuation aligned with De-Fi, with constant rate over the 4 years; small increase to the ICER

Company (technical engagement)

- Routine follow-up not available from De-Fi after participants discontinue treatment, but did receive an EOT assessment if a scan had not been conducted within the last 3 months of treatment.
- Data suggests premature discontinuation not anticipated to impact progression/ORR or have large impact on results; disagree with EAG assumption these patients would experience same progression risks as BSC

EAG comments

- People who discontinue nirogacestat not regularly monitored; progression risk (and if same as BSC) is uncertain
- Early discontinuation (e.g after 1 month) unlikely to see same benefits as nirogacestat treatment for 2 years
- Limited by data available; prefer to model early discontinuation

Patient and clinical expert comments (technical engagement)

- Proportion stopping treatment prior to 2 years unknown. Some may choose to stop treatment due to adverse effects, practical difficulties in accessing treatment or personal circumstances

Do people stop nirocagestat due to side effects? What proportion? Can they rechallenge? Should discontinuation of nirogacestat be modelled? If yes, how?

Abbreviations: BSC, best supportive care; EOT, end of treatment

Additional EAG issues

1. Conduct of the De-Fi trial

- Proportion of refractory disease in placebo group (76.4%) higher than nirogacestat (61.4); imbalance favours nirogacestat
- Imbalance in dropouts between treatment arms, with 4 people in nirogacestat group and 1 in placebo group censored due to no adequate disease status assessment. Missing data on tumour assessment for 4 nirogacestat participants means cannot know whether they had disease progression or not; risk of bias.
- EAG accept progression measured adequately in De-Fi, note PFS measured different in Gounder et al (sorafenib trial)

2. Assumed health-related resource use

- Company did not include resource use for CR. Assumed treatment-specific levels of GP and specialist visit resource use for SD, and underestimated specialist visits in PD, SD and PR.
- EAG preferred (informed by clinical opinion): 2 specialist visits per year in CR state, 6 in the PD state, 4 in the SD state and 2 in the PR state. These differences are not a major driver of the cost effectiveness. (See appendix for company and EAG base case assumptions on visits)

Are there any uncertainties regarding the conduct of De-Fi that committee should consider? How many healthcare visits per year, if any, would a person typically have in each of the following health states: CR, SD, PR and PD?

Abbreviations: CR, complete response; PD, progressed disease; PFS, progression-free survival; PR, partial response; SD, stable disease

Summary of company and EAG base case assumptions

Background

- At technical engagement, company accepted 2 of EAG preferred assumptions: 1) no additional progression after year 2. 2) way transition probabilities were calculated

Differences in assumptions in company and EAG base case after Technical Engagement

Assumption	Company base case	EAG base case
Stopping rule	2-Year stopping rule	2-Year stopping rule with 15% of patients on treatment past Year 2
Premature discontinuation	None	Included (to match De-Fi)
Utilities	From Shingler 2013	From Reichardt 2012
Ovarian dysfunction	Applied as intermittent lasting 28 days	Applied as a one-off event lasting for [redacted] days from initiation for 39% of patients
Resource use	No monitoring of CR and less specialist visits	Monitoring of CR and more specialist visits
Subsequent treatments	Doxorubicin	Vinorelbine, except after vinorelbine itself, where doxorubicin was used as subsequent treatment.
Chemotherapy treatment effect	Unanchored MAIC for CR, PR, SD, PD (using De-Fi and DESMOPAZ trials)	NMA for ORR (using De-Fi, DESMOPAZ and Gounder 2018 trials)
Chemotherapy dosage	60mg/m2 in cycle 1 then 80mg/m2 per cycle, for 2 years	90mg for 1 years
Response after year 2	No response after Year 2	Can respond after Year 2 (matches De-Fi)

Abbreviations: MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discount

When using confidential prices, the company and EAG base cases are above the range that NICE considers an acceptable use of NHS resources.

When using confidential prices, scenarios are above the range that NICE considers an acceptable use of NHS resources.

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Nirogacestat for treating desmoid tumours

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Uncaptured benefits

Company submission: "nirogacestat may offer some benefit to QALYs through increasing the capacity for some patients and caregivers to work and allowing patients to have a long-term outlook on life.

- Company noted no published data on this, so was not possible to capture in the economic analysis.

Company did include a scenario with societal perspective

- EAG: benefits would be modest given that only a subset of patients in the progressed disease health state; clinical advice suggests only a subset in the progressed disease state would experience pain and mobility issues substantial enough to impact activities of daily living, but that the impact would be important to this group.
- EAG scenario testing showed limited impact of carer utilities on the ICER.

Does the committee consider that the potential benefits discussed, including improved capacity for work and a longer-term outlook on life, represent uncaptured benefits in this appraisal, and are there any others to highlight?

Abbreviations: ICER, incremental cost-effectiveness ratio

Nirogacestat for treating desmoid tumours

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues - recap

EAR ID	Issue	ICER impact	Slide number
2	Uncertainty with the indirect treatment comparison	Unknown	Slides 17-18
3	Uncertainty related to the efficacy of nirogacestat and chemotherapy in reducing pain	Unknown	Slides 20-21
9	Health state utility values	Large	Slides 24-26
7	Assumed stopping rule	Small	Slides 27-28
8	Approach to discontinuation	Small	Slide 29

Abbreviations: EAR, evidence assessment report; ICER, incremental cost-effectiveness ratio.

Nirogacestat for treating desmoid tumours

Supplementary appendix

NICE National Institute for Health and Care Excellence

Key clinical trials – DeFi characteristics

Back to Clinical trial results – primary outcome

Table: Clinical trial designs and outcomes

	De-Fi
Design	Phase 3, multicentre, double blind, placebo controlled
Population	Adults with progressing desmoid tumours (≥20% within 12 months) according to the Response Evaluation Criteria in Solid Tumours, v1.1
Intervention	150 mg (three 50 mg tablets) nirogacestat twice daily
Comparator(s)	150 mg (three 50 mg tablets) placebo twice daily (reassigned to nirogacestat at the open-label extension)
Duration (median)	Nirogacestat: [redacted] months (range [redacted] to [redacted] months) Placebo: [redacted] months (range [redacted] to [redacted] months) *The double-blind period was approx. 20 months (August 2020 – April 2022), and the open-label extension continued to December 2024.*
Primary outcome	Progression-free survival.
Key secondary outcomes	Objective response rate (and duration of response) Change in patient-reported outcomes from baseline to Cycle 10 (BPI-SF, GODDESS DTIS, GODDESS DTSS, EORTC QLQ-C30
Locations	52 sites in Canada, the US, and Europe (2 in the UK) 37 sites randomised at least 1 participant

Abbreviations: ; BPI-SF, Brief Pain Inventory-Short Form; DTIS, Desmoid Tumour Impact Scale; DTSS, Desmoid Tumor Symptom Scale; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale.

Key clinical trial – baseline characteristics (1/3)

Back to Clinical trial results – primary outcome

Table: Participant baseline characteristics (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	37 (82)	37 (79)	74 (80)
Male	25 (36)	25 (35)	50 (35)
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%)
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)

EAG: in the nirogacestat arm, higher proportions of:

- White people
- People with a healthy weight
- People 46 years and older

No subgroup analysis was presented for these groups in the CS, but EAG's clinical experts did not suggest these would overtly bias the results.

Abbreviations: CS, company submission; ITT, intention-to-treat; SD, standard deviation

Key clinical trial – baseline characteristics (2/3)

Back to Clinical trial results – primary outcome

Table: Participant baseline disease characteristics (ITT population)

Characteristic	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)
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
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)

EAG: higher proportion of people whose tumour were refractory to treatment in the placebo arm. (see additional EAG issues slide)

EAG clinical expert: tumours refractory to treatment are less likely to respond to new treatment; imbalance in trial groups likely to favour the nirogacestat group. The company subgroup analyses (CS appendix C) did not entirely support this, but numbers too small to be certain.

Abbreviations: CS, company submission; ITT, intention-to-treat; SD, standard deviation

Key clinical trial – baseline characteristics (3/3)

Back to Clinical trial results – primary outcome

Table: Participant baseline disease characteristics (ITT population)

Characteristic	Nirogacestat (n=70)	Placebo (n=72)	Total (N=142)
Target tumour location(s), n (%)			
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)			
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

Abbreviations: ITT, intention-to-treat; RECIST; Response Evaluation Criteria in Solid Tumors; SD, standard deviation

Key clinical trial – summary of secondary endpoints

Table: summary of primary and secondary endpoints in DeFi

Endpoints	Results	
	Nirogacestat (n=70)	Placebo (n=72)
Secondary: Response		
Best overall response - Confirmed, n (%)		
Complete response	5 (7%)	0
Partial response	24 (34%)	6 (8%)
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Non-evaluable	[redacted]	[redacted]
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	
Time to confirmed response (months), median (range)	[redacted]	[redacted]
Probability of remaining in response, % (95% CI)		
At Month 12	[redacted]	[redacted]

Back to Clinical trial results – primary outcome

Abbreviations: CI, confidence interval; ITT, intention-to-treat; ORR, objective response rate

Key clinical trial – secondary PROs

Back to Clinical trial results – primary outcome
Back to Key Issue: Uncertainty related to the reduction in pain

Table: summary secondary PROs in DeFi

Endpoints	Results		One sided p value
	Nirogacestat (n=70)	Placebo (n=72)	
BPI-SF average worst pain intensity score			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo at Cycle 10, LS mean (SE)	-1.34 [redacted]		
DTSS total symptom score			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo, LS mean (SE)	[redacted]		
DTIS physical functioning score			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo, LS mean (SE)	[redacted]		
EORTC QLQ-C30 Global Health Status-QoL score			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo, LS mean (SE)	[redacted]		
EORTC QLQ-C30 physical functioning			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo, LS mean (SE)	[redacted]		
EORTC QLQ-C30 role functioning			
Change from baseline through Cycle 10, LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference to placebo, LS mean (SE)	[redacted]		

Full details of results in Table 2.8 (section 2.6) of company submission

Abbreviations: DTIS, Desmoid Tumour Impact Scale; DTSS, Desmoid Tumour Symptom Scale; EORTC, European Organisation for. Research and Treatment of Cancer ITT, intention-to-treat; LS, lease squares; QLQ, quality-of-life questionnaire; QoL, quality of life; SE, standard error

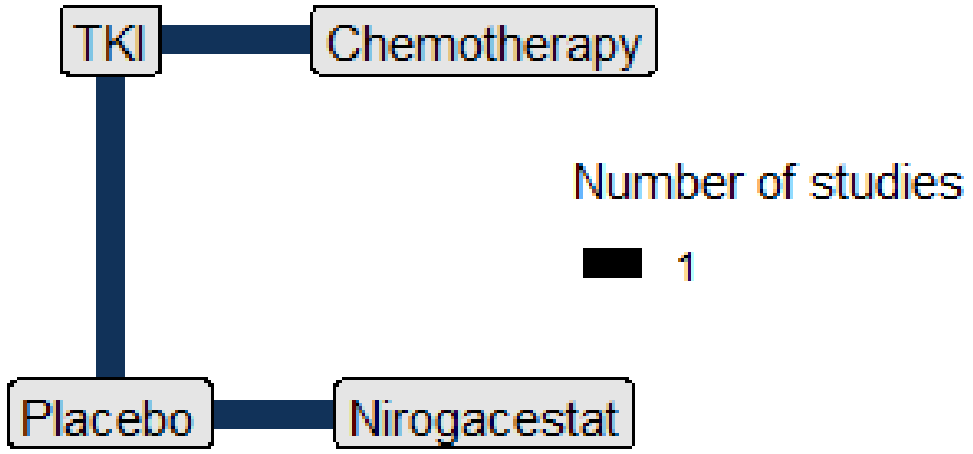
EAG – NMA methods

Back to Key issues: Uncertainty with the ITCs

- Due to time limitations and unclear evidence base, EAG took a pragmatic approach to NMAs
- A published NMA (Ou et al. 2024) was used to identify relevant RCTs (n=3):
  - De-Fi (nirogacestat versus placebo)
  - Gounder et al. 2018 (sorafenib versus placebo)
  - DESMOPAZ (pazopanib versus methotrexate plus vinblastine)
- No additional studies were identified through clinical expert advice and informal searches.

- Outcomes of interest: ORR, PFS and Grade 3 or higher AEs as considered most relevant for the cost-effectiveness analysis; pain was also considered important but a network could not be established (Gounder reported it as an outcome, but not the results).
- Bayesian approach with fixed effects was used; proportional hazards assumed for PFS.
- Non-informative prior distributions used for main treatment effects.

Figure: Network diagram of treatment



Abbrevaitions: AE, adverse event; ITC, indirect treatment comparison; NMA, network meta analysis; ORR, objective response rate; PFS, progression-free survival; RCT, randomised controlled trial

Company – MAIC methods

Back to Key issues: Uncertainty with the ITCs

- Evidence was identified through an extensive SLR performed by the company, which identified 2 full papers and 2 conference abstracts.
- DESMOPAZ used to inform the ITC; 3 other studies excluded due to significant limitations:
  - Costa et al. 2022 and Woods et al. 2022: abstracts on restrospective studies with small sample sizes, very different populations and follow up, outdated treatment periods, and limited reporting (baseline characteristics by treatment arm, missing outcome information).
  - Palassini et al. 2017: limitations in study design, population and outcome assessment
- Company considered the data (study design/population/outcomes) between DESMOPAZ and De-Fi sufficiently aligned for a MAIC; between-trial differences in characteristics to be adjusted via MAIC weighting.
- Based on feasibility assessment, ORR and PFS were available for comparison
- Covariates identified by SLR selected based on clinical relevance as prognostic factors – not all were reported consistently in both trials, so adjustment was made based on data availability.
- Univariate analysis was used to assess impact of each covariate, and covariates were incorporated in a stepwise approach to avoid overadjustment (ESS threshold ≥50% of the matched nirogacestat cohort).

Covariates adjusted for in MAIC
Intra-abdominal tumour location
Age
Prior systemic therapy
Prior radiation therapy
Prior surgery
Prior TKI exposure
CTNNB1 mutation
ECOG score
Sex

Abbrevaitions: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ORR, objective response rate; PFS, progression-free survival; RCT, randomised controlled trial; SLR, systematic literature review; TKI, tyrosine kinase inhibitors

Back to Key issues: Uncertainty with the ITCs

MAIC – studies considered for inclusion/exclusion (1/3)

Study identifier	DESMOPAZ
Company's inclusion decision	INCLUDE
Patient group	Adults with desmoid tumours
Age of patients	Median: 42 years
Line of treatment	First-line and second-line
Intervention	Methotrexate with vinblastine (n=22)
Comparator	Pazopanib
Baseline characteristics reported	Age, sex, ECOG performance status, tumour site, mutational status, Gardner syndrome, previous treatment, number of previous lines of systemic treatment
Scoped outcomes that were reported	Objective response rate, progression-free survival, overall survival, HRQoL, pain intensity, adverse events
Results for ORR and PFS	ORR: 26.3% One-year and two-year PFS: 79% [95% CI: 53.2, 91.5]
Study design	RCT (but only the chemotherapy arm was used)
Study time period	2012 to 2020
Time on treatment	12 months
Follow-up period	3 years
Country	France

Back to Key issues: Uncertainty with the ITCs

MAIC – studies considered for inclusion/exclusion (2/3)

Study identifier	Costa et al. (2022)	Palassini et al. (2017)	Wood et al. (2022)
Patient group	Teenagers and adults with desmoid tumours	Adults with desmoid tumours	Adults with desmoid tumours
Age of patients	Median: 37 years	Median: 36.6 years	Median: 33 years
Line of treatment	First-line only	First-line and second-line	First-line and second-line
Intervention	Sorafenib (n=32), doxorubicin with dacarbazine (n=13), liposomal doxorubicin (n=11), methotrexate with vinblastine (n=11), methotrexate with vinorelbine (n=8) and methotrexate monotherapy (n=1)	Methotrexate with vinblastine (n=30), methotrexate with vinorelbine (n=43), vinorelbine monotherapy (n=2)	Oral vinorelbine (n=37)
Comparator	None	None	None
Baseline characteristics	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

Back to Key issues: Uncertainty with the ITCs

MAIC – studies considered for inclusion/exclusion (3/3)

Study identifier	Costa et al. (2022)	Palassini et al. (2017)	Wood et al. (2022)
Scoped outcomes that were reported	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	Two-year PFS: 80%	ORR: 48%; Two-year PFS: 83%	ORR: 16%
Study time period	2000 to 2021	1989 to 2014	2020 to 2022
Time on treatment	Not stated	Median: 13.9 months	Median: 7 months
Follow-up period	Median: 5.6 years	Median: 6.6 years	Not stated
Country	USA	Italy	UK (London)

Results from nirogacestat vs. chemotherapy

	Company MAIC (ESS = 35)	EAG NMA		
		Niro vs chemo	Chemo vs niro	Chemo vs placebo
PFS, HR (95%CI), p-value	[redacted]	2.74 (0.56, 13.5)	0.37 (0.07, 1.80)	0.11 (0.02, 0.46)
ORR*, OR (95%CI), p-value	[redacted]	**7.28 (1.14, 49.3)****	0.14 (0.02, 0.88)	1.15 (0.23, 5.59)
CR, OR (95% CI), p-value	[redacted]	Not evaluated	Not evaluated	Not evaluated
PR, OR (95% CI), p-value	[redacted]	Not evaluated	Not evaluated	Not evaluated
SD, OR (95% CI), p-value	[redacted]	Not evaluated	Not evaluated	Not evaluated
PD, OR (95% CI), p-value	[redacted]	Not evaluated	Not evaluated	Not evaluated
Grade 3+ AEs, OR (95% CI)	Not evaluated	0.81 (0.14, 4.39)	1.23 (0.23, 7.08)	7.82 (1.81, 37.2)
BPI Pain, MD (95% CI) , p-value	[redacted]	Not evaluated	Not evaluated	Not evaluated
Global health status, MD (95% CI) , p-value	[redacted]	Not evaluated		
Physical functioning, MD (95% CI) , p-value	[redacted]	Not evaluated		

Abbreviations: AE, adverse events; BPI, brief pain inventory; CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; MD, mean difference; NMA, network meta-analysis; OR, odds ratio; ORR, objective response rate; PD, progressed disease; PFS, progression-free survival; PR, partial response; RCT, randomised controlled trial; SD, stable disease.

Key clinical trial – patient reported outcomes

Figure: BPI-SF average worst pain intensity score

Abbreviations: ITT, intention-to-treat.

Back to Key Issue: Uncertainty related to the reduction in pain

Post-hoc subgroup analysis of PFS

Back to Key Issue: Uncertainty related to the reduction in pain

Figure: Kaplan-Meier plot of progression-free survival in subgroup with controlled pain at baseline (BPI-SF API ≤4)

[redacted]

Figure: Kaplan-Meier plot of progression-free survival in sub-group with uncontrolled pain at baseline (BPI-SF API >4)

[redacted]

Mean change in pain (BPI) from baseline

Best overall response	Timepoint	Controlled		Uncontrolled	
		Nirogacestat (n)	BSC (n)	Nirogacestat (n)	BSC (n)
Complete response	Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]
Partial response	Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease	Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
	Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]

Probability of patients in each health state experiencing a tumour plateauing

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

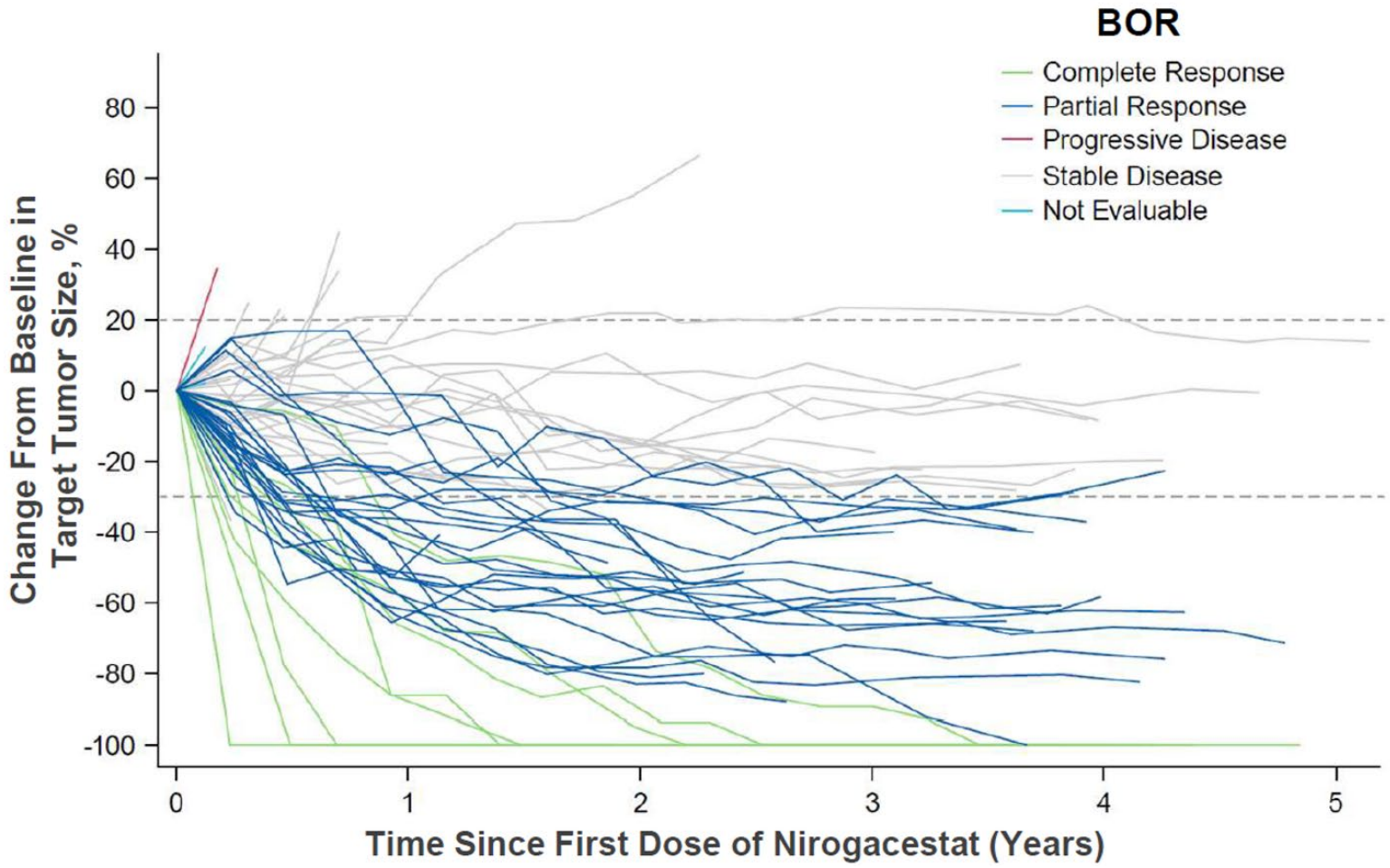
	Best Overall Response At Any Time Up to Year 1							
	Nirogacestat (N=70)				BSC (N=72)			
	CR	PR	SD	PD	CR	PR	SD	PD
Tumour size plateau	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue: Assumed stopping rule supplementary

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



Back to Key issue: Assumed stopping rule

Assumed health-related resource use: EAG and company

	SD nirogacestat		SD placebo		PR		CR		PD	
	Company	EAG	Company	EAG	Company	EAG	Company	EAG	Company	EAG
GP (per visit)	2.55	2.55	1.61	**2.55**	1.18	1.18	0.00	0.00	3.68	3.68
GP DT (per visit)	0.40	0.40	0.21	**0.40**	0.18	0.18	0.00	0.00	1.02	1.02
Specialist (per visit)	1.96	**4.00**	2.24	**4.00**	1.14	**2.00**	0.00	**2.00**	2.38	**6.00**

Differences between EAG and Company base case