Amsterdam, 19 June 2025
EMA/CHMP/82481/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ogsiveo

International non-proprietary name: nirogacestat

Procedure No. EMEA/H/C/006071/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AF	Aggressive fibromatosis
AI	Acceptable intake
APC	Adenomatous polyposis coli
API	Average pain intensity
BCS	Biopharmaceutics classification system
BPI	Brief Pain Inventory
C	Cycle
C30	Core 30
CDI	1,1'-Carbonyldiimidazole
CHMP	Committee for Medicinal Products for Human Use
CPCA	Carcinogenic potency categorization approach
CPP	Critical process parameter
CQA	Critical quality attribute
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTNNB1	Catenin β 1
DoE	Design of experiments
DoSD	Duration of stable disease
DSC	Differential scanning calorimetry
DTIS	Desmoid Tumor Impact Scale
DTRF	Desmoid Tumor Research Foundation
DTSS	Desmoid Tumor Symptom Scale
DTWG	Desmoid Tumor Working Group
EC	European Commission
EU	European Union
FAP	Familial adenomatous polyposis
GC	Gas chromatography
GMP	Good manufacturing practice
GODDESS	Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale
GS	Gamma secretase
GSI	Gamma secretase inhibitor
HDPE	High density polyethylene
Hey	Hairy ears, y-linked
HPLC	High performance liquid chromatography
IC	Ion chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma - mass spectrometry

IR	Infrared
JAG1	Jagged 1
KF	Karl Fischer titration
LDPE	Low density polyethylene
LS	Least squares
MAH	Marketing authorisation holder
MCC	Microcrystalline cellulose
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NICD	Notch intracellular domain
NMR	Nuclear magnetic resonance
NMT	Not more than
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
Ph. Eur.	European Pharmacopoeia
PIB	Powder in bottle
PROMIS PF	Patient-Reported Outcomes Measurement Information System Physical Function
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QC	Quality control
QP	Qualified person
QTPP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumors
RH	Relative humidity
SmPC	Summary of Product Characteristics
T-ALL/LBL	T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma
TAMC	Total Aerobic Microbial Count
TSE/BSE	Transmissible spongiform encephalopathy / Bovine spongiform encephalopathy
TYMC	Total combined yeasts/moulds count
UPLC-MS	Ultra performance liquid chromatography – mass spectrometry
UV-vis	Ultraviolet-visual
WOCBP	Women of child-bearing potential
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SpringWorks Therapeutics Ireland Limited submitted on 9 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Ogsiveo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 January 2022.

Ogsiveo, was designated as an orphan medicinal product EU/3/19/2214 on 17 October 2019 in the following condition: Treatment of soft tissue sarcoma.

The applicant applied for the following indication:

Ogsiveo is indicated for the treatment of adult patients with desmoid tumours.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ogsiveo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/ogsiveo

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0032/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance nirogacestat dihydrobromide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
27 February 2020	EMEA/H/SA/4361/1/2020/SME/II	Dr Walter Janssens and Prof. Markku Pasanen
12 November 2020	EMEA/H/SA/4361/2/2020/PA/SME/II	Dr Pierre Demolis, Dr Serena Marchetti and Dr Karri Penttilä

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Suitability of the proposed quality parameters and in particular: characterisation of the regulatory starting materials, active substance and finished product specification, dissolution method and impact on finished product performance, and stability studies.
- Suitability of the non-clinical programme to support the clinical development programme and benefit/risk assessment, and in particular on the carcinogenicity assessment.
- Adequacy of the design of the proposed Phase 3 study (NIR-DT-301) to support a marketing authorisation application and in particular on: population (with inclusion/exclusion criteria), primary and secondary endpoints (including patient reported outcomes), dose selection and statistical considerations (including sample size). Sufficiency of the clinical programme to be the basis of a marketing authorisation application and in particular: single pivotal study, safety database and safety analyses. Adequacy of the proposed clinical pharmacology programme to enable benefit/risk assessment.

In the scientific advice dated 12th of November 2020 (EMEA/H/SA/4361/2/2020/PA/SME/II) pertaining to the clinical development of nirogacestat with focus on the pivotal study NIR-DT-301–DeFi, the CHMP made a general remark that the usefulness of the advice to be given was hampered by the fact that the study was already ongoing (last patient randomised: 3 Aug 2020). However, in terms of the selected dose the CHMP concluded that this seemed reasonable based on the established MTD, non-clinical data and the PK/PD model using Notch effector HES4 as pharmacodynamic parameter.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Margareta Bego

The application was received by the EMA on	9 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 May 2024
The CHMP Co-Rapporteur's first Assessment was circulated to all CHMP and PRAC members on	21 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	09 April 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 June 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ogsiveo on	19 June 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	19 June 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation for the medicinal product Ogsiveo (nirogacestat) with the following therapeutic indication:

Ogsiveo is indicated for the treatment of adult patients with desmoid tumours.

2.1.2. Epidemiology and risk factors

Desmoid tumours (DT), also referred to as aggressive fibromatosis (AF), are rare, locally aggressive, slow growing soft tissue tumours that can cause severe pain, functional impairment, nerve damage, and bowel obstruction or perforation by infiltrating or exerting mass effects on vital structures (Lewis et al. 1999; Smith et al. 2000; Hosalkar et al. 2006; Shinagare et al. 2011; Constantinidou et al. 2012; Quintini et al. 2012; Penel et al. 2017a; Skubitz et al. 2017; Gounder et al. 2018).

Most cases of DT occur spontaneously in adults and are associated with a mutation in β-catenin (CTNNB1; also known as sporadic DT) (Tejpar et al. 1999; Lazar et al. 2008; Bo et al. 2012). β-catenin is an integral component of the Wnt/βcatenin/T-cell transcription factor signalling pathway, which is frequently dysregulated in cancer. Patients with DT carrying β-catenin mutations have a lower 5-year recurrence-free survival rate than patients with wildtype tumours (van Broekhoven et al. 2015; Guo et al. 2021). The incidence of DT is reported to be about 800- to 1000-fold higher in patients with familial adenomatous polyposis (FAP [Gardner Syndrome]), in which the adenomatous polyposis coli (APC) tumour suppressor gene is mutated (Skubitz et al. 2017). FAP is a serious condition with an almost 100% lifetime risk of colorectal cancer if untreated and is associated with other malignancies, including DT (Kyriakidis et al. 2023). FAP-associated DT are more frequently associated with abdominal tumours, especially in the Gardner variant of FAP (Skubitz et al. 2017).

Intra-abdominal DT are one of the leading causes of death in patients with FAP, resulting in mortality in approximately 10% of patients who have had a colectomy (Arvanitis 1990; Quintini 2012; Koskenvuo 2017). FAP-associated DT tend to be larger, have a multifocal pattern of distribution, exhibit more aggressive clinical behaviour, and are associated with a greater risk of recurrence compared to sporadic DT (Fallen 2006; Nieuwenhuis 2011; Koskenvuo 2017; Sanchez-Mete 2020). Table 1 summarizes the main differences between sporadic and FAP-associated DT.

Table 1. Sporadic vs Familial DT Characteristics

Characteristic	Sporadic (*CTNNB1*)	Familial (*APC*)
Predominance in females	63-73% female	45-55% female
Age of diagnosis*	~42 years	30-35 years
Tumor Location	Extra-abdominal/abdominal wall sites (50-90%)	Intra-abdominal (50-70%)

Reference: Fallen 2006; Nieuwenhuis 2011; Koskenvuo 2017; Sanchez-Mete 2020.
Based on data from 1216 patients with DT across 3 studies.
*Mayo Clinic study found similar age of diagnosis between sporadic and FAP-related DT.

DT most commonly occur in individuals between the ages of 15 and 60 years, with a peak age of about 30 years, and a 2- to 3-fold predominance in females (de Camargo et al. 2010; Skubitz et al. 2017; Anneberg et al. 2022). In the EU, the incidence of DT is about 3 to 5 cases per million per year in the general population (van Broekhoven et al. 2015; Orphanet Report Series 2022).

Data on the prevalence of DT in the EU is limited; however, based on a historical cohort study of patients with DT actively receiving treatment (active surveillance, systemic, locoregional or radiation therapy) in Denmark between 2009 and 2018, the prevalence of patients with DT is estimated to be about 3-4 times the incidence rate (Anneberget al. 2022; White et al. 2021).

2.1.3. Biologic features

According to the WHO, DT are defined as "clonal fibroblastic proliferations that arise in the deep soft tissue and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize" (Kasper et al. 2011). DT include soft tissue masses arising in any part of the body in different varieties of connective tissue, including muscle and fascia aponeurosis. The most common primary tumour sites include abdominal walls, limbs, girdles, and mesenteric areas. DT have been associated with elevated rates of local recurrence following surgery despite wide excisions (Penel et al. 2017). Mortality is occasionally observed owing to the locally aggressive nature and vital structure involvement of some DT (Smith et al. 2000).

Histologically, DT appear as poorly circumscribed proliferation of myofibroblastic cells with variable collagen deposition, and tumour margins are difficult to assess at the time of surgery. DT are morphologically heterogeneous and may exhibit striking morphological intratumoural and intertumoural heterogeneity (Skubitz et al. 2017). In some areas, tumours may resemble fibroblasts of inactive fibrous tissue, whereas other areas may resemble the active fibroblasts of wound healing (Carothers et al. 2012).

2.1.4. Clinical presentation, diagnosis

The clinical course of DT may be unusual and heterogeneous, characterised not only by tumour growth, proliferation, and disease progression, but also by stabilisation and spontaneous remission (Kasper et al. 2011). DT-specific morbidities can negatively impact school, work, and psychosocial functioning (Hosalkar et al. 2006; Schut et al. 2022).

2.1.5. Management

There are currently no approved therapies for the treatment of DT in the EU (DTWG, 2020; NCCN 2020), nor is there a golden standard of care. Treatment options vary for each patient and outcomes depend on the size, location, and morbidity associated with the tumour (Desmoid Tumor Working Group [DTWG] 2020; National Comprehensive Cancer Network [NCCN] 2020; Federman et al. 2022).

Active surveillance is currently recommended as the first approach in DT (DTWG 2020). This approach includes monitoring via magnetic resonance imaging (MRI) (or computed tomography [CT] if MRI is not feasible) within 1 to 2 months of diagnosis then at 3- to 6-month intervals. As described in the DTWG recommendations, a decision towards an active treatment should be postponed until the occurrence of subsequent progression or increase of symptomatic burden, assessed with ≥ 2 further assessments and possibly not before 1 year from diagnosis in the absence of fulfilling RECIST for progressive disease. Treatment may also be initiated sooner if the tumour is located near a vital structure (DTWG 2020).

Historically, surgery was the therapeutic option of choice for localized, extra-abdominal, small volume DT; however, surgery is no longer regarded as the cornerstone of DT treatment given the associated morbidity and local recurrence rates ranging from 24% to 77% after surgical resection, regardless of margin status, based on retrospective, observational data (Easter et al. 1989; Penel et al. 2017b; Crago et al. 2013; Tsagozis et al. 2017). Factors associated with local recurrence post-surgery include tumour location, age of the participant, tumour size, margin status, and prior recurrence.

Further, several studies have shown that surgery and active surveillance result in comparable event-free or progression-free survival rates and long-term disease control (Salas et al. 2011; Park et al. 2016; Penel et al. 2017b). The DTWG recommends surgery as a treatment only for patients with abdominal wall tumours and who require active treatment since these tumours have limited morbidity and risk of recurrence; surgery is not recommended to treat tumours in other locations (DTWG 2020).

Radiotherapy has been used both in the adjuvant setting after surgery and in the primary setting, mainly for extra-abdominal tumours (Kasper et al. 2011; DTWG 2020). While some reduction in the anticipated absolute risk of recurrence after surgery has been observed with the addition of radiotherapy (37% versus 25%), this reduction is not statistically significant; the absolute risk of progressive disease after radiotherapy alone is similar to the recurrence rate after surgery plus radiotherapy (23% versus 22%) (DTWG 2020). Cryoablation appears to be an effective treatment for local control of small- to medium-sized extra-abdominal tumours but is of limited utility for patients with large tumours near vital structures and is not widely available (Kujak et al. 2010; Havez et al. 2014; Schmitz et al. 2016; Redifer Tremblay et al.2019).

Various systemic therapies have been studied in patients with relapsed or recurrent DT, or for patients with DT that are not amenable to surgery or radiotherapy, or for whom surgery is potentially mutilating (including chemotherapy [e.g. anthracycline-based], TKIs [e.g. imatinib, sorafenib, and pazopanib], NSAIDs, and antihormonal therapy).

2.2. About the product

Nirogacestat (PF-03084014) is a small molecule, reversible, non-competitive inhibitor of the gamma secretase (GS) enzyme that was initially developed for investigation in Notch-driven tumours.

Nirogacestat has been shown to inhibit the Notch pathway by inhibiting GS, which prevents proteolytic cleavage of the Notch intracellular domain (NICD) leading to downregulation of the Notch target genes HES1 and C-MYC, resulting in tumour growth inhibition (Wei et al. 2010; Federman et al. 2022). Nirogacestat has been shown to inhibit the Notch pathway in DT by inhibiting NICD signalling and downstream HES1 expression (Shang et al. 2015).

The approved indication is:

Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumours who require systemic treatment.

Ogsiveo should be initiated and monitored by a physician experienced in the use of anticancer therapies.

Posology

The recommended dose is 150 mg Ogsiveo twice daily, one dose in the morning and one dose in the evening. This dose should not be exceeded.

Duration of treatment

Ogsiveo should be continued until disease progression or unacceptable toxicity.

Missed dose

If a dose of Ogsiveo is missed, patients should not take an additional dose. Patients should take the next prescribed dose.

Dose adjustments for adverse reactions

The recommended dose modifications for selected adverse reactions are provided in Table 2.

For other severe adverse reactions, or in the event of life-threatening adverse reactions, Ogsiveo should be withheld until the reaction is resolved to Grade ≤ 1 or baseline. Ogsiveo should only be restarted at a dose of 100 mg twice daily and only after carefully considering the potential benefit and likelihood of recurrence of the adverse reaction. Ogsiveo should be permanently discontinued for recurrence of severe or life-threatening adverse reaction upon rechallenge at the reduced dose.

Dose modifications should be made if patients experience the following adverse reactions (grades refer to Common Terminology Criteria for Adverse Events):

Table 2: Recommended dose modifications for adverse reactions in patients treated with Ogsiveo

Adverse reaction	Recommended action
Diarrhoea	
Grade 3 diarrhoea persisting for ≥ 3 days despite maximal medical therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Skin reactions	
Grade 3 folliculitis	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 maculopapular rash	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 hidradenitis	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Electrolyte abnormalities	
Grade 3 hypophosphataemia persisting for ≥ 7 days despite maximal replacement therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Grade 3 hypokalaemia despite maximal replacement therapy	Ogsiveo should be withheld until reaction is resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.
Hepatic abnormalities	
Alanine transaminase (ALT) or Aspartate transaminase (AST) ≥ 3 to 5 x ULN	Ogsiveo should be withheld until ALT, AST, or both are resolved to < 3 x ULN or baseline, then it should be restarted at a dose of 100 mg twice daily.
ALT or AST > 5 x ULN	Ogsiveo should be permanently discontinued.
Other adverse reactions	
Anaphylaxis or other severe hypersensitivity reaction	Ogsiveo should be permanently discontinued.

2.3. Type of application and aspects on development

The clinical development program for nirogacestat includes in total 14 clinical studies, however studies pertinent to the current application is the pivotal study NIR-DT-301 (DeFi) with studies A8641014 (dose finding study) and 14-C-0007 acting as supportive.

Table 3. History of Regulatory Interactions with CHMP

Date	Communication Type	Summary
27 Feb 2020	Scientific Advice (EU CHMP)	Written advice was obtained on the nonclinical and chemical, pharmaceutical, and biological development of nirogacestat including the acceptability of the starting materials for manufacture, proposed release specifications, the adequacy of the dissolution method, proposed stability studies for the registration batches and initial commercial batches, and the acceptability of the overall nonclinical package and on the proposed carcinogenicity programme.
12 Nov 2020	Scientific Advice (EU CHMP)	Written advice was obtained on the acceptability of the overall clinical pharmacology programme and to clinical development plan of nirogacestat in the target indication of progressing DT including the overall study design of the Phase 3 NIR-DT-301 study (dose selection, participant population, primary endpoint, PROs).
26 Oct 2023	MAA Pre-Submission Meeting with (Co)-Rapporteurs	A teleconference was held to discuss key elements of the MAA data package including, nonclinical and clinpharm packages, presentation of efficacy and safety, data cut off dates for efficacy and safety data, safety data display in SmPC, long-term safety for RMP.

Abbreviations: CHMP: Committee for Human Medicinal Products; EU: European Union; MAA: Marketing Authorisation Application; PRO: patient-reported outcome; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 50, 100 and 150 mg of nirogacestat as active substance. The product contains the dihydrobromide salt, also referred to as nirogacestat hydrobromide.

Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate.

Tablet coating: Macrogol polyvinyl alcohol graft copolymer (E 1209), talc (E553b), titanium dioxide (E171), glycerol monocaprylocaprate type 1/mono/diglycerides (E471), polyvinyl alcohol - partially hydrolyzed (E1203), FD&C yellow #6/sunset yellow FCF aluminium lake (E110), iron oxide yellow (E172).

The 50 mg tablet is available in HDPE bottles with child resistant closures and induction seals. The 100 and 150 mg tablets are available in clear PVC/PVDC blisters with aluminium lidding.

2.4.2. Active substance

General information

The chemical name of nirogacestat is (*S*)-2-(((*S*)-6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)amino)-*N*-(1-(2-methyl-1-(neopentylamino)propan-2-yl)-1*H*-imidazol-4-yl)pentanamide dihydrobromide, corresponding to the molecular formula $C_{27}H_{43}Br_2F_2N_5O$. It has a relative molecular mass of 651.48 g/mol (dihydrobromide salt) or 489.66 g/mol (free base), and the following structure:

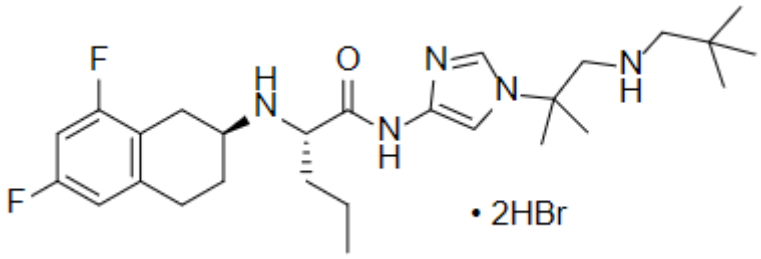


Figure 1: active substance structure

The structure of nirogacestat hydrobromide was elucidated by a combination of techniques such as elemental analysis, UV-Vis spectroscopy, IR spectroscopy, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, and mass spectrometry. The solid-state properties of the active substance were measured by x-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

Nirogacestat hydrobromide is a non-hygroscopic crystalline white to off-white powder. The active substance is sparingly soluble in water. Solubility increases at lower pH.

Nirogacestat hydrobromide exhibits stereoisomerism due to the presence of two chiral centres, resulting in four possible stereoisomers. The absolute configuration of the stereocentre at the C2 position in the tetrahydronaphtalene ring is (*S*). The absolute configuration of the stereocentre at the C2 position of the amide linkage is (*S*). There are no geometric isomers of nirogacestat. Enantiomeric and diastereomeric purity are controlled routinely in the active substance by chiral HPLC.

Polymorphism has been observed for nirogacestat hydrobromide. Twelve polymorphs were identified, the most stable of which (Form A), is generated routinely by the manufacturing process and is controlled in the active substance by XRPD.

Manufacture, characterisation and process controls

The active substance is manufactured at two manufacturing sites for which evidence of GMP compliance has been provided in the QP declaration.

Nirogacestat hydrobromide is synthesized in several stages including multiple convergent chemical transformation steps using well defined starting materials with acceptable specifications. The same process is used by both manufacturers with no alternate process being proposed.

Scheme 1: active substance manufacturing process

The initially proposed starting materials were only 2 synthetic steps from the active substance which was not considered enough, resulting in a major objection requesting redefinition of the starting materials. In response, the applicant re-defined one of the proposed starting materials as an intermediate. Information on the additional manufacturing steps was submitted and considered acceptable. The applicant maintained the other proposed starting material was adequately defined as steps upstream do not result in isolable intermediates. Furthermore, it has been demonstrated that impurities from the upstream steps do not impact the impurity profile of the active substance. Tight controls for impurities, including unknown impurities, are applied to the starting material. This was accepted by CHMP, and the major objection was resolved.

Batch analysis results for the starting materials from both sites were presented and are comparable. The starting material specification limits are adequately justified. It can be concluded that the quality of the final active substance is the same, irrespective of the starting material source and manufacturing site.

The manufacturing process and process controls are now described in adequate detail. The applicant has demonstrated that the chiral centres do not epimerise under the process conditions. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Adequate controls have been defined based on the results of Design of Experiments (DoE) studies.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. All identified genotoxic impurities are controlled according to ICH M7 Options 3 and 4 which is acceptable.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes were made to improve manufacturability quality, including control of impurities. Process steps were optimised using risk assessment and a combination of univariate and multivariate experiments. No design space is claimed.

The active substance is packaged in double, sealed, low-density polyethylene (LDPE) bags which comply with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), assay (HPLC), impurities (HPLC), stereoisomeric impurities (chiral HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), elemental impurities (ICP-MS), bromide counterion content (IC), and solid-state form (XRPD).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies, and appropriate specifications have been set.

The control strategy for residual solvents and elemental impurities has been detailed in the characterisation of the active substance section and the applied limits are in line with ICH Q3C and ICH Q3D, respectively.

The manufacturing process routinely delivers active substance with consistent particle size distribution. No impact has been observed on manufacturability or solubility in the finished product. Therefore, the omission of testing for particle size distribution is considered acceptable.

Justification for omission of testing for microbial contamination was provided. Nirogacestat finished product is a non-sterile tablet that is tested for TAMC, TYMC and absence of *E. coli* at release and on stability.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. Analytical methods used are the same across manufacturing sites with the exception of the method for elemental impurities.

Batch analysis data is presented for multiple production-scale, clinical and registration stability batches produced at both manufacturing sites. The results were within the specifications and consistent from batch to batch.

Stability

Stability studies have been initiated on 8 production scale batches including batches from both manufacturers, all stored in the proposed commercial container closure system. Stability data is

available from batches stored for up to 48 months under long term conditions (25 °C/60% RH) and up to 6 months under accelerated conditions (40 °C/75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, related substances, water content, chiral purity, solid-state form. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications. No significant trends were observed for any of the measured parameters and no changes in appearance or solid-state form were observed.

Photostability testing was conducted according to ICH Q1B Option 2. Exposure of the active substance as a solid and in aqueous solution to both visible and ultraviolet light for 10 days did not lead to any observable degradation of the active substance. The active substance is therefore considered photostable.

Forced degradation studies were conducted under acidic, basic, oxidative, heat, light and moisture conditions. Mass balance as well as peak purity were monitored during the forced degradation studies. Significant degradation was observed after exposure to acidic and oxidative conditions. The results indicate that the analytical methods for identification, assay and related substances are stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored at 15–25 °C in the proposed container closure system.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

Nirogacestat tablets are immediate release, film-coated tablets intended for oral administration containing 50, 100 or 150 mg of nirogacestat. The three strengths are differentiable by size, shape, and colour. The description of the nirogacestat tablet dosage forms is provided for all strengths in Table 4 below.

Table 4: description of the nirogacestat tablets

Nirogacestat Drug Product	Nirogacestat Dihydrobromide[a] Amount per Tablet (mg)	Description of the Dosage form
50 mg Tablet	66.525	Round, biconvex with an approximate diameter of 8 mm. They are film coated orange and debossed with “50” on one face and plain on the other face
100 mg Tablet	133.049	Round, with an approximate diameter of 10 mm. They are film coated light orange and debossed with “100” on one face and plain on the other face
150 mg Tablet	199.574	Oval, with an approximate dimension of 8.5 ×17.5 mm. They are film coated yellow orange and debossed with “150” on one face and plain on the other face

[a] USAN name is nirogacestat hydrobromide

. The tablets contain the same relative amount of each excipient.

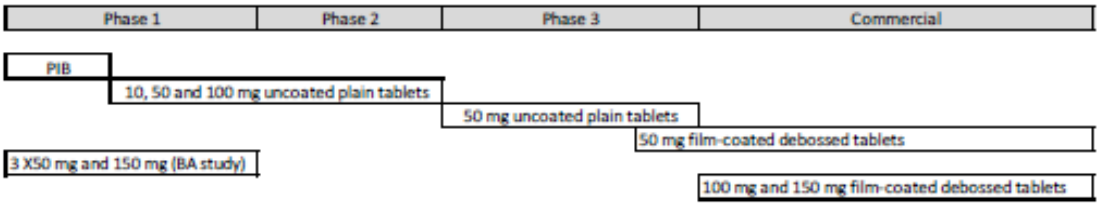
The selected excipients are commonly used for oral pharmaceutical dosage forms and their compatibility with the active substance has been adequately demonstrated. Their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the development was to produce an immediate release oral dosage form. A quality target product profile (QTPP) was defined as an immediate release dosage form that meets compendial and other relevant quality standards identified.

The finished product quality attributes were derived from the QTPP. Critical quality attributes (CQA) were identified based on the potential severity of harm to a patient in terms of safety and efficacy resulting from failure to meet the required quality standards. The CQAs identified are: appearance, identity, assay, content uniformity, dissolution, degradation products, and microbial quality.

Water content was demonstrated not to be a CQA since it does not impact dissolution or the impurity profile. The active substance quality attributes are suitably controlled in the active substance specification. Particle size was shown not to impact the finished product CQAs within the ranges routinely produced by the active substance manufacturing process. The impact of varying levels of disintegrant and lubricant in dissolution rate and stability was also studied and they were found not to have a significant impact.

Various formulations were developed and used at various stages of clinical development including powder in bottle (PIB), uncoated, and coated tablets of various strengths as indicated in Scheme 2.



Scheme 2: Illustration of Dosage Form Usages during development

The active substance is a sparingly soluble across the physiological pH range but highly permeable and is considered a BCS class 2 substance. The polymorphic form has been shown not to change during finished product manufacture or on storage.

Of the three proposed tablet strengths, only the 50 mg tablets were used in pivotal clinical studies. Bioequivalence between the 50 and 150 mg tablets was demonstrated in a relative bioavailability study. Since the three tablet strengths have quantitatively proportional compositions, a biowaiver was granted for the 100 mg tablet based on comparative dissolution profiles between strengths in pH 1.2, pH 4.5 and pH 6.8 media.

The parameters evaluated during development of the dissolution method were dissolution apparatus, rotation speed, pH, media volume and surfactant content. Active substance release is characterised by rapid initial release, irrespective of pH. Coning was observed at low rotation speeds attributed to insoluble excipients which prevent complete release of the active substance. Incomplete dissolution was also observed at pHs above 4.5. Addition of a surfactant increases solubility at neutral pH but does not allow development of a discriminatory method. Based on the extensive development studies, the apparatus and method parameters laid out in table 6 were selected for quality control (QC) purposes.

Table 5: Dissolution method parameters

Parameter	Setting
Apparatus type	USP dissolution apparatus 2 (paddle method)
Rotation speed	75 rpm
Media	pH 1.2 HCl buffer
Media volume	500 mL
Detection	UV at 247 nm
Sampling timepoints	10, 15, 30, 45, and 60 minutes

Discriminatory power was investigated by varying excipient content (disintegrant, lubricant) and process parameters (granulation parameter, compression force) with a potential impact on release profile. None of the parameters studied, alone or in combination, had a significant impact on release rate other than compression force where differences could be observed at the 5-minute timepoint. Considering the tight specification for release and rapid release profile of the active substance, the dissolution method is considered suitable for QC purposes.

The development of the manufacturing process relied upon risk assessment to identify process parameters potentially impacting the finished product CQAs. Based on this, the applicant univariate and multivariate experiments to optimise the different unit operations within the process. The process development is adequately discussed.

The primary packaging of nirogacestat 50 mg tablets is HDPEs bottles with child resistant closures and induction seals. The primary packaging of nirogacestat 100 and 150 mg tablets is clear PVC/PVDC blisters with aluminium lidding. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Adequate GMP documentation was provided by both finished product manufacturers.

The manufacturing process consists of ten main steps: pre-blending, screening, blending, lubrication, roller compaction and integrated milling, lubrication, compression, de-dusting, film-coating, packaging. The process is considered to be a standard manufacturing process.

A common pre-compression blend is used for all tablet strengths.

The manufacturing process was validated at both finished product manufacturing sites in the commercial equipment on production scale covering all unit operations. Active substance batches from both suppliers were incorporated. At least 3 batches of each tablet strength were produced. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The bulk tablets are packaged in HDPE drums lined with double polyethylene bags. Based on the presented bulk stability data the proposed bulk holding times of 12 months (50 mg tablets and 150 mg tablets) and 6 months (100 mg tablets) are acceptable.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual); identity (HPLC, IR); assay (HPLC); nitrosamine impurities (UHPLC-MS); individual unspecified degradation products (HPLC), total degradation products (HPLC); dissolution (Ph. Eur.); content uniformity (Ph. Eur.); microbiological quality (Ph. Eur.).

No degradation products were observed above the 0.2% identification threshold and therefore no control for specified impurities is proposed. The proposed acceptance criteria of ≤ 1.0% for total degradation products is therefore acceptable.

A nitrosamine risk assessment for the finished product was conducted in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The assessment evaluated the potential contributions from the active substance, excipients, and container closure system as well as the manufacturing process and associated cleaning procedures. A risk assessment was also conducted for the active substance and concluded that there was no risk of nitrosamine contamination due to the active substance synthetic process, raw materials or equipment and no other sources of nitrosamine formation were expected. The applicant initially concluded that there was no risk of nitrosamine contamination in nirogacestat tablets.

However, this nitrosamine risk assessment was not accepted since the active substance, present as the dihydrobromide salt, contains two secondary amines and excipients are used with known risks for presence of nitrite. A Major Objection was therefore raised at D120 requesting confirmatory testing on the finished product. Testing of NDSRIs was performed on all strengths including tablets of different ages, between 1 and 5 years old. Two nitrosamines ASYM-136911 and ASYM-136912 were detected above the acceptable intake (AI) of 1,500 mg/day in all tested tablets using a suitably sensitive analytical method, and the nitrosamines risk assessment was updated. The applicant proposed several approaches to reduce the levels of impurities below the AI, including the use of low nitrite microcrystalline cellulose (MCC) and re-formulating the product (e.g. introducing a nitrite scavenger), however, was unable to implement these changes within the timelines of the marketing authorisation procedure.

Considering the clinical context (unmet medical need for a severe condition with a beneficial clinical profile), the clinical judgement that long term treatment is unlikely, that both impurities are considered to have relatively low mutagenic potential, and the review and scientific opinion from NCWP indicating that the risk of cancer is near or below the accepted 1:100,000 for up to 7 years of continuous treatment at the maximum daily dose of 300 mg, it was agreed to exceptionally apply the "less than lifetime" multiplier of 6.7x from ICH M7 for products taken for between 1 and 10 years for an interim period, equating to limit of 20 µg/day for the sum of ASYM-136911 and ASYM-136912.

The applicant should further introduce finished product batches using low nitrite MCC by the end of 2025 and instigate formal ICH stability studies on these batches. Furthermore, the applicant is required to develop effective measures (i.e. an optimized formulation, manufacturing process and/or control strategy) to ensure the sum of ASYM-136911 and ASYM-136912 impurities does not exceed the AI of 1.5 µg/day throughout shelf-life and submit the appropriate variation to implement the change(s) and tighten the release and shelf-life specification limit to NMT 1.5 µg/day in the finished product by Q3 2027.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk

assessment and considering that elemental impurities are limited in the active substance specification, it is not necessary to include any elemental impurity controls in the finished product specification.

Water content testing is omitted on the finished product based on the presented release and stability data showing that the content of water is consistent from batch to batch and for each strength of the finished product and does not increase on storage.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for at least 3 production scale batches of each strength of the finished product manufactured by both manufacturers and using active substance batches sourced from both active substance manufacturers, thus confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data were provided from 3 registration/clinical batches of nirogacestat 50 mg, 100 mg, 150 mg stored for up to 48 months and from 3 commercial batches of nirogacestat 50 mg tablets stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines.

As the three tablet strengths are homothetic in composition, data for the 50 mg tablets is considered representative of the higher strength tablets.

Samples were tested for appearance, assay, degradation products, water content, dissolution, and microbiological quality. The analytical procedures used are stability indicating as demonstrated in forced degradation studies conducted under acidic, basic, oxidative, heated, and moisture conditions.

No significant changes or trend were observed under either condition. All parameters remained within the specifications and no significant trends were observed.

In addition, three batches (one per strength) were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant change was observed in the appearance, assay, degradation products or the dissolution performance following light exposure for all strengths of the finished product. Nirogacestat tablets are considered photostable.

The two nitrosamines detected during the course of the procedure were not included in the initial stability protocol, and therefore, the original stability data was not considered adequate to justify the originally proposed shelf-life of 48 months without specific storage conditions resulting in a major objection. In response, the applicant shortened the shelf-life to 24 months and applied more restrictive storage conditions (below 25 °C) to ensure the combined nitrosamine content in the finished product remains within the specification limit of 20 µg/day throughout shelf-life. The applicant should place all commercial batches on formal stability with nitrosamine testing every 3 months for the duration of time that the batch remains in commercial distribution. The applicant should amend the storage conditions and shelf-life as appropriate, based on the results of stability studies on batches manufactured with low nitrite MCC (REC).

Based on available stability data, the proposed shelf-life of 24 months when stored below 25 °C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products. A TSE/BSE statement from the supplier of the lactose monohydrate was provided. The material meets the current Ph. Eur. requirements for lactose.

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The major objection on the starting materials was resolved by re-definition of one of the starting materials and provision of argumentation demonstrating that the other was acceptable. Two nitrosamine impurities, ASYM-136911 and ASYM-136912, were detected during the course of the procedure in the finished product. Levels exceed the AI based on CPCA categorization. Considering the clinical context and that the risk of cancer is not increased for the likely duration of use, a higher combined specification limit of 20 µg/day was agreed. The applicant should take measures to reduce the levels of nitrosamine impurities below the AI limit as laid out in the recommendations section.

The quality of the product is in the meantime considered adequate to support a positive opinion based on the benefit/risk ratio of the product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP has identified the following measures necessary to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product:

The applicant is required to develop effective measures (i.e. an optimized formulation, manufacturing process and/or control strategy) to ensure the sum of ASYM-136911 and ASYM-136912 impurities does not exceed the AI limit of 1.5 µg/day throughout shelf-life and submit the appropriate variation to implement the change(s) and tighten the release and shelf-life specification limit to NMT 1.5 µg/day in the finished product' by Q3 2027 (see Annex II.D). A progress report should be submitted by Q3 2026.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should place all commercial batches on formal stability with nitrosamine testing every 3 months for the duration of time that the batch remains in commercial distribution.

2. The applicant should introduce finished product batches using low nitrite MCC by the end of 2025 and instigate formal ICH stability studies on these batches.
3. The applicant should amend the storage conditions and shelf-life as appropriate, based on the results of stability studies on batches manufactured with low nitrite MCC.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro evaluation of enzyme kinetics was completed with cell-free assays using the human isoform of GS extracted from HeLa cells and a recombinant human APP-C100-FLAG peptide purified in *E. coli*. Nirogacestat inhibited the enzymatic production of the $A\beta_{1-40}$ peptide in repeated experiments, resulting in a mean half-maximal inhibitory concentration (IC50) of 6.2 nM. Increasing concentrations of nirogacestat had no effect on Km but resulted in reduced Vmax, which is consistent with reversible and noncompetitive inhibition of the GS enzyme.

In a cellular assay using the human embryonic kidney (HEK) 293 stable cell line that expresses NΔE construct (containing aa1727-2813 of NOTCH1), nirogacestat displayed potent activity with IC50 of 7.7 nM (0.34 nM free) for Notch intracellular domain (NICD) inhibition. In human peripheral blood-acute lymphoid leukemia (HPB-ALL) cells that harbor *NOTCH1* mutations, nirogacestat displayed an IC50 of 41 nM (1.82 nM free) for NICD inhibition and an IC50 of 32 nM (1.4 nM) for growth inhibition. The growth inhibition observed in HPB-ALL cells after nirogacestat-mediated NICD inhibition is associated with induction of cell cycle arrest and apoptosis and is reversible upon cessation of nirogacestat exposure.

Nirogacestat was evaluated for antitumor effects in 7 patient-derived DT cell lines. *NOTCH1*, *JAG1*, and *HES1* were shown to be present in all patient lines, with high levels of nuclear localization of NICD confirming active Notch signaling. Dose-dependent decreases in NICD and *HES1* were confirmed by Western blot in 2 of the cell lines and a varying degree of growth inhibition was determined using cell proliferation assays in 5 of the cell lines at concentrations ranging from 0.01 to 10 μM over a 27-day treatment period. For these patient-derived cells, the IC50 for growth inhibition ranged from 4.19 μM in the most sensitive line to 158.8 μM in the most resistant line. Cell migration and invasion assays were conducted with 5 of the patient-derived cell lines and all showed significant reductions in migration and invasion after 7 days treatment with 10 μM nirogacestat.

The *in vivo* antitumor activity of nirogacestat was studied in a range of Notch-driven tumour models and a non-Notch-driven tumour model. Robust tumour growth inhibition (TGI) by nirogacestat at high dose levels (≥ 200 mg/kg/day) was obtained in 6 Notch-driven models, with greatest TGI (> 90%) in the T-ALL models (SupT1 and HPB-ALL). In contrast, the non-Notch-driven model, GTL-16, did not respond to nirogacestat treatment.

2.5.2.2. Secondary pharmacodynamic studies

Nirogacestat was evaluated for interaction with a number of other proteases, receptors, ion channels and kinases. Activity in a broad panel of common receptors was > 1 μM in all assays. The IC50 was determined for all receptors where inhibition was > 50% at the screening concentration of 10 μM. Testing at other aspartic proteases (pepsin A, BACE 1 and cathepsin D) or serine proteases (Chymotrypsin A, Trypsin) showed negligible inhibition at 20 μM. Nirogacestat also showed < 25% inhibition at 10 μM in a panel of 10 kinase enzymes, including ABL, CK1d, GSK3β, IKK2, IKKi, LCK, MK2, P38, PKA, PKCzeta. By comparison, the geometric mean human serum free Cmax observed at steady-state was 4.98 ng/mL (10.2 nM) after oral administration of 150 mg BID.

2.5.2.3. Safety pharmacology programme

The *in vitro* effects of nirogacestat on the hERG channel current expressed in HEK293 cells were assessed at concentrations of 0.3, 1, 3, and 10 μM. Under the conditions of this GLP study, the IC_{50} for the inhibitory effect of nirogacestat on hERG potassium current was 1.0 μM. This concentration is 98-fold over the human free geometric mean Cmax of 4.98 ng/mL (10.2 nM) after administration of 150 mg BID.

The respiratory effects of single oral doses of nirogacestat were assessed in male Sprague-Dawley rats (6/group) at doses of 5, 20, or 500 mg/kg using whole body plethysmography. There were no statistically significant effects on tidal and minute volumes during the 2-hour period of measurement that began immediately after dosing. There were no statistically significant effects on respiratory rate for the 5- and 20-mg/kg dose levels. However, at the 500-mg/kg dose, there was a statistically significant increase in respiratory rate. In the second and fourth 20-minute post-dose periods, the observed mean respiratory rate at this dose level increased by 40.2% and 27.5%, respectively. Because the increase was small in magnitude, the increased respiratory rate was not considered adverse. Based on the outcome of this GLP study, nirogacestat does not adversely affect pulmonary function in male rats.

The neurofunctional effects of single oral doses of nirogacestat were assessed in male Sprague-Dawley rats (6/group) at doses of 5, 20, or 500 mg/kg. The assessment included a functional observational battery (FOB), body temperature, and locomotor activity. There were no adverse effects in the FOB, body temperature, or locomotor activity. Based on the outcome of this GLP study, nirogacestat does not adversely affect neurofunctional activity in male rats.

The cardiovascular effects of nirogacestat were assessed in male Beagle dogs implanted with telemetry devices using a single-dose crossover design. Nirogacestat was administered orally to dogs at 2, 80, or 500 mg/kg. During the 23-hour post-dose observation period, no statistically significant changes in heart rate, blood pressure, or electrocardiogram (ECG) parameters were observed. Combined mean values of nirogacestat exposures ~ 6 hours postdose, were 10.5, 62.5 and 134 ng/mL for the 2, 80, and 500 mg/kg treatments respectively. The exposure in the dog at 500 mg/kg is below the human Cmax (508 ng/mL) after administration of 150 mg BID in DT patients.

2.5.2.4. Pharmacodynamic drug interactions

No PD drug interaction studies have been conducted.

2.5.3. Pharmacokinetics

Methods of analysis

Nirogacestat concentrations were quantified in plasma and serum samples from mouse, rat, and dog, as well as in buffer generated from *in vitro* studies, by LC-MS/MS. For GLP toxicology studies, the bioanalytical method validation was also conducted under GLP conditions.

Absorption

Pharmacokinetics of nirogacestat following single dose oral and intravenous (IV) administration was studied in male Sprague-Dawley rats and male and female Beagle dogs. The absolute bioavailability of nirogacestat was low (3.32% and 14.9% in the rat and dog, respectively). Following IV administration of nirogacestat, the estimated mean blood clearances in rat and dog were 52.3 and 20.4 mL/min/kg (plasma clearances corrected for blood-to-plasma partitioning), respectively. These values are 94.7% and 66.0% of the reference liver blood flow in the corresponding species, which indicates that nirogacestat is a high- and moderate-clearance compound in the rat and dog, respectively. The mean steady-state distribution volumes were 17.4 and 4.66 L/kg in the rat and dog, respectively. These values are > total body water and suggest that nirogacestat partitions into tissues.

Distribution

Protein binding was determined for mouse (CD1), rat (Sprague-Dawley), and dog (Beagle) with unbound free fractions of 0.2% for all three species. The fraction unbound of 0.4% was determined for human plasma and serum.

The extent of nirogacestat distribution into red blood cells (RBCs) was determined in rat, dog, and human whole blood. Mean blood-to-plasma (Cb/Cp) ratios of nirogacestat were 0.514, 0.387, and 0.517 in rat, dog, and human, respectively.

In a study conducted in mdr1a/1b (-/-) knockout and wild-type mice following an oral dose of 10 mg/kg nirogacestat, the knockout to wild-type asymmetry ratio of brain-to-plasma AUC ratios was 5.9. The brain-to-plasma AUC ratios were 1.12 and 6.57 for the wild-type and mdr1a/1b knockout mice, respectively.

The tissue distribution of [^{14}C] nirogacestat radioequivalents in male Long Evans (pigmented) rats was evaluated by whole body autoradiography after a single oral administration (20 mg/kg, ~190 µCi/kg) of [^{14}C] nirogacestat. [^{14}C] nirogacestat-derived radioactivity was widely distributed into tissues and fluids of rats at 0.5 hour after dosing. Concentrations of radioactivity in most tissues were higher than those observed in blood, consistent with the large volume of distribution for nirogacestat in the rat. Concentrations of [^{14}C] nirogacestat-derived radioactivity reached Cmax in most tissues between 2 to 4 hours after dosing. Excluding excreta, tissues with the highest levels of radioactivity at Cmax were uveal tract, liver, adrenal gland, spleen, and pituitary gland. [^{14}C] nirogacestat-derived radioactivity exhibited a prominent affinity for pigmented tissues (e.g. ocular tissues, excluding the lens of the eye). Affinity to pigmented tissues is commonly observed for lipophilic basic compounds, like nirogacestat, and is due to reversible binding to melanin (Jakubiak et al. 2018). Low concentrations of [^{14}C] nirogacestat-derived radioactivity were present in the non-circumventricular central nervous system (CNS) tissues, with AUC and Cmax achieving approximately half of that observed in the blood, indicating that drug-derived radioactivity did not readily distribute across the blood-brain barrier. However, exposure to [^{14}C] nirogacestat-derived radioactivity was higher in the choroid plexus than in the blood (approximately 7.5-fold higher AUC and 4.4-fold higher Cmax), which may suggest that nirogacestat does cross the blood-CSF barrier. Sustained levels of radioactivity were present in most tissues for at least 48 hours. The only non-melanin containing tissues with prolonged radioactivity levels (>10% of tissue Cmax at 168 hours) were the pituitary gland and testes.

The distribution of radioactivity in the tissues of male Beagle dogs was investigated 672 hours after a single oral administration of [^{14}C] nirogacestat at 5 mg/kg. Drug-related radioactivity was present and widely distributed in the majority of tissues analyzed, except for the brain and stomach contents where

concentrations were close to or below the limit of quantification. Based on mean data, highest concentrations were in the liver, eyes, adrenal glands, thyroid and kidney (0.086 - 0.399 µg equiv./g). For the majority of tissues analyzed, mean concentrations were > plasma (0.008 µg equiv./g) at 672 hours after dosing. Where calculable, the tissue:plasma ratios were generally > unity with the highest in liver, approximately 50:1.

Metabolism

Preliminary metabolism studies using non-radiolabeled nirogacestat were conducted using *in vitro* systems and with plasma and serum samples obtained from studies in rat, dog, and human. Nirogacestat was highly metabolized in hepatic (human, rat, and dog) and intestinal (human) microsomes. Nirogacestat appears to be metabolized into several oxidative metabolites. *In vitro*, CYP3A4 (85.7%) was the major CYP enzyme responsible for the metabolism of nirogacestat.

A study was conducted using rat, guinea pig, dog, and human liver microsomes (HLM), and human hepatocytes as well as plasma samples from rat, guinea pig, and dog. Metabolites of nirogacestat were observed in all samples apart from plasma obtained from the guinea pig. In total, 10 metabolites were identified, with the major metabolites, as assessed by ultraviolet response, resulting from products of oxidation and N-dealkylation (loss of neopentyl). Metabolite profiles were generally similar across species for *in vitro* samples with some minor differences between the *in vitro* and plasma sample profiles.

Mass balance, tissue distribution, and metabolite identification studies with [^{14}C] nirogacestat were conducted in both rat and dog, the two species utilized for the general toxicology studies.

The biotransformation of [^{14}C] nirogacestat in rats was extensive with numerous metabolites observed in plasma, urine and feces. There were 4 components in plasma each representing ≥ 2% of the sample radioactivity; the most significant component, P1, represented 74.9%. Metabolites that were identified in plasma resulted from N-dealkylation (loss of neopentyl) and oxidation, including a metabolite M283 (PF-03015273), representing 2.23% of the sample radioactivity, that has been characterized as the carboxylic acid derivative resulting from amide cleavage. P1 was unretained on the high-performance liquid chromatography system, suggesting it is a low molecular weight, polar compound and forms through further metabolism of M283 (PF-0315273), likely through loss of the difluorotetrahydronapthalene group. The presence of the related difluorotetrahydronapthylamine (M183(PF06450557-09)) metabolite of [^{14}C] nirogacestat was confirmed by using an authentic standard, even though the [^{14}C]-label has been lost. Metabolite P1 was not identified, but it is anticipated that subsequent metabolism of P1 results in the loss of $^{14}CO_2$, potentially through the formation of a polar, low molecular weight derivatives such as L-norvaline.

The metabolism of [^{14}C] nirogacestat was also extensive in the dog, with numerous metabolites observed in plasma, urine, and feces. Of more than 10 components observed in plasma, only 2 components represented greater than 10% of the sample radioactivity and were designated P1 and P9. Unidentified P1, representing 10.6% of the pooled plasma sample radioactivity, exhibited the same characteristics as the corresponding metabolite seen in rat. Component P9, representing 11.1% of the plasma radioactivity, comprised 2 unresolved metabolites that resulted from N-dealkylation (loss of neopentyl) and oxidation. M283 (PF-03015273; 3.19% of the plasma sample radioactivity) and M183 (PF06450557-09) were also observed.

Additionally, mass balance studies have been conducted in humans.The most abundant metabolites were P1 and M283, representing 44% to 48% and approximately 6% of the total radioactivity, respectively. In both human studies, poor recovery (approximately 62% to 65%) of the administered radioactive dose of [^{14}C] nirogacestat was observed. It was notable that in the clinical study and the

rat mass balance study, where expired air was collected, a significant amount of the [^{14}C]-administered radioactive dose (between 7% to 25%) was recovered as $^{14}CO_2$. Low recoveries in the dog mass balance study may also be due, in part, to the fact that expired air and associated $^{14}CO_2$ was not collected.

Excretion

Excretion of nirogacestat-derived radioactivity was studied in intact and bile duct cannulated (BDC) male and female Wistar Hanover rats following oral administration of a single 20-mg/kg dose of [^{14}C] nirogacestat. Collectively, the data suggest that the primary route of excretion occurs via the feces, considering that the [^{14}C] nirogacestat-derived radioactivity pathway following oral administration to rats is hepatic clearance and biliary excretion.

Excretion of nirogacestat-derived radioactivity was also studied in male Beagle dogs following a single oral administration of [^{14}C] nirogacestat at a dose level of 5 mg/kg. After 168 hours, most of the dose (mean of 74.0% of the radioactivity), was excreted in the feces with a mean of 3.1% recovered in urine. The mean total recovery including cage wash was 77.7%. Expired air was not collected in this study.

2.5.4. Toxicology

Toxicology of nirogacestat was assessed in a series of non-clinical toxicology studies in mice, rats, and dogs.

The oral route of exposure was selected for these studies since it is the intended clinical route of administration. The rat and dog were selected as the toxicology species based on nirogacestat pharmacokinetic and metabolism properties compared across species.

2.5.4.1. Single dose toxicity

Single dose toxicity studies were not conducted with nirogacestat.

2.5.4.2. Repeat dose toxicity

Exploratory and definitive GLP repeat-dose toxicity studies were conducted with nirogacestat in rats and dogs up to 3 months of duration. In all the repeat-dose toxicology studies, the dihydrobromide salt form of nirogacestat was used, and the reported dose level within each *in vivo* study was corrected for salt content and purity.

Rat

In a 1-month GLP-compliant study (06GR067), nirogacestat was not tolerated at 150 mg/kg/day with early termination of dosing. Treatment-related findings included effects on lymphoid and gastrointestinal organs consistent with inhibition of GS and the Notch pathway. Lymphoid depletion of the thymus, spleen, lymph nodes, and galactose-1-phosphate uridylyltransferase (GALT) and decreased thymic weight was observed. A concomitant decrease in total lymphocyte count along with a decrease in T-cell population, natural killer (NK) and B cells was observed. IgD and IgM expression was decreased. Hyperplasia of the mucosa of the gastrointestinal tract, characterized by increased numbers of enterocytes from the duodenum to the ileum, along with degeneration of the colonic epithelium was

observed. Other findings included retention of the hypertrophic zone of the growth plate and articular cartilage in the bone, and atrophy of the ovary with associated decrease in ovary weight and asynchrony of the estrous cycle. The lymphoid and gastrointestinal changes were reversible.

Hepatocellular vacuolation, consistent with lipid accumulation in the cytoplasm of periportal hepatocytes, was noted in a few individual rats. Other treatment-related effects observed in early deaths or moribund animals included increased numbers of foam cell foci in the lung, protein casts in kidneys of female rats with associated increases in blood urea nitrogen, and individual cell necrosis of glandular epithelial cells of the salivary gland. These changes were reversible.

Based on retention of the hypertrophic zone of articular cartilage, ovarian atrophy and asynchrony of the estrous cycle, depletion of lymphoid organs, and hepatocellular vacuolation noted at 20 mg/kg/day, 5 mg/kg/day was identified as the NOAEL and was associated with a C_{max} of 19.3/42.7 ng/mL (male/female) and an AUC_{0-24} of 50.7/137 ng•h/mL (male/female) on Day 30.

Similar findings were observed in a 3-month repeat dose study in rats (08GR493), but at lower doses. Nirogacestat was administered by oral gavage to Sprague-Dawley rats at doses of 0 (vehicle control), 5, 20, or 50 mg/kg/day (2.5, 10, or 25 mg/kg/dose 6 hours apart) BID for 3 months (91 consecutive days), followed by a 1-month recovery period. Due to mortality and adverse clinical signs in female rats at the 50-mg/kg/day dose level, dose administration was terminated for female rats at this dose level after 88 consecutive days. In female rats at 50 mg/kg/day, euthanized early treatment-related changes in WBC parameters and hemostatic parameters were observed. Morphological changes observed microscopically in RBCs consistent with increased RBC turnover with a concomitant regenerative response were observed. These hemostatic changes were reversible. Treatment-related clinical chemistry changes observed in female rats at 50 mg/kg/day euthanized early included increased ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin, which correlated to microscopic centrilobular hepatic necrosis. Increases in blood urea nitrogen and creatinine correlated with nephropathy.

Significant treatment-related microscopic findings included fibrinoid necrosis of pulmonary arteries, pulmonary phospholipidosis with an increased incidence and severity with an increase in dose. Increased incidence and severity of chronic progressive nephropathy was associated with increased kidney weights. Salivary gland necrosis was present in the parotid gland and submandibular gland in females. These effects were considered adverse but were reversible, except chronic progressive nephropathy in male and female rats. Treatment-related changes consistent with direct or indirect pharmacologic activity of nirogacestat included retention of the hypertrophic zone of the growth plate and deposition of woven bone (tibia, femur, and sternum), ovarian atrophy associated with decreased ovary weights, anestrus and asynchrony of the estrus cycle, centrilobular hepatocellular hypertrophy in female rats with associated increased liver weights, epidermal cysts, cardiomyopathy/myonecrosis/myofibrosis, and mammary acinar hyperplasia in female rats. Mammary acinar hyperplasia was attributed to the hormonal perturbations because of the ovarian atrophy. At the end of the recovery period, increased metaphyseal bone and epidermal cysts in male and female rats, cardiomyopathy in male rats, and ovarian follicular cysts, disruption of the estrus cycle, decreased ovarian weights, increased liver weights, myonecrosis/myofibrosis, and hyperplasia of the mammary gland in female rats were present; additionally, increased heart weights in female rats at 50 mg/kg/day were observed. Treatment-related findings also included effects on the lymphoid and gastrointestinal organs consistent with GS inhibition. Decreased cellularity (depletion) was observed in the spleen; decreased thymus weights were observed due in part to decreased cellularity. Decreased cellularity was also observed in the inguinal lymph node, the mesenteric lymph node, and the GALT. A concomitant decrease in total peripheral blood lymphocyte count was observed, along with decreases in all T-cell subsets and decreased IgD expression on B cells, and increased NK cells. Hyperplasia of the small intestinal epithelium characterized by increased numbers of enterocytes/goblet cells from the

duodenum to the ileum with a decrease in incidence and severity in the distal segments of the intestinal tract was observed. Lymphoid and gastrointestinal changes were reversible at all dose levels, while a partial recovery in lymphocyte count, T-cell subsets, and NK cells was observed at the end of the recovery period.

Based on ovarian atrophy, alterations in the estrous cycle, and decreased cellularity in the GALT in female rats and mesenteric lymph nodes in male and female rats at 5 mg/kg/day, **a NOAEL was not identified**. Therefore, LOAEL for this study was 5 mg/kg/day and was associated with a C_{max} of 19.6/56.7 ng/mL (male/female) and AUC_{0-24} of 223/680 ng*h/mL (male/female) on Day 90.

Dog

In a 1-month dog study (06GR066), two 80 mg/kg/day dogs were euthanized in extremis on Days 10 and 11 due to gavage trauma. Clinical signs associated with nirogacestat included emesis and loose/liquid stools that were observed at ≥ 2 mg/kg/day with increased incidence at 80 mg/kg/day. Salivation and discolored feces/liquid stools were also seen at 80 mg/kg/day. Similar to the rat, many of the findings were related to GS inhibition. Treatment-related epithelial hyperplasia was observed in the intestinal tract in both sexes. Minimal to mild inflammation was observed in the liver and was considered by the applicant to likely be secondary to bacterial embolism of the liver from the disrupted intestinal mucosal barrier and through the hepatic portal vein. Increases in WBC counts, fibrinogen, ALT, AST, and globulin were associated with this inflammation. Treatment-related extramedullary hematopoiesis was observed in the spleen and was considered a response to blood loss from the intestinal hemorrhages associated with epithelial hyperplasia. Treatment-related decreases in B and T cells were observed in the peripheral blood. Concurrent treatment-related lymphoid depletion was noted in the spleen of male dogs. In the thymus, minimal to mild cortical thymic atrophy occurred in both sexes of all dose groups consistent with normal age-related thymic involution. However, there was a treatment-related increase in the incidence and/or severity of thymic atrophy in both sexes at 80 mg/kg/day.

Based on the intestinal mucosa hyperplasia, splenic lymphoid depletion, and cortical thymic atrophy noted at 80 mg/kg/day, 10 mg/kg/day was identified as the NOAEL. At 10 mg/kg/day, nirogacestat was associated with a C_{max} of 448 ng/mL and AUC_{0-24} of 1920 ng•h/mL on Day 30.

Similar toxicities were also observed in the 3-month toxicity study in dogs; however, ovary and testes were new target organs that were not present in the 1-month dog study.

In a 3-month study (08GR495), nirogacestat was administered by oral gavage to Beagle dogs (4 or 6/sex/dose) at doses of 0 (vehicle control) 2, 10, or 50 mg/kg/day (1, 5, or 25 mg/kg/dose) BID 6 hours apart for 3 months. A dose of 50 (25 BID) mg/kg/day was not tolerated and after 5 to 7 days of administration, dosing was suspended for 26 days, and the dose was lowered to 20 (10 BID) mg/kg/day for the remainder of the study. Two high-dose dogs and 1 mid-dose dog were euthanized early for humane reasons due to adverse clinical signs. Clinical signs observed before their euthanasia included decreased activity, watery/discolored stools, inappetence, weight loss, and overall poor condition. Emesis was noted in several male and female dogs at 10 mg/kg/day and all animals at 50/20 mg/kg/day. Several findings were considered secondary to treatment due to poor clinical condition and multisystemic inflammation in organs such as the intestines and liver. These findings included hepatic inflammation associated with necrosis and corresponded with elevations in liver enzymes. In addition, thymic atrophy, pancreatic acinar degeneration/fibrosis, and single cell necrosis of tubular epithelial cells of the kidney were also present. These changes were associated with alterations in clinical pathology parameters including leukocytosis, neutrophilia, increased fibrinogen, and monocytosis reflecting the ongoing inflammatory processes in the intestines and liver. Microscopic changes included minimal to moderate inflammation/necrosis and goblet cell hyperplasia in the intestinal tract (duodenum, jejunum, ileum, cecum and/or colon) in both sexes. Most of the clinical

pathology parameters and microscopic findings were absent in the recovery phase. Persistent findings in the recovery phase included duodenal inflammation/necrosis and colonic goblet cell hyperplasia of minimal severity, lymphocyte depletion in the spleen and lymph nodes, Sertoli cell degeneration in the testis, and oocyte mineralization in the ovaries. Treatment-related decreases in B cell numbers were observed and these reductions in B cells did not fully reverse during the 1-month recovery period.

Based on oocyte mineralization noted at the lowest dose of 2 mg/kg/day, **a NOAEL was not identified.** Therefore, the LOAEL for this study was 2 mg/kg/day and was associated with a C_{max} of 47.3/40.9 ng/mL (male/female) and AUC_{0-24} of 494/467 ng•h/mL (male/female) on Day 91.

Mouse

A 1-month repeat dose study was conducted using CByB6F1 hybrid (TgRasH2 non-transgenic littermates) mice (20174161) to set doses for the 6-month definitive TgRasH2 carcinogenicity study. Based on the results of a 5-day dose ranging finding (DRF) phase, the 1-month phase was initiated at daily dose levels of 0, 20, 100, and 300 mg/kg/day (10, 50, and 150 mg/kg/dose BID). Nirogacestat was not tolerated at 300 mg/kg/day, resulting in an early death of one female mouse, and due to severity of clinical signs (dehydration, hunched posture, ungroomed fur) in both males and females, dosing for the 300 mg/kg/day group was suspended from Days 9 through 13 and reinitiated on Day 14 at a lower dose (200 mg/kg/day). There were no nirogacestat-related changes in food consumption, body weights, or clinical chemistry parameters compared to vehicle controls. At ≥ 100 mg/kg/day in males and females, increases in neutrophils, monocytes, eosinophils, and basophils were observed.

There were no macroscopic findings at necropsy. A dose-dependent decrease in thymus weight, decreased epididymis weights, decreased ovarian weights and increased liver weights were observed. Microscopic findings were observed at ≥ 100 mg/kg/day in the small intestine (duodenum, jejunum, and ileum), liver, femoral physis, sternal cartilage, and thymus. In males only, there were changes in the mandibular salivary gland, and testes. In females only, there were changes in the ovary and uterus. Given the magnitude of severity, the changes in ovarian cellularity were considered adverse.

Based on these results, particularly the adversity of ovarian histologic changes, the MTD for the 28-day phase was 100 mg/kg/day and the NOAEL was 20 mg/kg/day.

2.5.4.3. Genotoxicity

The genotoxicity of nirogacestat was adequately tested in a battery of genotoxicity studies in accordance with ICH S2(R1) guidance. Nirogacestat was assessed *in vitro* in the bacterial mutagenicity assay (06GR106) using *Salmonella typhimurium* strains TA1535, TA1537, TA100 and *E.coli* strain WP2uvrA pkM101, the *in vitro* cytogenetic (human lymphocyte) assay (06GR107), and *in vivo* in a rat micronucleus study (01214020). The *in vitro* tests were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity or insolubility, while *in vivo* nirogacestat was dosed up to the limit dose of 2000 mg/kg/day. Nirogacestat was negative in both *in vitro* assays, as well as the *in vivo* micronucleus study.

Exposure was not measured in the *in vivo* study, however sufficient distribution to bone marrow was demonstrated in the whole-body autoradiography (WBA) study in the male rat following a single oral dose of 20 mg/kg.

An enhanced Ames test was conducted to evaluate the impurity ASYM-136911 for its ability to induce reverse mutations at the histidine locus in four strains of Salmonella typhimurium (TA98, TA100, TA1535 and TA1537). The reliability of the negative result of this study is questionable due to presence of high levels of DMSO. A second and third enhanced Ames test using a preincubation protocol and a

plate incorporation method were conducted using acceptable levels of DMSO. The results indicated that ASYM-136911 was negative in the enhanced Ames test for N-nitrosamines.

2.5.4.4. Carcinogenicity

The carcinogenicity of nirogacestat was assessed in a 6-month repeat-dose GLP study in Tg rasH2 mice. Nirogacestat was administered orally BID (approximately 10 hours apart) for a minimum of 26 weeks to CByB6F1/Tg rasH2 hemizygous mice. Survival, clinical signs, body weights, body weight gains, food consumption, toxicokinetic parameters, macroscopic necropsy findings, and microscopic examinations were evaluated.

No effects on survival or significant increase in neoplasms were observed at 10 or 30 mg/kg/day. At 100 mg/kg/day, administration of nirogacestat resulted in a higher incidence of early deaths in male and female mice with a statistically significant dose-related trend for increased mortality in female mice and increased incidence of whole body hemangiosarcoma in male and female mice. The applicant states that hemangiosarcoma (particularly the spleen) is a common spontaneous neoplasm in TgRasH2 mice, being reported up to 16% in untreated control male mice and up to 17% in untreated control female mice in the published literature, and up to 16% in each sex in the testing facility's historical control database. While there is no published historical control information for hemangiosarcoma of any tissue in TgRasH2 mice, the testing facility's historical control for hemangiosarcomas in any tissue reports an incidence up to 15% in control male mice and up to 20% in control female mice. In this study, the incidence of hemangiosarcoma of any tissue in male mice was highest at 100 mg/kg/day (32%, incidence 8/25), which exceeded the testing facility's historical control range, while the incidence (16%) in female mice was below the historical control range.

The NOAEL for survival and for increased neoplasms is considered to be 30 mg/kg/day.

A carcinogenicity study was not conducted in the rat.

2.5.4.5. Reproductive and developmental toxicity

The developmental and reproductive toxicology assessment of nirogacestat consisted of two separate fertility studies in male and female rats and a preliminary embryo-foetal toxicity study in pregnant rats. The first fertility study was conducted by simultaneous treatment of male and female rats before mating. The second fertility study was conducted by treating male rats with nirogacestat then mating with untreated female rats, along with treated female rats mated with untreated known breeding male rats.

In the first rat fertility study (01214013), nirogacestat was administered to male and female rats via oral gavage QD at dose levels of 0 (vehicle), 5, 20, or 80 mg/kg/day. Male rats were treated for 28 days prior to mating with female rats that were treated with nirogacestat for 14 days.

Based on clinical observations and adverse effects on body weight and food consumption that led to mortality and moribundity for male and female rats at 80 mg/kg/day, 20 mg/kg/day was considered to be the NOAEL for male and female systemic toxicity of nirogacestat. Based on adverse effects on sperm parameters for males and reproductive performance for male and female rats at all dosage levels, resulting in no gravid female rats at 20 and 80 mg/kg/day, as well as lower reproductive organ weights at 20 and 80 mg/kg/day, and lower numbers of corpora lutea and implantation sites at 5 mg/kg/day, the NOAEL for male and female reproductive toxicity could not be determined. There was no effect on intrauterine survival at 5 mg/kg/day (the only test article-treated group with gravid female rats); therefore, the NOAEL for embryonic toxicity was considered to be 5 mg/kg/day.

In the second fertility study (01214026), rats were dosed via oral gavage at dose levels of 0 (vehicle) 2.5, 10, or 20 mg/kg BID approximately 6 hours apart. Male rats were dosed for 28 days before mating with treatment-naive female rats and continuing through 1 day before euthanasia. Female rats were dosed for 14 days before mating with treatment-naive known breeding male rats and continued to be dosed through Gestation Day 7. On Gestation Day 13, a laparohysterectomy was conducted for macroscopic examination, foetal collection, and tissue collection.

Based on effects on sperm parameters at ≥ 5 mg/kg/day, decreased epididymal weights (correlating microscopically to minimal cellular debris), and markedly reduced pregnancy and fertility indices for male rats at ≥ 20 mg/kg/day, as well as impairment of implantation at 5 and 20 mg/kg/day, the NOAEL for male rat reproductive toxicity could not be determined. For female rats, lower ovary/oviduct weights correlating microscopically to ovarian atrophy (accompanied by hypertrophy of the vaginal mucosa with mucification) and markedly reduced pregnancy and fertility were noted at 20 and 40 mg/kg/day; therefore, a dose level of 5 mg/kg/day was the NOAEL for female rat reproductive toxicity. Based on higher post-implantation loss and a lower mean number of viable embryos at 20 mg/kg/day, a dose level of 5 mg/kg/day was the NOAEL for early embryonic toxicity.

The embryo-foetal toxicity of nirogacestat was assessed in pregnant rats administered 0 (vehicle), or nirogacestat at 5, 20, 50, or 150 mg/kg/day (study 01214011). Rats were dosed by oral gavage QD during Gestation Days 6 through 17.

Adverse clinical observations and body weight and food consumption were noted at 150 mg/kg/day; the severity of the effects resulted in moribundity of 5 of 8 females. Complete or nearly complete resorptions of litters were noted at 50 and 150 mg/kg/day, and a higher mean litter proportion of post-implantation loss with correspondingly lower mean number of viable foetuses and lower mean foetal body weights were noted at 20 mg/kg/day. The NOAEL for embryo-foetal toxicity is considered to be 5 mg/kg/day in this study.

2.5.4.6. Toxicokinetic data

Toxicokinetic data was obtained in the repeat-dose studies performed in the rat, dog and the mouse as well as in the carcinogenicity study performed in the mouse and in the preliminary embryo-foetal development study in pregnant rats. Safety margins were calculated by dividing the total AUC_{0-24} from the respective toxicology study at the NOAEL, or LOAEL with the human total steady state AUC_{0-24} (12860 ng•hr/mL). Total exposures were used given that nirogacestat is highly protein bound in mouse, rat, dog and human plasma with fraction unbound of 0.2%, 0.2%, 0.2%, and 0.4%, respectively. It should be noted that toxicokinetics were not performed in the fertility and embryonic development studies in the rat and the TK results from the 1-month or the 3-month repeat-dose toxicity studies were used for exposure margin calculations.

Table 6: Calculated Safety Margins from Definitive Repeat Dose Toxicity Studies

Study Type (Study Number)	Dose[a] (mg/kg/day)	AUC(0-24)[b] (ng•h/mL)	Cmax[b] (ng/mL)	Exposure Margins[c,*]
Repeat Dose Studies				
1-month study in mice (20174161)	20	42.9	30.1	**0.003**
1-month study in rats (06GR067)	5	50.7 (M) 137 (F)	19.3 (M) 42.7 (F)	**0.004** **0.01**
3-month study in rats (08GR493)	5	223 (M) 680 (F)	19.6 (M) 56.7 (F)	**0.02** **0.05**
1-month study in dogs (06GR066)	10	1920	448	**0.1**
3-month study in dogs (08GR495)	2	481	44.1	**0.04**
Carcinogenicity Study				
6-month study in TgRasH2 mice (20174162)	100[d]	2200	716	**0.2**
Reproductive Toxicity Studies				
Fertility and early embryonic development in rats (01214013)	5[e]	50.7 (M) 137 (F)	19.3 (M) 42.7 (F)	**0.004** **0.01**
Fertility and early embryonic development in rats (01214026)	5[f]	223 (M) 680 (F)	19.6 (M) 56.7 (F)	**0.02** **0.05**
Embryo-fetal development in pregnant rats (01214011)	5	1400	202	**0.1**

Abbreviations: AUC: area under the concertation time curve; Cmax: maximum concentration; F: Female; M: Male

[a] Dose is either the NOAEL or LOAEL for the study.

[b] Total exposure derived from the end of the study.

[c] Margins were calculated by dividing the total animal AUC0-24 by the total human steady state AUC0-24 (12860 ng•hr/mL) after administration of nirogacestat at 150 mg BID.

[d] The AUC exposure value is derived from 0-10 hours. Converting this to average concentration is 220 ng/mL and dividing by the human average exposure of 536 ng/mL results in a safety margin of 0.4.

[e] TKs was not assessed in this study; therefore, the exposure from the 1-month rat study was used as nirogacestat was dosed QD in this study and the 1-month study.

[f] TKs was not assessed in this study; therefore, the exposure data from the 3-month repeat dose toxicity study in rats was used because nirogacestat was administered BID in this study and in the 3-month study.

2.5.4.7. Local tolerance

Given the oral route of delivery, the local tolerance after oral dosing was assessed in the repeat-dose toxicology studies.

Emesis, loose stools, inflammation in the GI-tract accompanied by microscopical changes were observed in the repeat-dose toxicity studies in the rat and the dog. GI effects, such as diarrhoea and nausea, were also observed in clinical trials.

2.5.4.8. Other toxicity studies

A GLP 28-day repeat-dose toxicity study was conducted in Sprague Dawley rats to qualify impurities at 1.6% for a nirogacestat dose of 300 mg.

There were no treatment-related adverse effects in clinical signs, body weights, clinical pathology, or after macro- and microscopic examinations. Slight decreases in adrenal weights that were associated with vacuolation in 3 of 5 male rats was observed. These minor changes are not considered adverse and the NOAEL for each of these impurities are 0.5 mg/kg/day.

2.5.5. Ecotoxicity/environmental risk assessment

The Applicant provided a Log K_{ow} study in accordance with OECD 123 showing Log Dow values at pH 5, 7 and 9 of 2.4, 5.2 and 5.7 respectively, indicating potential PBT-properties. Nirogacestat was found not to be readily biodegradable in OECD 301B.

Table 7: Summary of main study results

Substance (INN/Invented Name): Nirogacestat					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow} Study No. 20327710, GLP-compliant	OECD 123	Log Dow values at pH 5, 7 and 9 were 2.4, 5.2 and 5.7			Potential PBT: Y
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF	L/kg_{ww}			B/vB/not B
Persistence	DT50 Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C or ready biodegradability	D			P/vP/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is considered to be not PBT, nor vPvB The compound is considered to be vPvB The compound is considered to be PBT The compound is considered to be PBT and vPvB				
Phase I					
Calculation	**Value**			**Unit**	**Conclusion**
PEC_{sw}, refined	0.00207			µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)					N
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = type (e.g. sandy loam / clay / loamy sand) Sediment 2 = type	OECD 308	$DT_{50, water}$ = X / X d $DT_{50, sediment}$ = X / X d $DT_{50, whole\ system}$ = X / X d shifting to sediment = X% CO_2 = X% NER = X% Transformation products >10% = Y/N, TP1 = %, DT50 M1: d			DT50s at X°C 1 / 2 at day X at test end at test end
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC / EC_{10}		µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC / EC_{10}		µg/L	applicable endpoint(s)
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC / EC_{10}		µg/L	applicable endpoint(s)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC / EC_{10}		µg/L	Respiration

2.5.6. Discussion on non-clinical aspects

Pharmacology

Nirogacestat was shown to be a reversible, and noncompetitive inhibitor of GS that blocks the proteolytic activation of Notch receptors by preventing the cleavage of NICD. The potency of nirogacestat is evidenced from cell-free biochemical inhibition of GS-mediated production of Aβ (free IC50 = 6.2 nM) as well as cellular assays that demonstrated free IC50 against NICD production ranging from 0.34 to 1.8 nM. A clinical dose-ranging study when corrected for a human serum free fraction of 0.004, demonstrated free Cmax and free Cmin values of 10.2 nM and 2.2 nM, respectively, at steady state after 150 mg BID dosing.

The activity of nirogacestat in reducing NICD was associated with antitumour activity in a variety of Notch-driven tumour models. Results of clinical investigations in participants with solid tumours demonstrated evidence of therapeutic activity in participants with desmoid tumours (DT), a disease that is historically associated with dysregulation of the canonical Wnt signaling pathway. Experiments demonstrated the potential for a mechanism of action in which nirogacestat could inhibit Notch signaling that is downstream of the activated Wnt signaling that is typically expected in DT. While this mechanism is not well defined by non-clinical evaluations to date, some evidence of nirogacestat-mediated antitumour efficacy in DT has been established using patient-derived culture models.

Nirogacestat was evaluated for interaction with a number of other proteases, receptors, ion channels and kinases. Activity in a broad panel of common receptors was > 1 μM in all assays. By comparison, the geometric mean human serum free Cmax observed at steady-state was 4.98 ng/mL (10.2 nM) after oral administration of 150 mg BID. Thus, nirogacestat is selective for GS relative to other proteases, receptors, ion channels, and kinases tested.

Safety pharmacology studies did not identify any safety concerns related to cardiovascular, neurological or respiratory function. The hERG study showed an IC50 of 1.0 μM, which is 98-fold higher than the free human Cmax of 10.2 nM. In the dog cardiovascular study, Cmax was only determined for the mid-dose (80 mg/kg): 518 ng/ml. This represents a free fraction of 1.04 ng/ml. For comparison the free human Cmax is 2.03 ng/ml. For the 500 mg/kg dose only exposure at 6h was determined. The 6h exposure in this group was about 2-fold above that of the 80 mg/kg group. It can be concluded that the exposure in the 500 mg/kg was roughly comparable to clinical exposure. Thus, the dog study did not reach suprapharmacological exposure. This should be taken into account in the overall assessment of potential for QT prolongation.

Pharmacokinetics

Analysis methods for quantification of nirogacestat used in the GLP safety studies were adequately validated.

Nirogacestat demonstrated moderate systemic clearance in rats and dogs, with t½ values of 11.7 and 12.4 hours, respectively. Systemic exposure of nirogacestat increased with increasing dose in rats and dogs in the 3-month toxicity studies that was generally dose proportional in rats and slightly > dose proportional in dogs. Estimates of apparent volume of distribution at steady state for nirogacestat were > total body water in rats and dogs, suggesting that nirogacestat readily distributes to tissues in these species.

Nirogacestat showed high protein binding with average unbound free-fraction in serum of approximately 0.2% for mice, rats, and dogs at nominal concentrations of 5 μM, and 0.4% in humans. *In vitro* blood-to-plasma partitioning demonstrated preferential distribution into blood over plasma in rats, dogs, and humans. A whole-body autoradiography study showed that radioactivity derived from [^{14}C] nirogacestat is widely distributed throughout the body. A CNS distribution study showed that the

brain-to-plasma AUC ratio was approximately 6-fold higher in mdr1a/1b(-/-) knockout mice compared with wild type, suggesting that P-gp efflux may serve to prevent accumulation of nirogacestat in the brain.

In vivo mass-balance studies in rat and dog both identified P1 as the most abundant major metabolite. In rat P1 represented 74.9% of total plasma radioactivity and in dog 10.1%. In humans, P1 represented 44% of total plasma radioactivity. P1 was unretained on the high-performance liquid chromatography system, suggesting it is a low molecular weight, polar compound and forms through further metabolism of M283 (PF-0315273), likely through loss of the difluorotetrahydronapthalene group. Metabolite P1 was not identified. The absence of identification of component(s) in the P1 peak raises concerns on the presence of one or more metabolites which have not been adequately qualified in the non-clinical toxicity studies. However, the fact that extensive toxicity was observed at exposures at or below clinical exposure makes it unlikely that further elucidation of metabolite structures and possible nonclinical qualification studies would add to the safety assessment.

In radiolabeled mass-balance studies in rat and dog, the majority of radioactivity was recovered after 168 hours in feces (> 70%), with radioactivity in urine accounting for < 6% of administered dose.

Toxicology

Single dose toxicity studies were not conducted with nirogacestat. This is in accordance with current guidance where separate single-dose studies are not recommended since information on the acute toxicity is available from other toxicity studies.

In the non-clinical toxicology studies, nirogacestat was administered to mice, rats, and dogs in repeat-dose toxicology studies up to 3 months in duration.

In the 1-month mouse study, target organs in males and females included the small intestine (duodenum, jejunum, and ileum), liver, femoral physis, sternal cartilage, thymus, and sex organs in both male and female mice. The NOAEL was 5 mg/kg/day.

In the 3-month rat study, ovarian atrophy, alterations in the estrous cycle, decreased cellularity in GALT in females, and decreased cellularity of mesenteric lymph nodes in males and females at 5 mg/kg/day was observed. A NOAEL was not identified in this 3-month oral toxicity study in rats due to these effects. In addition, all dose levels showed chronic progressive nephropathy, pulmonary phospholipidosis, and salivary gland necrosis in a dose-dependent manner. The observed cardiomyopathy is a common spontaneous lesion in Sprague Dawley rats and was not considered related to nirogacestat as this was not observed in dogs or mice.

In the dog studies, treatment-related effects were present within the intestines, spleen, gall bladder, liver, kidney, testes, and ovary. The intestinal and liver findings were associated with generalized inflammation and associated clinical pathology changes in most of these animals. In the recovery dogs, the intestinal, testicular, and ovarian findings were persistent but at lower severity suggesting evidence of reversibility. Due to oocyte mineralization at the lowest dose in the 3-month dog study, a NOAEL was not identified. The lowest dose in the dog was 2 mg/kg/day (human equivalent dose of 70 mg/day).

Many of the toxicologic effects in the repeat-dose toxicology studies with nirogacestat in mice, rats, and dogs were ascribed to the intended pharmacological mode of action, i.e. inhibition of GS and decreased Notch signaling. Notch plays a key role in cellular differentiation in multiple tissues during early development and in adult tissues. The intestinal changes in rats and dogs, including goblet cell hyperplasia are consistent with the role of Notch within the intestine and these effects has been observed with other GS inhibitors. In addition, lymphoid depletion in multiple lymphoid tissues along with decreased WBC populations are associated with Notch inhibition based on the importance of this

pathway in cellular differentiation of lymphoid cells. Notch inhibition in endothelial cells also produces profound effects on angiogenesis, which can explain the growth plate changes observed in rats treated with nirogacestat. Similar to VEGF inhibitors, nirogacestat induced growth plate changes in the femorotibial joints of rats, which is known to occur by inhibition of angiogenesis, in both the 1- and 3-month repeat-dose toxicity studies. These growth plate changes in rats were also seen with another GS inhibitor.

A justification for not performing chronic repeat-dose toxicity studies (6-month) was provided as the exposures reported from the 3-month studies in rats and dogs demonstrated very low exposures in both species compared to the intended clinical exposure. Considering the toxicological findings in multiple organs across all tested species at no exposure margins to the clinical exposure further non-clinical toxicity studies of longer duration is not considered to add to the clinical safety assessment. A comprehensive discussion was provided on the toxicity profile of nirogacestat with implications to clinical use with special emphasis on those effects which are hard or impossible to see and measure in humans and were not reversible in animals, for example mineralisation of oocytes, degeneration of Sertoli cells, increased bone deposition, kidney degeneration, effect on lymphoid system. Monitoring of Ovarian Toxicity is described in section 4.6 of the SmPC and male fertility will be monitored via reporting of adverse effects. Clinical routine care is considered sufficient for monitoring effects on the kidney. The non-clinical toxicity findings are adequately described in section 5.3 of the SmPC.

Reproductive and developmental toxicity

Nirogacestat produced embryo toxicity when administered to pregnant rats, and impaired fertility in both male and female rat which correlated with ovarian atrophy, reduced testes weights, and decreased sperm motility and effects on sperm morphology. In the embryo foetal developmental toxicity study in rats, nirogacestat induced significant embryo loss, early resorptions and decreased fetal weights in surviving embryos. These effects occurred at 20 mg/kg/day resulting in systemic exposures below (approximately 0.45-fold) human exposures after administration of nirogacestat at 150 mg BID.

These observed developmental and reproductive toxicities of nirogacestat were also ascribed to GS inhibition. The effects on embryonic development were anticipated based on studies in transgenic mice demonstrating that the loss of Notch signaling is embryonically lethal. The changes in reproductive organs in nirogacestat treated male and female rats were also anticipated based on the known role of the Notch pathway in the ovary and testes. The ovarian changes in rats and dogs, along with altered estrous cyclicity, are likely due to inhibition of Notch signalling in the ovaries, as this signalling pathway is critical in the regulation of mammalian folliculogenesis. In the testes, the Notch signalling is critical for spermatogenesis.

Further embryo-foetal toxicity studies in rats and rabbits as well as a pre- and post-natal development (PPND)-study in the rat is not warranted. It can be concluded that the observed effects in the preliminary embryo-foetal toxicity study in the rat align with the known requirement of Notch for embryonic development. These effects occurred without exposure margins to human exposure and the available data is sufficient for concluding on human risk and the need for risk mitigation measures.

In accordance with ICH S11 guideline, juvenile animal studies were not conducted based on the weight of evidence approach. PDCO concurred that no juvenile toxicology studies were needed as reflected in the agreed PIP (P/0032/2022).

Nirogacestat was negative in the standard battery of *in vitro* and *in vivo* genetic toxicity studies with and without metabolic activation.

Carcinogenicity

An increased incidence of haemangiosarcomas was observed in Tg mice after 6-months of treatment. Hemangiosarcoma is a common background tumour in the spleen of TgRasH2 mice, and in this study the increased incidence in other tissues was significant in male rats after oral dosing of 100 mg/kg/day. Nirogacestat was not mutagenic or clastogenic suggesting the increase in hemangiosarcomas in mice occurs through a nongenotoxic mechanism. A rat 2-year carcinogenicity study was not conducted given that non-melanoma skin cancers have been reported in humans treated with nirogacestat and the fact that human systemic exposures exceed those that can be achieved in animal toxicology studies due to low tolerance in the rat and excess of toxicological findings. The observed non-melanoma skin cancers were not believed to be due to nirogacestat directly causing new skin cancers, but rather to it changing skin homeostasis to permit the growth of skin cancers emerging due to known causes. It is accepted not to perform a 2-year rat carcinogenicity study since the results of such study would not add to the clinical safety assessment. However, inhibition of GS can lead to several pharmacodynamic effects interfering with cellular regulation and differentiation in multiple tissues. In order to complement the cancer risk assessment, a weight of evidence based discussion according to ICH S1B Part II Addendum and based on all existing data (preclinical, clinical and existing literature) was conducted. Information on the dual role of Notch pathway is included in SmPC section 5.3: "Notch signalling has been reported to have both an oncogenic and tumour suppressor function". Nirogacestat was non-genotoxic in standard tests.

The exposure margins based on NOAEL/LOAEL observed in all repeat-dose studies performed in the rat, dog and mouse, reproductive toxicity studies performed in the rat, as well as the carcinogenicity study performed in the TgRasH2 mouse are considerable below 1, indicating a lack of safety margins to the adverse effects observed in the non-clinical studies. The applicant concludes that this lack of safety margins demonstrate that humans can tolerate much higher systemic levels compared to the toxicology species. The precise mechanism for this difference is unknown and surprising given that the GS pathway is highly conserved. Therefore, the applicant proposed that safety endpoints in humans rather than additional studies in animals are necessary to assess the actual human adverse event profile for nirogacestat. It is agreed that additional studies in animals are not warranted as significant findings relevant for risk assessment and risk mitigation in humans already is identified. To note, the finding of ovarian toxicity as observed in the rat and dog studies is also confirmed in humans. It is highly likely that also effects on testes and spermatogenesis would be affected in male humans at the clinical dose. These effects will affect both female and male fertility and embryotoxicity.

In male rats effects on sperm motility and morphology leading to embryotoxicity was observed. This finding will have implications on the need for use of contraceptives for treated men and their female partners of childbearing potential.

Nitrosamine impurities

During the procedure, nitrosamines impurities (ASYM-136911 and ASYM-136912) above the acceptable intake as per M3 guidelines have been detected in the finished medicinal product. Three enhanced Ames tests were provided indicating that these impurities are not mutagenic.

Considering the clinical context (unmet medical need for a severe condition with a beneficial clinical profile), the clinical judgement that long term treatment is unlikely, that both impurities are considered to have relatively low mutagenic potential, a product specific acceptable intake limit of 20 µg/day (corresponding to 66,667 ppb/day based on a maximum daily dose of 300 mg) for the sum of ASYM-136911 and ASYM-136912 was proposed.

The NcWP has been consulted on the product specific limit proposed by the applicant and concluded that the theoretical excess cancer risk (TECR) for total NDSRI (ASYM 136911 + ASYM 136912) levels is

near or below the acceptable TECR of 1:100,000 for 7 years of treatment duration or less. The average treatment in NIR-DT-301 was 33.6 months, (2.8. years) with 97% of patients discontinuing nirogacestat before reaching 5 years of treatment

The findings in non-clinical studies are adequately described in section 5.3 of the SmPC.

ERA

$PEC_{surfacewater}$ for nirogacestat is below the action limit of 0.01 µg/L. The Phase I $PEC_{surfacewater}$ was calculated to 0.00207 µg/L using a refined Fpen of 0.0000138, taking into account the prevalence of desmoid tumours, and the maximum daily dose of 300 mg. This is accepted, and a Phase II assessment is not required.

Nirogacestat is a potential PBT substance as log K_{ow} does exceed 4.5. A PBT-assessment is therefore required, and the Applicant indicated that studies are ongoing/planned and the results of all of the studies will be provided once available by Q4 2025. The study plan presented by the Applicant appears sufficient and acceptable. The conclusion regarding the potential impact of nirogacestat on the environment and the risk mitigation strategy can only be made after the assessment of the study results once they are submitted.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of nirogacestat to the environment.

The applicant commits to perform the following studies as follow-up measures:

- to submit an updated ERA including all final study reports by Q4 2025 (**Recommendation**).

2.5.7. Conclusion on the non-clinical aspects

The pharmacology and pharmacokinetics non-clinical programs are considered acceptable and no issues requiring further evaluation have been identified.

A sufficient toxicology program in mice, rats and dogs have identified several target organs such as the kidney, liver, GI-tract, hematopoietic/lymphoid/immune system, bone growth plates, ovaries, testes, negative effects on embryonic development as well as male and female fertility. Many of these effects can be ascribed to the intended pharmacological mechanism of nirogacestat and were observed at exposure levels below the intended clinical exposure. Additional non-clinical toxicity studies are not considered required to add to the clinical safety assessment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Pertinent to the current application is the pivotal study NIR-DT-301 (DeFi) with studies A8641014 and 14-C-0007 acting as supportive (each contributing with 2 and 17 patients, respectively, who were administered the recommended dose of nirogacestat 150 mg BID).

Study	Objectives	Population	Design	Dose Level	N	Data Cut
Primary Analysis Population						
NIR-DT-301 (Phase 3) (DB Phase) Completed	To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT/AF.	Participants ≥ 18 years with histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.	R, DB, PC	Nirogacestat 150 mg BID or Placebo Continuous 28-day cycles	142[a] 70 nirogacestat /72 placebo	07Apr 2022 (primary analysis)
Integrated DT Efficacy Population						
NIR-DT-301 (Phase 3) (DB Phase) Completed	To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT/AF.	Participants ≥ 18 years with histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.	R, DB, PC	Nirogacestat 150 mg BID or Placebo Continuous 28-day cycles	142[a] 70 nirogacestat /72 placebo	30Jun2022 (final database lock)
14-C-0007 (Phase 2) Ongoing	To determine the response rate (CR + PR) of nirogacestat in participants with DT/AF.	Participants ≥ 18 years with histologically confirmed DT not amenable to curative resection or definitive radiation therapy that has progressed after receiving at least one line of standard treatment; adequate organ function.	OL	Nirogacestat 150 mg BID Continuous 21-day cycles	17[b] 17 nirogacestat	02Dec 2022 (interim efficacy data cut)
A8641014 (Phase 1) Completed	To determine the MTD and to define the RP2D of nirogacestat when administered twice daily for 21 days alone in participants with advanced malignancies.	Participants with advanced solid tumor malignancies that were resistant to standard therapy or for which no standard therapy was available; or patients with acute T-ALL/LBL that were refractory or resistant to current treatment options or for which no standard therapy was available. Men and women, with an age of ≥ 16 years and a life expectancy >2 months, an ECOG performance status of ≤1 for patients with advanced solid tumor and of ≤2 for patients with refractory or	OL	Nirogacestat 150 mg BID Continuous 21-day cycles	2[c] 2 nirogacestat	22Nov 2016 (final data cut)

Study	Objectives	Population	Design	Dose Level	N	Data Cut
		relapsed T-ALL/LBL, were enrolled.				
OLE Population						
NIR-DT-301 (OL Extension Phase) Ongoing	To determine the efficacy (as defined by PFS) of nirogacestat in adult participants with progressing DT/AF.	Participants who experienced radiographic disease progression during the DB phase or were ongoing at the time of the primary analysis of the DB phase.	OL	Nirogacestat 150 mg BID Continuous 28-day cycles	84 Nirogacestat	24Oct2022 (interim data cut)

Abbreviations: AF: aggressive fibromatosis; BID: twice daily; CR: complete response; DB: double-blind; DT: desmoid tumors; ECOG: Eastern Cooperative Oncology Group; MTD: maximum tolerated dose; N: number of participants; OL: open-label; PC: placebo-controlled-; PFS: progression-free survival; PR: partial response; R: randomized; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended Phase 2 dose; SCE: Summary of Clinical Efficacy; T-ALL/LBL: T-cell lymphoblastic leukemia/lymphoblastic lymphoma.

[a] A total of 70 participants were randomized to nirogacestat (69 participants took at least 1 dose) and 72 were randomized to placebo.

[b] A total of 17 participants were treated and analyzed as part of the Safety Population but only 16 participants were evaluable for response.

[c] A total of 64 adult participants with solid tumors (including 9 participants with DT) and 8 participants with T-ALL/LBL were enrolled at dose levels ranging from 20 mg to 330 mg BID; however, only data from the 2 participants with DT who received a dose of nirogacestat at the 150 mg BID dose level were included in this SCE.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

Bioanalysis

Validated LC-MS/MS methods were developed for the analysis of nirogacestat concentrations in serum and urine.

Pharmacokinetic data analysis

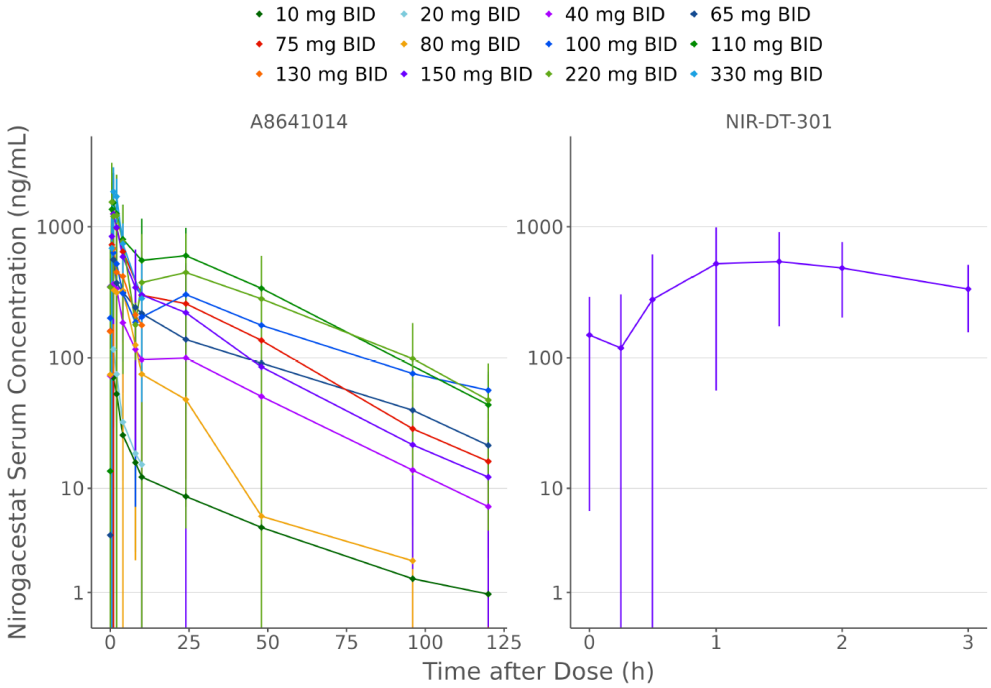
Standard non-compartmental analysis was performed in the early studies where rich sampling was applied, and population PK (popPK) was used for all PK data, including analysis of the target population. In addition, physiologically based pharmacokinetic (PBPK) modelling was applied.

Population pharmacokinetic analysis

The objective of the PopPK analysis was to develop a PopPK model to characterize the PK of nirogacestat in healthy subjects and patients with DT.

The pharmacokinetic data used in the population analysis included 5473 PK samples from 335 subjects from studies A8641001, A8641002, A8641008, A8641014, NIR-DT-101, NIR-DT-102, NIR-DT-103 and NIR-DT-301.

Figure 2 shows mean (± standard deviation (SD)) log-normal nirogacestat serum concentrations over time across the patient studies.



Colored diamonds and lines: mean nirogacestat serum concentrations at evaluated doses; **Error bars:** standard deviation; data points with less than two observations were omitted; **BID:** twice per day

Figure 2 Mean (± SD) Nirogacestat Serum Concentrations vs. Time after Dose stratified by Dose – Patients

The PK analyses were carried out using NONMEM (Version 7.4,). Model development in NONMEM was carried out using the importance sampling (IMP) estimation method.

In the base model, distribution and elimination was described by a three-compartment disposition model with first-order elimination from the central compartment. The absorption was characterized by a lag-time, first-order absorption process.

Pre-specified primary covariates including the effect of patients relative to healthy volunteers on CL, the effect of bioanalytical lab on residual variability, and the effect of body weight on disposition and elimination were evaluated manually (and assessed by comparison of the objective function value [OFV] using the likelihood ratio test). Following this, exploratory covariates were evaluated which included sex, age, race, ECOG status, bilirubin, ASAT, ALAT, albumin, creatinine clearance, co-medications and formulation. In general, only the exploratory covariates which showed a significant trend in eta vs covariate plots were tested manually.

Parameter estimates of the final model are presented in Table 9: Cut-offs for the evaluation of interaction potential. All parameters were estimated with sufficient precision (i.e. relative standard error [RSE] of <50%). CL in T-ALL/LBL patients was estimated to be 48.4% (4.4 L/h) of the CL in healthy volunteers and DT patients (9.09 L/h). A body weight proportional increase was identified for Vp2. Weight on Vc and Vp1 were not supported. Although weight on CL was above the statistical threshold (ΔOFV of 6.63), the effect was inverse proportional and physiologically implausible (inconsistent with allometric theory, where CL scales to weight to the power of 0.75). Strong,

itraconazole-mediated CYP3A inhibition resulted in approximately 2-fold higher F and 4.7-fold lower CL (CL = 1.94 L/h) of nirogacestat. Weak CYP3A4 inhibitors and inducers, as well as other comedications which affect P-gp or gastric pH, did not appear to have an influence on nirogacestat PK. A negative relationship between CLcr and age on CL was observed during univariate analysis, which were physiologically implausible (i.e. decrease in renal function results in higher CL) and clinically not impactful.

Residual unexplained variability was described by a proportional error, with separate estimates for the Pfizer, Alta/Intertek, Intertek and Alliance (joint error model) bioanalytical labs and a joint error model for the patient studies A8641014 and NIR-DT-301. Overall, the residual unexplained variability (RUV) was larger in the patient studies compared to the healthy volunteer studies.

A prediction-corrected visual predictive check (pcVPC) of the final PopPK model stratified by study is shown in Figure 3.

Table 8: Parameter Estimates of the Final PopPK Model

Parameter	Descriptor	Estimated	Estimate	CI95
$F1$	Bioavailability	fixed	0.192	NA
k_a	Absorption Rate Constant (1/h)	estimated	0.876	(0.838 - 0.915)
CL	Clearance (L/h)	estimated	9.09	(8.65 - 9.54)
V_c	Central Volume of Distribution (L)	estimated	7.74	(6.40 - 9.35)
Q_1	Intercompartmental Clearance - Shallow Compartment (L/h)	fixed	5.16	NA
V_{p1}	Peripheral Volume of Distribution - Shallow Compartment (L)	estimated	11.5	(10.8 - 12.3)
Q_2	Intercompartmental Clearance - Deep Compartment (L/h)	fixed	5.64	NA
V_{p2}	Peripheral Volume of Distribution - Deep Compartment (L)	estimated	115	(110 - 121)
T_{lag}	Absorption Lag Time (h)	estimated	0.313	(0.287 - 0.341)
F_{rel}-Form	Bioavailability - PiB Formulation (logit)	estimated	-0.326	(-0.503 - -0.148)
k_a-301	Absorption Rate Constant - NIR-DT-301 (ratio)	estimated	0.433	(0.385 - 0.488)
T_{lag}-301	Absorption Lag Time - NIR-DT-301 (ratio)	estimated	0.604	(0.543 - 0.672)
T_{lag}-Form	Absorption Lag Time - PiB Formulation (ratio)	estimated	0.589	(0.460 - 0.753)
F_{rel}-Dose	Bioavailability - Dose <10 mg (logit)	estimated	-0.686	(-1.03 - -0.340)
CL_{rel}-other tumor	Clearance - Solid Tumor/T-ALL/LBL (ratio)	estimated	0.484	(0.430 - 0.544)
F_{rel}-ITZ	Bioavailability - Itraconazole Co-administration (ratio)	estimated	1.98	(1.90 - 2.06)
CL_{rel}-ITZ	Clearance - Itraconazole Co-administration (ratio)	estimated	0.213	(0.209 - 0.216)
ω^2_{F1}	$\omega^2_{Bioavailability}$	estimated	0.385	(0.305 - 0.465)
ω^2_{ka}	$\omega^2_{AbsorptionRateConstant}$	estimated	0.0169	(0.00533 - 0.0284)
ω^2_{CL}	$\omega^2_{Clearance}$	estimated	0.108	(0.0748 - 0.141)
ω^2_{Vc}	$\omega^2_{CentralVolumeofDistribution}$	estimated	0.878	(0.438 - 1.32)
ω^2_{Vp2}	$\omega^2_{PeripheralVolumeofDistribution-DeepCompartment}$	estimated	0.0909	(0.0645 - 0.117)
ω^2_{Tlag}	$\omega^2_{LagTime}$	estimated	0.0739	(0.0419 - 0.106)
ω^2_{CL-ITZ}	$\omega^2_{ItraconazoleInhibition}$	estimated	0.143	(0.0583 - 0.227)
$\sigma^2_{Prop-BALAB1}$	$\sigma^2_{ProportionalError-Alta/Intertek}$	estimated	0.0316	(0.0282 - 0.0350)
$\sigma^2_{Prop-1014/301}$	$\sigma^2_{ProportionalError-Patients}$	estimated	0.222	(0.204 - 0.240)
$\sigma^2_{Prop-BALAB0}$	$\sigma^2_{ProportionalError-Pfizer}$	estimated	0.058	(0.0501 - 0.0659)
$\sigma^2_{Prop-BALAB2/3}$	$\sigma^2_{ProportionalError-Intertek/Alliance}$	estimated	0.0178	(0.0164 - 0.0191)

CI95: 95% Confidence interval; **NA**: not applicable for fixed parameters; ω^2_X: variance of inter-individual variability of parameter X; **Vp1:** Peripheral volume of distribution - shallow compartment; **Vp2:** Peripheral volume of distribution - deep compartment

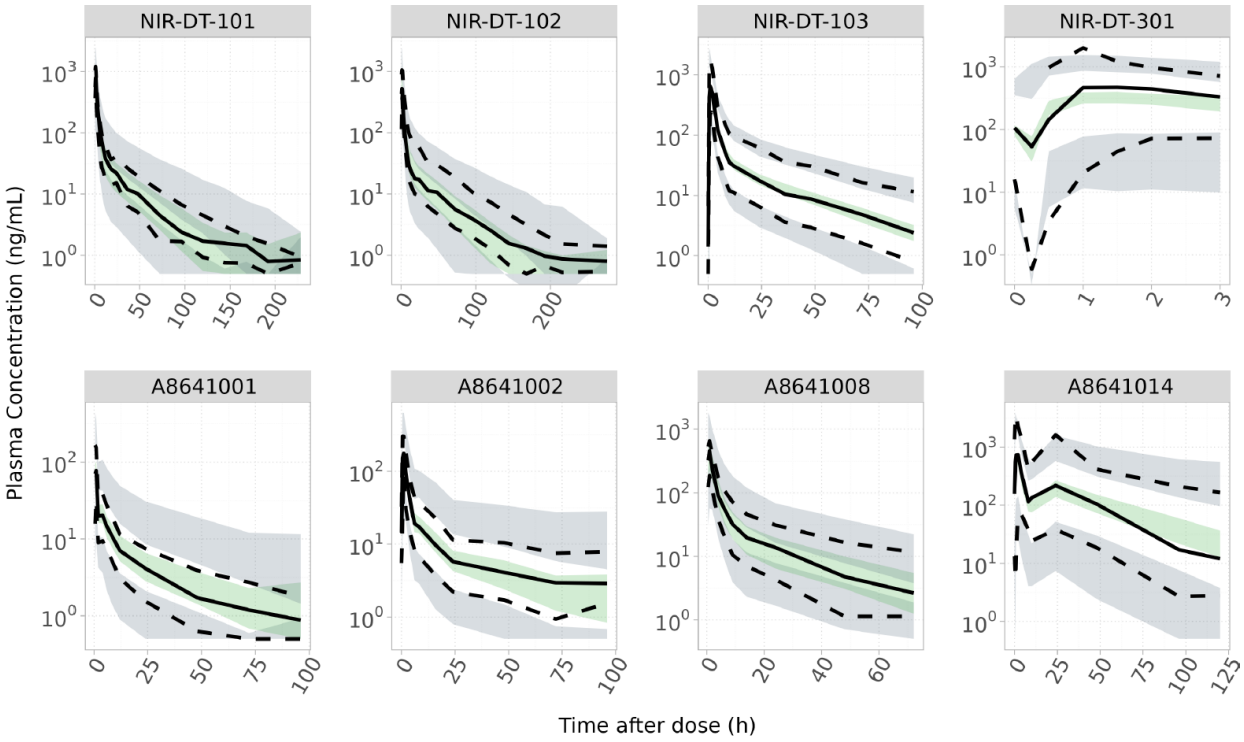


Figure 3: Prediction-corrected Visual Predictive Check by Study Excluding Observations - Final PopPK Model.
Solid Blue Line: Median of the observed nirogacestat concentrations, Dashed Lines: 2:5th and 97:5th percentiles of the observed nirogacestat concentrations, Shaded Area: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2:5th and 97:5th percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. (Bergstrand et al., 2011); data was truncated at 0.5 ng/mL (LLOQ)

Physiologically based pharmacokinetic modelling

Physiologically based pharmacokinetic (PBPK) modelling for nirogacestat were submitted by the Applicant based on the available in vitro and clinical PK data. Version 19 of the Simcyp Population-Based Simulator was used for all PBPK modelling and simulation. The modelling for this project was split into model development, refinement, verification, and application.

CYP3A4 inactivation data were re-analysed in order to derive initial estimates KI and kinact, accepting the caveat of potential enzyme co-operativity. Induction data were also included in the model. In order to recover the observed PK profiles following multiple dosing in healthy volunteers (Clinical study A8641002, Part 1, 95 mg QD), the balance between time dependency inhibition (TDI) and induction was evaluated and optimised. Thus, auto-induction and auto-inhibition were simulated within the model.

The final PBPK model was verified using several of the available clinical pharmacology studies. The verifications when using the most relevant clinical pharmacology studies are included below. Note that verification using additional clinical pharmacology studies were performed (data not shown).

The simulated single and multiple dose data for the proposed dose (150 mg BID) are illustrated in Figure 4 for Day 1 and Day 14 compared to the clinical data from clinical study A8641014.

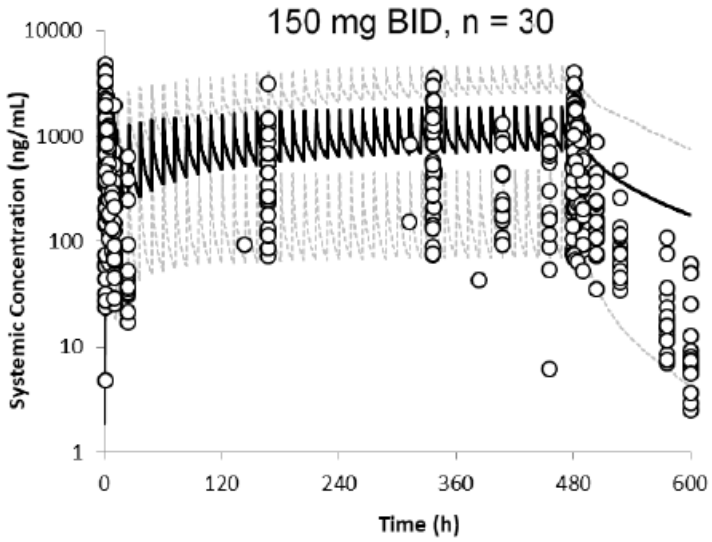
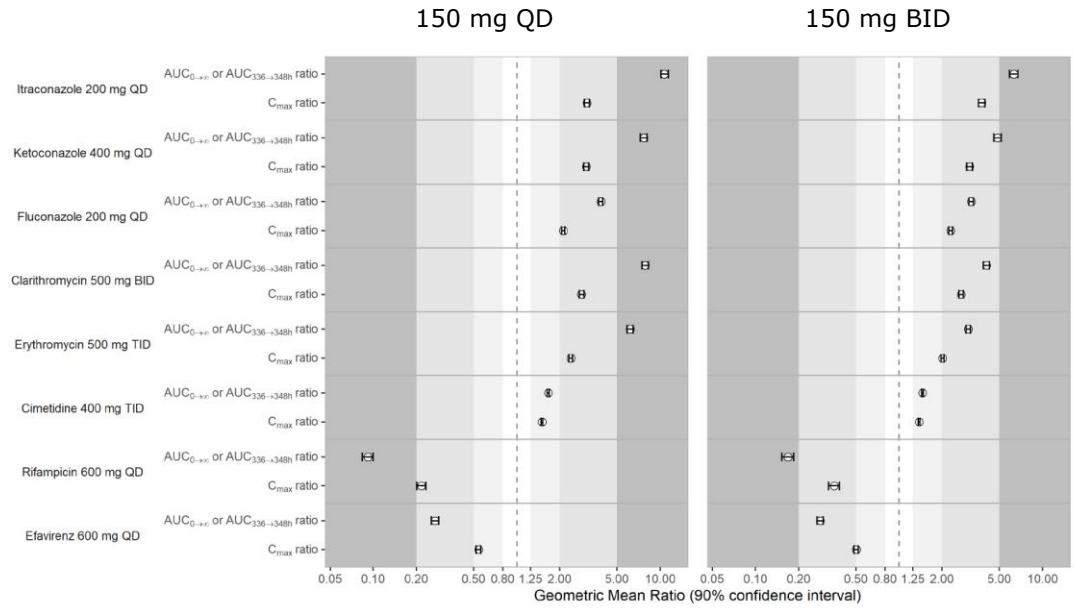


Figure 4 Log-linear simulated and observed mean plasma concentration-time profiles following oral dosing of nirogacestat for 14 days in cancer patients. Simulated (lines) and observed data (circles; Clinical Study A8641014). The grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n = 10 x n).

Simulated geometric mean AUC and Cmax ratios when nirogacestat (150 mg) was administered as either a single dose or following multiple doses are summarised in Figure 5.



For single dose nirogacestat the AUC is extrapolated to infinity; for multiple dose nirogacestat the AUC is for the interval of 0-tau [Source simulated data: 150mg-sd-itra-672h-cancer; 150mg-sd-keto-672h-cancer; 150mg-sd-fluc-672h-cancer; 150mg-sd-clar-672h-cancer; 150mg-sd-ery-672h-cancer; 150mg-sd-cim-672h-cancer; 150mg-sd-rif-672h-cancer; 150mg-sd-efv-672h-cancer-2b6induction; 150mg-bid-itra-348h-cancer; 150mg-bid-keto-348h-cancer; 150mg-bid-fluc-348h-cancer; 150mg-bid-clar-348h-cancer; 150mg-bid-ery-348h-cancer; 150mg-bid-cim-348h-cancer; 150mg-bid-rif-348h-cancer; 150mg-sd-efv-672h-cancer-2b6induction].

Figure 5: Summary of simulated geometric mean AUCinf, AUCtau and Cmax ratios for nirogacestat in the absence and presence of CYP3A4 inhibitors and inducers following single (150 mg) and repeat oral dosing of 150 mg nirogacestat BID in cancer patients

PBPK models were also developed with alternative absorption models including an advanced compartmental and transit (ACAT) model and an advanced dissolution, absorption and metabolism (ADAM) model with the main objective to predict the PK-DDIs following co-administration with acid-reducing agents (data not shown).

Absorption

Nirogacestat is rapidly absorbed, with a tmax of 1.5 hours and an absolute bioavailability of 19.2% (Range: 16.2%-24.3%). The effect of food (high-fat, high-calorie) on the PK of nirogacestat was evaluated in a sub-study to a dose finding phase-1 study in patients with advanced solid tumors. 14 patients receiving either 150 mg or 220 mg nirogacestat BID were included in the sub-study. Comparing the fed with the fasted state the dose normalized GMR (90% CI) was for C_{max} 93% (55, 166) and for AUC_{tau} 114% (76, 171) when two outliers were removed from the analysis. Including the outliers in the analysis gave a dose normalized GMR (90% CI) for C_{max} of 71% (40, 127) and for AUC_{tau} of 91% (60, 140). In the pivotal phase-3 study in patients with desmoid tumors nirogacestat was administrated without regard to food.

Based on in vitro data, nirogacestat is a substrate of P-gp but not of BCRP and it has not been demonstrated to be a high permeability compound. The solubility is pH-dependent with a significant decrease of solubility at pH > 6.0, only 2.6% of the 150 mg dose is estimated to be soluble at a pH of 6.5. According to ICH M9 nirogacestat is classified as an BCS class IV substance.

Distribution

After IV dosing in NIR-DT-102 Vz was 541 L. After a 150 mg single dose the Vz/F varied between 1500-3300 L in different studies. The geometric mean (%CV) Vz/F was predicted to be 1430 L (64.9%) following a single 150 mg dose according to the PopPK model.

Nirogacestat is highly protein bound, with a mean fu in human plasma and serum of 0.4% (corresponding to a protein binding of 99.6%) and with no signs of concentration dependency. Nirogacestat was highly bound to both albumin and alpha-1 acid glycoprotein (AAG), but with a greater affinity for AAG.

Protein binding was also investigated for the metabolite M283 at a concentration of 5µM, resulting in a mean unbound fraction of 6.15%.

The human blood/plasma ratio of nirogacestat is approximately 0.5.

Elimination

Nirogacestat has an apparent terminal half-life of 23 hours.

Two mass balance studies have been performed, the second including an IV-arm to estimate absolute bioavailability. As the first study had poor recovery a second study was performed including expired air trapping. Both studies indicate that the main elimination pathway for nirogacestat is metabolism followed by faecal excretion of the metabolites.

Following a single dose of 150 mg of ^{14}C-labelled nirogacestat in the second study the average total recovery of radioactivity following oral administration of radiolabelled nirogacestat was 65% (49%-90%) with 17%, 38%, and 9.7% in urine, faeces, and expired air respectively. The average total recovery of radioactivity following IV-administration was 79% (71%-94%) with 21%, 33%, and 25% in urine, faeces, and expired air respectively. Release of the ^{14}C-label as CO_2 occurred rapidly following both oral and IV administration with quantifiable levels in expired air already after 15 minutes. Following ^{14}C-nirogacestat tracer intravenous dose the geometric mean (CV%) clearance was estimated to be 12.4 L/h (19.3%). Following a single oral administration ^{14}C-nirogacestat the CL/F was 64 L/h (24%). Renal CL was estimated to be 0,0183 L/h (91.7%). Based on popPK the CL in patients with DT was estimated to be 9.09 L/h in the typical DT patient with associated inter-individual variability of 33%CV.

Less than 0.5% of the administered dose is excreted as unchanged nirogacestat in both faeces and urine. In urine 10 metabolites each representing less than 5% of the dose were detected. In faeces M434 and isomer forms of M436 represented 12 % of the dose, six other metabolites, all below 10% of the administrated dose, were also detected.

In serum and whole blood the total radioactivity reached 2-fold higher maximum concentrations and also exhibited an extended terminal elimination phase resulting in far greater systemic exposure to total radioactivity than to that of nirogacestat. The mean terminal elimination half-life ($t_{1/2}$) for nirogacestat in serum was approximately 37 hours. The mean $t_{1/2}$ for total radioactivity was approximately 415 hours in serum and 456 hours in blood. The Applicant mainly explained this with the C^{14}-label being released and incorporated in endogenous substances. The apparent oral systemic clearance is approximately 45 L/hr.

In serum only parent nirogacestat and another peak, P1, represented more than 10% of the radioactivity. In the 0-72 hour AUC pool P1 represented 44% and nirogacestat 26% of the radioactivity. The P1 peak was unretained on the chromatographic column and has not been identified,

but the Applicant claimed it a mixture of polar, low molecular weight substances. The major serum radioactive peak (P1) was present in serum across species.

Based on in vitro data, nirogacestat is extensively metabolised and CYP3A4 is the main enzyme responsible for metabolism of nirogacestat, with minor involvement of CYP2C19, 2C9 and 2D6. In vitro data also indicate that CYP3A4 is involved in formation of metabolites M183 and M283.

Nirogacestat is not a substrate of OATP1B1 or OATP1B3.

Dose proportionality and time dependencies

In the phase-1 study in the Japanese population dose proportionality after a single dose was investigated over the dose range 50-150 mg, with trends toward greater than proportional increases in both C_{max} and AUC with increasing dose (slope estimates 1.3-1.5). In the early MAD study nirogacestat exposures were slightly greater than dose proportional across the dose groups 7 mg BID to 95 mg QD (oral solution, PIB). In the PopPK analysis dose was identified as a covariate on bioavailability where doses below 10 mg led to higher than dose proportional increases in the exposure.

Nirogacestat is a sensitive CYP3A4 substrate. In vitro it has been shown to be a direct and time-dependent inhibitor as well as an inducer of CYP3A4. No evaluation of time dependency comparing AUCinf after single dose and AUCtau,ss (based on NCA) has been provided. Time dependency in the nirogacestat PK profile was included in the PBPK model development. According to the final PBPK model, nirogacestat has autoinduction and autoinhibition where the final PBPK model predicted a net decrease in the CYP3A4 levels over time on treatment which leads to time dependent PK on treatment.

Pharmacokinetics in target population and therapeutic window

In the PopPK analysis no significant differences in the PK was noted between healthy volunteers and DT patients. However, patients with other solid tumours or T-ALL/LBL were found to have approximately 50% lower clearance.

Inter-individual variability was quantified in the final PopPK model where CL was associated with inter-individual variability of 33%CV. The Vc was associated with inter-individual variability of 94%CV. An additional source of variability is inter-variability in bioavailability.

Based on the variability range observed in PK evaluations, including Phase 1 PK studies and predictions from the PopPK analysis, a no-effect boundary of 0.5 to 2.0 for Cmax and AUCtau is proposed. Exposure differences within these boundaries are unlikely to be clinically meaningful. The dose can be reduced by 33% in case of certain adverse events and in the pivotal phase-3 study where this was applied there were no clear signs of lack of efficacy in subjects with dose reduction.

Special populations

No dedicated renal impairment study was conducted given the low excretion of unchanged nirogacestat in urine (less than 0.5% of the dose). Renal function was not identified as a clinically significant covariate in thePopPK. The potential effect of severe renal impairment (RI) on CYP3A4-activity/levels and thus the metabolism of nirogacestat has not been discussed.

A dedicated HI-study using both the Child-Pugh (CP) Classification system and the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for liver dysfunction was conducted. Mainly subjects with moderate hepatic impairment by either classification system were included, one subject had severe HI by Child-Pugh, though moderate HI by NCI. The Applicant failed to measure fraction unbound (fu) for technical reasons and thus the unbound exposure was not determined in the

study. The total nirogacestat exposure (AUC) was not affected by moderate hepatic impairment, but peak exposure was reduced by 28% (CP) or 42% (NCI) depending on classification system. Also higher Vz/F, and longer t½ were noted. Lower binding to serum proteins in vivo may allow nirogacestat to be more easily distributed from the central compartment (blood), thus resulting in lower C_{max} values and higher Vz/F. The single subject with severe HI based on CP-criteria had the most affected PK-parameters with a 1.8-fold higher AUC and a 58% reduction of Cmax. Ogsiveo is not recommended in patients with severe hepatic impairment, as reflected in sections 4.2 and 5.2 of the SmPC.

Sex, race, age and weight were investigated by PopPK where none was considered a clinically relevant covariate. Cross study comparisons between different phase-1 studies showed similar exposures in the Japanese subjects as non-Japanese subjects.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	21/335	4/335	0/335

Pharmacokinetic interaction studies

Table 9: Cut-offs for the evaluation of interaction potential

	50×Cmax(u)[a] (µM)	25×Inlet Cmax(u)[a] (µM)	0.1×dose/250 ml[b] (µM)
Nirogacestat	1.3	2.5	122.5
Metabolite M283[c]	1.5	NA	NA

a Multiple dose Cmax, 150 mg BID dose (study A8641014), fu 1%,
b Based on a 150 mg dose
c Cut-off of metabolite determined as 20% of parent Cmax of 2.5 µM (ie 0.5 µM) and fu of 6.15%. Note however that this metabolite is not major and thus not mandatory to investigate as perpetrator of interactions.
NA - Not applicable

PBPK modelling was used to predict the effect of mild, moderate and strong CYP3A4 inhibitors and moderate and strong CYP3A4 inducers on nirogacestat exposure, to predict the effect of a clinical dose of nirogacestat on midazolam exposure and to predict the effect of nirogacestat on substrates of CYP2B6, CYP2C8, CYP2C9 and CYP2C19.

Results from in vivo DDI studies is summarised in the table below.

Table 10: Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	AUC_{inf}	
Victim			
Effect of co-administration with itraconazole	250 (233, 268)	823 (720, 941)	Concomitant treatment with strong and moderate CYP3A4 inhibitors not recommended.
Perpetrator			
Effect on midazolam	131 (122, 140)	159 (150, 168)	Should not be used with CYP3A4 substrates that have narrow therapeutic

			indices (e.g. cyclosporine, tacrolimus).
Effect on dabigatran etexilate	97 (79, 119)	99.5 (84, 118)	-

Nirogacestat as victim of drug-drug interactions

Study NIR-DT-103 (part 1) was intended to investigate the effects of a single dose (P-gp inhibition) and multiple doses (CYP3A4 induction) of rifampicin on the PK of a single dose of nirogacestat, but this part of the study was not performed due to a notice concerning genotoxic impurities in the rifampicin drug product.

Study NIR-DT-103 (part 2) investigated the effect of multiple doses of the strong CYP3A4 inhibitor itraconazole (200 mg) on the PK of a single dose of nirogacestat (100 mg) in 24 healthy volunteers. PK sampling occurred up to 96 hours post dose. When administered with itraconazole dosed to steady-state, nirogacestat C_{max}, AUC_{last} and AUC_{inf} were increased by approximately 2.5-fold, 6.3-fold, and 8.2-fold compared to nirogacestat administered alone. The median T_{max} for serum nirogacestat when administered alone was 1 hour (range: 0.50 to 1.52 hours) and increased to 1.5 hours (range: 1.00 to 2.03 hours) when administered with itraconazole at steady-state. The mean half-life increased from 27 hours to 58 hours and mean CL/F decreased from 59 to 8 L/h.

Increased gastric pH: Nirogacestat has pH-dependent solubility as it is highly soluble at low pH, but the solubility significantly decreases at pH > 6.0. No in vivo study investigating the potential effect of drugs which increase gastric pH has been performed.

Nirogacestat as perpetrator of drug-drug interactions

Study A8641002 (part 2): In part 2 of the MAD study, the effects of nirogacestat at a dose of 95 QD given during 10 days on the sensitive CYP3A4 substrate midazolam was investigated in 16 healthy volunteers using a two-sequence cross-over design. PK sampling of midazolam was performed up to 36 hours post dose. Co-administration of nirogacestat 95 mg QD and midazolam 2 mg resulted in increases in plasma systemic exposure of midazolam by approximately 58.9% (approximately 1.6-fold increase) and 30.7% (approximately 1.3-fold increase) for AUC_{inf} and C_{max}, respectively.

Substrates of CYP2B6, CYP2C8, CYP2C9 and CYP2C19: No in vivo study has been performed.

Contraceptive steroids: No in vivo study has been performed.

Study NIR-DT-103 (part 3): The effects of a single 150 mg dose of nirogacestat on the sensitive P-gp substrate dabigatran etexilate (75 mg) was investigated in 22 healthy volunteers. PK sampling occurred up to 48 hours post-dose. The plasma C_{max} and all evaluated AUC parameters for total dabigatran (free dabigatran and dabigatran acyl glucuronide) were similar when administered alone or with nirogacestat.

Pharmacokinetics using human biomaterials

In vitro CYP inhibition by nirogacestat is summarised in the table below. In conclusion, there is an in vitro signal of CYP3A4 inhibition by nirogacestat at clinically relevant concentrations (both direct inhibition and time-dependent inhibition) but no in vitro signal of inhibition of any other CYP enzyme by nirogacestat.

Table 11: Summary of in vitro enzyme inhibition by nirogacestat (pooled human liver microsomes)

Enzyme	Substrate	Positive control inhibitors (Direct/MBI)	Competitive inhibition	TDI	Positive signal to evaluate further
			Ki* (µM)		Yes/No
CYP1A2	Phenacetin	A-Naphtho-flavone Furafylline	>25	No	No
CYP2B6	Bupropion	Orphenadrine Phenacyclidine	>25	No	No
CYP2C8	Paclitaxel	Montelukast Gemfiprozol glucuronide	>25	No	No
CYP2C9	Diclofenac	Sulfaphenazole Tienilic acid	>25	No	No
CYP2C19	S-Mephenytoin	Modafinil S-fluoxetine	>25	No	No
CYP2D6	Dextromethorphan	Quinidine Paroxetine	>25	No	No
CYP3A4/5	Testosterone Midazolam Nifedipine	Ketoconazole Troleandomycin	5.5 >25 3.45	Yes	Yes (direct inhibition and TDI)

There are no in vitro signals of inhibition of CYP enzymes by the metabolite M283.

There are in vitro signals that nirogacestat induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 at clinically relevant concentrations, but not for CYP1A2.

In vitro transporter inhibition by nirogacestat is summarised in the table below. In conclusion, there is an in vitro signal of P-gp inhibition by nirogacestat at clinically relevant concentrations but no in vitro signal of inhibition of any other transporter by nirogacestat.

Table 12: In vitro transporter inhibition by nirogacestat

Transporter	Substrate	Positive control inhibitor	In vitro system	IC50 (µM)	Ki* (µM)	Positive signal (Y/N)
P-gp	digoxin	PSC833	Transfected MDCKII cells	2.3		Y
BCRP	pitavastatin	Ko143	Transfected MDCKII-LE cells	>120		N
OATP1B1	atorvastatin	Rifamycin SV	Transfected HEK293 cells	>13.8		N
OATB1B1	rosuvastatin	Rifampicin	Transfected HEK293 cells	>10		N
OATP1B3	atorvastatin	Rifamycin SV	Transfected HEK293 cells	>13.8		N

OATP1B3	rosuvastatin	Rifampicin	Transfected HEK293 cells	>100		N
OAT1	PAH	Probenecid	Transfected HEK293 cells	>13.8		N
OAT3	urosemide	Probenecid	Transfected HEK293 cells	>13.8		N
OCT2	MPP+	Imipramine	Transfected HEK293 cells	>13.8		N
OCT1	Not studied					-
MATE1	metformin	Cimetidine	Transfected HEK293 cells	>13.8		N
MATE2k	metformin	Pyrimethamine	Transfected HEK293 cells	>13.8		N
BSEP	Not studied					-

* If IC50 is used instead of Ki a justification should be provided (including linearity, choice of substrate concentration etc.)

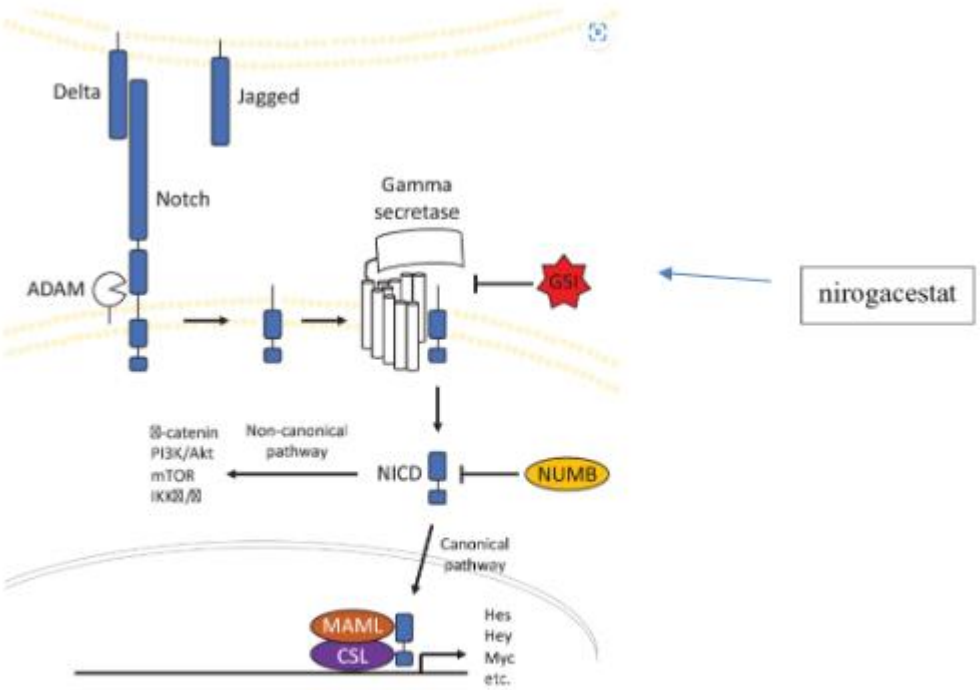
2.6.2.2. Pharmacodynamics

Mechanism of action

Nirogacestat (PF-03084014) is a small molecule, reversible, noncompetitive inhibitor of the GS enzyme that was initially developed for investigation in Notch-driven tumours.

Nirogacestat has been shown to inhibit the Notch pathway by inhibiting GS, which prevents proteolytic cleavage of the Notch intracellular domain (NICD) leading to downregulation of the Notch target genes HES1 and C-MYC, resulting in tumour growth inhibition (Wei et al. 2010; Federman et al. 2022). Nirogacestat has been shown to inhibit the Notch pathway in DT by inhibiting NICD signalling and downstream HES1 expression (see figure below: Shang et al. 2015).

Figure 6: Schematic Representation of Notch Signaling Pathway with Nirogacestat-related GS Inhibition



Abbreviations: GS: gamma secretase; GSI: gamma secretase inhibition; NICD: Notch intracellular domain.
A Notch receptor binds to cell-bound or soluble Delta/jagged ligands. Bound Notch is first cleaved by a disintegrin and metalloprotease (ADAM) to release the extracellular portion. GS then catalyzes a second cleavage event, liberating NICD into the intracellular space.
Adapted from (McCaw 2021)

Primary and secondary pharmacology

The molecular mechanism for the oncogenic activity of NICD may include inhibiting differentiation, promoting survival, or accelerating proliferation. Potential oncogenic targets of NOTCH1 include cMyc, cyclin D1, and several other factors. In the case of cMyc, evidence demonstrates that cMyc is a direct target gene of NOTCH1 and essential for development of both T-cell leukaemia and mammary tumours in mice (Sharma et al. 2006; Klinakis et al. 2006).

DT is historically associated with deregulation of the canonical Wnt signalling pathway, with activating mutations in CTNNB1 being commonly identified in patients with DT and a common occurrence of DT in patients with FAP with mutations in APC. Studies suggest crosstalk between the Wnt and Notch pathways (Rodilla et al. 2009; Rampazzo et al. 2013). Expression of NOTCH1 and HES1 has been observed in mesenchymal stromal cells found in DT, suggesting that the Notch pathway is possibly related to DT tumourigenesis (Shang et al. 2015; Federman et al. 2022).

Evidence for nirogacestat-mediated antitumour efficacy in association with reduction in activated Notch signalling was established in DT using patient-derived culture models (Shang et al. 2015). An additional potential mechanism of action for nirogacestat in the treatment of DT involves GS inhibition, which prevents the release of cytoplasmic β-catenin by blocking the proteolytic cleavage of cadherin complexes (Marambaud et al. 2002; Jang et al. 2011). This well-conserved feature of cell-cell adhesion has been shown to be an important factor in the regulation of Wnt signalling. The critical components of this regulation of the Wnt pathway are active in DT. Collectively, these observations support a plausible therapeutically relevant mechanism of nirogacestat-mediated GS inhibition that reduces activated Notch and possibly β-catenin signalling resulting in antiproliferative and apoptotic responses.

Cardiac electrophysiology

The effects of nirogacestat on QT interval corrected by Fridericia's formula (QTcF) could not be evaluated in a TQT study because the MTD of 220 mg BID does not support administering a supratherapeutic dose (>2-fold exposures over the 150 mg dose) to healthy participants. A C-QT model was developed using data from healthy participant studies and two studies in participants with cancer diagnoses to estimate the relationship between nirogacestat concentration and QTcF interval. In participants with DT, the C-QT model predicted a 3.80 msec increase (90% CI 0.877 to 6.37 msec) in QTcF interval at concentrations that are 2-fold higher than the predicted increase in Cmax with strong CYP3A4 inhibition. In participants with advanced malignancies, the C-QT model predicted a 5.86 msec increase (90% CI: 1.35, 9.81) in QTcF interval at concentrations that are 2-fold higher than the predicted increase in Cmax with moderate CYP3A4 inhibition.

A risk of nirogacestat-related QT prolongation is not anticipated at therapeutically relevant exposures.

Relationship between plasma concentration and effect

Several types of PK/PD models were submitted as part of this procedure. This includes exposure-response analyses of various efficacy and safety-related endpoints as well as a concentration-QTc analysis.

Concentration-QTc analysis

The objectives of this C-QT analysis were to evaluate the relationship between serum nirogacestat concentrations and QTcF interval and to predict nirogacestat-related changes in QTcF interval at therapeutic and at 2x therapeutic concentrations.

Concentration-time, ECG, and demographic data were combined from seven studies (studies A8641001, A8641002, A8641014, NIR-DT-101, NIR-DT-102, NIR-DT-103, and NIR-DT-301). The C-QT dataset included 2587 time-matched PK and ECG samples from 359 subjects. Only paired concentrations and QT measurements were used in the analysis. An ECG and serum concentration was considered paired if taken within 10 minutes of each other, except for pre-dose. The mean of triplicate values was used in the analysis.

Population C-QT analysis was performed using NONMEM program version 7.4.4 () and first-order conditional estimation with interaction (FOCE-I). Below follows a very brief description of the model development. The details concerning the model development generally adhered to the Garnett 2018 et al. paper.

Exploratory analyses confirmed that the key assumptions (effect of nirogacestat on HR, QTcF adequately controls for the effect of HR on QT interval, time delay between nirogacestat concentrations and QT interval, relationship between concentrations and QTcF is linear) were not violated to a significant degree.

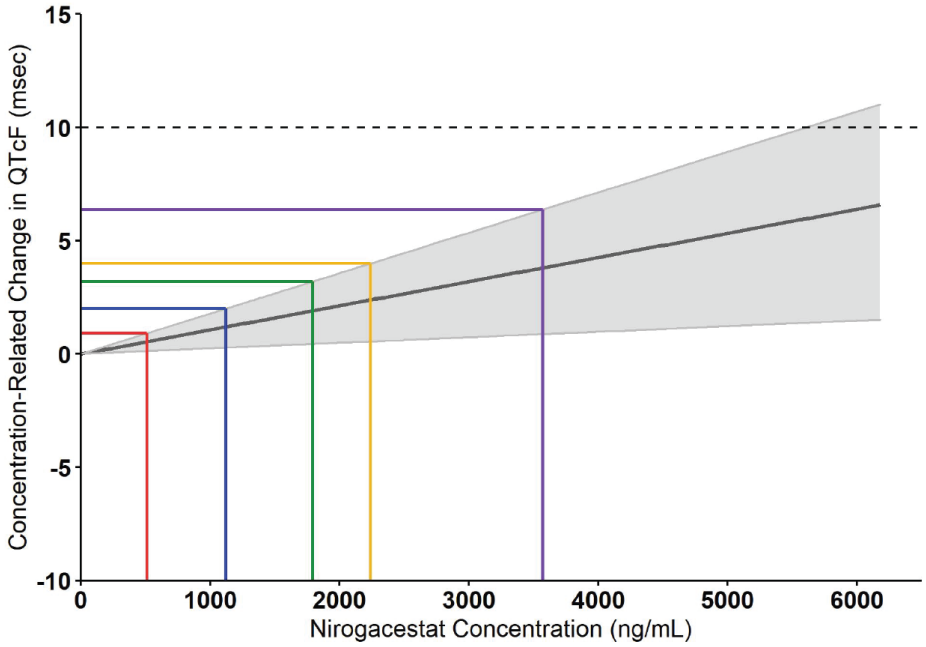
The model included a significant effect of sex and age. The estimated nirogacestat concentration-related slope in the full model was 0.0011 msec/ng/mL. The parameter estimates of the full model are shown in Table 13. The model described the observed data well according to a visual predictive check (VPC).

Table 13: final parameter estimates for the full C-QT model

Parameter	Description	Estimate	%RSE
$QTCF_{abs}$	Baseline QTcF (msec)	402	0.267%
SLPSEX	Increase in baseline QTcF for females [effect size]	0.0468 [≈5% increase for females]	9.65%
SLPAGE	Effect of age on baseline QTcF [effect size]	0.0282 [17 msec increase as age increases from 18 to 80 years]	21.4%
SLPNIRO	Effect of nirogacestat concentration on QTcF	0.00111	35.9%
IIV on Baseline QTcF (msec) [Shrinkage]		15.9 [2.8%]	7.86%
Additive residual error (msec)		7.53	2.99%

IIV = inter-individual variability; QTcF = QT with Fridericia's correction; RSE = relative standard error, calculated as 100*(Standard Error)/(Estimate); IIV and residual error are reported as standard deviation, calculated as sqrt(ETA) and sqrt(EPS), respectively. Epsilon shrinkage was computed to be 6.7%.

The final nirogacestat C-QT model was used to predict the ΔQTcF and two-sided 90% CI at concentrations of interest (Figure 7).



Dashed line = 10 msec reference line; Grey line and shaded area = linear regression of the model-predicted concentration-related change in QTcF and 90% prediction interval versus observed concentration values; Colored lines = upper 90% CI of the model-predicted concentration-related effect at each concentration of interest; Red = PopPK model-predicted Cmax,ss in DT patients with 150 mg BID (510 ng/mL); Blue = Cmax,ss with moderate CYP3A4 inhibition (1120 ng/mL); Green = Cmax,ss with strong CYP3A4 inhibition (1790 ng/mL); Yellow = 2x Cmax,ss with moderate CYP3A4 inhibition (2240 ng/mL); Purple = 2x Cmax,ss with strong CYP3A4 inhibition (3570 ng/mL)

Figure 7 Plot of Predicted ΔQTcF Upper 90% Confidence Interval at Concentrations of Interest in the Desmoid Tumor Patient Population

Exposure-response analyses

Model-based exposure-response models were developed for several efficacy- and safety related endpoints. This included desmoid tumour size, PFS, BOR, DOR, follicle-stimulating hormone (FSH), ovarian dysfunction, phosphate levels and various other treatment-related AEs.

Data of 214 subjects from studies A8641014 and NIR-DT-301 were available for the PK/PD, efficacy, and safety analyses. Of these, 149 were from DT patients (where 72 patients received placebo).

Model development was carried out sequentially, first describing disease progression and placebo response, followed by assessment of the nirogacestat exposure-response relationship (ERR). Nonlinear mixed effects modeling was employed to develop PK/PD models to characterize safety and efficacy of nirogacestat in DT patients, patients with solid tumours other than DT, and patients with T-ALL/LBL. The previously developed nirogacestat PopPK model was used to derive individual exposure parameters. Bayesian post hoc PK parameter estimates were used to estimate nirogacestat exposures (nominal steady state or exposure at day of onset) for the subsequent exposure-response analysis.

A significant ERR was identified between nirogacestat exposure and FSH. FSH was found to linearly increase with nirogacestat serum concentrations and a delay between serum concentrations and FSH change was characterized by an indirect response model.

Grade 3+ hypophosphatemia was found to have a relationship with nirogacestat exposure. Compared to treatment, Cmax was found to be the best predictor of grade 3+ hypophosphatemia occurrence (Figure 8). At a 100 mg dose, the probability of a grade 3+ hypophosphatemia occurrence was calculated to be 5.89%. For a 150 mg dose, the probability of a grade 3+ hypophosphatemia occurrence was calculated to be 6.78%. For various other treatment-related AEs that were explored, no significant exposure-response trend was identified.

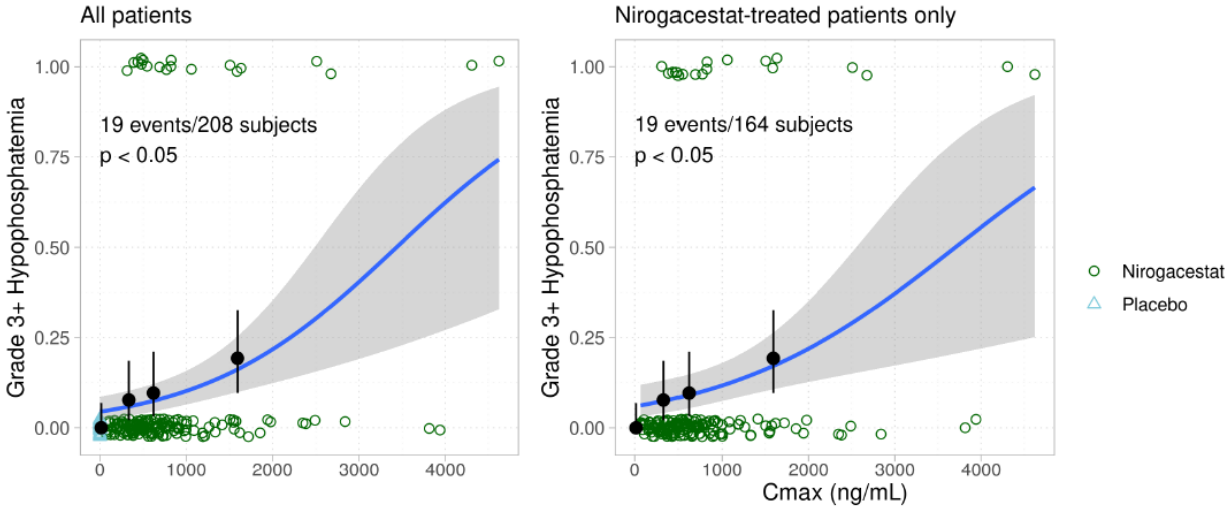


Figure 8 Logistic Regression Relationships for Grade 3+ Hypophosphatemia in All Patients and Nirogacestat-Treated Patients Only.

Note: The solid black points represent the mean exposure and event rates in the placebo treated patients or patients stratified by nirogacestat exposure quartile. Vertical black bars represent the 5th to 95th percentile CI on the event rate. The solid blue line indicates the logistic regression model fit (regardless of p-value). The shaded gray region represents the 95% CI on the modeled event rate. The p-value for the slope is indicated. The data points for patients with and without an event are shown at the top and bottom of the plots, respectively. Cmax: Nominal maximum concentration at day of onset or steady state; Cmin: Nominal minimum concentration (trough) at day of onset or steady state; AUC: Nominal area under the time-concentration curve at day of onset or steady state; CI: Confidence interval.

For PFS, which was the primary endpoint in the NIR-DT-301 study, no significant exposure-response relationship was found although PFS probability was associated with nirogacestat treatment.

No significant exposure-response relationships were identified for desmoid tumour size, BOR, DOR, ovarian dysfunction and phosphate maximum reduction from baseline.

Dose justification

PK/PD evaluations have been conducted at various points during the development of nirogacestat to support justifications for clinical dose recommendations. Support for initial dose ranging was provided based on non-clinical evaluations of tumour growth in association with inhibition of Notch signalling. The recommended phase 2 dose was selected based on identification of a maximum tolerated dose and comparative evaluation of efficacy and tolerability observed in study A8641014. Based on an assumption that GS inhibitor-mediated inhibition of Notch signalling is the primary mechanism of antitumour efficacy, PK/PD analysis of an additional biomarker (HES4 expression) in study A8641014 was also supportive of the phase 2 dose selection. Additional PK/PD and exposure-response analyses based on data from participants with DT in studies A8641014 and NIR-DT-301 were employed to support identification of an optimal dose selection for clinical use (see above).

2.6.3. Discussion on clinical pharmacology

ADME

The mass balance data provided and the moderate in vitro permeability of nirogacestat it is not possible to conclude on high permeability as defined in ICH M9 for BCS classification. Considering the low solubility at pH above 6, nirogacestat is classified as a BCS-class IV substance.

A relative BA study comparing 3x 50 mg and 1x 150 mg uncoated tablets showed bioequivalence. Further in vitro dissolution studies comparing uncoated and film-coated tablets have been performed and are assessed as acceptable (see section 2.4.). Most clinical data in the target population was generated with 3x50 mg uncoated tablet. The intended commercial film-coated 100 and 150 mg tablet have not been used in any clinical study. However, as the only difference is the non-functional coating the presented data is considered sufficient.

No studies were conducted to bridge relative BA between the powder in bottle formulation (PIB) formulation used in early phase 1 studies to the tablet formulations. This is considered acceptable, since the PIB formulation was used at dose levels mostly below the proposed therapeutic dose and key PK characterization comes from later studies utilising oral solution and tablet formulation.

The food effect sub-study was performed in patients with different types of tumours and at different dose levels. Based on the pop-PK model, patients with advanced solid tumours have lower CL compared to healthy volunteers and target population (patients with Desmoid tumours). PK-sampling in the study was quite sparse. These are factors which may contribute to uncertainties and variability making it difficult to establish a food-effect. Nirogacestat was dosed without regard to food in the pivotal NIR-DT-301 study. Based on these data it is agreed that no restrictions with regards to food are proposed in the SmPC.

In vitro-data indicate that nirogacestat is a substrate of P-gp but not of BCRP. A clinical DDI study was performed with the strong CYP3A4/P-gp inhibitor itraconazole (see DDI part below).

In the mass balance studies the ^{14}C-label is not in a stable position, as early as in 15 min after both IV and oral administration a quantifiable amount is detected in expired air as CO_2. Metabolites resulting from the decarboxylation-metabolism are not identified since these possible metabolites are unlabelled in the studies. No (< 0.5%) unchanged nirogacestat was detected in either faeces or urine. 7 and 10 other peaks representing metabolites were detected in faeces and urine respectively, however few have been structurally characterized. Approximately 14% of the dose excreted in faeces and 1% of the dose excreted in urine has been structurally characterized.

Based on in vitro data, nirogacestat is extensively metabolised and CYP3A4 is the main enzyme responsible for metabolism of nirogacestat. This has been confirmed in the in vivo DDI study with ketoconazole (strong CYP3A4 inhibitor) where an 8-fold increase in nirogacestat exposure was observed. Overall, the data is sufficient to conclude that metabolism by CYP3A4 is the main elimination pathway with metabolites being excreted mainly in faeces but ultimately also as CO_2 in expired air. This is consistent with the mass balance results from rat and dog. Another major elimination pathway is unlikely considering the totality of the data and from this perspective no further mass balance studies are required.

In the serum, the parent compound is detected as a major constituent and also the unidentified P1 peak, which is unretained on the column (C18-column) and consists of at least two components. All other metabolite-peaks represented less than 10% of the radioactivity. The P1-peak was also present in non-clinical studies, in rat it represented 79% of the total radioactivity but in dog only 10%, and to some extent at least then covered in tox-studies, though it is not proven that the composition of the peaks is the same in humans and non-clinical species. The total radioactivity in serum and whole blood exhibited an extended terminal elimination phase resulting in far greater systemic exposure to total radioactivity than to that of nirogacestat. Also in non-clinical studies the plasma half-life radioactivity was long. The Applicant mainly explained this with the ^{14}C-label being released and incorporated in endogenous substances, while a plausible explanation it remains theoretical and slow eliminating metabolites cannot be excluded.

Overall, the circulating components related to nirogacestat have been poorly characterized, and there are uncertainties as to whether there are any major and/or active plasma metabolites. Considering the important fact that in non-clinical species extensive toxicity was observed at exposures at or below clinical exposure, it is unlikely that further elucidation of the metabolite structures would add to the safety assessment of nirogacestat.

The data from the performed clinical studies include both effect and toxicity of the formed metabolites (if pharmacologically active). The risks associated with the lack of knowledge of metabolite profile and activity are related to situations/populations not common in the performed clinical studies.

Considering the totality of the data, another major elimination pathway is unlikely, and it is agreed that nirogacestat is extensively metabolized by CYP3A4 with numerous metabolites. The margin of exposure is negative for the parent compound and several of the potential risks stemming from the uncertainties regarding the exposure of particular metabolites are at least partly mitigated by already proposed restrictions in the SmPC or proposed DDI-studies. In conclusion, the issue of a not fully satisfactory investigation of the metabolism of nirogacestat is not further pursued.

Nirogacestat is not a substrate of OATP1B1 or OATP1B3. It is not necessary to perform substrate studies with renal transporters as renal excretion of parent drug is not a major route of elimination.

Target population

Pharmacokinetics in the target population was described using a PopPK approach and overall, PopPK is found acceptable for description of PK in DT population. A total of 5473 PK samples from 335 adult subjects were used for PK model development which is appropriate.

Post-dose samples below LLOQ (5.54%) and 134 additional samples (for various reasons such as missing date/time, PK without dosing) were excluded from the analysis. Reasons for exclusion of additional samples should have been described in more detail (especially those samples that were flagged as inconsistent with PK of nirogacestat). However, those samples are in minority and are not expected to have significant effect on the overall model development.

The covariate distributions are considered overall reasonable. Covariates of particular interest are those related to co-medications with potential for interaction with nirogacestat. Only strong CYP3A inhibitors was identified as a significant covariate. The potentially relevant co-medications CYP3A inducers, weak CYP3A inhibitors, moderate CYP3A inhibitors, P-gP inducers, P-gP inhibitors, antacids and H2 receptor antagonists were not represented by a sufficient number of subjects. Concomitant PPI was represented by ~30 subjects and was explored as a covariate on absorption but was not found to be a meaningful covariate. Of note, the covariate analysis of concomitant PPI is not considered sufficient to waive the request for a PPI DDI study due to uncertainties in the analysis (for instance, PPI compliance and timing of PPI intake in relation to nirogacestat intake were unknown).

An overall standard workflow was used to develop the PopPK model. During the covariate model development, highly correlated covariates were not tested, which is plausible. Pre-specified primary covariates were investigated by manually testing them in the model which is endorsed. Eta vs covariate plots were used for exploratory covariates and could generally be considered an acceptable approach when the eta shrinkage is reasonably low (<20-30%). The eta shrinkages were reasonable for all parameters except ka and Tlag. The covariate analysis is considered acceptable.

The final model is considered overall reasonable, including the structural 3-compartment model. The fact that the inter-compartmental clearance parameters (Q1 and Q2) had to be fixed is considered a limitation. Based on this it is not entirely clear if the 3-compartment model is indeed supported by the data or if a two-compartment model would have sufficed. Nevertheless, the parameter estimates of the final model were estimated with acceptable precision (<30%). Weight was only included on Vp2 and not on CL or Vc since it was not considered statistically significant. A more mechanistic implementation would be to include body weight using fixed vs estimated allometric exponents on all clearance and volume parameters, respectively. However, the implementation of body weight in the final model is considered acceptable given the limited impact of the PopPK model in the current procedure.

The VPC stratified by study showed an acceptable description of the observed data. VPCs stratified by Cycle 1/Day 1 vs later cycles did not indicate any signs of time-dependent PK (data not shown).

A therapeutic window defined as a 0.5-2-fold difference in Cmax and AUCtau is considered overall reasonable for nirogacestat given the rather high variability in nirogacestat PK. According to the dose reduction algorithm, the dose can be reduced by 33% in case of certain adverse events. This dose reduction algorithm was applied in study NIR-DT-301 and there were no clear signs of lack of efficacy in subjects with dose reduction.

Special populations

Renal elimination is not a primary clearance pathway for nirogacestat, thus it is expected that renal impairment should not have a significant impact on nirogacestat PK. Pharmacokinetic alterations may occur in severe renal impairment (RI) because of a reduction in hepatic and/or intestinal CYP metabolism. No subjects with severe RI were included in the clinical phase 3 study. Overall severe RI is not expected to be common in the target population However, a wording in section 4.2 of the SmPC has been included to state that nirogacestat is not recommended in patients with severe RI which is acceptable.

The degree of hepatic impairment was determined using both the Child-Pugh Classification system (CP) which is in accordance with relevant EMA guideline I and NCI-ODWG criteria (NCI). The total nirogacestat exposure (AUC) was not affected by moderate hepatic impairment, but peak exposure was reduced by 28% (CP) or 42% (NCI) depending on classification system. These results are not considered clinically relevant and do not warrant any dose adjustments. The limited effect on nirogacestat PK by hepatic impairment is somewhat unexpected given the extensive metabolism by CYP3A4 and large effect seen by the strong CYP3A4 inhibitor itraconazole. With only one subject

classified with severe hepatic impairment (HI) (by CP), conclusions cannot be drawn for severe HI, but this subject did have the most altered exposure (both AUC and Cmax) and possibly the effect in moderate HI is underestimated as there appears to be few individuals being affected in factors indicative of affected elimination capacity.

The Applicant failed to measure fraction unbound (fu) in the hepatic impairment (HI) study for technical reasons and thus the unbound exposure was not determined. The intended target population is relatively young and severe forms of HI anticipated to be rare. In section 4.2 of the SmPC dose reductions are proposed based on several different adverse reactions. In the SmPC it is concluded that treatment in severe HI is not recommended, which is considered adequate.

DDI

PBPK model

The Applicant developed different PBPK models which differed in the absorption part (first-order absorption model, ACAT model and ADAM model).

The first-order absorption model was applied to support dosing recommendations for various DDIs. However, the PBPK model is not considered sufficiently qualified for these purposes. Overall, a standard workflow was used for developing the PBPK model. The elimination part of the model includes both autoinduction and autoinhibition of CYP3A4 which renders the final PBPK model very complex and makes it very difficult to accept this model for extrapolation of unstudied scenarios. Moreover, several critical input parameters related to CYP3A4 inhibition were optimised based on clinical data which is another limitation of the model. Taken together, the complex nature of the PBPK model and the fact that important parameters were optimised based on clinical data means that the models' credibility is questioned. Regarding model verification, the first-order absorption model did not describe the observed patient data well. The model overpredicts the observed data for the 150 mg BID group. Since 150 mg BID is the proposed dosing regimen, this is considered a major limitation of the analysis. The fact that the proposed dose is not described well negatively impacts the credibility of the model for predicting unstudied scenarios (e.g. DDI scenarios).

The ACAT and ADAM models were applied to predict a PK DDI study with concomitant PPI. However, the presented PBPK models are not considered sufficiently credible.

The ACAT and ADAM models are, at best, considered supportive evidence and is not acceptable for waiving a clinical study (which would imply high regulatory impact and hence would require substantial model validation).

Nirogacestat as victim of drug-drug interactions

Based on in vitro data, CYP3A4 is the main enzyme involved in the metabolism of nirogacestat, with minor involvement of CYP2C19, 2C9 and 2D6. Other CYP enzymes are not expected to contribute to $\geq$ 25% of drug elimination based on in vitro data, and in vivo data with itraconazole confirm that CYP3A4 is the main enzyme involved in metabolism. In vivo data investigating the effect of inhibitors of other CYP enzymes are thus not needed. Nirogacestat is a substrate of P-gp based on in vitro-data.

Based on the results of the itraconazole study, nirogacestat can be considered a sensitive CYP3A4 substrate as AUC_{inf} increased 8-fold following treatment with multiple doses of the strong CYP3A4 inhibitor (and P-gp inhibitor) itraconazole. C_{max} increased less than AUC (2.5-fold) and half-life increased, which indicates that the effect was both on bioavailability/first pass effect and on systemic elimination. It is not possible to exclude an effect of P-gp inhibition on the overall observed increase in AUC, but the effect of itraconazole on nirogacestat exposure is likely caused mainly by CYP3A4, considering also that nirogacestat is excreted unchanged to a very low extent. In addition, most CYP3A4 inhibitors also inhibit P-gp and it is not considered necessary to have a separate warning

regarding P-gp inhibitors that do not inhibit CYP3A4. The recommendation in section 4.5 of the SmPC to avoid concomitant treatment with strong CYP3A4 inhibitors is agreed considering the significant effect on nirogacestat exposure.

There is no in vivo study with a moderate CYP3A4 inhibitor, and the PBPK model cannot be used to predict the magnitude of the effect of moderate inhibitors. According to the definition in the DDI guideline, a moderate inhibitor can cause a 2-fold to 5-fold increase in AUC of a sensitive probe drug. Thus, the effects of a moderate CYP3A4 inhibitor are also expected to be clinically relevant based on the therapeutic window of nirogacestat and it is agreed that concomitant use should be avoided, as recommended in section 4.5 of the SmPC.

Regarding mild CYP3A4 inhibitors, these are generally defined as causing 1.25-to-2-fold increase in AUC. As a 2-fold increase in exposure of nirogacestat is considered safe, concomitant use with mild CYP3A4 inhibitors would be acceptable and there is thus no need to mention them in section 4.5 of the SmPC.

No in vivo data is available regarding the effects of an inducer on the exposure of nirogacestat and the PBPK model cannot be used to predict the magnitude of effects. However, based on the effects of itraconazole on nirogacestat exposure it is agreed that moderate and strong inducers are expected to result in clinically relevant decreases in exposure (at least by 50%) of a sensitive CYP3A4 substrate such as nirogacestat. Concomitant use with strong or moderate inducers should therefore be avoided due to a risk of reduced efficacy as stated in section 4.5 of the SmPC. On the other hand, a mild inducer is not expected to result in a clinically relevant decrease in exposure (<50% decrease), considering the therapeutic window of nirogacestat.

According to the EU DDI guideline, if the solubility of the drug or the dissolution of the formulation is markedly pH dependent in the physiological pH range, the potential effect of drugs which increase gastric pH, such as proton pump inhibitors, H2-receptor antagonists or antacids, should be investigated in vivo. This is the case for nirogacestat, as the solubility is greatly reduced above pH 6 (starts decreasing already between pH 5 and 6). A dedicated in vivo DDI study investigating the effect of multiple-dose treatment with a PPI on nirogacestat exposure was therefore requested, and the Applicant has agreed to perform an in vivo study with a proton pump inhibitor (and a H2 antagonist) post-approval (**RECOMMENDATION**). Until data is available, it is acceptable that section 4.5 of the SmPC states that concomitant use with PPIs and H2-antagonists is not recommended while staggered use with antacids may be used if needed.

Nirogacestat as perpetrator of drug-drug interactions

The cut-off calculation for nirogacestat is based on a value of C_{max} estimated at steady state (C1D21) in participants with advanced solid tumours at 150 mg BID in study A8641014 (rich sampling). In the pivotal phase 3 study NIR-DT-301 the popPK-model derived $C_{max,ss}$ was lower, 508 ng/ml. Using the higher value observed in study A8641014 is considered worst-case and can be agreed.

Inhibition by nirogacestat of all mandatory CYP enzymes has been investigated. There is an in vitro signal of in vivo relevant direct inhibition of intestinal CYP3A4 and also potential for time-dependent inhibition of CYP3A4, but no signal of inhibition of other CYP enzymes.

Several in vitro induction studies were performed. There are in vitro induction signals for CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 but not for CYP1A2.

Inhibition of all mandatory transporters (and some non-mandatory transporters) by nirogacestat have been investigated in vitro. There is an in vitro-signal of P-gp inhibition by nirogacestat but nirogacestat is not a clinically relevant inhibitor of any other transporters based on in vitro-data.

In study A8641002 investigating the effects of nirogacestat on the sensitive CYP3A4 substrate midazolam, a different (lower) dose is given than the clinical dose (95 QD instead of 150 mg BID). There are in vitro signals of both inhibition (direct and time-dependant) and induction of CYP3A4. The net effect on the sensitive CYP3A4 substrate midazolam was inhibition in this study (midazolam AUC_{inf} and C_{max} increased by 59% and 31%, respectively). It cannot however be firmly concluded if a higher systemic and intestinal exposure would affect the balance between induction and inhibition and also not if a more pronounced inhibition would be observed with the clinical dose. It is reflected in section 4.5 of the SmPC that the effect of a clinical dose may be different. Based on pop-PK data there seems to be no apparent time-dependent PK behaviour of nirogacestat, which gives some reassurance that the balance between induction and inhibition would not be significantly different with the clinical dose compared to the studied dose (nirogacestat being itself a sensitive CYP3SA4 substrate). The proposed recommendation that nirogacestat should not be used together with CYP3A4 substrates that have narrow therapeutic indices also to some extent mitigates the uncertainty regarding the effect of a clinical dose.

In vitro data indicate Pregnane X Receptor (PXR) induction, and the midazolam study cannot be used to confirm the absence of PXR induction as there was both inhibition and induction of CYP3A4 in vitro. Also, the PBPK model cannot be used to assess the impact of nirogacestat on substrates of CYP2B6, CYP2C8, CYP2C9 and CYP2C19. The Applicant has agreed to perform an in vivo CYP induction cocktail study (**RECOMMENDATION**). Until the results of this study are available, the absence of data is adequately reflected in section 4.5 of the SmPC.

Nirogacestat is a teratogen/embryo-foetal toxic drug, and therefore an in vivo study regarding its effects on contraceptive steroids should normally be performed as the drug is intended for use in fertile women. Although the midazolam study demonstrated inhibition as net effect, there are in vitro signals of both inhibition and induction of CYP3A4 and it is not known if both inhibition and induction occur in vivo. There are also in vitro signals of induction of CYP enzymes that are not inhibited by nirogacestat (including CYP2C9, involved in metabolism of ethinyl estradiol, and CYPC19, involved in the metabolism of progestins). The Applicant argued that a PK DDI study would not be sufficient to conclude on the absence of an effect on systemic contraceptives due to potential PD effects and also that the use of hormonal contraception is low in this patient group. A PK/PD study in healthy female volunteers is not considered feasible and a study in patients is challenging; thus it can be agreed to not perform a study with oral contraceptives in this case. Section 4.5 of the SmPC adequately reflects this uncertainty.

Based on part 3 of study NIR-DT-103, nirogacestat is not a clinically relevant inhibitor of P-gp, as the exposure of the sensitive P-gp substrate dabigatran etexilate was not significantly affected by nirogacestat (AUC within BE acceptance criteria, C_{max} almost within BE acceptance criteria and with a point estimate of 97%).

Relationship between plasma concentration and effect

A concentration-QTc analysis is considered supportive of the assessment on the nirogacestat QT prolonging potential. Section 5.1 of the SmPC is based on the results of the analysis which is considered acceptable. The analysis supports that nirogacestat do not cause clinically relevant QT prolongation at therapeutic exposures. However, there are limitations of the analysis which means that the results should be interpreted with caution. Firstly, there seems to be only limited amount of data available from patients with supratherapeutic exposure. Secondly, this is a pooled analysis which could lead to biased results in case the included studies are heterogenous (lack of standardization of measurements, etc).

The predictions of QT prolongation at various exposures of interest seem overall reasonable, although the data should be interpreted with caution due to the highlighted limitations of the analysis. The

selected exposure scenarios that were included in the predictions is not entirely clear. As an example, the QT prolongation was predicted for patients cotreated with strong and moderate CYP3A4 inhibitors which is not fully relevant since moderate and strong inhibitors are to be avoided according to the proposed SmPC. Nevertheless, it is agreed that sufficiently high exposure scenarios have been simulated and they indicate that the mean and 90% CI of the predicted increase in QT is below 10 ms. The overall conclusion that nirogacestat does not cause clinically relevant QT prolongation is based on the totality of evidence also including pre-clinical data and the clinical (cardiovascular) safety database, in addition to the concentration-QT analysis.

Several additional exposure-response analyses for efficacy and safety endpoints were conducted. For most endpoints, no significant exposure-response trends were evident, however, this finding is rather inconclusive due to design limitations in the clinical data; the observed exposure range in the DT patient data was narrow due to the lack of robust dose finding data in DT patients and in study NIR-DT-301, patients were subject to dose reductions which could confound the results. Exposure-response trends were evident for FSH, dose reductions and for phosphate levels. The latter supports the recommend dose reduction in case of Grade 3+ hypophosphatemia AEs.

Dose justification

Overall, a reasonable justification for the proposed posology has been provided. Nevertheless, the proposed dose (150 mg BID) was studied in a considerable number of patients in study NIR-DT-301 which means that it is possible to assess the appropriateness of the proposed dose based on efficacy and safety data.

2.6.4. Conclusions on clinical pharmacology

A rather limited clinical pharmacology package has been included in this application, resulting in several restrictions of nirogacestat use in the SmPC. With the implemented SmPC restrictions the limited clinical pharmacology package supports the granting of the MA.

2.6.5. Clinical efficacy

2.6.5.1. Dose-response studies

Study A8641014

Study A8641014 was a first-in-human, open-label, phase 1 dose-finding study (Messersmith 2015) in participants with advanced solid tumours that was conducted to determine the MTD and Recommended Phase 2 Dose (RP2D) for the clinical development of nirogacestat.

The study had three components which included a dose-finding component in solid tumour patients (ESCALATING-S), an expansion cohort in solid tumour patients (EXPAND-S) and a dose-finding component in T-ALL/LBL patients (ESCALATING-L).

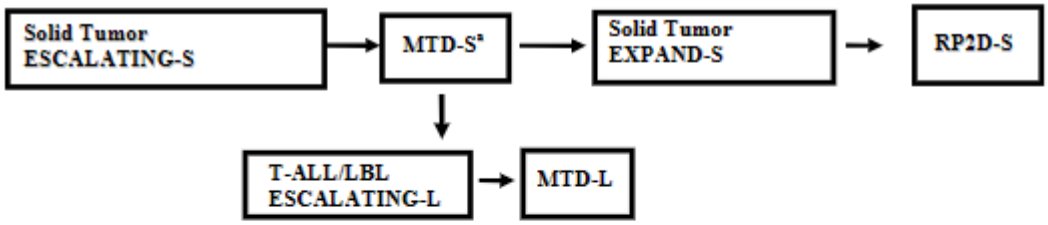
The data cut-off date was 09 January 2013.

Table 14. Study Design Overview

Study Component	Patient Population	Study Treatment	Goal	Number of Patients
ESCALATING-S	Advanced solid tumor	PF-03084014	MTD-S	3+3 design as required
EXPAND-S	Advanced solid tumor	PF-03084014	RP2D-S	Approximately 22
ESCALATING-L	Refractory or relapsed T-ALL/LBL	PF-03084014	MTD-L	3+3 design as required

Source: Protocol (Section 16.1.1)
Abbreviations: ESCALATING-S=dose-finding cohort in solid tumor patients, ESCALATING-L=dose-finding cohort in T-ALL/LBL patients, EXPAND-S=expansion cohort in solid tumor patients, MTD=maximum tolerated dose, MTD-S=MTD in a dose-finding cohort of solid tumor patients, MTD-L=MTD in a dose-finding cohort of T-ALL/LBL patients, RP2D-S=recommended Phase 2 dose in solid tumor patients, T-ALL/LBL=T cell acute lymphoblastic leukaemia/lymphoblastic lymphoma.

Figure 9: Trial Design Workflow



Source: Protocol (Section 16.1.1)
Abbreviations: ESCALATING-S=dose-finding cohort of solid tumor patients, ESCALATING-L=dose-finding cohort of T-ALL/LBL patients, EXPAND-S=expansion cohort in solid tumor patients, MTD=maximum tolerated dose, MTD-S=MTD in a dose-finding cohort of solid tumor patients, MTD-L=MTD in a dose-finding cohort of T-ALL/LBL patients, RP2D-S=recommended Phase 2 dose in solid tumor patients, T-ALL=T-cell Acute lymphoblastic leukaemia, T-LBL=T-cell lymphoblastic lymphoma.
[a] An expansion cohort was planned once the MTD-S was determined.

In the dose-finding portion of the study, the MTD of nirogacestat administered BID continuously for 21 days was established at 220 mg BID in participants with advanced solid tumours. Additional participants were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID.

The primary objectives were to determine the MTD and define the RP2D for nirogacestat when given continuously BID in participants with solid tumours. The dose level of 220 mg BID was determined to be the MTD based on the 3+3 study design of the dose-finding component of the study.

The safety and tolerability of nirogacestat was further evaluated in the study's expansion cohort enrolling additional participants at the 220 and 150 mg BID dose levels. The RP2D was established at 150 mg BID, based upon the higher frequency of Grade 3 treatment-related AEs in the 220 mg BID dosing cohort as compared to that in the 150 mg BID dosing cohort.

2.6.5.2. Main study

Study NIR-DT-301 (DeFi): a randomized (1:1), double-blind, placebo-controlled, phase 3 study of nirogacestat versus placebo in adult patients with progressing Desmoid Tumours/Aggressive Fibromatosis (DT)

Participants remained in the double-blind (DB) phase until one of the following:

- The participant experienced death
- Central imaging review determined that the participant had radiographic progressive disease (using RECIST v 1.1)

- The investigator determined the participant was experiencing clinical progression
- The participant prematurely discontinued study treatment for any reason
- The study was stopped by the sponsor for any reason
- The estimated number of PFS events (approximately 51 events) was observed and the primary PFS analysis was completed (based on statistical assumptions, this was anticipated to be approximately 2 years after the first participant was randomized).

At completion of the DB phase (once the estimated number of events were observed and the primary PFS analysis was completed), the remaining participants in the DB phase had their study treatment assignment unblinded and if eligible, had the opportunity to enrol in the optional open-label extension (OLE) phase.

The first participant randomised: 15 May 2019

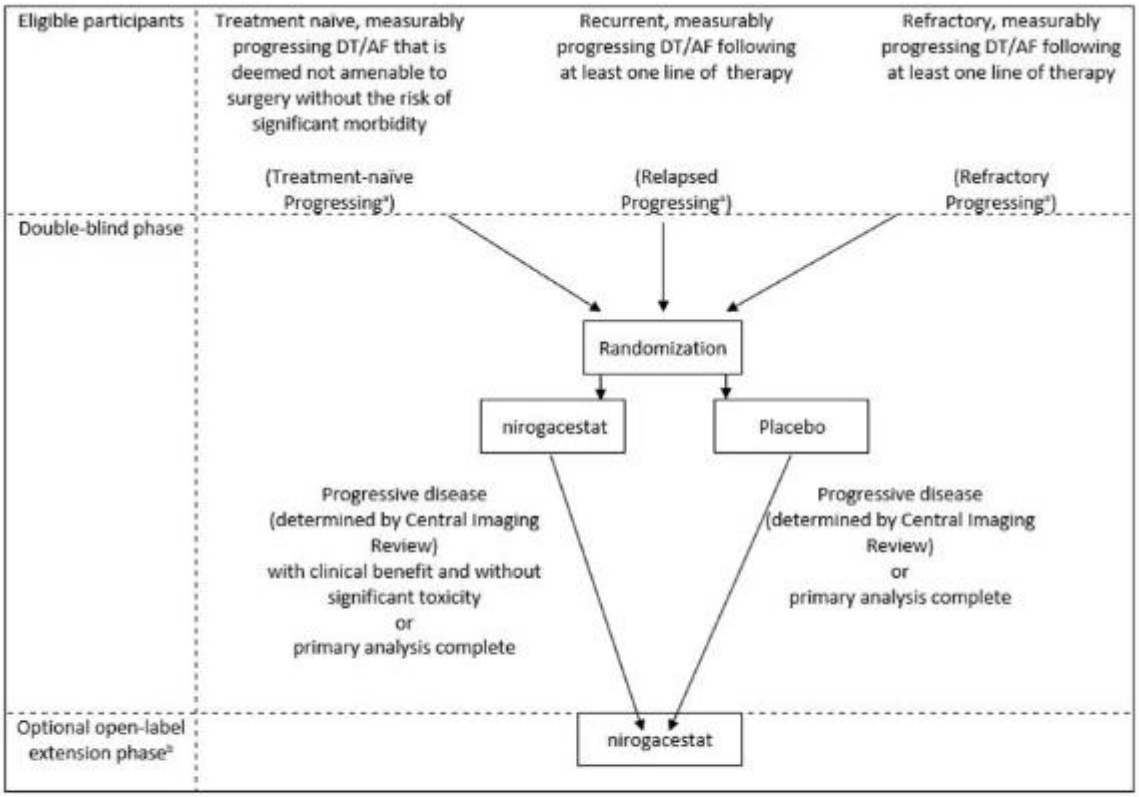
The last patient randomised: 3 Aug 2020

Data cut-off date for primary analysis: 07 April 2022

Database lock: 17 May 2022

Study status: The DB Phase is completed while the Optional Open label extension is ongoing.

Figure 10: Study schema



Abbreviations: DF/AF: desmoid tumor/aggressive fibromatosis.

[a] All eligible participants must have histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by Response Evaluation Criteria in Solid Tumors version 1.1 within 12 months of the screening visit s can (inclusion criteria 2).

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

Methods

- **Study participants**

Approximately 135 participants were planned to be screened to achieve 118 participants randomly assigned to nirogacestat or placebo in a 1:1 ratio.

Key inclusion criteria

1. Participant was at least 18 years of age at the time of signing the ICF.

2. Participant had histologically confirmed DT (by local pathologist prior to informed consent) that had progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.

3. Participant had any of the following:

a) Treatment naïve, measurably progressing DT that was deemed not amenable to surgery without the risk of significant morbidity

b) Recurrent, measurably progressing DT following at least 1 line of therapy (systemic, radiation or surgical)

c) Refractory, measurably progressing DT following at least 1 line of therapy (systemic, radiation or surgical)

4. Participant had a DT where continued progressive disease did not result in immediate significant risk to the participant.

5. Participant agreed to provide archival or new tumour tissue for re-confirmation of disease.

6. If the participant was being treated with any therapy for the treatment of DT, this must have been completed at least 28 days (or 5 half-lives, whichever was longer) prior to first dose of study treatment. All toxicities from prior therapy must have been resolved to ≥ Grade 1 or clinical baseline.

7. Participants who received chronic nonsteroidal anti-inflammatory drugs as treatment for conditions other than DT must have been receiving them prior to the documented DT progressive disease (inclusion criterion 2) and on a stable dose for at least 28 days prior to first dose of study treatment.

8. Participant had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening.

9. Participant gave signed informed consent which included compliance with the requirements and restrictions listed in the informed consent form and in the protocol.

10. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. **Male participants:**
Male participants are eligible to participate if they agree to the following during the treatment period and for at least 90 days after the last dose of study treatment:
- Refrain from donating or preserving sperm;
PLUS either:
- Be abstinent from sexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent;
OR

- Must agree to use a male condom when having sexual intercourse with women of childbearing potential (WOCBP). An additional form of contraception should also be used by the female partner, if she is of childbearing potential.

b. **Female participants:**
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
- Is not of childbearing potential (not WOCBP).
OR
- Is of childbearing potential but is abstinent or using 1 highly effective contraceptive method, during the treatment period and until 6 months after the last dose of active study treatment. A second method of contraception is required if the participant is using hormonal contraception, as coadministration with nirogacestat may alter the plasma concentrations of hormonal contraceptives resulting in reduced efficacy. Additionally, the participant agrees not to harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 6 months after the last dose of active study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
- A WOCBP must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the baseline visit prior to the first dose of study treatment.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Key exclusion criteria

1. Participant had known malabsorption syndrome or preexisting 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.

2. Participant experienced any of the following within 6 months of signing informed consent: Clinically significant cardiac disease (NYHA 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.

3. 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 electrocardiogram [ECG] readings, done approximately 2 to 3 minutes apart and averaged) at screening.

4. Participant was using concomitant medications that were known to prolong the uncorrected QT (QT)/QTcF interval including Class Ia (e.g. quinidine, procainamide, disopromide) and Class III (e.g. dofetilide, ibutilide, sotalol) antiarrhythmics at the time of informed consent. 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.

5. Participant previously received or was receiving therapy with GS inhibitors or anti-Notch antibody therapy.

6. Participant was using any treatment for DT including TKIs, nonsteroidal anti-inflammatory drugs (chronic daily use), or any investigational treatment 28 days (or 5 half-lives, whichever was longer) prior to the first dose of study treatment.

OR

Participant had started any treatment for DT after the documented DT progressive disease (inclusion criteria 2)

- **Treatments**

Patients received 150 mg nirogacestat or placebo orally twice daily in 28-day cycles until disease progression, death, or unacceptable toxicity.

Table 15. Study Treatment Characteristics

Treatment Arm Name	Experimental	Control
Treatment Name	Nirogacestat	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	50 mg	N/A
Dosage Level(s)	150 mg BID	N/A
Route of Administration	Oral	Oral

- **Objectives**

Primary objective

- To determine the efficacy of nirogacestat in adult participants with progressing DT.

Secondary objectives

• To determine the ORR (CR + PR) of nirogacestat in participants with progressing DT.

• To determine DOR.

• Change in PRO measures from baseline over time (defined in NIR-DT-301 SAP).

- **Outcomes/endpoints**

Primary efficacy endpoint

The primary efficacy endpoint is PFS defined as the time from randomisation until the date of assessment of progression or death by any cause (whichever occurs first).

Progression was determined radiographically by independent, blinded Central Imaging Review using RECIST v1.1 or clinically as assessed by the investigator and confirmed via blinded, independent, central review (the latter was added within Amendment 5 [9 February 2021]).

Secondary efficacy endpoints

• ORR as defined in NIR-DT-301 Statistical Analysis Plan (SAP)

  – DOR (in months) as defined in NIR-DT-301 SAP

• To evaluate DT symptoms and impacts using PRO instruments as follows:

- Mean change from baseline at Cycle 10 in BPI Average Pain Intensity (API)

The BPI-SF (hereafter BPI) is a measurement tool for assessing clinical pain and allows participants to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. The BPI consists of 9 questions and utilizes an 11-point NRS from 0-10 (0 being "no pain" and 10 being "highest pain level") with a 24-hour recall period.

- Mean change from baseline at Cycle 10 in GODDESS Desmoid Tumor Symptom Scale Total Symptom Score (DTSS TSS)
- Mean change from baseline at Cycle 10 in GODDESS Desmoid Tumor Impact Scale Physical Functioning (DTIS PF)

The GODDESS tool (Gounder et al. 2023) was developed to measure signs and symptoms of desmoid tumours and their impact on participants' lives, using 2 separate scales – the DTSS and the DTIS. The DTSS consists of 11 items assessing the severity of key signs and symptoms, including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumour location-specific signs/symptoms. The DTIS includes 17 items that measure the impact of DT symptoms on daily life.

- 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 QLQ-C30 Physical Functioning (PF)
- Mean change from baseline at Cycle 10 in EORTC QLQ-C30 Role Functioning (RF)

The EORTC QLQ-C30 is a quality of life (QoL) questionnaire used for assessing the health-related quality of life of cancer participants participating in international clinical trials. EORTC QLQ-C30 version 3.0 was used in this study, with a 7-day recall period. It consists of 30 questions, with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the GHS/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The recall period for each question is "during the past week."

- **Sample size**

The study was initially estimated to enrol 94 participants, but this number was increased to 118 in protocol amendment 2, dated 14 October 2019. At the time, 113 participants had been enrolled.

The initial sample size calculation assumed 90% power, 51 PFS events, a 1-sided type 1 error rate of 0.025, a 10% dropout rate, and a median PFS of 20 months in the nirogacestat arm and 8 months in the placebo arm (corresponding to a hazard ratio of 0.4). The updated sample size calculation was similar; the only difference was that an assumption of 20% spontaneous regression rate was added.

Although the study planned to randomize approximately 118 participants, all eligible participants in Screening at the time of achieving the target enrolment, were allowed to enrol, resulting in a total of 142 participants randomized.

Furthermore, the analysis was performed after 49 events had been reported, instead of the target 51 events, because the Applicant decided to issue the double-blind end of study notification on 07 April 2022. This decision was made because additional follow-up data from the ongoing 14-C-0007 study demonstrated that the original nirogacestat assumption of 20 months to median progression was too

conservative. In addition, no new events had been reported in the NIR-DT-301 study between 20 September 2021 and 07 April 2022.

- **Randomisation and blinding (masking)**

Participants were centrally randomised to nirogacestat or placebo in a 1:1 ratio using an interactive response technology.

Randomisation was stratified by tumour location, intra-abdominal (including mesentery and pelvis) or extra-abdominal (including head/neck, para-spinal, extremities, abdominal wall, chest wall, and other locations). If the participant had multiple target tumours that were located both in the intra- and extra-abdominal location, the tumour was classified as intra-abdominal. The tumour location used for stratification was the same as the reported target lesion(s) used for assessment of the primary endpoint.

For the double-blind phase, the participant, investigator, and all other clinical site personnel were blinded to the assigned treatment allocation. All sponsor personnel were also blinded except for the sponsor's quality assurance designee(s), safety/safety reporting designee(s), and clinical supply material designee(s).

The blind was not to be broken unless one of the following criteria applied:

- Emergency situations

  In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the blind was broken for emergency reasons, the unblinded participant will be permanently discontinued from the study and it not eligible to enter the open-label extension phase.

- Central Imaging Review determined that a participant had radiographic progressive disease (using RECIST v1.1);

  Prior to unblinding in this situation, the following criteria must have been met:

  a) all double-blind end-of-treatment study assessments have been completed in a blinded manner.

  b) All ongoing AEs/SAEs from the double-blind phase have been assessed for causality by the investigator or qualified designee in a blinded manner and recorded in the eCRF.

  c) Sponsor designee has confirmed that the criteria above have been met.

  If eligible, participants may still have entered the open-label extension phase.

- The required number of PFS events have been observed and the primary PFS analysis has been completed.

Unblinding at the clinical site for any other reason was considered a protocol deviation, and the unblinded participant would have been permanently discontinued from the study.

If a participant prematurely discontinued study treatment for any reason other than radiographic progressive disease, including clinical progression, the study treatment allocation was not unblinded.

- **Statistical methods**

Planned analyses

Analysis Populations

The intent-to-treat population was used for efficacy analyses, the per-protocol population was used for supportive analyses, and the safety population was the analysis population for the safety analyses.

These populations were defined as follows:

- Intent-to-treat (ITT): all participants who were enrolled and randomized. Participants were analyzed according to the treatment they were randomized to.
- Per-Protocol (PP): those participants who received study treatment and had no major protocol deviations. Major protocol deviations were defined in the statistical analysis plan prior to unblinding. In addition to major protocol deviations, those participants who met the following criteria were excluded from this population:

  − Did not have confirmed diagnosis of DT per inclusion criterion 2 or were found not to have DT per central confirmatory review

  − Permanent discontinuation due to non-compliance with study treatment

  − Participants who received < 60% of the planned dose (300 mg) of study treatment during their treatment period

  − Mis-randomization.

  Participants were analyzed according to the study treatment actually received.
- Safety: all participants randomly assigned to study treatment and who took at least 1 dose of study treatment. Participants were analyzed according to the treatment they actually received.

Primary efficacy analysis

PFS was calculated from time of randomization to the earlier date of progression or death due to any cause. Participants were counted as events or censored as explained in the table below.

For the analysis of PFS, a stratified log-rank test was performed (1-sided alpha level of 0.025). Kaplan-Meier curves were presented, and HR and the 95% confidence interval (CI) were estimated using a stratified Cox proportional hazards model (stratification variable: tumour location, intra-abdominal vs extra-abdominal).

Table 16: Primary PFS censoring methodology

Situation	Date of Censoring of Event	Outcome
No adequate disease status assessment	Date of randomization	Censored
No documented progression or death	Date of last adequate disease status assessment	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 do 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

A number of sensitivity analyses were planned for the primary endpoint:

a) Calculation of PFS using only events confirmed by central radiographic review per RECIST v1.1

b) Calculation of PFS including all PI-determined clinical progressions

c) Analysis using the PP set using the primary endpoint censoring rules

d) Using the date of the first missing assessment as the date of progression for participants who progressed radiographically right after 2 or more consecutively missed radiological assessments

e) Using local RECIST results of PI selected target tumour, instead of results from the central review, for the 15 participants whose scans are read prior to the implementation of Protocol Amendment 2 (which included the implementation of PI selection of target lesions for central review)

f) Additional sensitivity analyses using only subjects with centrally confirmed diagnosis of DT/AF

g) A sensitivity analysis using interval-censoring methodology for PFS will be performed. When the exact date of progression is not observed due to scheduled assessment, these progression events are considered interval censored. The right side of the interval will be the date of progression as defined in the above table, and the left side of the interval will be the last adjudicated assessment for disease progression before the right side of the interval. If there is no adjudicated assessment before the date of progression, the left side of the interval will be the randomization date. Participants without a PFS qualified event will be right censored with the same censoring rules as specified in the above table.

   A generalized stratified log-rank test stratified by the stratification factor will be performed for treatment comparison using SAS PROC ICLIFETEST (Guo et al. 2014). This procedure will also be used to estimate the survival function for PFS with the

EMICM method, which is a combination of the EM algorithm and iterative convex minorant algorithm. A multiple imputation method will be used to estimate the standard error of the survival function using SEED =138207.

h) In addition, to estimate the median PFS follow-up time at the time of analysis, a time-to censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e. the censored becomes an event and the PFS event becomes censored.

Secondary efficacy endpoints

ORR was calculated for each treatment arm, and the proportions were compared using the Cochran-Mantel-Haenszel test, stratified by randomization factor. 95% confidence intervals (estimated using the exact method) were presented for each arm separately. Response was defined as having a confirmed best overall response (BOR) of CR or PR by RECIST v1.1 during the blinded portion of the study.

Duration of Objective Response (DoOR) was defined as the duration in months from the time measurement criteria are met for CR or PR (whichever came first) until the date of progression or death (whichever came first). DoOR was analyzed using the Kaplan-Meier method based on participants with a documented response (CR or PR) only.

Duration of Stable Disease (DoSD) was defined as the duration in months from the start of treatment until the date of progression or death (whichever came first). DoSD was analyzed using the Kaplan-Meier method based on participants with CR, PR, or SD.

There was no formal testing between the two treatment arms for either DoOR or DoSD because the number of participants available for these analyses was random. The censoring rules were the same as for the primary endpoint.

Each PRO endpoint was analyzed using a restricted maximum likelihood (REML) based repeated measures approach (mixed model for repeated measures (MMRM)). The response variable was the change from baseline to each PRO assessment. Data from all scheduled timepoints were reported, although the analyses were limited to time points at which at least 10 participants had non-missing data in both treatment arms through Cycle 10 (i.e. Cycle 11 and beyond were not included in the model).

The models included the treatment arm and timepoint as fixed-effect categorical factors, the baseline PRO score and stratification factor (target tumour location: intra-abdominal vs extra-abdominal) as fixed effects covariates, and the baseline x time and treatment x time interactions. Both main effects and the interaction terms remained in the model, regardless of significance.

The model assumed unstructured covariance among the within participant repeated measurements. If the algorithm did not converge, a heterogeneous Toeplitz was tried first, followed by heterogeneous autoregressive (ARH) (1) as a covariance structure to achieve convergence. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

As a sensitivity analysis, a pattern mixture model (PMM) was used to assess the robustness of the MMRM estimate with regard to missing data, when the missing at random (MAR) assumption was replaced by assumptions that were likely to be relatively less favourable to the experimental treatment. The MAR assumption was replaced by three different assumptions (patterns) depending on reason and timing of missingness:

- **Missing before or at Cycle 10 due to death:** The worst score (e.g. 10 for DTSS Total Symptom Score) was assigned as a penalty for unobservable values up to Cycle 10 after participant's death. This was applied to both treatment arms.

- **Missing before or at Cycle 10 due to AEs or progression (clinical or radiographic):** A control-based approach was used for the nirogacestat arm. For the placebo arm, multiple imputation under MAR assumption was used.
- **Missing values before or at Cycle 10 with missingness that does not satisfy either of the conditions above:** Data were assumed to be MAR in both treatment arms.

After the endpoint data had been imputed, the endpoints were analysed using MMRM, as in the main analysis.

Planned subgroup analyses

In the statistical analysis plan, several subgroup analyses were planned for the primary endpoint (PFS), as shown in the table below.

Table 17: Subgroup for efficacy analyses

Stratification	
Stratification factor as reported in randomization	
Demographics	
Sex (Male vs Female)	Age (by quartile)
Race (White vs Non-White)	Ethnicity
Geographic region (North America vs the rest of world)	BMI (18.5 kg/m^2,18.5 - < 25 kg/m^2, 25 - < 30 kg/m^2, ≥ 30 kg/m^2)
Disease Characteristics	
Multi-focal disease vs single tumor	Baseline target lesion size by quartile
Baseline target lesion locations[1]	
Prior Treatment	
Any prior therapy (Yes vs No)	Number of prior lines of therapies (0, 1-3, 4+)
Prior systemic therapy (Yes vs No)	Prior surgical treatment (Yes vs No)
Prior radiation treatment (Yes vs No)	Previous exposure with sorafenib (Yes vs No)
Prior chemotherapy exposure (Yes vs No)	Prior tyrosine kinase inhibitor exposure (Yes vs No)
	Desmoid tumor treatment status[2]
Dose Modification	
Dosed per protocol vs reduction (Yes vs No)	Relative Dose Intensity (≤ 80% vs > 80%)
Genetic Mutation	
History of familial adenomatous polyposis (FAP)	Presence of any CTNNB1 mutation, somatic CTNNB1 mutation, or germline CTNNB1 mutation
Presence of any APC mutation, somatic APC mutation, or germline APC mutation	
Adverse Event	
Highest Reported FSH in women of childbearing potential (WOCBP) by range indicator (Low/Normal, High)	WOCBP with events of ovarian dysfunction (as defined by a narrow list of terms per Section 7.5.1) that have resolved versus those that have not resolved
Participants with AEs of Rash or Alopecia (as defined by all narrow terms in Section 7.5.2).	Participants with AEs of Diarrhea within the first 3 cycles

[1] Baseline target lesion location is based on actual target tumor location from the Electronic Database. Baseline target lesion locations: Intra-Abdominal (including mesentery and pelvis) and Extra-Abdominal (including head/neck, para-spinal, extremities, abdominal/chest wall, and other locations). If a participant has multiple target tumors that are located in both the intra and extra-abdominal location, the tumor will be classified as intra-abdominal.
[2] Desmoid tumor treatment status: 1) Treatment naïve, measurably progressing DT/AF, 2) Recurrent, measurably progressing DT/AF following at least one line of therapy, and 3) Refractory, measurably progressing DT/AF following at least one line of therapy

Error probabilities, adjustment for multiplicity and interim analyses

Error probabilities

Hypothesis tests were conducted at the 0.025 level (1 sided). 95% confidence intervals were calculated.

Multiplicity

To control for multiplicity, the primary and secondary efficacy endpoints were tested in a hierarchical stepdown procedure; that is, if the null hypothesis was rejected at the 1-sided significance level of 0.025, the testing could proceed to the next endpoint. If the null hypothesis was not rejected, all subsequent results were considered descriptive only.

The order of the endpoints was not specified in the protocol, but the following order was specified in version 1 of the statistical analysis plan:

- PFS
- ORR
- BPI-SF Average Pain Intensity (API) score
- Desmoid Tumour Symptom Scale (DTSS) Total Symptom Score
- Desmoid Tumour Impact Scale (DTIS) Physical Functioning Domain Score
- EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL)
- EORTC QLQC30 Physical Functioning
- EORTC QLQC30 Role Functioning

Version 1 of the statistical analysis plan was not completed until late in the study on 7 April 2022, which was the same day as the data cut-off date. Database freeze took place one and a half months later on 17 May 2022.

Some of the secondary endpoints were excluded from the hierarchical stepdown procedure: duration of response, tumour volume, and the PROMIS questionnaire. Duration of response was excluded because the Applicant considered this endpoint to be supportive of ORR. Tumour volume was excluded because it was downgraded to being an exploratory endpoint in the statistical analysis plan (according to the Applicant, this was done per FDA comment). The PROMIS questionnaire was also downgraded to being an exploratory endpoint (according to the Applicant, this was to avoid duplications to the other PROs).

Interim analyses

No interim analyses were performed in this study. However, the protocol allowed 1 interim analysis after 26 PFS events (approximately 50% of the total events) had been observed, at which time the study could be stopped for overwhelming efficacy or futility. The protocol specified stopping criteria and an alpha-spending function.

Changes from protocol-specified analyses

Notable changes from the protocol-defined statistical analyses compared to this statistical analysis plan are described below:

I. "Change in tumour volume from baseline as assessed by MRI volumetric" was moved from secondary to exploratory endpoint, per FDA comment.

II. "Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks" was moved from secondary to exploratory endpoint, due to duplications to other PROs.

III. Duration of Response and Duration of Stable disease was removed from the hierarchical testing of secondary endpoints as they were considered supportive of ORR.

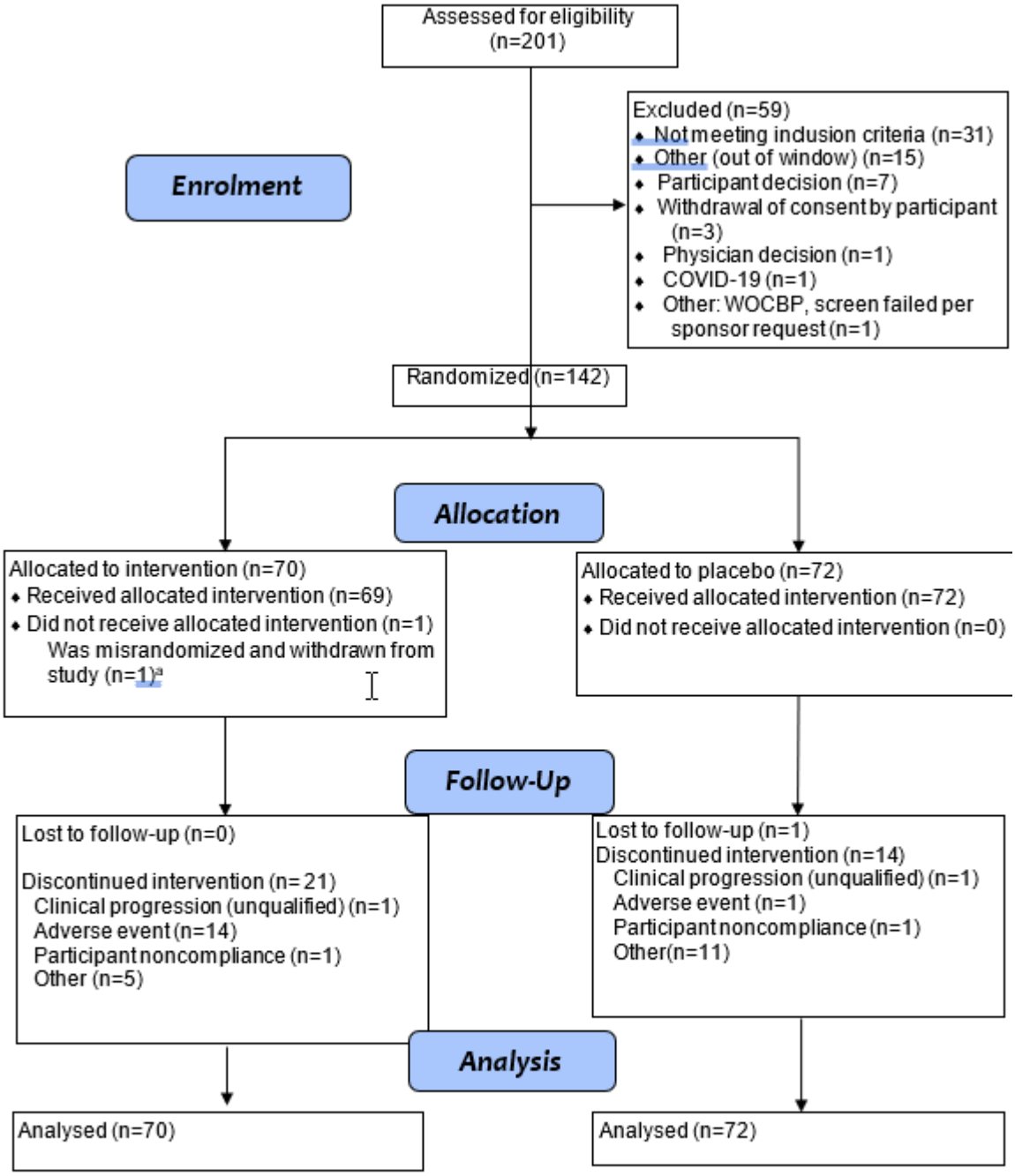
IV. Proportion of participants with improvement in BPI-SF API score at Cycle 10 were removed from the hierarchical testing of secondary endpoints.

V. Estimates of duration of response at Months 6, 12 and 24 were added.

Results

- **Participant flow**

Figure 11: Participant flow Diagram for Double-Blind Phase of NIR-DT-301



Abbreviations: ITT: Intent-to-Treat; WOCBP: women of childbearing potential.
Analysis represents ITT Population, defined as all participants who were enrolled and randomized to study treatment. The ITT Population was the analysis population for the efficacy analyses.

a. This participant was a WOCBP and was considered misrandomised because she was enrolled while WOCBP were on hold for screening after the identification of ovarian toxicity and was therefore not able to be dosed.

- **Recruitment**

The study was conducted in 52 sites across seven countries: Belgium, Canada, Germany, Italy, Netherlands, UK, and the US participated in the study including 42 sites that consented a participant and 37 sites that randomized at least one participant.

The first participant randomised: 15 May 2019

The last patient randomised: 3 August 2020

Data cutoff date for primary analysis: 07 April 2022

Database lock: 17 May 2022

Study status: The DB Phase is completed whilst the Optional Open label extension is ongoing.

The median follow-up time in the DB Phase (ITT population) was 19 months (min 0, max 31) for the nirogacestat treated participants and 11 months (min 0, max 31) for participants receiving placebo.

- **Conduct of the study**

The original global study protocol was finalised on 03 August 2018 and amended five times. In summary, notable changes pertain to the following:

In amendment 2 (14 October 2019) the sample size was increased from 105 to 135 screened patients and from 94 to 118 randomised patients. Considering however that the study is double blinded, it is assumed that this change will not negatively affect the integrity of the study. The second notable amendment pertain to a change in the definition of the primary endpoint PFS (Amendment 5 [9 February 2021]) to include not only radiologically confirmed progression but also clinically observed progression. The Applicant has however performed relevant sensitivity analyses whereby it is demonstrated that this change to the definition of PFS does not negatively affect the integrity of the study.

Protocol amendment 2 (14 October 2019):

Twenty-five participants were initially consented under Protocol Amendment 2, which included the following changes:

- Sample size increased from 105 to 135 screened participants and from 94 to 118 randomized participants.
- Data from Phase 3 sorafenib study were updated (Gounder et al. 2018).
- Updated inclusion/exclusion criteria.
- Added potential risk of nirogacestat to interact with drugs which are substrates of cytochrome P450 3A4.
- Added potential risk of gastric acid reducing agents to reduce absorption and lower exposure prior to dosing of nirogacestat.
- Added new section for AESIs.
- Changed serial PK draw and observation period from 2 hours to 3 hours.
- Updated the methodology for selecting target lesions to specify that target lesions will be selected by the investigator. The location of the target tumour(s) selected by the investigators as the basis for inclusion in the study were documented on the Pre-Randomization RECIST v1.1 Calculation Worksheet.

Protocol amendment 5 (09 February 2021)

No participants were initially consented under Protocol Amendment 5 as screening had previously closed. This amendment included the following changes:

- Revised the definition of PFS to include events of clinical progression in the analysis of PFS for the primary endpoint.

- **Baseline data**

Table 18: Demographics and Other Baseline Characteristics (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Sex, n (%)			
Male	25 (36)	25 (35)	50 (35)
Female	45 (64)	47 (65)	92 (65)
Women of childbearing potential[a], n (%)			
Yes	37 (82)	37 (79)	74 (80)
No	8 (18)	10 (21)	18 (20)
Infertility history, n (%)			
Yes	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	1 (4)	1 (2)
No	25 (100)	23 (92)	48 (96)
Unknown	0	1 (4)	1 (2)
Infertility history – females[a], n (%)			
Yes	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 (8)	1 (3)	4 (5)
History of menstrual irregularities, n (%)			
Yes	11 (30)	10 (27)	21 (28)
No	23 (62)	26 (70)	49 (66)
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)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
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	3 (4)	3 (2)
Not reported	2 (3)	5 (7)	7 (5)
Age at informed consent (years)			
n	70	72	142
Mean (SD)	37.5 (14.43)	37.0 (12.89)	37.2 (13.62)
Median (Q1, Q3)	33.5 (26, 50)	34.5 (28, 44)	34.0 (27, 46)
Min, max	18, 73	18, 76	18, 76
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)
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 (%)			
North America	44 (63)	53 (74)	97 (68)
Europe	26 (37)	19 (26)	45 (32)
Country			

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
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)
United States	40 (57)	50 (69)	90 (63)

Source: Table 14.1.2.1.1.
Abbreviations: BMI: body mass index; ITT: intent-to-treat; max: maximum; min: minimum; Q: quartile; SD: standard deviation.
Note: Percentages were based on the number of participants in the ITT Population, unless otherwise noted.
Note: Infertility and child-bearing potential were defined by the investigator.
[a] Percentages were based on the number of the sex summarized.
[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.

In addition concerning the ECOG status, 73% had an ECOG performance status (PS) of 0, 27% had an ECOG PS of 1, and < 1% had an ECOG PS of 2.

Table 19: Disease Characteristics (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Time since diagnosis to randomization (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 tumor treatment status, n (%)			
Treatment I	18 (26)	14 (19)	32 (23)
Refractory	43 (61)	55 (76)	98 (69)
Recurrent	9 (13)	3 (4)	12 (8)
Number of target tumors, n (%)			
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 tumors			
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 tumor 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 tumor size per RECIST (mm)[c]			
N	69	72	141

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
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 tumor size group (mm), n (%)[c]			
Baseline target tumor size < 68.90	19 (27)	16 (22)	35 (25)
Baseline target tumor size 68.90 to < 100.35	21 (30)	14 (19)	35 (25)
Baseline target tumor size 100.35 to < 155.35	15 (21)	20 (28)	35 (25)
Baseline target tumor size ≥ 155.35	14 (20)	22 (31)	36 (25)
Number of non-target tumors, 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 tumors			
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 tumors where tumor 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 tumor 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

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
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 Mutation, n (%)			
Yes	54 (77)	58 (81)	112 (79)
No	15 (21)	13 (18)	28 (20)
Unknown	1 (1)	1 (1)	2 (1)
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 Germline Mutation, n (%)			
Yes	9 (13)	12 (17)	21 (15)
No	59 (84)	59 (82)	118 (83)
Unknown	2 (3)	1 (1)	3 (2)
Any APC Mutation, n (%)			
Yes	13 (19)	16 (22)	29 (20)
No	56 (80)	55 (76)	111 (78)
Unknown	1 (1)	1 (1)	2 (1)
Any APC Somatic Mutation, n (%)			
Yes	11 (16)	11 (15)	22 (15)
No	41 (59)	43 (60)	84 (59)
Unknown	18 (26)	18 (25)	36 (25)
Any APC Germline Mutation, n (%)			
Yes	9 (13)	12 (17)	21 (15)
No	59 (84)	59 (82)	118 (83)
Unknown	2 (3)	1 (1)	3 (2)
Any CTNNB1 Mutation, n (%)			
Yes	43 (61)	42 (58)	85 (60)
No	26 (37)	29 (40)	55 (39)
Unknown	1 (1)	1 (1)	2 (1)
Any CTNNB1 Somatic Mutation, n (%)			

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Any CTNNB1 Somatic Mutation, n (%)			
Yes	43 (61)	42 (58)	85 (60)
No	9 (13)	12 (17)	21 (15)
Unknown	18 (26)	18 (25)	36 (25)
Any CTNNB1 Germline Mutation, n (%)			
Yes	0	0	0
No	68 (97)	71 (99)	139 (98)
Unknown	2 (3)	1 (1)	3 (2)

Source: Table 14.1.2.2.1.

Abbreviations: FAP: Familial adenomatous polyposis; ITT: intent-to-treat; max: maximum; min: minimum; Q: quantile; SD: standard deviation.

Note: Percentages were based on the number of participants in the Intent-to-Treat Population, unless otherwise noted.

Note: Per Listing 16.2.4.2, Participant PPD had a target lesion located in the buttock; however, the number of target lesions was not reported. Due to this missing data, this participant was not included in the summary of number of target lesions.

Note: Number of target and non-target tumors and location(s) of tumors were as assessed by the central reviewers. Number of target tumors was not included for participant PPD who was not treated.

[a] Time since diagnosis to randomization was calculated as: (Date of randomization – Date of Diagnosis + 1)/30.4375. Diagnosis dates were imputed where necessary.

[b] Participants could have had a tumor that presented in more than one location. Therefore, population counts could not be summed across the locations.

[c] Baseline target tumor size was calculated by summing the longest diameter for each tumor and reviewer and then averaging the sum across reviewers.

Table 20: Prior desmoid tumour therapies Intent to treat Population

	Nirogacestat (N=70)	Placebo (N=72)	Total (N=142)
Radiation Therapy, n (%)			
Yes	16 (23%)	16 (22%)	32 (23%)
No	54 (77%)	56 (78%)	110 (77%)
Surgery Therapy, n (%)			
Yes	31 (44%)	44 (61%)	75 (53%)
No	39 (56%)	28 (39%)	67 (47%)
Systemic Therapy, n (%)			
Yes	43 (61%)	44 (61%)	87 (61%)
No	27 (39%)	28 (39%)	55 (39%)
Chemotherapy, n (%)			
Yes	24 (34%)	27 (38%)	51 (36%)
No	46 (66%)	45 (63%)	91 (64%)

Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022

Note: Percentages were based on the number of participants in the Intent-to-Treat Population.

[1] Participant may have received more than one prior systemic therapy; thus counts cannot be summed across types of systemic therapies.

[2] Best Response was presented once per participant as the Best observed objective response from all lines of therapy.

[3] Time from most recent prior systemic therapy to randomization was calculated as: (Date of Randomization - Date of Stop of Most Recent Prior Systemic Therapy + 1)/30.4375. Partial dates for date of stop of most recent prior systemic therapy were imputed per the Statistical Analysis Plan.

Source: Listing 16.2.4.6, Listing 16.2.4.7 and Listing 16.2.4.8, Dataset(s): ADSL, ADCM, Program: t_prior_th.sas, Date/time of run: 24JUL2023:11:13

- **Numbers analysed**

Table 21: Participant Disposition (All Participants Enrolled)

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
Participants screened[a]			201
Participants randomized	70	72	142
Intent-to-treat Population[b]	70 (100)	72 (100)	142 (100)
Safety Population[c]	69 (99)	72 (100)	141 (>99)
Per-protocol Population[d]	62 (89)	67 (93)	129 (91)
Participants by randomized strata			
Intra-abdominal	17 (24)	18 (25)	35 (25)
Extra-abdominal	53 (76)	54 (75)	107 (75)
Participants by CRF reported tumor location			
Intra-abdominal	16 (23)	17 (24)	33 (23)
Extra-abdominal	54 (77)	55 (76)	109 (77)
DB treatment status			
Progressions meeting study endpoint[e]	12 (17)	35 (49)	47 (33)
Radiographic progressive disease	11 (16)	29 (40)	40 (28)
Qualified clinical progression	1 (1)	6 (8)	7 (5)
Completed DB treatment due to achieving the target event rate	0	0	0
Ongoing	36 (51)	23 (32)	59 (42)
Premature discontinuation of DB treatment	21 (30)	14 (19)	35 (25)
Clinical progression (unqualified)	1 (1)	1 (1)	2 (1)
Adverse event	14 (20)	1 (1)	15 (11)
Participant non-compliance	1 (1)	1 (1)	2 (1)
COVID-19[f]	0	0	0
Other	5 (7)	11 (15)	16 (11)
Study status – DB Phase			
Discontinued	30 (43)	21 (29)	51 (36)
Primary reason for discontinuation – DB Phase			
Death	0	1 (1)	1 (<1)
Radiographic progressive disease	7 (10)	1 (1)	8 (6)
Qualified clinical progression	1 (1)	6 (8)	7 (5)
Unqualified clinical progression	1 (1)	1 (1)	2 (1)

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
Withdrawal of consent by participant	4 (6)	7 (10)	11 (8)
Adverse event	11 (16)	1 (1)	12 (8)
Physician decision	2 (3)	0	2 (1)
Sponsor decision	0	0	0
Lost to follow-up	0	1 (1)	1 (<1)
COVID-19[f]	0	0	0
Other	4 (6)	3 (4)	7 (5)
Participants who were able to continue into the Open-label Phase[g]	11 (16)	29 (40)	40 (28)
Participants who enrolled in the Open-label Phase[h]	4 (36)	28 (97)	32 (80)
Participants who did not enroll in Open-label Phase[h]	7 (64)	1 (3)	8 (20)

Source: Table 14.1.1.1.1.

Abbreviations: AE: adverse event; CRF: case report form; DB: double-blind.

Note: Percentages were based out of the number of participants randomized in each arm (unless otherwise specified).

[a] Participants screened included all participants who signed a DB informed consent.

[b] The Intent-to-Treat Population consisted of all participants who were enrolled and randomized to study treatment.

[c] The Safety Population consisted of all randomized participants who took at least 1 dose of study treatment.

[d] The Per-Protocol Population consisted of all those participants who received study treatment, had no major protocol deviations, were not mis-randomized, had confirmed DTs/aggressive fibromatosis per Central Review, and did not discontinue due to non-compliance with study treatment.

[e] Number of progression events reflected total events in the discontinuation of study treatment not in the analysis of PFS.

[f] Discontinuations due to COVID-19 were COVID-19 related restrictions. Discontinuation due to COVID-19 related AEs were summarized as AEs.

[g] Participants who were allowed to transition into the Open-label Extension of the study included those participants who experienced radiographic progression confirmed by central review or who were ongoing at the time the target event rate was achieved.

[h] Percentages were out of the number of participants who were able to continue into the Open-label Extension.

- **Outcomes and estimation**

Primary endpoint: Progression free survival (PFS)

Table 22: Summary of PFS from Randomization – DB Phase (ITT Population)

	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)
Number of participants censored, n (%) Reason for censoring:	58 (83)	35 (49)
No adequate disease status assessment	4 (6)	1 (1)
No documented progression or death	53 (76)	32 (44)
Early discontinuation by study investigator and not adjudicated as qualified event	1 (1)	1 (1)
New anticancer therapy or procedure started prior to radiographic or clinical progression	0	1 (1)
Probability of being event free at Month 6 (95% CI[a])	91.8 (81.4, 96.5)	69.8 (57.5, 79.2)
Probability of being event free at Month 12 (95% CI[a])	84.7 (72.5, 91.7)	52.8 (40.1, 63.9)
Probability of being event free at Month 24 (95% CI[a])	76.4 (60.5, 86.6)	44.0 (31.6, 55.7)
Kaplan-Meier estimates of time to event (months) Quartiles (95% CI):		
25%	NE (9.3, NE)	5.6 (3.2, 8.3)
50%	NE (NE, NE)	15.1 (8.4, NE)
75%	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.29 (0.15, 0.55)	
One-sided p-value[c]	< 0.001	

Reference: NIR-DT-301 CSR Table 14.2.1.1.1.1.1.

Abbreviations: CI: confidence interval; DB: double-blind; ITT: intent-to-treat; NE: not estimable; PFS: progression-free survival.

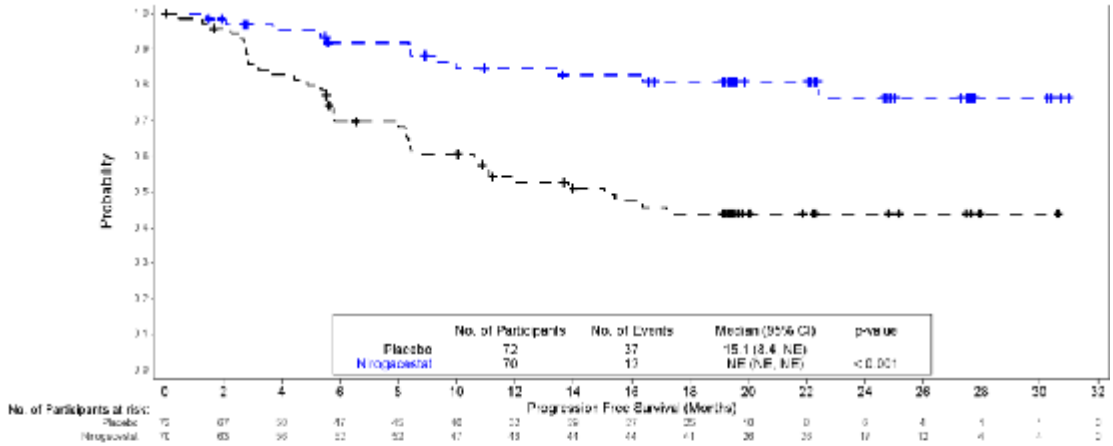
Note: Progression free survival was calculated as: (earliest date of death/(centrally-read radiographic/qualified clinical) progression or censoring- randomization date +1)/30.4375. Censoring was defined in NIR-DT-301 SAP Section 4.3.1.

Note: Qualified clinical progression events were clinical progression events assessed by the investigator that were adjudicated by an independent Endpoint Adjudication Committee.

Note: Percentages were based on the number of participants in the ITT population.

[a] Calculated from the product-limit method.

Figure 12: Kaplan-Meier Plot of PFS from Randomization – DB Phase (ITT Population)



Reference: NIR-DT-301 CSR Figure 14.2.1.1.1.2.1.

Abbreviations: CI: confidence interval; CSR: clinical study report; DB: double-blind; ITT: Intent-to-Treat; PFS: progression-free survival.

Note: PFS was calculated as: (date of death or [radiographic/qualified clinical] progression or censoring date – randomization date + 1)/30.4375. Censoring was defined in NIR-DT-301 SAP Section 4.3.1.

Note: Qualified clinical progression events were clinical progression events assessed by the investigator that were adjudicated by an independent Endpoint Adjudication Committee.

Note: Median and 95% CIs were estimated from the Kaplan-Meier method.

Upon request, the Applicant provided the following table to clarify the number of potentially informatively censored participants.

Table 23: Participant Disposition by Progression-Free Survival Status and Treatment Status – Double-Blind Phase – Intent-to-Treat Population

Type of Event or Censoring	Treatment Status Discontinuation Reason	Nirogacestat (N=70) n (%)	Placebo (N=72) n (%)
Number of participants with event	**Discontinued**	**12 (17)**	**37 (51)**
Type of event			
Radiographic progression	Met study endpoint (radiographic progressive disease - as confirmed by central review)	11 (16)	29 (40)
	Other*	0	1 (1)
Qualified clinical progression	Met study endpoint (qualified clinical progression)	1 (1)	6 (8)
Death before progression	Other**	0	1 (1)
Number of participants censored		**58 (83)**	**35 (49)**
Non-informative censoring	On treatment	36 (51)	23 (32)
Potential informative censoring	Discontinued	22 (31)	12 (17)
	Adverse event	14 (20)	1 (1)
	Noncompliance	1 (1)	1 (1)
	Other	5 (7)	9 (13)
	Participant mis-randomised and discontinued from the study on physician decision without treatment	1 (1)	0
	Unqualified clinical progression	1 (1)	1 (1)

Database lock: 17May2022; data cutoff: 07Apr2022

Abbreviations: N: number of participants in the Intent-To-Treat Population; n: number of participants in a category.

Note: Percentages were based on the number of participants in the Intent-To-Treat Population.

'Non-informative censoring': participants were censored for reaching data cut-off.

'Potential informative censoring': participants were censored due to withdrawal from study.

*Other: the participant dropped from the study due to patient decision. She had suspected progression of disease but did not wish to delay additional treatment for central review of her imaging.

**Other: drug hold for planned surgery.

Secondary endpoints:

ORR:

Table 24: Summary of ORR – DB Phase (ITT Population)

BOR - Confirmed, n (%)	Nirogacestat (N = 70)	Placebo (N = 72)
CR	5 (7)	0
PR	24 (34)	6 (8)
SD	35 (50)	55 (76)
Progressive disease	1 (1)	10 (14)
NE	4 (6)	1 (1)
ORR (ORR: CR+PR)[a], n (%)	29 (41)	6 (8)
95% CI[b], %	(29.8, 53.8)	(3.1, 17.3)
Two-sided p-value[c]	< 0.001	
DCR (CR+PR+SD)[d], n (%)	64 (91)	61 (85)
95% CI[b], %	(82.3, 96.8)	(74.3, 92.1)
Two-sided p-value[c]	0.218	

Reference: NIR-DT-301 CSR, Table 14.2.2.1.1.

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; DB: double-blind; DCR: disease control rate; ITT: Intent-to-Treat; NE: not estimable; ORR: objective response rate; PR: partial response; SD: stable disease; v: version.

Note: Confirmed best response was defined as having at least 2 sequential scans demonstrating CR or PR.

[a] Objective response rate was defined as having a confirmed best response of CR or PR by RECIST v1.1.

[b] Obtained using exact method based on binomial distribution.

[c] Obtained using a Cochran-Mantel-Haenszel test for general association stratified by tumor location. Placebo was the reference treatment.

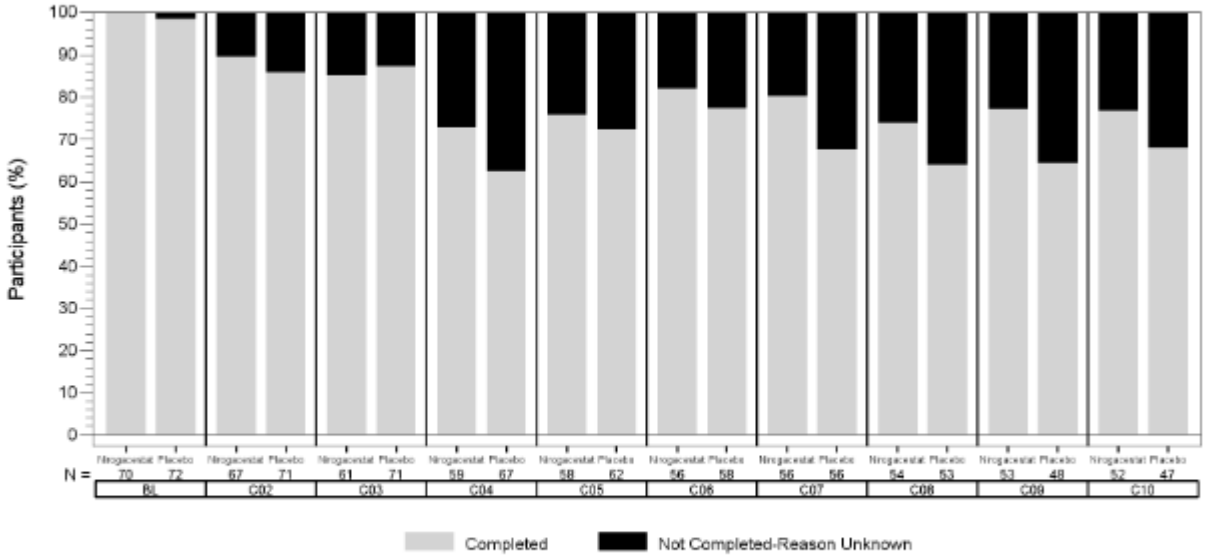
[d] Disease control rate was defined as having a best response of CR, PR, or SD by RECIST v1.1.

PRO assessments

PRO compliance rate

All PRO instruments examined exhibited similar compliance rates. Through Cycle 3, both arms gradually declined at the same rate to ~85%; at Cycle 4, the arms diverged with nirogacestat dropping to ~75% whereas placebo dropped to the 60% range (likely due to a greater rate of disease progression). Whilst there was some variation by Cycle and PRO, the 75% to 60% ratio largely persisted through Cycle 10.

Figure 14.1.1.4.8.1.1
Figure of Compliance Rate for DTSS - Double-Blind Phase
Intent-to-Treat Population



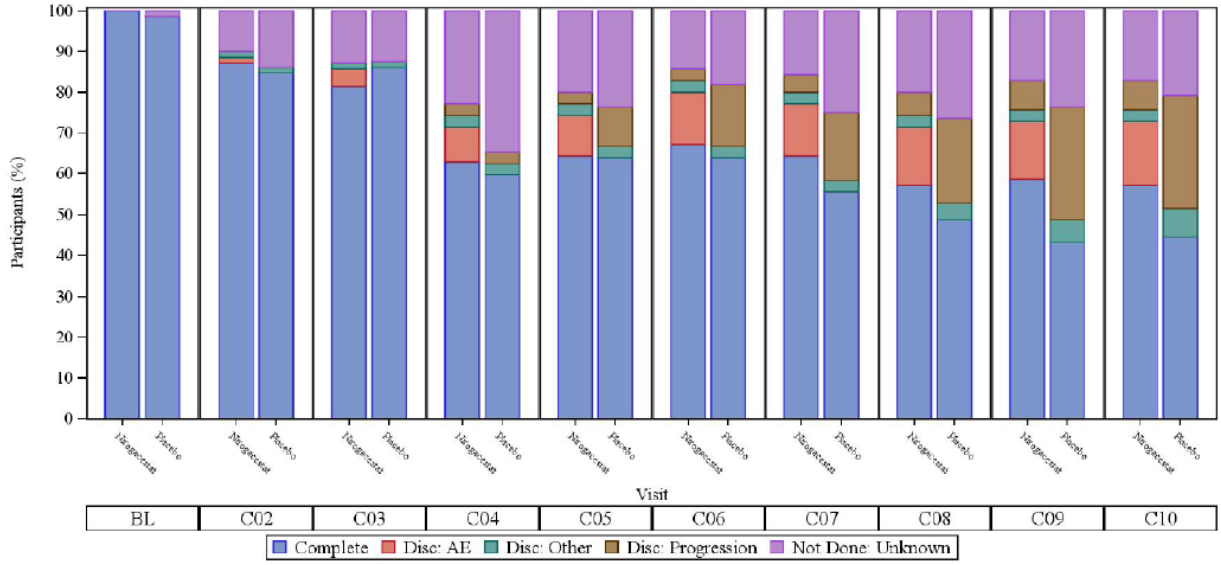
Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022
DTSS = Desmoid Tumor Symptom Scale
Note: Minimum requirements for scoring was defined as at least one scale with non-missing values. Scales were calculated: (1) if all questions within a scale were non-missing for a day (2) a weekly average was calculated if 4 or more daily scores could be calculated.
Source: Listing 16.2.6.7.1.1.1, Dataset(s): ADSL, ADQV, Program: f_icr.sas, Date/time of run: 25JUL2023: 9:39

PRO completion rate

All PRO instruments examined (DTSS, DTIS, BPI, QLQ-C30) exhibited similar completion rates. Both arms exhibited the same trajectory, with values abruptly falling from ~80% to 60% between Cycle 3 and 4 before stabilizing through Cycle 6. At Cycle 7 the arms diverged with participants in the nirogacestat arm discontinuing at a slower rate from AEs compared to the placebo arm, whose

participants were more rapidly lost to disease progression. By Cycle 10, the completion rate for nirogacestat was ~55% vs. ~40% for placebo.

Figure 13: Completion Rate for DTSS – Double-Blind Phase - ITT



Note. Completion rate is defined the percentage of the ITT population who met the minimum requirements for scoring

Abbreviations: DTSS =Desmoid Tumor Symptom scale

Summary table of PRO results

Table 25: Secondary PRO Endpoints: Change from Baseline at Cycle 10

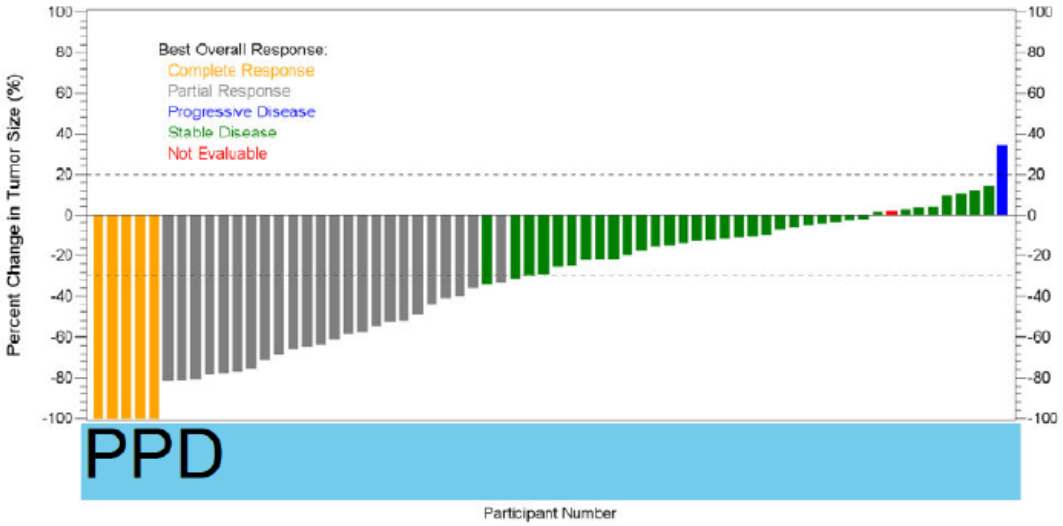
PRO Assessment	LS mean (SE)		LS mean difference (SE)	p-value
	Nirogacestat	Placebo		
GODDESS DTSS	-1.110 (0.2316)	0.457 (0.2355)	-1.567 (0.3178)	<0.001
GODDESS DTIS	-0.613 (0.0984)	0.094 (0.1041)	-0.706 (0.1384)	<0.001
BPI-SF API	-1.583 (0.2897)	-0.241 (0.2931)	-1.342 (0.3976)	<0.001
EORTC QLQ-C30				
Global health status/HRQoL	2.935 (3.0385)	-8.466 (3.3218)	11.401 (4.4211)	0.006
Physical Functioning	9.143 (1.7722)	-5.225 (1.9309)	14.368 (2.5415)	<0.001
Role functioning	13.293 (3.1303)	-5.590 (3.3932)	18.884 (4.5067)	<0.001

Reference: NIR-DT-301 CSR Table 14.2.13.3.3.1, Table 14.2.14.3.3.1, Table 14.2.15.3.3.1, and Table 14.2.16.3.3

Abbreviations: API: Average Pain Intensity; BPI-SF: Brief Pain Inventory – Short Form; 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; GODDESS: GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; HRQoL: health-related quality of life; LS mean: least squares mean; PRO: patient-reported outcome; SE: standard error.

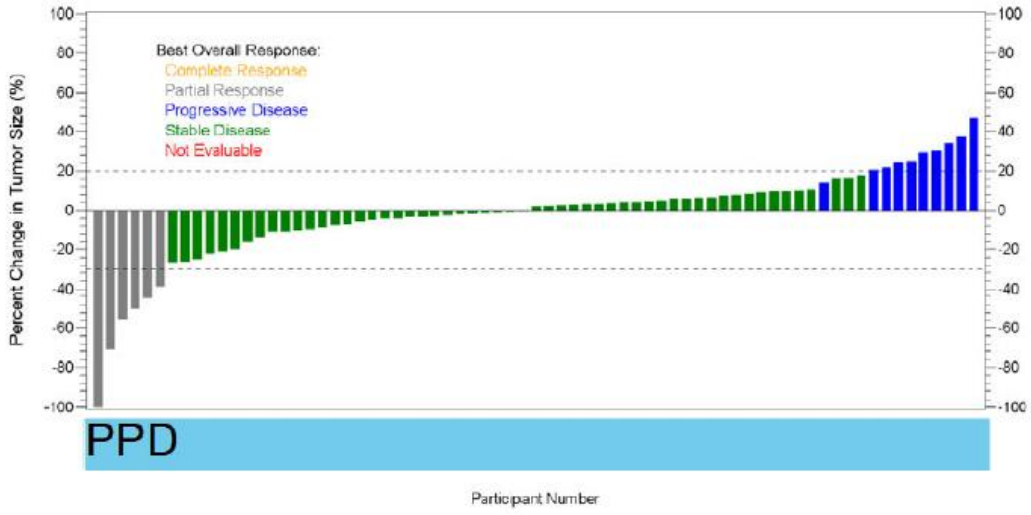
Exploratory/supportive endpoints

Figure 14: Waterfall Plot of Lowest Percent Change from Baseline in Tumour Size by RECIST 1.1 in Nirogacestat Arm – DB Phase (ITT Population)



Source: Figure 14.2.1.4.1.1.
Abbreviations: DB: double-blind; ITT: intent-to-treat; RECIST: Response Evaluation Criteria in Solid Tumours.

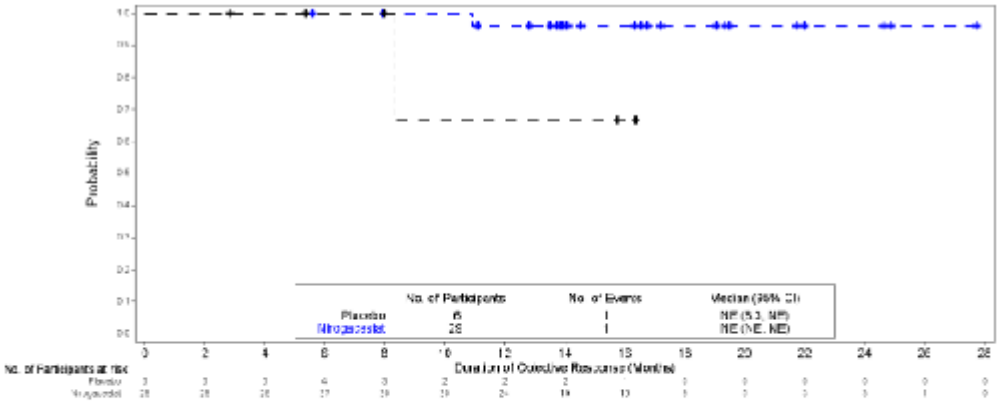
Figure 15: Waterfall Plot of Lowest Percent Change from Baseline in Tumour Size by RECIST 1.1 in Placebo Arm – DB Phase (ITT Population)



Source: Figure 14.2.1.4.1.1.
Abbreviations: DB: double-blind; ITT: intent-to-treat; RECIST: Response Evaluation Criteria in Solid Tumours.

Duration of Response

Figure 16: Kaplan-Meier Plot of Duration of Objective Response – DB Phase (ITT Population)



Reference: NIR-DT-301 CSR, Figure 14.2.3.2.1.

Abbreviations: CI: confidence interval; DB: double-blind; DOR: duration of response; ITT: intent-to-treat; NE: not estimable.

Note: DOR was calculated as: (date of death or disease progression - date of documented complete response or partial response + 1)/30.4375, if death or documented disease progression occurred OR, (date of last adequate disease status assessment - date of documented complete response or partial response + 1)/30.4375, if censored due to no documented progression or death or early discontinuation by study investigator OR, (date of last adequate disease status assessment before new therapy - date of documented complete response or partial response + 1)/30.4375, if censored due to new anticancer therapy or procedure.

Note: Median and 95% CI were estimated from Kaplan-Meier method.

- **Ancillary analyses**

Post hoc exploratory analyses for the treatment naïve, progressing DT subgroup in study NIR-DT-301

In terms of the primary endpoint PFS, the HR for the treatment naïve population was 0.77 (95% CI: 0.18, 3.23) with 3/18 (17%) progression events in the nirogacestat arm versus 5/14 (36%) in the placebo arm. For comparison, in the overall population at the data cut-off date of 7th of April 2022, the HR was 0.29 (95% CI 0.15, 0.55), p-value < 0.001 (one-sided).

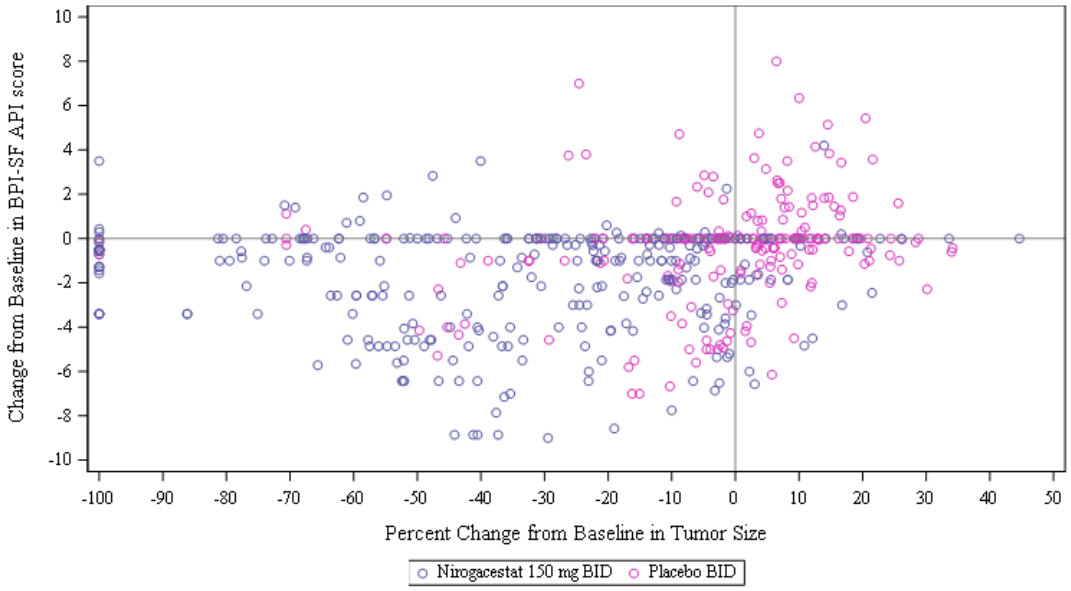
ORR was 50% (95% CI: 26.0, 74.0) for the treatment naïve population nirogacestat arm compared to 7% (95% CI: 0.2, 33.9) for the placebo arm.

The safety profile in the treatment naïve population appears consistent with what was observed for the overall population.

Post hoc analysis plotting change in BPI pain score as a function of change in tumour size

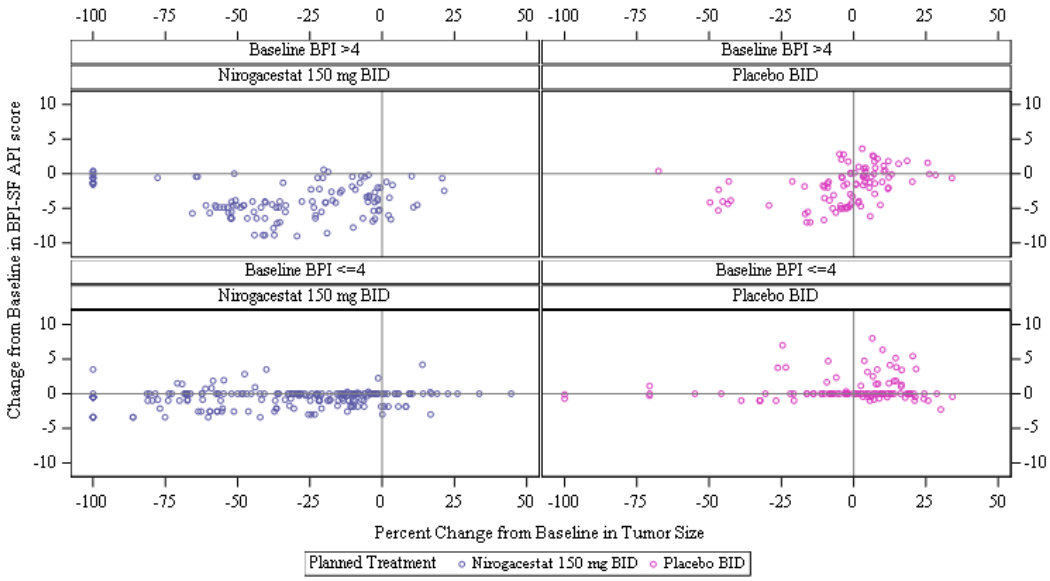
Upon CHMP's request, the Applicant plotted change in BPI pain score as a function of change in tumour size. The purpose of this analysis was to assess the possibility of functional unblinding.

Figure 17: Change in BPI-SF API Score from Baseline vs Percent Change of Tumour Size from Baseline in Double-Blind Phase – Intent-to-Treat Population



Abbreviations: BID: twice daily; BPI-SF API: Brief Pain Inventory Short Form Average Pain Inventory.
Database lock: 17May2022; data cutoff: 07Apr2022.
Note: Tumour size at each tumour assessment was calculated as the sum of the longest diameter of target lesions.

Figure 18: Change in BPI-SF API Score from Baseline vs Percent Change of Tumour Size from Baseline by BPI-SF API Score at Baseline in Double-Blind Phase – Intent-to-Treat Population



Abbreviations: BID: twice daily; BPI-SF API: Brief Pain Inventory Short Form Average Pain Inventory.
Database lock: 17May2022; data cutoff: 07Apr2022.
Note: Tumour size at each tumour assessment was calculated as the sum of the longest diameter of target lesions.

Table 26: Sensitivity Analysis: Comparison of MMRM vs PMM Estimates of Differences Between Arms at Cycle 10 for Select PROs

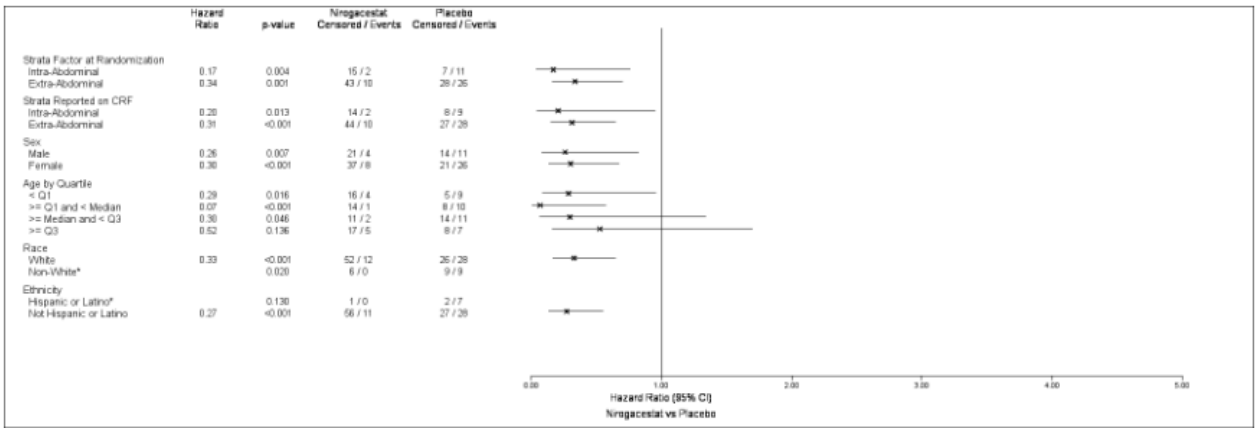
Measure	Scale Range	Better Value	MMRM			PMM		
			Difference	95% CI	*p*	Difference	95% CI	*p*
Secondary Endpoints								
BPI Worst Pain	0-10	↓	-1.342	[-2.131, -0.553]	<.001	-1.170	[-1.886, -0.455]	<.001
DTSS Total Symptom	0-10	↓	-1.567	[-2.197, -0.937]	<.001	-1.368	[-2.007, -0.730]	<.001
DTIS Physical Function	1-5	↓	-0.706	[-0.981, -0.432]	<.001	-0.623	[-0.883, -0.363]	<.001
QLQ-C30								
Global Health Status / QoL	0-100	↑	11.401	[2.602, 20.200]	0.006	9.482	[1.494, 17.471]	.010
Physical Function	0-100	↑	14.368	[9.313, 19.424]	<.001	10.742	[5.953, 15.530]	<.001
Role Function	0-100	↑	18.884	[9.937, 27.830]	<.001	15.182	[6.770, 23.595]	<.001
Exploratory Endpoints								
DTSS								
Total Symptom (5-item)	0-10	↓	-1.579	[-2.160, -0.998]	<.001	-1.365	[-2.016, -0.714]	<.001
Pain	0-10	↓	-2.118	[-2.863, -1.373]	<.001	-1.779	[-2.562, -0.996]	<.001
QLQ-C30 Pain	0-100	↓	-29.361	[-38.872, -19.850]	<.001	-23.799	[-32.532, -15.067]	<.001
PROMIS (T-score)								
Physical Function (10a)	0-100	↑	6.011	[3.823, 8.200]	<.001	5.068	[2.871, 7.265]	<.001

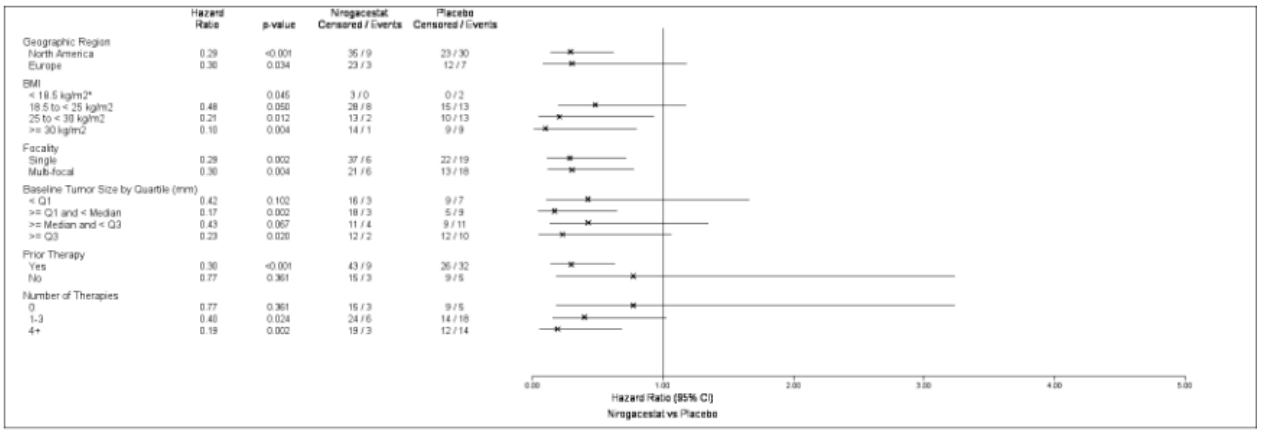
Notes. Difference = nirogacestat - placebo value. For a given measure, the number of cycles included in the PMM model matched those used in the MMRM

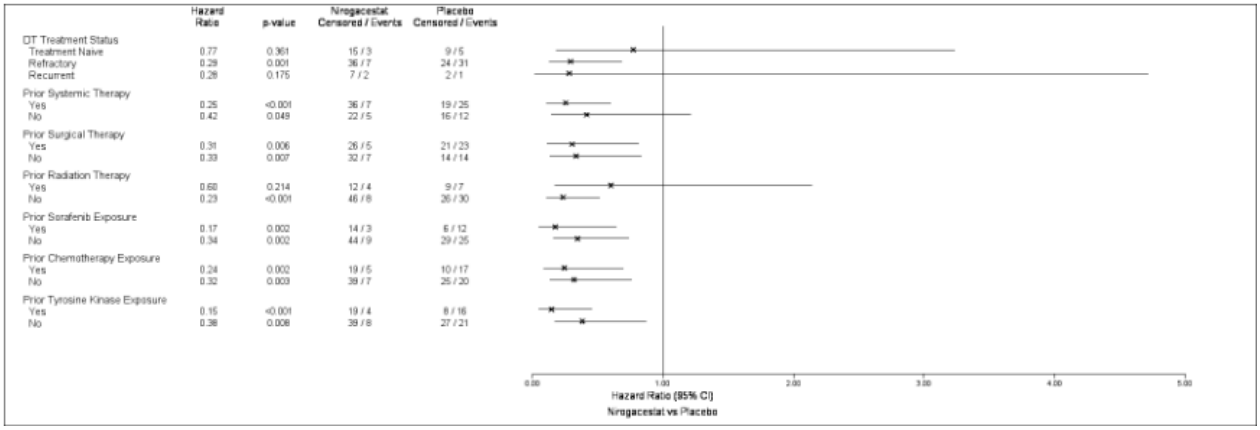
BPI = Brief Pain Inventory Short Form; DTIS = Desmoid Tumor Impact Scale; DTSS = Desmoid Tumor Symptom Scale; QLQ-C30 = European Organisations for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MMRM = Mixed model repeated measures; PMM = Pattern mixture model; PRO = Patient-Reported Outcomes Measure

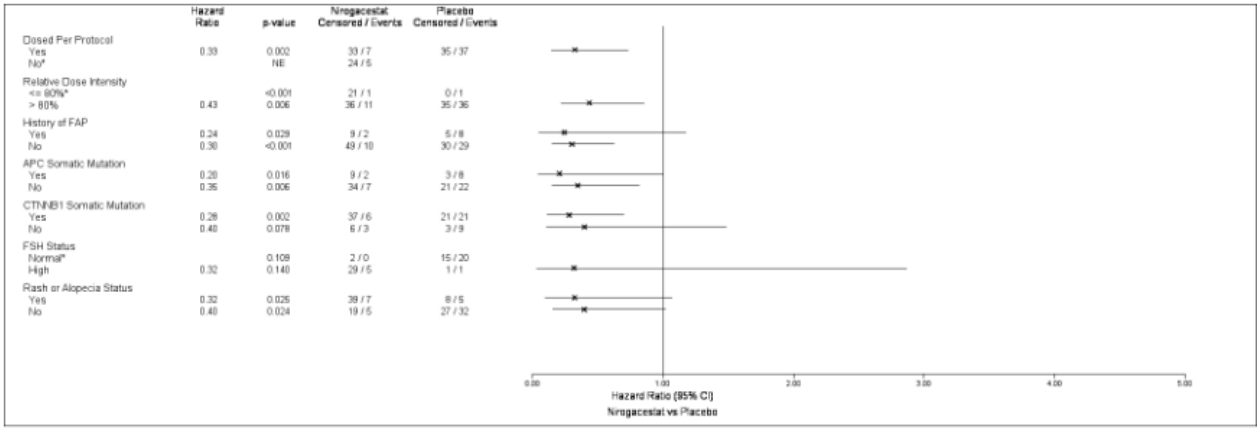
Subgroup analyses

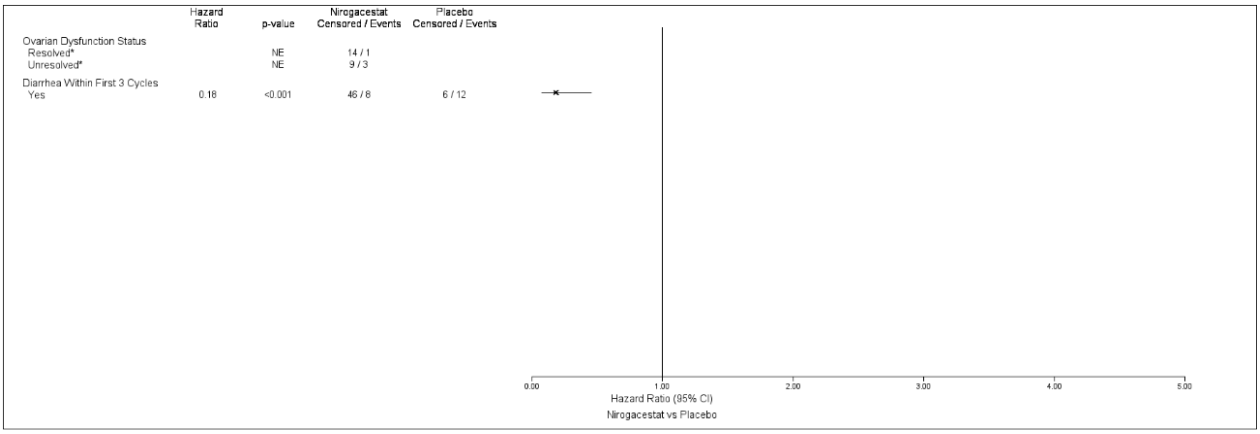
Figure 19: Forest Plot of PFS by Subgroups - DB Phase ITT Population











Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022
Note: Progression free survival was calculated as:
(Earliest date of death/(centrally-read radiographic/qualified clinical) progression or censoring- randomization date +1)/30.4375.
Censoring was defined in section 4.3.1 of the Statistical Analysis Plan.
Note: Qualified clinical progression events were clinical progression events assessed by the investigator that were adjudicated by an independent Endpoint Adjudication Committee.
Note: Hazard ratio was estimated from the stratified Cox proportional hazards model using the exact method for ties, stratified by tumor location except for subgroups by tumor location. A * indicates the HR was not estimable.
Note: Ovarian dysfunction subgroups only included women of child-bearing potential.
Source: Table 14.2.1.2.1.1, Dataset(s): ADSL, ADTTE, Program: f_forest.sas, Date/time of run: 24AUG2023:15:09

2.6.5.2.1. Optional OLE phase

The C1D1 visit (baseline visit) of the OLE phase was conducted on the same day as, or within 24 hours after, the double-blind (DB) end of treatment (EOT) visit.

Participants were enrolled in the OLE phase using the interactive response technology (IRT) only after (1) all ongoing adverse events (AEs)/serious AEs (SAEs) from the DB phase were assessed for

causality in a blinded manner by the investigator or qualified designee, and (2) all AE/SAE causality assessments were entered into the electronic case report form (eCRF). In addition, all DB EOT visit assessments were completed prior to unblinding and administering the first dose of open-label study treatment.

Following the OLE baseline visit (C1D1), participants who were previously randomized to receive placebo in the DB phase returned to the clinic for study visits at OLE Cycle 1 (Days 8, 15, and 22) and OLE Cycle 2 (Day 28). Participants who were previously randomized to nirogacestat in the DB phase did not return to the clinic until the OLE C4D1.

All participants had study visits on OLE C4D1 and then on Day 1 of every 3 cycles thereafter.

Table 27: Participant Disposition (OLE Population)

Category	Placebo to Nirogacestat 150 mg BID (N = 45) n (%)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N = 39) n (%)	Total (N = 84) n (%)
Participants who Enrolled in OLE Phase	45 (100%)	39 (100%)	84 (100%)
Treatment Status			
Discontinued	13 (29%)	3 (8%)	16 (19%)
Radiographic Progression	3 (7%)	2 (5%)	5 (6%)
Clinical Progression	0	1 (3%)	1 (1%)
Adverse Event	7 (16%)	0	7 (8%)
Other	3 (7%)	0	3 (4%)
Ongoing	32 (71%)	36 (92%)	68 (81%)
Study Status			
Discontinued	11 (24%)	3 (8%)	14 (17%)
Ongoing	34 (76%)	36 (92%)	70 (83%)
Primary Reason for Discontinuation from Study			
Radiographic Progression	2 (4%)	2 (5%)	4 (5%)
Clinical Progression	0	1 (3%)	1 (1%)
Adverse Event	6 (13%)	0	6 (7%)
Other	3 (7%)	0	3 (4%)

Reference: Table SCE.1.2.
Abbreviations: BID: twice daily; OLE: open-label extension.

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 Summary of efficacy for trial NIR-DT-301

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumours/Aggressive Fibromatosis (DT)			
Study identifier	NIR-DT-301		
Design	Study NIR-DT-301 was a multi-centre, randomized, double-blind (DB), placebo-controlled, parallel arm, Phase 3 study to evaluate the efficacy, safety, and tolerability of nirogacestat in adult participants with progressing DT.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		The DB phase ended once the estimated number of events were observed and the primary PFS analysis was completed. Not applicable The OLE phase is currently ongoing.
Hypothesis	Superiority		
Treatments groups	Experimental		Nirogacestat 150 mg BID continuously in 28-day cycles
	Control		Placebo BID continuously in 28-day cycles
Endpoints and definitions	Primary endpoint	PFS	PFS, defined as the time from randomization until the date of assessment of progression or death by any cause. Progression was determined radiographically using RECIST v1.1 or clinically as assessed by the investigator. 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 tyrosine kinase inhibitors) for DT.
	Secondary endpoint	ORR	Objective response rate, defined as the proportion of participants with CR + PR assessed via central reader using RECIST v1.1 Criteria
	Secondary endpoint	DoR	Duration of response for participants whose best response was CR or PR

	Secondary endpoint	PROs	Symptoms and impacts were assessed by evaluating change from baseline on the following PROs: • GODDESS • BPI • PROMIS PF short form 10a plus 3 additional items from PROMIS item banks • EORTC QLQ-C30
Database lock	07 April 2022		
Results and Analysis			
Analysis description	**Primary and Secondary Analyses**		
Analysis population and time point description	Efficacy analyses were conducted using the intention-to-treat (ITT) population.		
Descriptive statistics and estimate variability	Treatment group	Nirogacestat 150 mg BID	Placebo
	Number of subjects	70	72
	Kaplan-Meier Estimates Median PFS (95% CI), months	NE	15.1 (8.4, NE)
	Hazard Ratio (95% CI)	0.29 (0.15, 0.55)	
	p-value (one-sided; stratified log-rank test with placebo as reference)	<0.001	
Analysis description	**Secondary Endpoint: ORR**		
Analysis population and time point description	Efficacy analyses were conducted using the intention-to-treat (ITT) population.		
Descriptive statistics and estimate variability	Treatment group	Nirogacestat 150 mg BID	Placebo
	Number of subjects	70	72
	ORR, n (%)	29 (41%)	6 (8%)
	95% CI	(29.8, 53.8)	(3.1, 17.3)

	p-value (two-sided; Cochran-Mantel-Haenszel test for general association stratified by tumor location)	0.218	
Analysis description	**Secondary Endpoint: DoR**		
Analysis population and time point description	Efficacy analyses were conducted using the intention-to-treat (ITT) population.		
Descriptive statistics and estimate variability	Treatment group	Nirogacestat 150 mg BID	Placebo
	Number of subjects	70	72
	ORR, n (%)	Not estimable for either treatment arm	
Analysis description	**Secondary Endpoint: PRO Analyses**		
Analysis population and time point description	Efficacy analyses were conducted using the intention-to-treat (ITT) population.		

	PRO endpoints	Comparison groups	Nirogacestat 150 mg BID vs Placebo
	Change from baseline at Cycle 10 in BPI API	LS mean scores	-1.583 vs -0.241
		LS mean difference	-1.342
		P-value	<0.001
	Change from baseline at Cycle 10 in DTSS total symptom score	LS mean scores	-1.110 vs 0.457
		LS mean difference	-1.567
		P-value	<0.001
	Change from baseline at Cycle 10 in DTIS physical functioning domain score	LS mean scores	-0.613 vs 0.094
		LS mean difference	-0.706
		P-value	<0.001
	Change from baseline at Cycle 10 in EORTC QLQ-C30 global health status/quality of life	LS mean scores	2.935 vs -8.466
		LS mean difference	11.401
		P-value	0.006
	Change from baseline at Cycle 10 in EORTC QLQ-C30 physical functioning scores	LS mean scores	9.143 vs -5.225
		LS mean difference	14.368
		P-value	<0.001
	Change from baseline at Cycle 10 in EORTC QLQ-C30 role functioning scores	LS mean scores	13.293 vs -5.590
		LS mean difference	18.884
		P-value	<0.001

Notes	Treatment with nirogacestat demonstrated superiority over placebo in adult participants with DT, with a substantial reduction in the risk of disease progression, an increase in the objective response rate, and significant and clinically meaningful improvements in pain, DT-specific symptom burden and their impact on participant lives, physical functioning, role functioning, and health-related quality of life.

2.6.5.4. Clinical studies in special populations

Table 29: Clinical Studies in Special Populations

	Controlled Trials in DT	Noncontrolled Trials in DT	
	NIR-DT-301 DB Phase (N=70) n (%)	NIR-DT-301 OLE Placebo to Nirogacestat (N=45) n (%)	A8641014 and 14-C-0007 (N=19) n (%)
Renal impairment patients[a]	0	2 (4)	0
Hepatic impairment patients[b]	5 (7)	3 (7)	0
Paediatric patients <18 years	0	0	0
Age 65-74	3 (4)	0	1 (5)
Age 75-84	0	1 (2)	0
Age 85+	0	0	0

Reference: EMA Table 11 – MAA D120 Efficacy; Listing 99 (MAA D120 Safety); Listing 100 (MAA D120 Safety).

Data cutoff: 02APR2024.

Abbreviations: DB: double-blind; DT: desmoid tumours; EMA: European Medicines Agency; GFR: glomerular filtration rate; N: number of participants in Safety Population; n: number of participants with data available; OLE: open-label extension.

Percentage (%) was based on Safety Population.

a Renal impairment is defined as having GFR <90 mL/min prior to nirogacestat administration. For placebo-to-nirogacestat participants, >2 occurrences of GFR <90 mL/min prior to nirogacestat administration are considered.

b Hepatic impairment is defined as having bilirubin above upper limit of normal prior to nirogacestat administration. For placebo-to-nirogacestat participants, >2 occurrences of bilirubin above upper limit of normal prior to nirogacestat administration are considered.

2.6.5.5. Supportive study(ies)

Study A8641014

This study only contributed with two patients with DT treated at the recommended dose of nirogacestat. Please refer also to section 2.6.5.1. *Dose response studies.*

Study 14-C-0007

This study is an open-label Phase 2 study conducted to determine the ORR (CR + PR) of nirogacestat in participants with DT; no randomization or blinding was performed.

Nirogacestat was administered orally at a dose of 150 mg BID continuously in 21-day cycles.

Efficacy Endpoints:

- The primary endpoint was the ORR, defined as the proportion of participants who have objective response as CR or PR assessed by RECIST v1.1 using CT scans or MRI scans.
- ORR and DCR by mutation type of APC and CTNNB1 genes.

Results

All 17 participants were treated and analysed as part of the Safety Population. A total of 16 participants were evaluable for response.

Primary Endpoint Analysis

Table 30. Objective Response Rate – Evaluable for Response Population

	Total (N = 16) n (%)
BOR – Derived	
CR	0
PR	5 (31%)
SD	10 (63%)
NE	1 (6%)
PD	0
Confirmed BOR – Derived[a]	
CR	0
PR	5 (31%)
SD	10 (63%)
NE	1 (6%)
PD	0
Objective Response Rate (CR + PR)[b]	5 (31%)
95% Exact CI[c]	(11.0-58.7)

Reference: 14-C-0007 CSR Table 14.2.1.1.
Abbreviations: BOR: Best Overall Response; CI: confidence interval; CR: Complete Response; NE: Not Evaluable; PD: Progressive Disease; PR: Partial Response; SD: Stable Disease.
Percentages were based on the Evaluable for Response Population. % = n/N.
[a] Confirmation criteria: CR = ≥4 weeks; PR = ≥4 weeks; SD: Documented at least once ≥4 weeks from baseline; PD: no prior SD, PR. Or CR.
[b] Based on confirmed BOR.
[c] Using exact method based on binomial distribution.

2.6.6. Discussion on clinical efficacy

This application is supported by the pivotal study NIR-DT-301 (DeFi) with studies A8641014 and 14-C-0007 acting as supportive (each contributing with 2 and 17 patients, respectively, administered the recommended dose of nirogacestat 150 mg BID).

NIR-DT-301 (DeFi)

This study is a randomized, double-blind (DB), placebo-controlled, phase 3 study of nirogacestat versus placebo in adult patients with progressing desmoid tumours (DT).

The study was conducted in 52 sites across the EU (BE, DE, IT, NL), Canada, UK and the US. The first patient in was randomised on 15th of May 2019.

A total of 142 patients were randomised (1:1) to either nirogacestat (N=70) or placebo (N=72).

Design and conduct of the clinical studies:

In the scientific advice dated 12th of November 2020 (EMEA/H/SA/4361/2/2020/PA/SME/II), pertaining to the clinical development of nirogacestat with focus on the pivotal study NIR-DT-301–DeFi, the CHMP made a general remark that the usefulness of the advice to be given was hampered by the fact that the study was already ongoing (last patient randomised on 3rd of Aug 2020). However, in terms of the selected dose the CHMP concluded that this seemed reasonable based on the established MTD, non-clinical data and the PK/PD model using Notch effector HES4 as pharmacodynamic parameter.

The choice of a placebo-controlled study is relevant given the heterogenous nature of DT ranging from tumour progression to spontaneous stabilisation/remission and by the fact that there is no universal standard of care nor approved therapeutic option for the treatment of progressing DT.

To enter the study, the patients should have histologically confirmed DT that had progressed by≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.

There were five amendments made to the study protocol whereof two are noteworthy. In amendment 2 (14 October 2019) the sample size was increased from 105 to 135 screened patients and from 94 to 118 randomised patients (but the target number of PFS events was unchanged). The second notable amendment pertain to a change in the definition of the primary endpoint PFS to include not only radiologically confirmed progression but also clinically observed progression (Amendment 5 [9 February 2021]). These amendments are discussed in the subsection Statistical methods below.

At completion of the DB phase, the remaining participants in the DB phase had their study treatment assignment unblinded and if eligible, had the opportunity to enrol in the optional open-label extension (OLE) phase (ongoing).

Statistical methods

Sample size

Considerably more patients were recruited into the study than initially intended: 142 instead of 94. This was in part due to a decision to allow all patients who were eligible at screening to enter the study, even after the target sample size had been reached. It was also due to protocol amendment 2, in which the target sample size was increased from 94 to 118 patients. This increase was not explained, but a new assumption was added to the sample-size calculation, specifying that a spontaneous regression rate of 20% was anticipated (previously, there had not been such an assumption). The increase in sample size is acceptable because the study was event driven, so it does not increase the type 1 error.

Although the sample size was increased, the study was stopped before the target number of PFS events had been observed (49 out of 51). This decision was based on both external data, which suggested that the median time to progression in the nirogacestat arm had been too conservatively estimated (20 months), and the fact that no PFS events had been observed in the trial for several months. This justification is acceptable.

Change in primary endpoint definition

While the study was ongoing, the definition of PFS (the primary endpoint) was changed to include not only radiologically confirmed progression, but also clinically observed progression. Making such major changes can inflate the type-1 error of a study and harm its integrity in other ways. In this case however, the change is unproblematic because the results are virtually identical regardless of which definition is used (hazard ratio of 0.29 versus 0.31, $p<0.001$ in both cases).

Multiplicity

The strategy to control for multiplicity in the analysis of the secondary endpoints was not fully specified until late in the study. According to the protocol, a hierarchical testing procedure would be specified in the statistical analysis plan, which was not completed until the data cut-off date of 7 April 2022 (database freeze took place one and a half month later on 17 May 2022). In addition to specifying the testing order, the statistical analysis plan downgraded 3 of the secondary endpoints to the status of exploratory or supportive endpoints: duration of response, tumour volume, and the PROMIS questionnaire. Therefore, these endpoints were excluded from the hierarchical testing procedure.

It is unfortunate that the hierarchical testing procedure was specified late in the study. The order in which the endpoints were tested is unimportant, as all endpoints were significant; however, significant effects were not seen for all 3 of the secondary endpoints that were downgraded to the status of exploratory or supportive in the statistical analysis plan. Only the effect on the PROMIS Physical Functioning 10a Score was significant, while no statistical test has been reported for duration of response, and the effect on tumour volume was statistically significant at some time points but not at the end of treatment. Despite this limitation, there is no direct evidence that the decision to exclude three endpoints from the hierarchical testing procedure was data driven, so the testing procedure is acceptable. This means that all but 3 of the originally specified secondary endpoints (duration of response, tumour volume, and the PROMIS questionnaire) are controlled for multiplicity.

Missing data

The discontinuation rate from the study was high, especially in the nirogacestat arm due to adverse events. In total, 30% (n=21/70) of the patients in the nirogacestat arm and 17% (n=12/72) of patients in the placebo arm discontinued the study due to withdrawal of consent, adverse event, physician decision, loss to follow-up, or other reason.

A major contributing factor to the high dropout rate from the study was probably the study design, as patients were routinely excluded from the study if they discontinued the randomised treatment. This is not a recommendable way to perform a study, as it violates the intention-to-treat principle and may incur bias. The Applicant was asked to address the impact of such discontinuations on PFS with relevant sensitivity analyses (see *Efficacy data and additional analyses* below).

The statistical analysis plan did not clearly describe how missing data would be handled in the ORR analysis. According to the clinical study report, 5 participants were classified as ORR non-responders because their overall response was "not estimable". The term "not estimable" was not defined, and these patients clearly do not include all dropouts. However, given that ORR means "best overall response", it can be assumed that the patients who dropped out after responding were counted as responders and patients who dropped out without having responded were counted as non-responders. This would be a standard procedure.

Although the discontinuation rate was higher in the nirogacestat arm, there were more missing data for PRO endpoints in the placebo group. The reason for this was that the placebo group had a higher rate of disease progression, which also led to discontinuation from the study.

For the PRO endpoints, the primary MMRM analysis assumed that data were missing at random. A sensitivity analysis was conducted with imputation of worst-score values after death, control-based imputation (jump to reference) for patients in the nirogacestat arm who withdrew from the study due to an adverse event or disease progression, and imputation assuming missing-at-random for all other patients. As explained below, a sensitivity analysis with jump-to-reference imputation for all missing data was requested.

Censoring rules

In the clinical study report, it was unclear how many patients were censored in the PFS analysis because they discontinued treatment and were therefore excluded from the trial. Unfortunately, the lack of post-discontinuation data means that it was not possible to conduct a reanalysis that ignores treatment discontinuations (a treatment policy strategy). However, the results were considered statistically robust based on the results of sensitivity analyses (see *Efficacy data and additional analyses* below).

The statistical analysis plan stated that patients would be censored analysis if they initiated new anti-cancer treatment. This is not consistent with the EMA guideline (EMA/CHMP/27994/2008/Rev.1), which recommends ignoring new anti-cancer treatments in the analysis. However, only 1 patient was censored with this reason, so it will have had a negligible effect on the results.

The EMA guideline (EMA/CHMP/27994/2008/Rev.1) also recommends ignoring the event that a patient misses one or more visits before progressing. Although the statistical analysis plan stated that patients would instead be censored if they missed two or more consecutive assessments before progressing, no patient was censored for this reason.

Demographics and baseline characteristics

Demographics and baseline characteristics appear similar between treatment arms. Overall, most participants were female (65%) whereof 80% of childbearing potential. The median age was 34 years (min, max: 18, 76). The majority of participants had received prior treatment for DT and were classified as refractory or recurrent, 69% and 8%, respectively.

There were 35 (23%) participants with intra-abdominal tumour location, and 107 (77%) with extra-abdominal tumours (stratification factor). 81% of participants who were evaluable for somatic mutations had somatic mutations in CTNNB1. A total of 15 participants had germline mutations of APC. 24 participants had a family history of FAP including 12 with confirmed APC mutations. The remaining 12 participants with FAP did not have germline mutations identified or did not have samples available.

The median baseline target tumour size per RECIST was 100.35 mm, with a range from 19.9 to 400.9 mm with a slightly larger target tumour size of 115.7 mm in the placebo arm as compared to 91.6 mm in the nirogacestat arm.

Differences between treatment arms were observed in regard to race, ethnicity, and BMI with more participants in the nirogacestat arm identifying as White and Not Hispanic/Latino, enrolling in rest of world, and having a normal BMI as compared to placebo. These differences, however, are not considered to have any major impact on the study outcome.

Efficacy data and additional analyses

At the data cut-off date of 7th of April 2022, 49 PFS events had occurred (34.5% maturity) in the ITT population.

Regarding the primary endpoint of PFS, a statistically significant improvement was observed for nirogacestat compared to placebo, with a 71% reduction in the risk of disease progression or death (HR 0.29 [95% CI: 0.15, 0.55]; $p < 0.001$).

Premature discontinuation from the trial (that is, potentially informative censoring) was more common in the nirogacestat arm than in the placebo arm (31% vs 17%; n=22 vs n=12). The difference was explained by the fact that more patients in the nirogacestat arm discontinued due to an adverse event (20% vs. 1%; n=14 vs n=1).

To examine the robustness of the primary efficacy results, the Applicant conducted a worst-case sensitivity analysis and a tipping-point analysis (data not shown). The worst-case analysis showed that nearly all of the between-group difference in PFS disappeared (hazard ratio: 0.93; 95% confidence

interval: 0.58 to 1.49) when potential informative censoring was counted as a PFS event in the nirogacestat arm but as censoring at the time of data cut-off in the placebo arm.

The tipping-point analysis showed that the between-arm difference in PFS ceases to be statistically significant if the following criteria are met:

- A PFS event occurred in ≥60% (n≥13) of the 22 patients who were potentially informatively censored patients in the nirogacestat arm.

AND

- A PFS event occurred in an equal or lower proportion of the 12 potentially informatively censored patients in the placebo arm.

It was considered implausible that a PFS event would have occurred in ≥60% of potentially informatively censored patients when the event rate was only 25% (n=12/48) in patients who were not informatively censored (that is, in patients who either had an event or were administratively censored). Therefore, the results of the primary efficacy analysis are considered to be robust.

Kaplan-Meier estimates of median PFS was NE (NE, NE) in the nirogacestat arm vs. 15.1 (8.4, NE) in the placebo arm.

The median follow-up time in the DB Phase (ITT population) was 19 months (min 0, max 31) for the nirogacestat treated participants and 11 months (min 0, max 31) for participants receiving placebo.

Subgroup analyses showed similar PFS results across all prespecified subgroups including demographics (gender, race, region), disease characteristics (single tumour/multi-focal), prior treatment, gene mutations (history of FAP, presence of any AFP mutation) and adverse events.

ORR in the ITT population was also statistically significantly improved with 41% in the nirogacestat arm versus 8% in the placebo arm. A total of 7% of the participants achieved CR and 34% PR in the nirogacestat arm as compared to zero and 8% respectively in the placebo arm. Median time to objective response for participants receiving nirogacestat was 5.6 months as compared to 11.1 months in the placebo arm.

The PRO instruments used were DTSS, DTIS, BPI, and QLQ-C30 (please refer to section 2.6.5. . *Outcomes/endpoints* for description). All reached statistical significance at the prespecified assessment time at Cycle 10. Despite the large amount of missing data, the DTSS, DTIS, and BPI also reached statistical significance in a requested sensitivity analysis in which all missing data were handled using jump-to-reference imputation (data not shown). This sensitivity analysis did not show statistical significance for the QLQ-C30 global health status score (p=0.025, one-sided). Since the endpoints were tested hierarchically, the non-significant result for the QLQ-C30 global health status score meant that statistical significance could not be claimed for the QLQ-C30 physical functioning and QLQ-C30 role functioning scores either (although the p-values were <0.001), as these endpoints were below the global score in the testing hierarchy.

Since the QLQ-C30 scores did not reach statistical significance in the sensitivity analysis, the effects were not considered statistically robust, so they were not included in the SmPC.

Although the effects on DTSS and DTIS were statistically significant in the sensitivity analysis, these scales had not been psychometrically validated before they were used in the phase-3 trial of nirogacestat. An endpoint scale should be validated in independent studies before it is used to claim the efficacy of a medicinal product, unless the scale is widely used in clinical practice. Since neither of these criteria is met, the efficacy claims for DTSS and DTIS are not included in section 5.1 of the SmPC.

The BPI scale is well-established for measuring pain, and the efficacy of nirogacestat on this scale was statistically significant in both the original analysis and in the sensitivity analysis. The effect was also considered clinically relevant.

A concern was raised that the results for the BPI pain score were biased by functional unblinding. Two plots depicting the change in BPI pain score as a function of the change in tumour size were submitted upon request, one for all patients and one grouped by baseline BPI score (low vs. high, defined as BPI pain scores ≤4 vs. >4). These plots indicated that tumour shrinkage was associated with pain reduction in both study arms, predominantly in patients with high baseline BPI pain scores (>4). As might be expected, there was no clear association between tumour shrinkage and pain reduction in patients with low baseline BPI pain scores (≤4). Moreover, tumour growth appeared to be associated with increased pain in the placebo arm. It was concluded that the observed pain reduction in the nirogacestat arm reflects the antitumour activity of nirogacestat.

Results of the BPI scale are reflected in section 5.1 of the SmPC as supporting PFS results by change from baseline in patient-reported worst pain favouring the nirogacestat arm at Cycle 10 (-1.6 vs -0.2; LS mean difference: -1.3; 95% confidence interval: -2.1 to -0.6; $p < 0.001$).

OLE Phase

At completion of the DB 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 (ongoing). At the data cut-off date, a total of 84 participants were included in the OLE population consisting of 45 participants from the placebo arm and 39 participants from the nirogacestat arm. In the OLE Population, the median duration of exposure to nirogacestat was 29 months (range: 13.7-38.4) in the nirogacestat-to-nirogacestat group versus 13 months (range: 0.3-31.9) in the placebo-to-nirogacestat arm. The median participant years of exposure was 2.45 years (range: 1.13.2) in the nirogacestat-to-nirogacestat group versus 0.59 years (range: 0-2.7) in the placebo-to-nirogacestat arm.

The Applicant will submit the clinical study report with all appendices for the OLE phase of Study NIR-DT-301. (**RECOMMENDATION**)

Healthcare and patient engagement

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedicated process and FAQs document: https://www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcareprofessional-organisations-process-and-faqs_en.pdf). In this context 2 healthcare professional organisations (EORTC and EURACAN) shared their perspectives regarding the assessment of Ogsiveo for the applied indications on behalf of their members.

The feedback from EORTC and EURACAN confirmed the view that desmoid tumors have an unpredictable evolution but can have a significant impact on patients' lives and that there is a need for new treatments for patients in Europe.

2.6.7. Conclusions on the clinical efficacy

The efficacy demonstration of nirogacestat 150 mg BID for the treatment of progressive DT derives from the DB phase of the pivotal study NIR-DT-301 in which a statistically significant and clinically relevant benefit have been demonstrated in terms of PFS supported by subgroup-analyses and secondary endpoints such as ORR.

2.6.8. Clinical safety

The safety and tolerability data of nirogacestat 150 mg BID monotherapy in patients with desmoid tumours is derived from the pivotal phase 3 study NIR-DT-301, consisting of a placebo-controlled double-blind (DB) phase and an open label extension (OLE) phase, and 2 supportive studies, 14-C-0007 and A8641014.

Table 31. Summary of Studies included in the SCS Analysis Populations

Study	Study Description	N	LPLV or visit cutoff	Study Status
Primary Analysis Population				
NIR-DT-301 DB phase	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Participants with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)	69 Nirogacestat/ 72 Placebo	07Apr2022 (primary analysis data cutoff)	Completed
Integrated DT Safety Population				
NIR-DT-301 DB phase	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)	69 Nirogacestat/ 72 Placebo	30Jun2022 (database lock)	Completed
14-C-0007	Phase II Trial of the γ-secretase Inhibitor PF-03084014 in Adults with Desmoid Tumors/Aggressive Fibromatosis	17 Nirogacestat	01Dec2022	Ongoing
A8641014	A Phase 1 Trial of PF 03084014 in Patients With Advanced Solid Tumor Malignancy and T Cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma	DT: 9 Nirogacestat	22Nov2016	Completed
OLE Population				
NIR-DT-301 OLE phase	Open-Label Extension of Phase 3 Trial of Nirogacestat Versus Placebo in Adult Participants with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)	84 Nirogacestat	24Oct2022	Ongoing

AF: aggressive fibromatosis; CM: cancer monotherapy; DB: double-blind; DT: desmoid tumor; HV: healthy volunteer; LBL: lymphoblastic lymphoma; LPLV: last participant last visit; OLE: Open-label extension;

2.6.8.1. Patient exposure

Table 32. Patient exposure

				Participants with long term safety data [2]	
	Patients enrolled	**Patients exposed [1]**	**Participants exposed to the proposed dose range (50-150 mg BID)**	**≥ 6 Months**	**≥ 12 Months**
Blinded studies (placebo-controlled), n	69	69	24	55	46
Open-label studies, n	185	185	25	64	44
Post marketing, n	N/A	790*	790*	None, due to limited post marketing experience (≤6 months data for Ogsiveo in U.S. market)	
Compassionate use, n	249	249	249[a]	108[b]	52[c]

n = Number of participants with data available, N/A= Not available.

Ongoing Studies: NIR-DT-301 double-blind phase, data cutoff 30Jun2022; NIR-DT-301 OLE, data cutoff 24Oct2024; 14-C-007, data cutoff 01Dec2022; Compassionate use, data cutoff 23Oct2023.

Blinded studies (placebo-controlled): NIR-DT-301-double-blind phase.

Open-label studies:14-C-0007, A8641014, A8641016, A8641019, A8641020, NIR-DT-301-OLE.

*Post marketing: There are no post marketing studies. Post marketing reflects post market exposure as of 27 May 2024. Exposure numbers represent estimated patient exposure based on the number of patients that have been reported through specialty pharmacies, patient support programs, and medically integrated dispensing pharmacies.

[1] Received at least 1 dose of active treatment.

[2] In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

a. Exposure numbers represent participants that had at least one compassionate use order shipped, and the program was not notified otherwise that the participant did not start treatment. One participant is included who had initial dose greater than 150 mg BID. This dose was provided in error and subsequently corrected.

b. Participants with exposure Greater than 6 months (cumulative treatment days/30.4735) are counted in respective columns. Compassionate use participants potential cumulative exposure is calculated using the number of days of quantity shipped per the participant ordered dose for each shipment. The compassionate use program does not collect the actual participant nirogacestat treatment start and stop dates.

c. Participants with exposure Greater than 12 months (cumulative treatment days/30.4735) are counted in respective columns. Compassionate use participants potential cumulative exposure is calculated using the number of days of quantity shipped per the participant ordered dose for each shipment. The compassionate use program does not collect the actual participant nirogacestat treatment start and stop dates.

Note: NIR-DT-301 DB phase includes participants who received nirogacestat in double blinded phase and also who had additional follow-up from OLE Phase on nirogacestat.

NIR-DT-301-OLE includes participants who received placebo in double blinded phase and nirogacestat in OLE Phase.

Table 33: Extent of exposure

	Study NIR-DT-301		Nirogacestat			
	Placebo (N=72)	Nirogacestat 150 mg BID (N=69)	< 150 mg BID (N=2)	150 mg BID (N=88)	≥ 220 mg BID (N=5)	Total (N=95)
Number of Participants Treated, n (%)	72 (100%)	69 (100%)	2 (100%)	88 (100%)	5 (100%)	95 (100%)
Duration of Exposure (months) [1]						
n	72	69	2	88	5	95
Mean	13.482	17.583	82.382	24.560	16.815	25.370
SD	8.6193	10.0534	0.3485	23.5786	21.7974	24.6664
Median	11.400	20.928	82.382	21.503	14.160	21.388
Min	0.23	0.30	82.14	0.30	0.33	0.30
Max	32.99	33.58	82.63	106.84	53.55	106.84
Duration of Exposure Category, n (%)						
< 1 month	72 (100%)	69 (100%)	2 (100%)	88 (100%)	5 (100%)	95 (100%)
≥ 1 month	71 (99%)	67 (97%)	2 (100%)	86 (98%)	3 (60%)	91 (96%)
≥ 2 months	70 (97%)	61 (88%)	2 (100%)	80 (91%)	3 (60%)	85 (89%)
≥ 3 months	67 (93%)	59 (86%)	2 (100%)	77 (88%)	3 (60%)	82 (86%)
≥ 6 months	54 (75%)	55 (80%)	2 (100%)	72 (82%)	3 (60%)	77 (81%)
≥ 12 months	34 (47%)	45 (65%)	2 (100%)	59 (67%)	3 (60%)	64 (67%)
≥ 24 months	8 (11%)	19 (28%)	2 (100%)	31 (35%)	1 (20%)	34 (36%)
≥ 36 months	0	0	2 (100%)	12 (14%)	1 (20%)	15 (16%)
Actual Dose Intensity (mg/day) [2]						
n	72	69	2	88	5	95
Mean	296.4	261.9	157.2	256.2	387.4	261.0
SD	12.08	45.57	1.93	46.48	153.07	64.01
Median	300.0	288.3	157.2	276.9	374.0	276.7
Min	239	163	156	138	256	138
Max	300	300	159	300	630	630
Actual Dose Intensity Category, n (%)						
< 200 mg/day	0	11 (16%)	2 (100%)	16 (18%)	0	18 (19%)
≥ 200 - < 260 mg/day	3 (4%)	14 (20%)	0	20 (23%)	2 (40%)	22 (23%)
≥ 260 - < 300 mg/day	10 (14%)	20 (29%)	0	28 (32%)	0	28 (29%)
300 mg/day	59 (82%)	24 (35%)	0	24 (27%)	0	24 (25%)
> 300 - 440 mg/day	0	0	0	0	2 (40%)	2 (2%)
> 440 mg/day	0	0	0	0	1 (20%)	1 (1%)
Relative Dose Intensity (%) [3]						
n	72	69	2	88	5	95
Mean	98.803	87.305	98.268	85.410	74.628	85.113
SD	4.0277	15.1898	1.2053	15.4934	24.9527	16.0715
Median	100.000	96.104	98.268	92.293	85.010	92.358
Min	79.74	54.36	97.42	45.99	38.74	38.74
Max	100.00	100.00	99.12	100.00	95.45	100.00
Relative Dose Intensity Category, n (%)						
< 80%	1 (1%)	22 (32%)	0	31 (35%)	2 (40%)	33 (35%)
≥ 80%	71 (99%)	47 (68%)	2 (100%)	57 (65%)	3 (60%)	62 (65%)
Participant Years of Exposure [4]						
n	72	69	2	88	5	95
Mean	1.12	1.47	6.87	2.05	1.40	2.11
SD	0.718	0.838	0.029	1.965	1.816	2.056
Median	0.95	1.74	6.87	1.79	1.18	1.78
Min	0.0	0.0	6.8	0.0	0.0	0.0
Max	2.7	2.8	6.9	8.9	4.5	8.9
Sum	80.9	101.1	13.7	180.1	7.0	200.8
Participants Dose Reduced (NIR-DT-301 and A8641014 only)						
Yes	0	29 (42%)	0	30 (42%)	2 (40%)	32 (41%)
No	72 (100%)	40 (58%)	2 (100%)	41 (58%)	3 (60%)	46 (59%)

Table 34: Extent of exposure in OLE population (Study NIR-DT-301)

	Placebo to Nirogacestat 150 mg BID (N=45)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N=39)	Total (N=84)
Number of Participants Treated, n (%)	45 (100%)	39 (100%)	84 (100%)
Duration of Exposure (months) [1]			
n	45	39	84
Mean	12.876	30.711	21.157
SD	9.9262	4.7950	11.9512
Median	7.064	29.405	26.530
Min	0.30	13.67	0.30
Max	31.93	38.37	38.37
Duration of Exposure Category, n (%)			
< 1 month	45 (100%)	39 (100%)	84 (100%)
≥ 1 month	42 (93%)	39 (100%)	81 (96%)
≥ 2 months	38 (84%)	39 (100%)	77 (92%)
≥ 3 months	38 (84%)	39 (100%)	77 (92%)
≥ 6 months	34 (76%)	39 (100%)	73 (87%)
≥ 12 months	21 (47%)	39 (100%)	60 (71%)
≥ 24 months	8 (18%)	38 (97%)	46 (55%)
≥ 36 months	0	7 (18%)	7 (8%)
Actual Dose Intensity (mg/day) [2]			
n	45	39	84
Mean	269.8	252.1	261.6
SD	50.95	46.19	49.31
Median	300.0	273.0	293.6
Min	53	167	53
Max	300	300	300

Actual Dose Intensity Category, n (%)			
< 200 mg/day	5 (11%)	8 (21%)	13 (15%)
≥ 200 - < 260 mg/day	8 (18%)	11 (28%)	19 (23%)
≥ 260 - < 300 mg/day	9 (20%)	14 (36%)	23 (27%)
300 mg/day	23 (51%)	6 (15%)	29 (35%)
Relative Dose Intensity (%) [3]			
n	45	39	84
Mean	89.921	84.037	87.189
SD	16.9840	15.3980	16.4372
Median	100.000	91.003	97.877
Min	17.76	55.81	17.76
Max	100.00	100.00	100.00
Relative Dose Intensity Category, n (%)			
< 80%	11 (24%)	17 (44%)	28 (33%)
≥ 80%	34 (76%)	22 (56%)	56 (67%)
Participant Years of Exposure [4]			
n	45	39	84
Mean	1.07	2.56	1.76
SD	0.827	0.400	0.996
Median	0.59	2.45	2.21
Min	0.0	1.1	0.0
Max	2.7	3.2	3.2
Sum	48.3	99.8	148.1
Participants Dose Reduced			
Yes	15 (33%)	22 (56%)	37 (44%)
No	30 (67%)	17 (44%)	47 (56%)

Patient disposition

Table 35. Disposition for Participants who Received Nirogacestat 150 mg BID and Placebo - Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Treatment Status					
Ongoing	23 (32%)	36 (52%)	0	0	3 (3%)
Discontinued	49 (68%)	33 (48%)	50 (69%)	33 (48%)	49 (56%)
Radiographic Progression	29 (40%)	11 (16%)	29 (40%)	11 (16%)	11 (13%)
Qualified Clinical Progression[a]	6 (8%)	1 (1%)	6 (8%)	1 (1%)	1 (1%)
Unqualified Clinical Progression[b]	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Adverse Event	1 (1%)	14 (20%)	1 (1%)	14 (20%)	15 (17%)
Death	0	0	0	0	1 (1%)
Non-Compliance	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Withdrawal By Participant	0	0	0	0	14 (16%)
Other	11 (15%)	5 (7%)	12 (17%)	5 (7%)	5 (6%)

Reference: Table SCS.2.3, and NIR-DT-301 CSR Table 14.1.1.1.1.

AE: adverse event; BID: twice daily; DT: desmoid tumor; N: number of participants; mg: milligram.

[a] Qualification of events of clinical progression was only performed in the NIR-DT-301 study.

[b] 1 participant died in the NIR-DT-301 placebo arm due to an SAE of sepsis; however, this participant discontinued study treatment prior to his death due to a pre-planned surgery which was captured as a reason of "other".

OLE population (Study NIR-DT-301)

Table 36. Disposition for Participants who Received Nirogacestat 150 mg BID - OLE Population

	OLE Population (24Oct2022)		
Treatment Group	**Placebo to Nirogacestat 150 mg BID**	**Nirogacestat 150 mg BID to Nirogacestat 150 mg BID**	**Total**
Total N	**45**	**39**	**84**
Treatment Status			
Ongoing	32 (71%)	36 (92%)	68 (81%)
Discontinued	13 (29%)	3 (8%)	16 (19%)
Radiographic Progression[a]	3 (7%)	2 (5%)	5 (6%)
Clinical Progression	0	1 (3%)	1 (1%)
Adverse Event	7 (16%)	0	7 (8%)
Other	3 (7%)	0	3 (4%)

Reference: Table SCS.2.4

BID: twice daily; OLE: open-label extension; N: number of participants; mg: milligram

[a] Qualification of events of clinical progression was only performed in the NIR-DT-301 study.

2.6.8.2. Adverse events

Table 37. Overall AE Profile for Participants who Received Nirogacestat 150 mg BID or Placebo – Primary Analysis Population and Integrated DT Safety Population

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Participants with ≥1 TEAE, n (%)	69 (96%)	69 (100%)	69 (96%)	69 (100%)	88 (100%)
Events	661	1445	661	1463	2641
Participants with ≥1 treatment-related TEAE, n (%)	53 (74%)	68 (99%)	53 (74%)	68 (99%)	87 (99%)
Events	204	862	203	868	1285
Participants with ≥1 SAE, n (%)	8 (11%)	14 (20%)	8 (11%)	13 (19%)	21 (24%)
Events	14	19	14	18	34
Participants with ≥1 treatment-related SAE, n (%)	0	9 (13%)	0	8 (12%)	11 (13%)
Events	0	10	0	9	12
Participants with ≥1 Grade 3 or higher TEAE, n (%)	12 (17%)	38 (55%)	12 (17%)	38 (55%)	53 (60%)
Events	38	73	38	74	134
Participants with ≥1 Grade 3 or higher treatment-related TEAE, n (%)	2 (3%)	29 (42%)	2 (3%)	29 (42%)	39 (44%)
Events	3	44	3	44	63

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Participants with ≥1 TEAE by maximum severity, n (%)					
Grade 1	18 (25%)	3 (4%)	18 (25%)	3 (4%)	4 (5%)
Grade 2	39 (54%)	28 (41%)	39 (54%)	28 (41%)	31 (35%)
Grade 3	10 (14%)	36 (52%)	10 (14%)	36 (52%)	50 (57%)
Grade 4	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (2%)
Grade 5	1 (1%)	0	1 (1%)	0	1 (1%)
Participants with ≥1 treatment-related TEAE by maximum severity, n (%)					
Grade 1	35 (49%)	12 (17%)	35 (49%)	12 (17%)	14 (16%)
Grade 2	16 (22%)	27 (39%)	16 (22%)	27 (39%)	34 (39%)
Grade 3	2 (3%)	29 (42%)	2 (3%)	29 (42%)	39 (44%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Participants with TEAEs leading to treatment discontinuation, n (%)	2 (3%)	16 (23%)	2 (3%)	16 (23%)	17 (19%)
Events	2	23	2	23	24
Participants with TEAEs leading to death, n (%)	1 (1%)	0	1 (1%)	0	1 (1%)
Events	1	0	1	0	1
Participants with ≥1 TEAE by Cycle of onset, n (%)					
Cycle 1	58 (81%)	67 (97%)	57 (79%)	67 (97%)	86 (98%)
Cycle 2	5 (7%)	1 (1%)	5 (7%)	1 (1%)	1 (1%)
Cycle 3	2 (3%)	0	3 (4%)	0	0
Cycle 4	0	0	0	0	0
Cycle 5	0	0	0	0	0
Cycle 6	1 (1%)	0	1 (1%)	0	0
Cycle 7-12	3 (4%)	1 (1%)	3 (4%)	1 (1%)	1 (1%)
Cycle 13 or later	0	0	0	0	0
Participants with ≥1 treatment-related TEAE by Cycle of onset, n (%)					
Cycle 1	44 (61%)	66 (96%)	44 (61%)	66 (96%)	85 (97%)
Cycle 2	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Cycle 3	3 (4%)	1 (1%)	3 (4%)	1 (1%)	1 (1%)
Cycle 4	1 (1%)	0	1 (1%)	0	0
Cycle 5	0	0	0	0	0
Cycle 6	0	0	0	0	0
Cycle 7-12	1 (1%)	0	1 (1%)	0	0
Cycle 13 or later	3 (4%)	0	3 (4%)	0	0

Reference: NIR-DT-301

BID: twice daily; DT: desmoid tumour; N: number of participants; mg: milligram; TEAE: treatment-emergent adverse event; SAE: serious adverse event.

Note: TEAEs are those events that occur on or after the initiation of study treatment through 30 days after the last dose of study treatment.

Note: AEs severity is Graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or investigator assessment.

OLE population (Study NIR-DT-301)

Table 38. Overall AE Profile -NIR-DT-301 OLE Population

	OLE Population (24Oct2022)		
Treatment Group	**Placebo to Nirogacestat 150 mg BID**	**Nirogacestat 150 mg BID to Nirogacestat 150 mg BID**	**Total**
N	45	39	84
Participants with ≥1 TEAE, n (%)	45 (100%)	28 (72%)	73 (87%)
Events	676	98	774
Participants with ≥1 treatment-related TEAE, n (%)	45 (100%)	15 (38%)	60 (71%)
Events	359	28	387
Participants with ≥1 SAE, n (%)	10 (22%)	2 (5%)	12 (14%)
Events	11	5	16
Participants with ≥1 treatment-related SAEs, n (%)	3 (7%)	0	3 (4%)
Events	3	0	3
Participants with ≥1 Grade 3 or higher TEAE, n (%)	21 (47%)	5 (13%)	26 (31%)
Events	36	10	46
Participants with ≥1 Grade 3 or higher treatment-related TEAE, n (%)	16 (36%)	2 (5%)	18 (21%)
Events	19	2	21
TEAEs by maximum severity, n (%)			
Grade 1	2 (4%)	4 (10%)	6 (7%)
Grade 2	22 (49%)	18 (46%)	40 (48%)
Grade 3	20 (44%)	5 (13%)	25 (30%)
Grade 4	1 (2%)	0	1 (1%)
Grade 5	0	0	0
Participants with TEAEs leading to treatment discontinuation, n (%)	6 (13%)	0	6 (7%)
Events	6	0	6
Participants with TEAEs leading to death, n (%)	0	0	0
Events	0	0	0
TEAEs by Cycle of onset, n (%)	0	0	0
Cycle 1	44 (98%)	9 (23%)	53 (63%)
Cycle 2	1 (2%)	6 (15%)	7 (8%)
Cycle 3	0	3 (8%)	3 (4%)
Cycle 4	0	6 (15%)	6 (7%)
Cycle 5	0	2 (5%)	2 (2%)
Cycle 6	0	1 (3%)	1 (3%)
Cycle 7-12	0	1 (3%)	1 (3%)
Cycle 13 or later	0	0	0

BID: twice daily; N: number of participants; OLE: open-label extension; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Note: TEAEs are those events that occur on or after the initiation of study treatment through 30 days after the last dose of study treatment.

Note: AE severity is graded using CTCAE version 5.0 or investigator assessment.

Common TEAEs

Table 39. Incidence of Frequently (⩾15% of Participants) Occurring TEAEs in Participants who Received 150 mg BID Nirogacestat and Placebo – Primary Analysis and Integrated DT Population

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Any TEAE	69 (96%)	69 (100%)	69 (96%)	69 (100%)	88 (100%)
Diarrhoea	25 (35%)	58 (84%)	25 (35%)	58 (84%)	75 (85%)
Nausea	28 (39%)	37 (54%)	28 (39%)	39 (57%)	52 (59%)
Fatigue	26 (36%)	35 (51%)	26 (36%)	35 (51%)	44 (50%)
Hypophosphataemia	5 (7%)	29 (42%)	5 (7%)	30 (43%)	44 (50%)
Headache	11 (15%)	20 (29%)	11 (15%)	20 (29%)	35 (40%)
Rash maculo-papular	4 (6%)	22 (32%)	4 (6%)	22 (32%)	32 (36%)
Stomatitis	3 (4%)	20 (29%)	3 (4%)	20 (29%)	26 (30%)
Aspartate aminotransferase increased	8 (11%)	11 (16%)	8 (11%)	12 (17%)	24 (27%)
Vomiting	14 (19%)	14 (20%)	14 (19%)	15 (22%)	22 (25%)
Alanine aminotransferase increased	6 (8%)	12 (17%)	6 (8%)	13 (19%)	22 (25%)
Hot flush	4 (6%)	13 (19%)	4 (6%)	13 (19%)	22 (25%)
Dermatitis acneiform	0	15 (22%)	0	15 (22%)	22 (25%)
Abdominal pain	9 (13%)	11 (16%)	9 (13%)	11 (16%)	19 (22%)
Cough	3 (4%)	11 (16%)	3 (4%)	11 (16%)	18 (20%)
Dry skin	5 (7%)	11 (16%)	5 (7%)	11 (16%)	16 (18%)
Alopecia	1 (1%)	13 (19%)	1 (1%)	13 (19%)	16 (18%)
Rash	5 (7%)	13 (19%)	5 (7%)	13 (19%)	15 (17%)
COVID-19	12 (17%)	12 (17%)	12 (17%)	12 (17%)	14 (16%)
Decreased appetite	8 (11%)	11 (16%)	8 (11%)	11 (16%)	14 (16%)
Weight increased	5 (7%)	11 (16%)	5 (7%)	11 (16%)	14 (16%)
Dyspnoea	4 (6%)	11 (16%)	4 (6%)	11 (16%)	14 (16%)
Ovarian failure	0	13 (19%)	0	13 (19%)	13 (15%)
Premature menopause	0	11 (16%)	0	11 (16%)	11 (13%)

BID: twice daily; DT: desmoid tumor; N: number of participants; mg: milligram; TEAE: treatment-emergent adverse event.

OLE population (Study NIR-DT-301)

Table 40. Incidence of Frequently (≥15% of Participants) Occurring TEAEs in Participants who Received Nirogacestat 150 mg BID -NIR-DT-301 OLE Population

	OLE Population (24Oct2022)		
Treatment Group	**Placebo to Nirogacestat 150 mg BID**	**Nirogacestat 150 mg BID to Nirogacestat 150 mg BID**	**Total**
Total N	**45**	**39**	**84**
Any TEAE	45 (100%)	28 (72%)	73 (87%)
Diarrhoea	37 (82%)	6 (15%)	43 (51%)
Fatigue	18 (40%)	3 (8%)	21 (25%)
Nausea	18 (40%)	2 (5%)	20 (24%)
COVID-19	9 (20%)	6 (15%)	15 (18%)
Headache	13 (29%)	2 (5%)	15 (18%)
Hypophosphataemia	14 (31%)	1 (3%)	15 (18%)
Cough	9 (20%)	3 (8%)	12 (14%)
Stomatitis	11 (24%)	1 (3%)	12 (14%)
Alanine aminotransferase increased	10 (22%)	1 (3%)	11 (13%)
Aspartate aminotransferase increased	10 (22%)	1 (3%)	11 (13%)
Ovarian failure	11 (24%)	0	11 (13%)
Weight decreased	9 (20%)	1 (3%)	10 (12%)
Pruritus	9 (20%)	0	9 (11%)
Rash maculo-papular	8 (18%)	1 (3%)	9 (11%)
Vomiting	8 (18%)	0	8 (10%)
Hot flush	7 (16%)	0	7 (8%)

N: number of participants; OLE: open-label extension, TEAE: treatment-emergent adverse event

TEAEs of grade ≥3

Table 41. Incidence of Grade ⩾3 TEAEs Occurring in ⩾2 Participants who Received 150 mg BID Nirogacestat or Placebo – Primary Analysis and Integrated DT Safety Population

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Any Grade ≥3 TEAE in all participants	12 (17%)	38 (55%)	12 (17%)	38 (55%)	53 (60%)
Diarrhoea	1 (1%)	11 (16%)	1 (1%)	11 (16%)	14 (16%)
Hypophosphataemia	0	2 (3%)	0	2 (3%)	11 (13%)
Folliculitis	0	4 (6%)	0	4 (6%)	4 (5%)
Rash maculo-papular	0	4 (6%)	0	4 (6%)	4 (5%)
Weight increased	1 (1%)	2 (3%)	1 (1%)	2 (3%)	4 (5%)
Anaemia	1 (1%)	2 (3%)	1 (1%)	2 (3%)	3 (3%)
Hypertension	0	2 (3%)	0	2 (3%)	5 (6%)
Stomatitis	0	3 (4%)	0	3 (4%)	3 (3%)
Alanine aminotransferase increased	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (2%)

Aspartate aminotransferase increased	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (2%)
Fatigue	0	2 (3%)	0	2 (3%)	3 (3%)
Tumour pain	2 (3%)	1 (1%)	2 (3%)	1 (1%)	1 (1%)
Hypokalaemia	0	1 (1%)	0	2 (3%)	3 (3%)
Sepsis	3 (4%)	0	3 (4%)	0	0
Abdominal pain	0	1 (1%)	0	1 (1%)	2 (2%)
COVID-19	2 (3%)	0	2 (3%)	0	0
Skin infection	0	1 (1%)	0	1 (1%)	2 (2%)

BID: twice daily; DT: desmoid tumor; N: number of participants; mg: milligram; TEAE: treatment-emergent adverse event.

OLE population (Study NIR-DT-301)

Table 42. Incidence of Grade ≥3 TEAEs Occurring in ≥2 Participants Who Received 150 mg BID Nirogacestat and Placebo - NIR-DT-301 OLE Population

	OLE Population (24Oct2022)		
Treatment Group	**Placebo to Nirogacestat 150 mg BID**	**Nirogacestat 150 mg BID to Nirogacestat 150 mg BID**	**Total**
Total N	**45**	**39**	**84**
Any Grade ≥3 TEAE in all participants	21 (47%)	5 (13%)	26 (31%)
Diarrhoea	5 (11%)	2 (5%)	7 (8%)
Stomatitis	3 (7%)	0	3 (4%)
Folliculitis	2 (4%)	0	2 (2%)
Nausea	2 (4%)	0	2 (2%)
Rash maculo-papular	2 (4%)	0	2 (2%)
Small intestinal obstruction	1 (2%)	1 (3%)	2 (2%)
Weight increased	1 (2%)	1 (3%)	2 (2%)

N: number of participants; OLE: open-label extension; TEAE: treatment-emergent adverse event

Gastro-intestinal events

In the primary analysis, **Diarrhoea** was reported with a median time to onset in the nirogacestat arm of 9 days (range 2-434 days) and in the placebo arm 16 days (range 1-372 days). Diarrhoea was managed with anti-diarrhoeal medicines as well as dose modifications. In the nirogacestat arm, diarrhoea led to dose reduction in 9% of patients with diarrhoea, treatment interruption in 16% and treatment discontinuation in 6%. In the placebo arm, treatment was interrupted in 4% of patients with diarrhoea.

Table 43. Summary of mucositis and stomatitis – Integrated Desmoid Tumour Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Mucositis and Stomatitis Disorder Adverse Event	5 (7%)	26 (38%)	0	35 (40%)	1 (20%)	36 (38%)
GASTROINTESTINAL DISORDERS	3 (4%)	24 (35%)	0	30 (34%)	0	30 (32%)
Stomatitis	3 (4%)	20 (29%)	0	26 (30%)	0	26 (27%)
Mouth ulceration	0	4 (6%)	0	4 (5%)	0	4 (4%)
Oral pain	0	2 (3%)	0	3 (3%)	0	3 (3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (4%)	5 (7%)	0	9 (10%)	1 (20%)	10 (11%)
Oropharyngeal pain	3 (4%)	5 (7%)	0	9 (10%)	1 (20%)	10 (11%)

In the Primary analysis population, median time to onset of **stomatitis** was 8.5 days with nirogacestat vs. 2 days for placebo. Stomatitis was treated symptomatically and led to dose reduction in 3 patients (15% of patients with stomatitis).

Non-melanoma skin cancer (NMSC)

Table 44. Treatment-Emergent Non-Melanoma Skin Cancers – Primary analysis and Integrated Desmoid Tumor Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Non-Melanoma Skin Cancer Adverse Event	0	2 (3%)	0	3 (3%)	0	3 (3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (3%)	0	3 (3%)	0	3 (3%)
Squamous cell carcinoma of skin	0	2 (3%)	0	2 (2%)	0	2 (2%)
Basal cell carcinoma	0	1 (1%)	0	1 (1%)	0	1 (1%)
Squamous cell carcinoma	0	0	0	1 (1%)	0	1 (1%)

Nirogacestat does not directly cause NMSCs but may potentiate their development through interference with skin homeostasis.

Cognitive disorder events

Table 45. Participants who Reported Cognitive Disorder Events Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Memory impairment	2 (3%)	4 (6%)	2 (3%)	4 (6%)	8 (9%)
Disturbance in attention	0	2 (3%)	0	2 (3%)	3 (3%)
Mental impairment	0	1 (1%)	0	1 (1%)	1 (1%)
Cognitive disorder	0	0	0	0	2 (2%)

BID: twice daily; DT: desmoid tumor; N: number of participants.

Primary analysis population

Cognitive disorders were reported at a low frequency, with a numerically slightly higher incidence in the nirogacestat arm. Treatment discontinuation was reported in 1 patient (1%) on nirogacestat, due to mental impairment, vs. none on placebo. No concerns were raised regarding effects on the central nervous system in the neurofunctional study in rats. Furthermore, based on non-clinical data, nirogacestat is not likely to accumulate in the central nervous system.

Peripheral oedema

Table 46. Participants who Reported Peripheral Oedema Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	NIR-DT-301 Placebo (07Apr2022)	NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)	NIR-DT-301 Placebo (30Jun2022)	NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)	Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)
Total N	**72**	**69**	**72**	**69**	**88**
Oedema peripheral	1 (1%)	4 (6%)	1 (1%)	4 (6%)	10 (11%)

BID: twice daily; DT: desmoid tumor; N: number of participants

In the Primary analysis population, peripheral oedema was reported at a higher incidence with nirogacestat (n=4; 6%) compared with placebo (n=1; 1%). Frequency in the Integrated DT population was 11% (10 patients) and in the OLE population 2% (1 patient in each subgroup). The role of Notch signalling in regulating vascular permeability and endothelial barrier function is context-dependent and the net effect of GSI inhibition on vascular permeability is not clear.

Pulmonary disorders

In the Primary analysis population, an imbalance in respiratory events was reported for cough (nirogacestat vs. placebo: 16% vs. 4%) and dyspnoea (16% vs. 6%). Data in the Integrated DT population were consistent with the Primary analysis population.

In the integrated cancer monotherapy population, 1 case of pneumonitis (grade 2; non-serious) was reported 20 days after the last dose of nirogacestat (study A8641014).

Musculoskeletal events

Effects on Mature Bone

Table 47. Treatment-Emergent Musculoskeletal Disorder Adverse Events by System Organ Class and Preferred Term - Integrated Desmoid Tumor Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Musculoskeletal Disorder Adverse Event	1 (1%)	2 (3%)	0	4 (5%)	0	4 (4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1%)	2 (3%)	0	4 (5%)	0	4 (4%)
Osteoporosis	0	1 (1%)	0	2 (2%)	0	2 (2%)
Bone pain	0	1 (1%)	0	1 (1%)	0	1 (1%)
Exostosis	0	0	0	1 (1%)	0	1 (1%)
Osteopenia	1 (1%)	0	0	0	0	0

Bone Fracture Events with nirogacestat

Table 48. Participants who Reported Bone Fracture Events Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Participants with a Fracture Event[a]	0	4	0	4	8
Foot fracture	0	2 (3%)	0	2 (3%)	2 (2%)
Foot fracture Grade 2	0	1 (1%)	0	1 (1%)	1 (1%)
Onset cycle[b]	0	1 (1), ≥13 (1)	0	1 (1), ≥13 (1)	1 (1), ≥13 (1)
Hand fracture	0	1 (1%)	0	1 (1%)	1 (1%)
Onset cycle[b]	0	4 (1)	0	4 (1)	4 (1)
Radius fracture	0	1 (1%)	0	1 (1%)	1 (1%)
Radius fracture Grade 2	0	1 (1%)	0	1 (1%)	1 (1%)
Onset cycle[b]	0	6 (1)	0	6 (1)	6 (1)
Fracture	0	0	0	0	4 (5%)
Fracture Grade 2	0	0	0	0	3 (3%)
Onset cycle[b]	0	0	0	0	≥13 (4)
Hip fracture	0	0	0	0	1 (1%)
Hip fracture Grade 2	0	0	0	0	1 (1%)
Onset cycle[b]	0	0	0	0	≥13 (1)

BID: twice daily; DT: desmoid tumor; N: number of participants.

Note: There were no Grade 4 or 5 fracture events

a Fracture Event values were summed using listed PTs from NIR-DT-301 Participants with multiple fracture events were only counted once.

b cycle number (number of participants with first onset that cycle).

Cardiac rhythm disturbances

Table 49. Participants who Reported Cardiac Disorders SOC Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Atrial fibrillation	0	1 (1%)	0	1 (1%)	2 (2%)
Bradycardia	0	1 (1%)	0	1 (1%)	1 (1%)

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Cardiac failure	0	0	0	0	1 (1%)
Palpitations	1 (1%)	1 (1%)	1 (1%)	1 (1%)	3 (3%)
Sinus bradycardia	0	2 (3%)	0	2 (3%)	2 (2%)
Sinus tachycardia	2 (3%)	2 (3%)	2 (3%)	2 (3%)	3 (3%)
Supraventricular tachycardia	0	0	0	0	1 (1%)
Tachycardia	0	3 (4%)	0	3 (4%)	3 (3%)

BID: twice daily; DT: desmoid tumor; N: number of participants.

Cardiac Disorders SOC TEAEs occurred in 9 (13%) participants in the nirogacestat arm and 3 (4%) of participants in the placebo arm of Study NIR-DT-301.

2.6.8.3. Serious adverse events, deaths, and other significant events

2.6.8.3.1. Serious adverse events (SAEs)

Table 50. SAEs - Primary Analysis Population and Integrated DT Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Serious Treatment-Emergent Adverse Event	8 (11%)	13 (19%)	1 (50%)	21 (24%)	3 (60%)	25 (26%)
INFECTIONS AND INFESTATIONS	5 (7%)	4 (6%)	0	6 (7%)	0	6 (6%)
Skin infection	0	0	0	2 (2%)	0	2 (2%)
Abdominal abscess	0	1 (1%)	0	1 (1%)	0	1 (1%)
Abdominal infection	0	1 (1%)	0	1 (1%)	0	1 (1%)
Appendicitis	0	1 (1%)	0	1 (1%)	0	1 (1%)
Bronchitis	0	0	0	1 (1%)	0	1 (1%)
Groin abscess	0	1 (1%)	0	1 (1%)	0	1 (1%)
Infected cyst	0	1 (1%)	0	1 (1%)	0	1 (1%)
COVID-19	2 (3%)	0	0	0	0	0
Infection	1 (1%)	0	0	0	0	0
Sepsis	3 (4%)	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	3 (4%)	0	4 (5%)	0	4 (4%)
Premature menopause	0	3 (4%)	0	3 (3%)	0	3 (3%)
Vulvovaginal inflammation	0	0	0	1 (1%)	0	1 (1%)
GASTROINTESTINAL DISORDERS	3 (4%)	3 (4%)	0	3 (3%)	0	3 (3%)
Abdominal pain	0	1 (1%)	0	1 (1%)	0	1 (1%)
Small intestinal obstruction	0	1 (1%)	0	1 (1%)	0	1 (1%)
Stomatitis	0	1 (1%)	0	1 (1%)	0	1 (1%)
Diarrhoea	1 (1%)	0	0	0	0	0
Duodenal perforation	1 (1%)	0	0	0	0	0
Gastrointestinal fistula	1 (1%)	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (50%)	1 (1%)	1 (20%)	3 (3%)
Head injury	0	0	0	1 (1%)	0	1 (1%)
Injury	0	0	0	0	1 (20%)	1 (1%)
Joint dislocation	0	0	1 (50%)	0	0	1 (1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (3%)	2 (3%)	0	3 (3%)	0	3 (3%)
Spindle cell sarcoma	0	1 (1%)	0	1 (1%)	0	1 (1%)
Squamous cell carcinoma	0	0	0	1 (1%)	0	1 (1%)
Tumour haemorrhage	1 (1%)	1 (1%)	0	1 (1%)	0	1 (1%)
Tumour pain	1 (1%)	1 (1%)	0	1 (1%)	0	1 (1%)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	3 (3%)	0	3 (3%)
Hip arthroplasty	0	0	0	1 (1%)	0	1 (1%)
Hysterectomy	0	0	0	1 (1%)	0	1 (1%)
Splenectomy	0	0	0	1 (1%)	0	1 (1%)
IMMUNE SYSTEM DISORDERS	0	0	0	1 (1%)	1 (20%)	2 (2%)
Drug hypersensitivity	0	0	0	0	1 (20%)	1 (1%)
Hypersensitivity	0	0	0	1 (1%)	0	1 (1%)
VASCULAR DISORDERS	0	0	0	2 (2%)	0	2 (2%)
Haematoma	0	0	0	2 (2%)	0	2 (2%)
Embolism	0	0	0	1 (1%)	0	1 (1%)
CARDIAC DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Atrial fibrillation	0	1 (1%)	0	1 (1%)	0	1 (1%)
HEPATOBILIARY DISORDERS	1 (1%)	1 (1%)	0	1 (1%)	0	1 (1%)
Cholecystitis	0	1 (1%)	0	1 (1%)	0	1 (1%)
Hepatic function abnormal	1 (1%)	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	0	1 (20%)	1 (1%)
Hypophosphataemia	0	0	0	0	1 (20%)	1 (1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	1 (1%)	0	1 (1%)
Back pain	0	0	0	1 (1%)	0	1 (1%)
NERVOUS SYSTEM DISORDERS	0	0	0	1 (1%)	0	1 (1%)
Cerebrovascular accident	0	0	0	1 (1%)	0	1 (1%)
RENAL AND URINARY DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Haematuria	0	1 (1%)	0	1 (1%)	0	1 (1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1%)	0	0	1 (1%)	0	1 (1%)
Bronchospasm	0	0	0	1 (1%)	0	1 (1%)
Pulmonary embolism	1 (1%)	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Rash maculo-papular	0	1 (1%)	0	1 (1%)	0	1 (1%)

OLE population (Study NIR-DT-301)

Table 51. SAEs - NIR-DT-301 OLE Population

SYSTEM ORGAN CLASS Preferred Term	Placebo to Nirogacestat 150 mg BID (N=45) n (%)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N=39) n (%)	Total (N=84) n (%)
Number of Participants with Any Serious Treatment-Emergent Adverse Event	10 (22%)	2 (5%)	12 (14%)
GASTROINTESTINAL DISORDERS	4 (9%)	2 (5%)	6 (7%)
Small intestinal obstruction	1 (2%)	1 (3%)	2 (2%)
Intestinal fistula	0	1 (3%)	1 (1%)
Obstruction gastric	1 (2%)	0	1 (1%)
Proctalgia	1 (2%)	0	1 (1%)
Stomatitis	1 (2%)	0	1 (1%)
INFECTIONS AND INFESTATIONS	3 (7%)	1 (3%)	4 (5%)
Abdominal abscess	0	1 (3%)	1 (1%)
Appendicitis	1 (2%)	0	1 (1%)
Pyelonephritis	1 (2%)	0	1 (1%)
Pyelonephritis acute	1 (2%)	0	1 (1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2%)	0	1 (1%)
Cyst	1 (2%)	0	1 (1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (2%)	0	1 (1%)
Papillary thyroid cancer	1 (2%)	0	1 (1%)
RENAL AND URINARY DISORDERS	1 (2%)	0	1 (1%)
Hydronephrosis	1 (2%)	0	1 (1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2%)	0	1 (1%)
Rash	1 (2%)	0	1 (1%)

2.6.8.3.2. AEs of special interest

Ovarian toxicity (OT)

Table 52. Summary and Characterization of OT Events Reported Among Nirogacestat 150 mg BID and Placebo Participants – Primary Analysis Population and Integrated DT Safety Population

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Total Women, n (%)	47 (65%)	44 (64%)	47 (65%)	44 (64%)	59 (67%)
Total WOCBP	37	36	37	36	48
Total WOCBP with OT (narrow search), n (%)	0	27 (75%)	0	27 (75%)	29 (60%)
Total WOCBP without OT (narrow search), n (%)	37 (100%)	9 (25%)	37 (100%)	9 (25%)	19 (40%)
Reported PTs (narrow terms)					

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Ovarian failure, n (%)	0	13 (36%)	0	13 (36%)	13 (27%)
Premature menopause, n (%)	0	11 (31%)	0	11 (31%)	11 (23%)
Amenorrhoea, n (%)	0	3 (8%)	0	3 (8%)	5 (10%)
Menopause, n (%)	0	1 (3%)	0	1 (3%)	1 (2%)
Oligomenorrhoea, n (%)	0	0	0	1 (3%)	1 (2%)
Characterization of OT Events (narrow terms)					
Number of Participants with OT Events by Outcome[a]					
Recovered/Resolved, n (%)	0	17 (63%)	0	18 (67%)	20 (69%)
Recovering/Resolving, n (%)	0	1 (4%)	0	0	0
Not recovered/Not resolved, n (%)	0	10 (37%)[b,c]	0	10 (37%)	10 (34%)
Unknown, n (%)	0	1 (4%)	0	1 (4%)	1 (3%)
Number of Participants with OT Events with Dose modifications[a]					
Reduced, n (%)	0	2 (7%)	0	2 (7%)	2 (7%)
Interrupted, n (%)	0	2 (7%)	0	2 (7%)	3 (10%)
Withdrawn, n (%)	0	4 (15%)	0	4 (15%)	4 (14%)
Concomitant Medications					
Number of WOCBP with OT with use of concomitant meds, n (%)	0	4 (15%)	0	4 (15%)	4 (14%)
Mean duration of use of con meds (Std)	NE	367.5 (377.49)	NE	443.3 (472.45)	443.3 (472.45)

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Median duration of use of con meds	NE	307.5	NE	360.0	360.0

BID: twice daily: desmoid tumor; OT: ovarian toxicity; N: number of participants; NE: not estimable, PT: preferred term; Std: standard deviation; WOCBP: women of childbearing potential;

[a] Denominator is out of the total number of participants with an event of OT. Participants can be counted in more than one group (modification or outcome).

[b] One participant had an event of OT considered not resolved at the time of study withdrawal; however, because this participant withdrew consent for further follow-up; this participant was considered "not resolved" in this table and lost-to follow-up for the purposes of OT follow-up in Figure 1 (Listings SCS 2.3.1 and SCS 5.3.1).

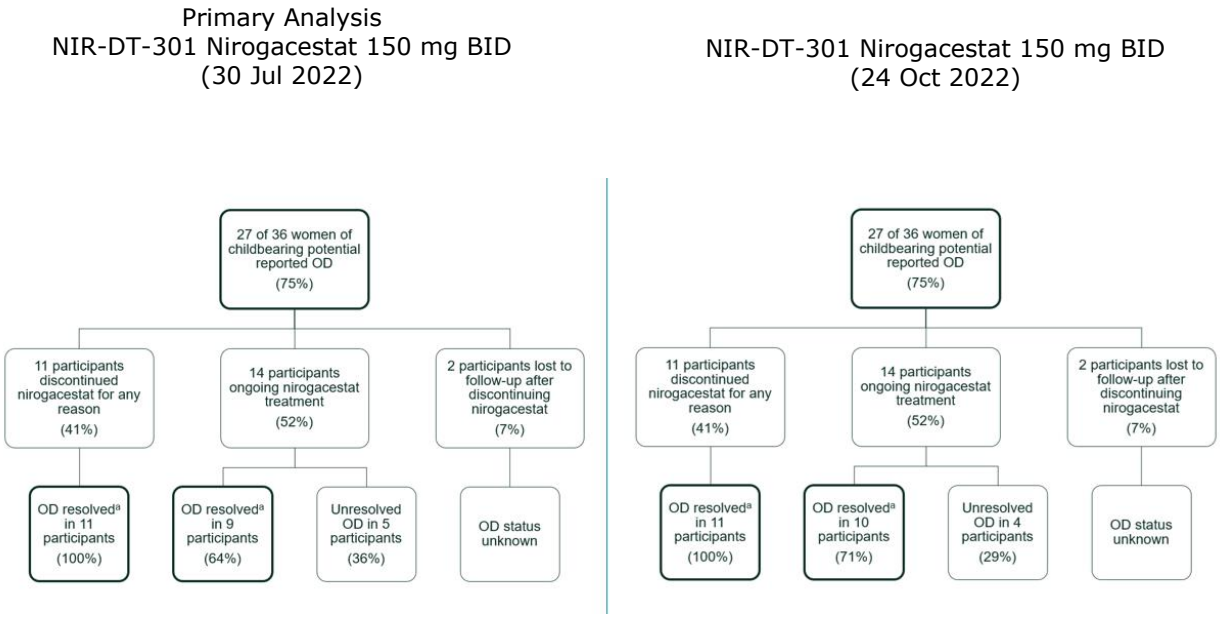
[c] One participant was considered unresolved in the primary analysis but has since been assessed as resolved in the nirogacestat 150 mg BID arm in the Integrated DT Safety Population.

The median time to first onset of OT events was 62 days (range: 1-381 days) after the initiation of nirogacestat. The median duration of OT events was 132 days (range: 11days to 215 weeks).

Resolution of OT events (NIR-DT-301)

Resolution of OT was determined by the investigator for each case based on the features that prompted the reporting of the event for that participant (e.g. cessation of menses, hormone abnormality). OT was reported to resolve in women of child bearing potential (WOCBP) both while continuing nirogacestat and after stopping nirogacestat.

Figure 20. OT by Outcome - Double-Blind Phase



OT: ovarian toxicity

[a] One participant had an event of OT considered not resolved at the time of study withdrawal; however, because this participant withdrew consent for further follow-up; this participant was considered lost-to follow-up for the purposes of OT follow-up

Off-treatment resolution

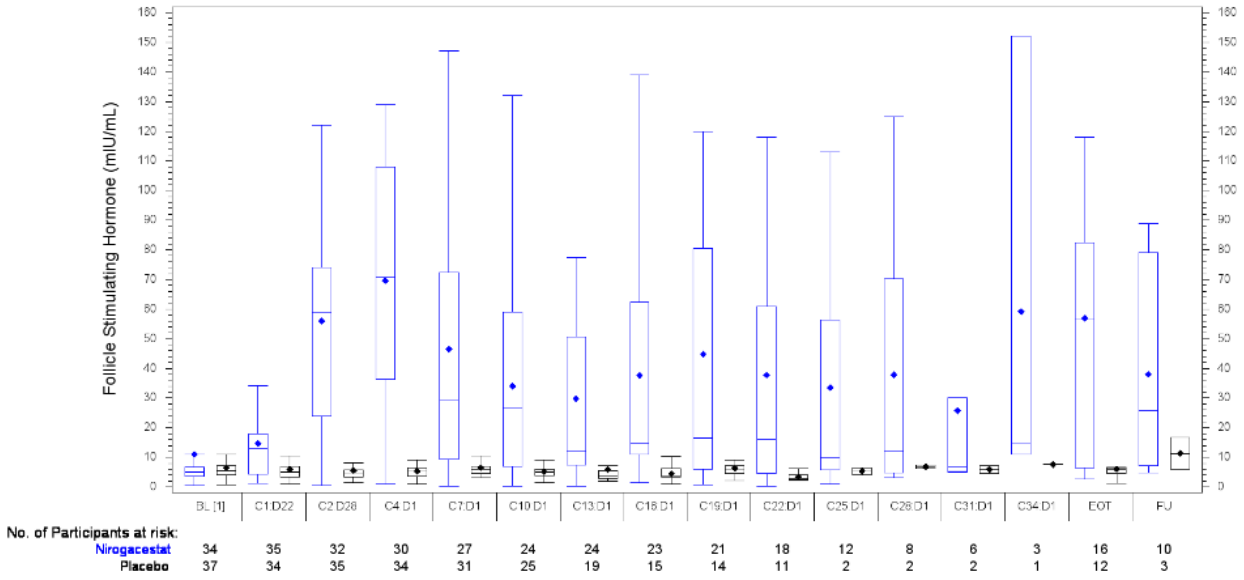
Of the 27 WOCBP with OT events, 13 patients discontinued nirogacestat for any reason. Of these, no data on resolution of OT was available in 2 patients, as both were lost to follow-up. In the remaining 11 patients, OT was reported as resolved. In 2 patients no information on the return of menstruation was available; however, hormone levels had returned to normal. The remaining 9 patients reported return of menstruation, although FSH and/or oestradiol levels had not normalised in 4 patients. Of the latter 4 patients, evaluation of resolution of OT event in terms of hormone levels was hampered in 1 patient due to peri-menopausal age (48 years) and in 1 patient due to use of combined oral contraceptive.

On-treatment resolution

Of the 14 WOCBP with OT events continuing nirogacestat treatment, OT was reported as resolved in 10 patients and as not resolved in 4 patients (as of 24 October 2022). In the 10 patients reporting return of menstruation, FSH and/or oestradiol levels had not returned to normal in 3 patients. As of the latest follow-up (2 August 2024), the OT event was ongoing in 3 patients continuing nirogacestat, including in 1 patient with an age close to natural menopause.

Reproductive Hormone Summary

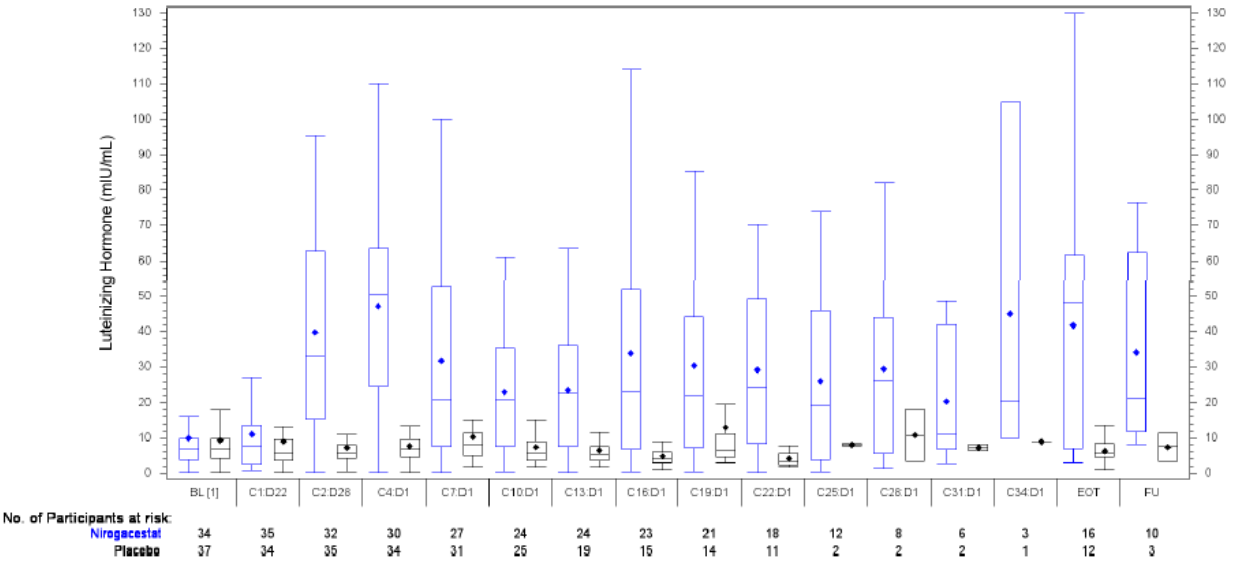
Figure 21. Box and Whisker Plot of FSH in WOCBP – Double-Blind Safety Population



Reference: NIR-DT-301 CSR Figure 14.3.4.1.4.5.1.
[1] Baseline was defined as the most recent measurement prior to the first administration of study treatment.
Note: BL: Baseline, Cx:Dx: Cycle x Day x, EOT: End of Treatment, FU: Follow-Up.
Note: Box plots were presented with whiskers at min and max, outlines of box at q1 and q3, dot at the mean and middle line at the median. Values below Q1-1.5*IQR or above Q3+1.5*IQR are excluded.

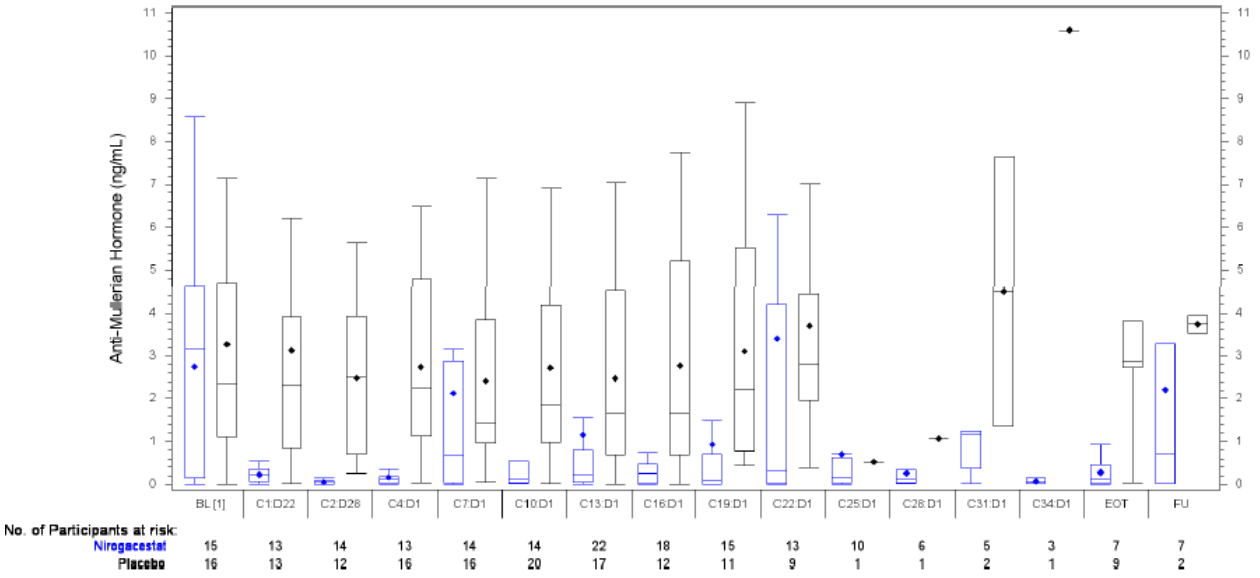
While FSH values appeared elevated for the population of WOCBP receiving nirogacestat, fluctuations were observed in FSH levels for individual participants.

Figure 22. Box and Whisker Plot of LH in WOCBP – Double-Blind Safety Population



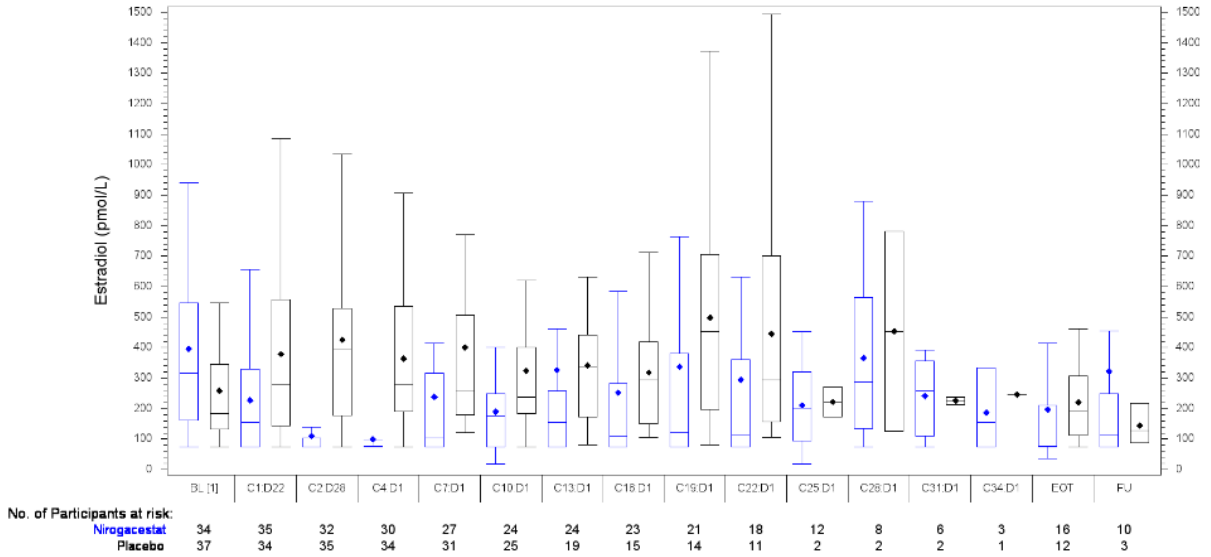
Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022
IQR = Interquartile range
Note: BL = Baseline, Cx:Dx = Cycle x Day x, EOT = End of Treatment, FU = Follow-Up.
Note: Box plots were presented with whiskers at min and max, outlines of box at q1 and q3, dot at the mean and middle line at the median. Values above Q3+1.5*IQR are excluded. If the removal of outliers resulted in a max value less than the mean, then the mean value was not presented on the plot.
[1] Baseline was defined as the most recent measurement prior to the first administration of study treatment.

Figure 23. Box and Whisker Plot of AMH in WOCBP – Double-Blind Safety Population



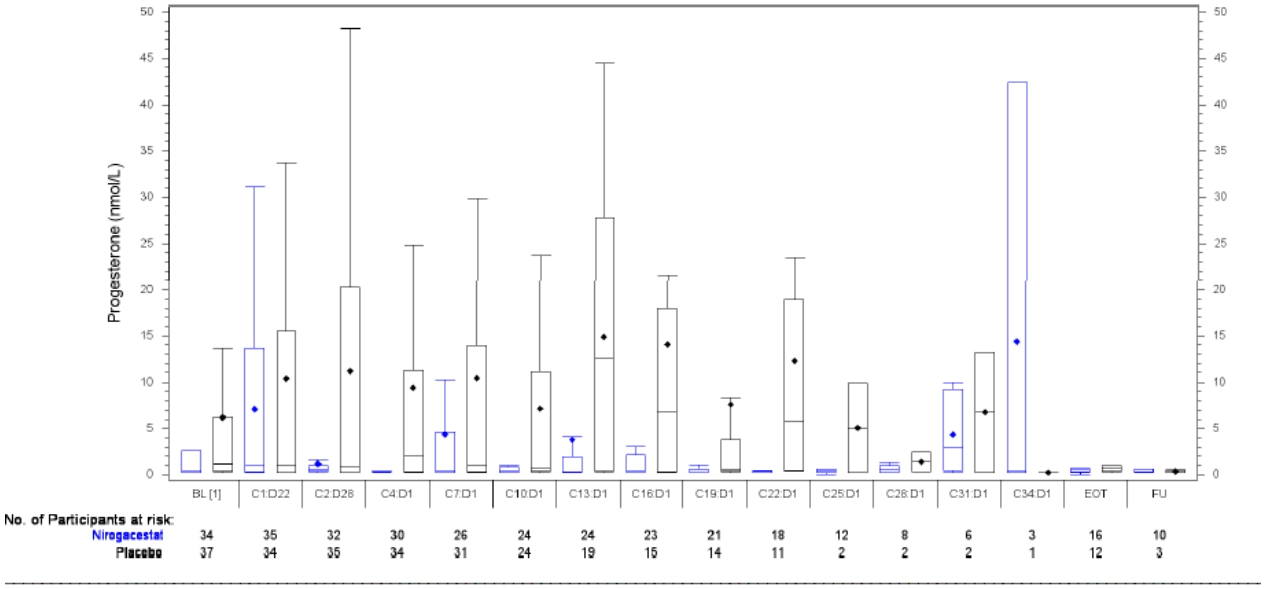
Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022
IQR = Interquartile range
Note: BL = Baseline, Cx:Dx = Cycle x Day x, EOT = End of Treatment, FU = Follow-Up.
Note: Box plots were presented with whiskers at min and max, outlines of box at q1 and q3, dot at the mean and middle line at the median. Values above Q3+1.5*IQR are excluded. If the removal of outliers resulted in a max value less than the mean, then the mean value was not presented on the plot.
[1] Baseline was defined as the most recent measurement prior to the first administration of study treatment.

Figure 24. Box and Whisker Plot of Estradiol in WOCBP – Double-Blind Safety Population



Reference: NIR-DT-301 CSR Figure 14.3.4.1.4.5.1.
[1] Baseline was defined as the most recent measurement prior to the first administration of study treatment.
Note: BL: Baseline, Cx:Dx: Cycle x Day x, EOT: End of Treatment, FU: Follow-Up.
Note: Box plots were presented with whiskers at min and max, outlines of box at q1 and q3, dot at the mean and middle line at the median. Values below Q1-1.5*IQR or above Q3+1.5*IQR are excluded.

Figure 25. Box and Whisker Plot of progesterone in WOCBP – Double-Blind Safety Population



Database Lock: 17-May-2022, Data Cutoff: 07-Apr-2022
IQR = Interquartile range
Note: BL = Baseline, Cx:Dx = Cycle x Day x, EOT = End of Treatment, FU = Follow-Up.
Note: Box plots were presented with whiskers at min and max, outlines of box at q1 and q3, dot at the mean and middle line at the median. Values above Q3+1.5*IQR are excluded. If the removal of outliers resulted in a max value less than the mean, then the mean value was not presented on the plot.
[1] Baseline was defined as the most recent measurement prior to the first administration of study treatment.

In summary, in WOCBP, median levels of FSH and LH were higher with nirogacestat compared with placebo; the increase in hormone levels started during the first (C1D22 for FSH) or second cycle (C2D28 for LH) and levels remained elevated during treatment with nirogacestat. Median anti-mullerian hormone (AMH) levels were generally low during nirogacestat treatment compared with placebo, with the decrease from baseline first reported during cycle 1 (C1D22). Note that data for AMH were available for approximately half the number of patients in both study arms, likely reflecting WOCBP enrolled after protocol amendment no. 3.

Median oestradiol levels were generally lower with nirogacestat compared with placebo during treatment, with the most pronounced decrease being observed from the second cycle (C2D28) to the fourth cycle (C4D1). From cycle 7 onwards, oestradiol levels tended to return to baseline levels.

Median progesterone levels with nirogacestat were low compared with placebo, with the decrease starting during the second cycle (C2D28).

Prolonged oestrogen suppression

Table 53. Summary of WOCBP Receiving Nirogacestat who Reported Prolonged Estrogen Suppression ≥6 months

Relevant MH	OT PT (Broad Term)[i]	Start	End	Outcome	Dose Reduction (Y/N)	Concomitant Hormone Therapy	Baseline Estradiol Level (pmol/L)[ii]
Participant Reported Event of OT (Narrow Term)							
Amenorrhea Menstrual Irregularities	Premature Menopause	15-Nov-19	16-Apr-21	Resolved	N	N	139.5
	Hot flush	05-May-20	Ongoing	Not Resolved	N	N	
Menstrual Irregularities	Ovarian failure	20-Dec-19	28-Jan-22	Resolved[iii]	Y	Y (levonorgestrel - IUD)	389
None	Blood follicle stimulating hormone increased	17-Jan-2020	11-Mar-20	Resolved	N	Y (desogestrel;ethinylestradiol)	NR
	Ovarian failure	17-Apr-20	05-Jun-20	Resolved	N	Y (desogestrel;ethinylestradiol)	
Menstrual Irregularities	Hot flush	17-Oct-19	Ongoing	Resolving	N	N	161.5
	Menopause	14-Jan-20	Ongoing	Not Resolved	N	N	
Amenorrhea Menstrual Irregularities	Menstruation irregular	30-Sep-20	22-Dec-20	Resolved	N	Y (ulipristal acetate)	436.7
	Ovarian failure	23-Dec-20	Ongoing	Not Resolved	N	Y (ulipristal acetate)	
Amenorrhea	Ovarian failure	25-Sep-20	Ongoing	Not Resolved	N	Y (intrauterine contraceptive device)	157.8
Menstrual Irregularities	Menstruation Irregular	03-Aug-20	02-Oct-20	Resolved	Y	Y (ethinylestradiol;norgestimate)	73.39
Amenorrhea Endometriosis	Vulvovaginal dryness	18-Oct-21	Ongoing	Not Resolved	Y	Y (levonorgestrel - IUD)	113.8
N	NA	NA	NA	NA	N	Y (desogestrel;ethinylestradiol)	649.6
N	NA	NA	NA	NA	Y	Y (levonorgestrel - IUD)	73.39

Reference: Listing SCS.33.5.1 NIR-DT-301 CSR Listing 16.2.4.5.2 (infertility history); Listing 16.2.4.4 (medical history); Listing 16.2.5.2.1.1 (concomitant medications).
IUD: intrauterine device; MH: medical history; N: no; NA: not applicable; NR: not reported; OT: ovarian toxicity; PT: preferred term; WOCBP: women of childbearing potential; Y: yes.
[i] For completeness, TEAEs were included using the broad definition of OT as described in the SCS SAP (Section 6.1); however, participants were categorized according to the narrow definition of OT which included the PTs of amenorrhea, menopause, ovarian failure, and premature menopause).
[ii] Baseline was defined as the last assessment prior to the first dose of study treatment.
[iii] Event resolution reported during additional follow-up via pharmacovigilance which was reported after the 30Jun2022 data cut through 30 July 2022 or as part of the OLE phase of the study (Listing SCS.5.4.1).

Oestrogen suppression for >6 months was reported in 10 out of 36 WOCBP in the nirogacestat arm. Of these 10 WOCBP with prolonged oestrogen suppression, 6 patients reported events of premature menopause or ovarian failure while 4 did not report such events. Four out of 6 WOCBP with OT events and all 4 patients without OT events used concomitant hormone therapy. Three patients, of which 1 patient reported OT, were of menopausal age.

Mechanistic review

As the Notch pathway is involved in the growth and maturation of ovarian follicles, inhibition of this pathway may lead to primary ovarian insufficiency, possibly via interference with angiogenesis and disruption in cell-to-cell signalling in thecal cells.

OLE population (study NIR-DT-301)

Table 54. Summary and Characterization of OT Events Reported Among Nirogacestat 150 mg BID and Placebo Participants -NIR-DT-301 OLE Population

	OLE Population (24Oct2022)		
Treatment Group	**Placebo to Nirogacestat 150 mg BID**	**Nirogacestat 150 mg BID to Nirogacestat 150 mg BID**	**Total**
Total N	**45**	**39**	**84**

Total Women, n (%)	32 (71%)	20 (51%)	52 (62%)
Total WOCBP	27	18	45
Total WOCBP with OT (narrow search), n (%)	18 (67%)	0	18 (40%)
Total WOCBP without OT (narrow search), n (%)	9 (33%)	18 (100%)	27 (60%)
Reported PTs (narrow terms)[a]			
Ovarian failure, n (%)	11 (41%)	0	11 (24%)
Premature menopause, n (%)	5 (19%)	0	5 (11%)
Amenorrhoea, n (%)	1 (4%)	0	1 (2%)
Ovarian disorder, n (%)	1 (4%)	0	1 (2%)
Characterization of OT Events (narrow terms)			
Number of participants with OT Events by Outcome[a,b]			
Recovered/Resolved, n (%)	2 (11%)	0	2 (11%)
Recovering/Resolving, n (%)	0	0	0
Not recovered/Not resolved, n (%)	16 (89%)	0	16 (89%)
Unknown, n (%)	0	0	0
Number of Participants with OT Events with Dose Modifications[a,b]			
Reduced, n (%)	2 (11%)	0	2 (11%)
Interrupted, n (%)	0	0	0
Withdrawn, n (%)	0	0	0
Concomitant Medications			
Number of WOCBP with OT with use of con meds[a,b], n (%)	2 (11%)	0	2 (11%)
Mean duration of use of con meds (Std)	469.5(154.86)	NE	469.5(154.86)
Median duration of use of con meds	469.5	NE	469.5

Reference: Table SCS 27

BID: twice daily; DT: desmoid tumor; OT: ovarian toxicity; OLE: open-label extension; N: number of participants; n/a: not available; NE: not evaluable, PT: preferred term; Std: standard deviation; WOCBP: women of childbearing potential

a Participants can be counted in more than one group (modification or outcome).

b Denominator is out of the total number of participants with an event of OT

In the OLE population (data cut-off: 24 October 2022), 18 of 45 WOCBP (40%) reported OT events, all in the placebo-nirogacestat group. Dose modification was reported as dose reduced in 11% (n=2) (frequency based on the number of patients with an event); none of the patients discontinued nirogacestat treatment. The median time to first onset of OT events was similar in the OLE Population compared with the Primary analysis population (53.5 days vs. 62 days). The median duration of OT events was longer in the OLE Population (188 days vs 149 days). Outcome of OT was reported as recovered/resolved in 11% (n=2) of patients with OT events and not recovered/resolved in the remaining 16 patients (89%).

As of the updated data cut-off date (2 April 2024), 22 patients (49%) reported OT, 19 patients in the placebo-nirogacestat group and 3 in the nirogacestat-nirogacestat group. Resolution of the OT event was reported in 12 of 22 patients (55%), in 5 patients after discontinuation of nirogacestat and in 7 patients continuing nirogacestat. Of the 10 patients with unresolved OT events, 1 patient was lost to follow-up. Six of 10 patients with ongoing OT reported a medical history of menstrual irregularities and 1 patient had an age close to natural menopause.

Long-term effects on fertility

As of the latest follow-up date (24 October 2022), resolution of OT events was reported in 21 of 27 WOCBP with OT (78%). Although this data suggests that OT events may be reversible in terms of return of menstruation and normalisation of hormone levels, the long-term effects on female fertility, e.g. in terms of pregnancies and live births, are not known.

In non-clinical studies, reduced testes weight and decreased sperm motility as well as a decrease in morphologically normal sperm were observed, at doses relevant for clinical use. No data on male fertility were captured in the pivotal study. Consequently, the effect of nirogacestat on male fertility is not known.

Skin events

Table 55. Participants who Reported Skin Disorder Events (Broad Terms) Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Rash maculo-papular	4 (6%)	22 (32%)	4 (6%)	22 (32%)	32 (36%)
Rash maculo-papular Grade 3	0	4 (6%)	0	4 (6%)	4 (5%)
Dermatitis acneiform	0	15 (22%)	0	15 (22%)	22 (25%)
Rash	5 (7%)	13 (19%)	5 (7%)	13 (19%)	15 (17%)
Dry skin	5 (7%)	11 (16%)	5 (7%)	11 (16%)	16 (18%)
Pruritus	6 (8%)	9 (13%)	6 (8%)	9 (13%)	12 (14%)
Rash erythematous	0	2 (3%)	0	2 (3%)	3 (3%)
Acne	0	1 (1%)	0	1 (1%)	1 (1%)
Dermatitis	0	1 (1%)	0	1 (1%)	1 (1%)
Pustule	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Rash papular	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Rash pruritic	0	1 (1%)	0	1 (1%)	1 (1%)
Erythema	1 (1%)	0	1 (1%)	0	0
Hidradenitis	0	6 (9%)	0	6 (9%)	6 (7%)

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Hidradenitis Grade 3	0	1 (1%)	0	1 (1%)	1 (1%)
Folliculitis	0	9 (13%)	0	9 (13%)	14 (16%)
Folliculitis Grade 3	0	4 (6%)	0	4 (6%)	4 (5%)
Alopecia	1 (1%)	13 (19%)	1 (1%)	13 (19%)	16 (18%)

BID: twice daily; DT: desmoid tumor; N: number of participants.

In the primary analysis population, TEAEs pertaining to rash (broad and narrow search) were reported at a higher incidence for nirogacestat (77%) compared with placebo (26%). Median time to onset for rash events was 19 days (range 2-603 days) for nirogacestat. Dose modifications for rash events (based on the number of patients with events) were reported as dose reduced in 8% (n=3), dose interrupted in 19% (n=7) and treatment discontinuation in 1 patient (3%).

Electrolyte insufficiency events

Hypophosphatemia

Table 56. Participants who Reported Hypophosphatemia Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Hypophosphatemia	5 (7%)	29 (42%)	5 (7%)	30 (43%)	44 (50%)
Grade 3	0	2 (3%)	0	2 (3%)	11 (13%)

BID: twice daily; DT: desmoid tumor; N: number of participants.
Note: There were no participants with Grade 4 or 5 events of hypophosphatemia.

In the Primary analysis population, both hypophosphatemia and hypokalaemia were reported at a higher incidence with nirogacestat (42% and 12%, respectively) compared with placebo (7% and 1%, respectively). Median time to onset for hypophosphatemia was 15 days (range 1-833 days) for nirogacestat. Dose modifications for hypophosphatemia (based on the number of patients with events) were reported as dose reduced in 9%, dose interrupted in 6% and treatment discontinuation in 1

patient (3%). Hypophosphatemia and hypokalaemia events were managed with replacement therapy and dose reductions.

Hypokalaemia

Table 57. Participants who Reported Hypokalemia Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
Hypokalemia	1 (1%)	8 (12%)	1 (1%)	8 (12%)	17 (19%)
Grade 3	0	1 (1%)	0	2 (3%)	3 (3%)

BID: twice daily; DT: desmoid tumor; N: number of participants.

Note: There were no participants with Grade 4 or 5 events of hypokalemia.

Hepatotoxicity

Table 58. Participants who Reported Elevated Liver Enzymes Among Participants who Received Nirogacestat 150 mg BID and Placebo – Primary Analysis and Integrated DT Safety Populations

	Primary Analysis Population		Integrated DT Safety Population		
Treatment Arm/Group	**NIR-DT-301 Placebo (07Apr2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (07Apr2022)**	**NIR-DT-301 Placebo (30Jun2022)**	**NIR-DT-301 Nirogacestat 150 mg BID (30Jun2022)**	**Integrated All DT Nirogacestat 150 mg BID (30Jun2022, 01Dec2022, 22Nov2016)**
Total N	**72**	**69**	**72**	**69**	**88**
ALT	6 (8%)	12 (17%)	6 (8%)	13 (19%)	22 (25%)
ALT Grade 3	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (2%)
AST	8 (11%)	11 (16%)	8 (11%)	12 (17%)	24 (27%)
AST Grade 3	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (2%)

BID: twice daily; DT: desmoid tumor; N: number of participants.

Note: There were no participants with Grade 4 or 5 events of ALT increased or AST increased.

Table 59. Treatment-Emergent Hepatotoxicity Adverse Events by System Organ Class and Preferred Term - Integrated Desmoid Tumour Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Hepatotoxicity Adverse Event	11 (15%)	18 (26%)	2 (100%)	31 (35%)	1 (20%)	34 (36%)
INVESTIGATIONS	11 (15%)	17 (25%)	2 (100%)	30 (34%)	1 (20%)	33 (35%)
Aspartate aminotransferase increased	8 (11%)	12 (17%)	1 (50%)	24 (27%)	1 (20%)	26 (27%)
Alanine aminotransferase increased	6 (8%)	13 (19%)	1 (50%)	22 (25%)	0	23 (24%)
Blood alkaline phosphatase increased	2 (3%)	0	0	5 (6%)	0	5 (5%)
Blood bilirubin increased	2 (3%)	1 (1%)	0	4 (5%)	0	4 (4%)
Gamma-glutamyltransferase increased	3 (4%)	2 (3%)	0	2 (2%)	0	2 (2%)
Transaminases increased	1 (1%)	0	1 (50%)	0	0	1 (1%)
International normalised ratio increased	1 (1%)	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	1 (1%)	0	6 (7%)	0	6 (6%)
Hypoalbuminaemia	0	1 (1%)	0	6 (7%)	0	6 (6%)
GASTROINTESTINAL DISORDERS	1 (1%)	0	0	0	0	0
Ascites	1 (1%)	0	0	0	0	0
HEPATOBILIARY DISORDERS	1 (1%)	0	0	0	0	0
Hepatic function abnormal	1 (1%)	0	0	0	0	0

In the Primary analysis population, ALT and AST increased was reported at a higher frequency with nirogacestat (17% and 16%, respectively; grade 3: 3%, each) compared with placebo (8% and 11%, respectively; grade 3: 1%, each). None of the patients on nirogacestat in the Primary analysis population had increased AST or ALT levels of >3xULN in combination with increased total bilirubin levels of >2xULN. There were no cases of DILI or cases meeting the Hy's law criteria reported with nirogacestat in any of the patient populations.

Hypersensitivity reactions

Table 60. Treatment-Emergent Hypersensitivity Events by System Organ Class and Preferred Term - Integrated Desmoid Tumour Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Hypersensitivity Event	1 (1%)	3 (4%)	0	5 (6%)	0	5 (5%)
GASTROINTESTINAL DISORDERS	0	1 (1%)	0	2 (2%)	0	2 (2%)
Lip swelling	0	1 (1%)	0	1 (1%)	0	1 (1%)
Mouth swelling	0	0	0	1 (1%)	0	1 (1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1%)	1 (1%)	0	2 (2%)	0	2 (2%)
Urticaria	1 (1%)	1 (1%)	0	2 (2%)	0	2 (2%)
EYE DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Periorbital oedema	0	1 (1%)	0	1 (1%)	0	1 (1%)

<u>OLE population</u>

Table 61. Treatment-Emergent Hypersensitivity Events by System Organ Class and Preferred Term - Open-Label Extension Population

SYSTEM ORGAN CLASS Preferred Term	Placebo to Nirogacestat 150 mg BID (N=45) n (%)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N=39) n (%)	Total (N=84) n (%)
Number of Participants with Any Treatment-Emergent Hypersensitivity Event	1 (2%)	0	1 (1%)
IMMUNE SYSTEM DISORDERS	1 (2%)	0	1 (1%)
Anaphylactic reaction	1 (2%)	0	1 (1%)

2.6.8.3.3. Deaths

Table 62. Deaths Reported in Nirogacestat Clinical Studies Included in Integrated DT Safety Population

Study	Participant Indication Under Study	Study Treatment and Dose	Cause of Death (PT)	Investigator Assessed Relationship to Study Treatment
NIR-DT-301	DT	Placebo	Sepsis (Sepsis)	Unrelated
NIR-DT-301	DT	Nirogacestat 100 mg(i)	Multi-organ failure (Multiple organ dysfunction syndrome), Spindle cell sarcoma diagnosis initially reported as a pulmonary nodule (Spindle cell sarcoma), Tumor hemorrhage (Tumour Haemorrhage)	Unrelated
14-C-0007	DT	Nirogacestat 150 mg BID	Cerebrovascular Accident	Unrelated

BID: twice daily; DT: desmoid tumor; mg: milligram; PT: preferred term

(i) Participant discontinued from the NIR-DT-301 study due to clinical progression more than 30 days prior to death. Dose listed was last dose level prior to discontinuing study treatment.

In study NIR-DT-301, one on-treatment death due to a TEAE of sepsis was reported in the placebo arm. In the nirogacestat arm, a death due to multiorgan failure in the context of disease progression was reported more than 30 days after last dose.

In study 14-C-0007, one on-treatment death due to cerebrovascular accident was reported in a patient long-standing hypertension; the latency time was 5 years.

2.6.8.4. Laboratory findings

Haematology

Primary analysis population

Median levels of **eosinophils**, both in absolute and relative counts, were higher in the nirogacestat arm compared with placebo. Increased levels were first observed during cycle 1 and persisted throughout the double-blind period. Shifts to grade 1 eosinophilia were observed at a higher incidence with nirogacestat (26%) compared with placebo (6%). Eosinophilia was reported as a TEAE in 3% of patients on nirogacestat vs. none on placebo.

Median levels of **monocyte** counts were higher with nirogacestat compared with placebo. Increased levels were observed from cycle 1 and persisted throughout the double-blind period.

There was a trend for increased **lymphocyte** counts with nirogacestat from cycle 4 through cycle 22 compared with placebo. There was no imbalance in shifts for lymphocyte counts across study arms, neither in terms of a decrease or an increase in lymphocyte count. There were no corresponding TEAEs.

No consistent trends over time or an imbalance in shifts were observed for other haematology parameters.

OLE population

Shifts in haematology parameters were generally consistent with the primary analysis population.

Chemistry

Primary analysis population

The most pronounces differences between the nirogacestat and the placebo arm concerned increases in ALAT and ASAT levels and decreases in phosphate and potassium.

Median levels of blood urate were consistently lower with nirogacestat compared with placebo. Decreased levels were first observed during cycle 1 and persisted throughout the double-blind period.

No consistent trends over time or an imbalance in shifts were observed for other chemistry parameters.

Hormone levels

Primary analysis population

Hormone levels in female patients are discussed in section 'adverse events of special interest'.

For male patients, blood sampling for hormone levels was implemented as per protocol amendment no. 3. Hormone levels, i.e. FSH, LH, progesterone, testosterone and free testosterone, have been captured throughout the double-blind phase of the pivotal study for 23 out of 25 male patients (92%) in both study arms. No trend over time was observed for any of the hormones; no relevant differences were observed between the study arms.

OLE population

No consistent trend over time was observed for any of the hormones. However, the assessment of data is hampered by the low number of male patients (placebo-nirogacestat: n=13; nirogacestat-nirogacestat: n=19). No TEAEs were reported with nirogacestat regarding changes in male hormone level or reproductive disorders.

Urinalysis

Primary analysis population

Proteinuria and glycosuria have been included in section 4.8 of the SmPC, based on an imbalance in urinalysis data between study arms and a pharmacologic rationale.

2.6.8.5. Vital signs and other observations related to safety

Vital signs

In the Primary analysis population, no clinically significant trends were identified in vital sign parameters with nirogacestat compared with placebo.

ECG

In the Primary analysis population, median change from baseline to the highest post-baseline value was 17.0 msec for nirogacestat (range: -2 to 57 msec) vs. 9 msec for placebo (range: -7 to 45 msec).

None of the patients in the Primary analysis population, Integrated DT population or OLE population, treated at the 150 mg BID dose, reported a QTcF interval of >500 msec or an increase in QTcF of >60 msec.

In study A8641014, a QTcF interval of >500 msec and/or an increase in QTcF of >60 msec was reported in 3 patients, 1 patient on 80 mg BID and 2 patients on 220 mg BID. The investigator considered these events as either related to poor lead placement, instrument malfunction, or not to be related to treatment.

The results from the concentration-QTc analysis indicated that the mean and 90% CI of the predicted increase in QT is below 10 ms (see section 'pharmacodynamics''for details). The results of this analysis are presented in section 5.1 of the SmPC.

2.6.8.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.7. Safety in special populations

Age

The dataset used for population pharmacokinetics (PopPK) analysis, which included 27 participants aged ≥65 years or older, found no significant effect of age on nirogacestat PK. The small number of patients ≥65 years of age in the Integrated DT population (3 with nirogacestat vs. 3 with placebo) does not allow for a meaningful assessment of safety per age category (≥65 years vs. <65 years).

Sex

Apart from ovarian toxicity being reported in WOCBP, alopecia was reported predominantly in females in the nirogacestat arm (n=12; 27%) vs. 1 male patient (4%). This event may be secondary to ovarian toxicity. Generally, assessment of the TEAE profile by sex is hampered by the small number of patients included across study arms in the pivotal study as well as per sex.

Table 63. AE by special population - Double-Blind Phase NIR-DT-301 Safety Population

	Nirogacestat				Placebo			
MedDRA Preferred Term	**Hepatically Impaired[a] (N=5) n (%)**	**Renally Impaired[b] (N=0) n (%)**	**Pregnant (N=0*) n (%)**	**Elderly (Age ≥65) (N=3) n (%)**	**Hepatically Impaired[a] (N=4) n (%)**	**Renally Impaired[b] (N=2) n (%)**	**Pregnant (N=0) n (%)**	**Elderly (Age ≥65) (N=3) n (%)**
Any TEAE	5 (100)	0	0	3 (100)	4 (100)	2 (100)	0	3 (100)
Serious TEAE	2 (40)	0	0	0	1 (25)	1 (50)	0	0
Fatal	0	0	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	1 (20)	0	0	0	1 (25)	1 (50)	0	0
Life-threatening	0	0	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	2 (40)	0	0	0	0	0	0	0
AE leading to study treatment discontinuation	1 (20)	0	0	1 (33)	1 (25)	0	0	0
Diarrhoea	0	0	0	1 (33)	0	0	0	0
Hepatic function abnormal	0	0	0	0	1 (25)	0	0	0
Premature menopause	1 (20)	0	0	0	0	0	0	0

Reference: Day 120 Table Q.101.

Data cutoff: 02Apr2024

Abbreviations: AE: adverse event; N: number of participants in Safety Population; n: number of participants with data meeting the definition for each special population; TEAE: treatment-emergent adverse event.

Percentage (%) was based on Safety Population.

a Hepatic impairment is defined as having bilirubin above upper limit of normal prior to nirogacestat administration. For placebo-to-nirogacestat participants, more than 2 occurrences of bilirubin above upper limit of normal prior to nirogacestat administration are also considered.

b Renal impairment is defined as having glomerular filtration rate <90 mL/min prior to nirogacestat administration. For placebo-to-nirogacestat participants, more than 2 occurrences of glomerular filtration rate <90 mL/min prior to nirogacestat administration are also considered.

Table 64. AE by special population - Open-Label Phase NIR-DT-301 Safety Population

	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID				Placebo BID to Nirogacestat 150 mg BID			
MedDRA Preferred Term	Hepatically Impaired[a] (N=5) n (%)	Renally Impaired[b] (N=0) n (%)	Pregnant (N=0) n (%)	Elderly (Age ≥65) (N=3) n (%)	Hepatically Impaired[a] (N=3) n (%)	Renally Impaired[b] (N=2) n (%)	Pregnant[c] (N=0) n (%)	Elderly (Age ≥65) (N=1) n (%)
Any TEAE	5 (100)	0	0	3 (100)	3 (100)	2 (100)	0	1 (100)
Serious TEAE	3 (60)	0	0	0	0	1 (50)	0	0
Fatal	0	0	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	2 (40)	0	0	0	0	1 (50)	0	0
Life-threatening	0	0	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	3 (60)	0	0	0	0	0	0	0
AE leading to study treatment discontinuation	1 (20)	0	0	2 (67)	0	0	0	0
Diarrhoea	0	0	0	2 (67)	0	0	0	0
Premature menopause	1 (20)	0	0	0	0	0	0	0

Reference: Day 120 Table Q.101.B.
Data cutoff: 02Apr2024.
Abbreviations: AE: adverse event; BID: twice daily; N: number of participants in Safety Population; n: number of participants with data meeting the definition for each special population; OLE: open-label extension; TEAE: treatment-emergent adverse event.
Percentage (%) was based on Safety Population.
a Hepatic impairment is defined as having bilirubin above upper limit of normal prior to nirogacestat administration. For placebo-to-nirogacestat participants, more than 2 occurrences of bilirubin above upper limit of normal prior to nirogacestat administration are also considered.
b Renal impairment is defined as having glomerular filtration rate <90mL/min prior to nirogacestat administration. For placebo-to-nirogacestat participants, more than 2 occurrences of glomerular filtration rate <90 mL/min prior to nirogacestat administration are also considered.
c A spontaneous abortion has been reported by a woman in NIR-DT-301 OLE phase (placebo-to-nirogacestat) who conceived while receiving nirogacestat who was not practicing effective birth control.

Renal impairment

As per protocol inclusion criterion 9f, patients could be included if serum creatinine was ≤1.5 x ULN or if creatinine was >1.5 x ULN then calculated creatinine clearance had to be ≥60 mL/min (using the Cockcroft-Gault formula). In the OLE population, 2 patients have been identified with mild renal impairment at baseline; the reported AEs in both patients are largely consistent with the safety profile of nirogacestat in general. Based on the limited data, no conclusions can be drawn regarding safety in patients with pre-existing renal impairment.

Hepatic impairment

As per protocol inclusion criterion 9d and 9e, patients could be included if total bilirubin was ≤1.5x ULN and ASAT/ALAT was ≤2x ULN. As per the protocol for study NIR-DT-301, patients with a current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones) were excluded from the study. In the clinical database, 8 patients were identified with a bilirubin level above ULN at baseline, 5 patients in the double-blind phase of study NIR-DT-301 and 3 patients in the OLE phase. Baseline bilirubin levels were <1.5x ULN in 7 patients. None of these patients had a post-baseline bilirubin level >2x ULN while on nirogacestat. The reported AEs in these patients were largely consistent with the safety profile of nirogacestat in general and do not raise a concern. Nevertheless, based on the limited data no firm conclusions can be drawn regarding safety in patients with pre-existing hepatic impairment.

Cardiovascular impairment

Patients with significant cardiovascular disease have been excluded from the pivotal study; thus, there is no data on safety in patients with pre-existing cardiovascular disease. No relevant effect of

nirogacestat on vital signs or QTc has been observed and no imbalance in cardiac rhythm disorders has been reported across study arms in the pivotal study.

2.6.8.8. Immunological events

Not applicable.

2.6.8.9. Safety related to drug-drug interactions and other interactions

See section 2.6.2.1. pharmacokinetics.

2.6.8.10. Discontinuation due to adverse events

Table 65. TEAEs leading to treatment discontinuation - Primary Analysis Population and Integrated DT Safety Population

	Study NIR-DT-301		Nirogacestat			
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=72) n (%)	Nirogacestat 150 mg BID (N=69) n (%)	< 150 mg BID (N=2) n (%)	150 mg BID (N=88) n (%)	≥ 220 mg BID (N=5) n (%)	Total (N=95) n (%)
Number of Participants with Any Treatment-Emergent Adverse Event Leading to Discontinuation of Study Drug	2 (3%)	16 (23%)	0	17 (19%)	2 (40%)	19 (20%)
GASTROINTESTINAL DISORDERS	1 (1%)	4 (6%)	0	4 (5%)	0	4 (4%)
Diarrhoea	0	4 (6%)	0	4 (5%)	0	4 (4%)
Vomiting	0	1 (1%)	0	1 (1%)	0	1 (1%)
Dysphagia	1 (1%)	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	4 (6%)	0	4 (5%)	0	4 (4%)
Premature menopause	0	3 (4%)	0	3 (3%)	0	3 (3%)
Ovarian failure	0	1 (1%)	0	1 (1%)	0	1 (1%)
INVESTIGATIONS	0	3 (4%)	0	3 (3%)	0	3 (3%)
Alanine aminotransferase increased	0	3 (4%)	0	3 (3%)	0	3 (3%)
Aspartate aminotransferase increased	0	2 (3%)	0	2 (2%)	0	2 (2%)
IMMUNE SYSTEM DISORDERS	0	0	0	1 (1%)	1 (20%)	2 (2%)
Drug hypersensitivity	0	0	0	0	1 (20%)	1 (1%)
Hypersensitivity	0	0	0	1 (1%)	0	1 (1%)
METABOLISM AND NUTRITION DISORDERS	0	2 (3%)	0	2 (2%)	0	2 (2%)
Decreased appetite	0	1 (1%)	0	1 (1%)	0	1 (1%)
Hypophosphataemia	0	1 (1%)	0	1 (1%)	0	1 (1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (1%)	0	1 (1%)	1 (20%)	2 (2%)
Rash	0	0	0	0	1 (20%)	1 (1%)
Rash maculo-papular	0	1 (1%)	0	1 (1%)	0	1 (1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Fatigue	0	1 (1%)	0	1 (1%)	0	1 (1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Sjogren's syndrome	0	1 (1%)	0	1 (1%)	0	1 (1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (1%)	0	1 (1%)	0	1 (1%)
Tumour haemorrhage	0	1 (1%)	0	1 (1%)	0	1 (1%)
NERVOUS SYSTEM DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Mental impairment	0	1 (1%)	0	1 (1%)	0	1 (1%)
RENAL AND URINARY DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Haematuria	0	1 (1%)	0	1 (1%)	0	1 (1%)
VASCULAR DISORDERS	0	1 (1%)	0	1 (1%)	0	1 (1%)
Hot flush	0	1 (1%)	0	1 (1%)	0	1 (1%)
HEPATOBILIARY DISORDERS	1 (1%)	0	0	0	0	0
Hepatic function abnormal	1 (1%)	0	0	0	0	0

OLE Population (Study NIR-DT-301)

Table 66. TEAEs leading to treatment discontinuation - Open-Label Extension Population

SYSTEM ORGAN CLASS Preferred Term	Placebo to Nirogacestat 150 mg BID (N=45) n (%)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N=39) n (%)	Total (N=84) n (%)
Number of Participants with Any Treatment-Emergent Adverse Event Leading to Discontinuation of Study Drug	6 (13%)	0	6 (7%)
INVESTIGATIONS	2 (4%)	0	2 (2%)
Alanine aminotransferase increased	2 (4%)	0	2 (2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (4%)	0	2 (2%)
Rash	1 (2%)	0	1 (1%)
Rash maculo-papular	1 (2%)	0	1 (1%)
GASTROINTESTINAL DISORDERS	1 (2%)	0	1 (1%)
Obstruction gastric	1 (2%)	0	1 (1%)
IMMUNE SYSTEM DISORDERS	1 (2%)	0	1 (1%)
Anaphylactic reaction	1 (2%)	0	1 (1%)

TEAEs leading to dose reduction

Table 67. Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term – Double-Blind Phase – Integrated Desmoid Tumour Safety Population

	NIR-DT-301		Nirogacestat			
System Organ Class Preferred Term	**Placebo (N=72) n (%)**	**Nirogacestat 150 mg BID (N=69) n (%)**	**<150 mg BID (N=2) n (%)**	**150 mg BID (N=88) n (%)**	**≥220 mg BID (N=5) n (%)**	**Total Nirogacestat (N=95) n (%)**
Any TEAE leading to dose reduction	0	29 (42)	0	39 (44)	1 (20)	40 (42)
Gastrointestinal disorders	0	9 (13)	0	11 (13)	1 (20)	12 (13)
Diarrhoea	0	6 (9)	0	8 (9)	0	8 (8)
Stomatitis	0	3 (4)	0	3 (3)	0	3 (3)
Nausea	0	0	0	0	1 (20)	1 (1)
Skin and subcutaneous tissue disorders	0	6 (9)	0	8 (9)	0	8 (8)
Rash maculo-papular	0	3 (4)	0	5 (6)	0	5 (5)
Hidradenitis	0	2 (3)	0	2 (2)	0	2 (2)
Dermatitis acneiform	0	1 (1)	0	1 (1)	0	1 (1)
Urticaria	0	1 (1)	0	1 (1)	0	1 (1)
Metabolism and nutrition disorders	0	4 (6)	0	5 (6)	0	5 (5)
Hypophosphataemia	0	3 (4)	0	3 (3)	0	3 (3)
Hypokalaemia	0	1 (1)	0	1 (1)	0	1 (1)
Hypocalcaemia	0	0	0	1 (1)	0	1 (1)
Investigations	0	2 (3)	0	4 (5)	0	4 (4)
Alanine aminotransferase increased	0	1 (1)	0	1 (1)	0	1 (1)
Aspartate aminotransferase increased	0	1 (1)	0	1 (1)	0	1 (1)
Blood follicle stimulating hormone increased	0	1 (1)	0	1 (1)	0	1 (1)
Blood luteinising hormone increased	0	1 (1)	0	1 (1)	0	1 (1)
Electrocardiogram QT prolonged	0	0	0	1 (1)	0	1 (1)
Weight decreased	0	0	0	1 (1)	0	1 (1)

	NIR-DT-301		Nirogacestat			
System Organ Class Preferred Term	**Placebo (N=72) n (%)**	**Nirogacestat 150 mg BID (N=69) n (%)**	**<150 mg BID (N=2) n (%)**	**150 mg BID (N=88) n (%)**	**≥220 mg BID (N=5) n (%)**	**Total Nirogacestat (N=95) n (%)**
General disorders and administration site conditions	0	1 (1)	0	2 (2)	1 (20)	3 (3)
Fatigue	0	1 (1)	0	2 (2)	0	2 (2)
Mucosal inflammation	0	0	0	0	1 (20)	1 (1)
Infections and infestations	0	2 (3)	0	2 (2)	0	2 (2)
Folliculitis	0	2 (3)	0	2 (2)	0	2 (2)
Staphylococcal abscess	0	1 (1)	0	1 (1)	0	1 (1)
Reproductive system and breast disorders	0	1 (1)	0	2 (2)	0	2 (2)
Ovarian failure	0	1 (1)	0	1 (1)	0	1 (1)
Breast tenderness	0	0	0	1 (1)	0	1 (1)
Blood and lymphatic system disorders	0	1 (1)	0	1 (1)	0	1 (1)
Anaemia	0	1 (1)	0	1 (1)	0	1 (1)
Congenital, familial and genetic disorders	0	1 (1)	0	1 (1)	0	1 (1)
Fanconi syndrome[(a)]	0	1 (1)	0	1 (1)	0	1 (1)
Eye disorders	0	1 (1)	0	1 (1)	0	1 (1)
Eye irritation	0	1 (1)	0	1 (1)	0	1 (1)
Hepatobiliary disorders	0	1 (1)	0	1 (1)	0	1 (1)
Cholecystitis	0	1 (1)	0	1 (1)	0	1 (1)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (20)	1 (1)
Arthralgia	0	0	0	0	1 (20)	1 (1)
Myalgia	0	0	0	1 (1)	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1)	0	1 (1)	0	1 (1)
Tumour pain	0	1 (1)	0	1 (1)	0	1 (1)
Psychiatric disorders	0	1 (1)	0	1 (1)	0	1 (1)
Insomnia	0	1 (1)	0	1 (1)	0	1 (1)
Nervous system disorders	0	0	0	1 (1)	0	1 (1)
Memory impairment	0	0	0	1 (1)	0	1 (1)

Data cutoff for NIR-DT-301: 30Jun2022 and for 14_C_0007: 01Dec2022.

Abbreviations: BID: twice daily; MedDRA: Medical Dictionary for Regulatory Activities.

Note: Nirogacestat groups are not mutually exclusive. Total nirogacestat includes all participants exposed to nirogacestat and can be derived by summing the <150 mg BID, 150 mg BID, and ≥220 mg BID groups.

Note: Adverse events are coded using MedDRA Dictionary Version 24.0.

Note: Treatment-emergent adverse events are those events that occur on or after the initiation of study treatment through 30 days, after the last dose of study treatment.

Note: A participant with dose interruption followed by reduction are counted in dose reduced.
Fanconi syndrome was term reported by investigator.

Table 68. Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term – NIR-DT-301 (Open-Label Extension Population)

System Organ Class Preferred Term	Placebo to Nirogacestat 150 mg BID (N=45) N (%)	Nirogacestat 150 mg BID to Nirogacestat 150 mg BID (N=39) N (%)	Total (N=84) N (%)
Any TEAE leading to dose reduction	17 (38)	4 (10)	21 (25)
Gastrointestinal disorders	9 (20)	1 (3)	10 (12)
Diarrhoea	5 (11)	1 (3)	6 (7)
Stomatitis	3 (7)	0	3 (4)
Nausea	1 (2)	0	1 (1)
Vomiting	1 (2)	0	1 (1)
Reproductive system and breast disorders	4 (9)	0	4 (5)
Ovarian failure	2 (4)	0	2 (2)
Ovarian disorder	1 (2)	0	1 (1)
Premature menopause	1 (2)	0	1 (1)
Skin and subcutaneous tissue disorders	3 (7)	0	3 (4)
Dermatitis acneiform	1 (2)	0	1 (1)
Hidradenitis	1 (2)	0	1 (1)
Rash maculo-papular	1 (2)	0	1 (1)
Investigations	1 (2)	1 (3)	2 (2)
Alanine aminotransferase increased	1 (2)	0	1 (1)
Weight decreased	0	1 (3)	1 (1)
Metabolism and nutrition disorders	1 (2)	1 (3)	2 (2)
Hypokalaemia	1 (2)	1 (3)	2 (2)
General disorders and administration site conditions	0	1 (3)	1 (1)
Fatigue	0	1 (3)	1 (1)
Infections and infestations	1 (2)	0	1 (1)
Folliculitis	1 (2)	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3)	1 (1)
Basal cell carcinoma	0	1 (3)	1 (1)

Abbreviations: BID: twice daily; N: number of participants in Safety Population; MedDRA: Medical Dictionary for Regulatory Activities; n: number of participants with data available; TEAE: treatment-emergent adverse events

Percentage (%) was based on Safety Population.

Note: Adverse events are coded using MedDRA Dictionary Version 24.0.

Note: TEAEs are those events that occur on or after the initiation of study treatment through 30 days, after the last dose of study treatment.

2.6.8.11. Adverse reactions in SmPC

Adverse reactions (ADRs) for nirogacestat are defined as those AEs considered related to nirogacestat based on the assessment of numerical frequency data (incidence, EAIR, EAER) and review of individual case details such as temporal association of the event with administration of nirogacestat, dechallenge and rechallenge information, and confounding factors such as intercurrent illnesses and administration of concomitant medications which could be plausible alternative causes for the reported events. The presence of a description of a plausible mechanism by which GS inhibition could lead to the reported event in the literature was also taken into account when considering if a reported event was an adverse reaction for nirogacestat.

The data described below reflect exposure to nirogacestat in 88 participants with DT across 3 studies who were treated with nirogacestat 150 mg BID (Integrated All DT nirogacestat 150 mg BID group in the Integrated DT Safety Population).

Table 69. Adverse Reactions Reported for Nirogacestat 150 mg BID (N=88)

System organ class	Adverse reaction	All grades	Grades 3-4
Gastrointestinal disorders	Diarrhoea	Very common (85%)	Very common (16%)
	Nausea	Very common (59%)	Common (1%)
	Stomatitis[a]	Very common (40%)	Common (3%)
	Dry mouth	Very common (17%)	--
Skin and subcutaneous disorders	Rash[b]	Very common (66%)	Common (5%)
	Alopecia	Very common (18%)	--
	Folliculitis	Very common (16%)	Common (5%)
	Hidradenitis	Common (7%)	Common (1%)
	Dry skin	Very common (18%)	--
	Pruritis	Very common (14%)	--
Neoplasms benign, malignant and unspecified	Basal cell carcinoma	Common (1%)	--
	Squamous cell[c] carcinoma	Common (3%)	--
Metabolism and nutrition disorders	Hypophosphataemia	Very common (50%)	Very common (13%)
	Hypokalaemia	Very common (19%)	Common (3%)
Nervous system disorders	Headache	Very common (40%)	--
	Dizziness	Very common (15%)	--
Investigation	Proteinuria	Very common (46%)	--
	Glycosuria	Very common (52%)	--
Blood and lymphatic system disorders	Eosinophilia	Very common (27%)	--
Renal and urinary disorders	Renal tubular disorder	Common (1%)	--
Injury, poisoning and procedural complications	Bone fracture [d]	Common (9%)	--
Hepatobiliary disorders	ALT increased	Very common (25%)	Common (2%)
	AST increased	Very common (27%)	Common (2%)
Reproductive system and breast disorders	Ovarian toxicity[e]	Very common (92%)	--
Respiratory, thoracic and mediastinal disorders	Cough	Very common (20%)	--
	Upper respiratory tract infection[f]	Very common (23%)	--
	Dyspnoea	Very common (16%)	--
	Epistaxis	Very common (16%)	--
General disorders and administration site conditions	Fatigue	Very common (50%)	Common (3%)
	Influenza-like illness	Very common (15%)	--

[a] Stomatitis includes stomatitis, mouth ulceration, oral pain, and oropharyngeal pain.
[b] Rash includes rash maculo-papular, dermatitis acneiform, rash, rash erythematous, rash pruritic, and rash papular.
[c] Squamous cell carcinoma included squamous cell carcinoma of skin and squamous cell carcinoma.
[d] Bone fracture includes fracture, foot fracture, hand fracture, radius fracture, hip fracture and rib fracture.
[e] Ovarian toxicity includes ovarian failure, premature menopause, amenorrhoea, oligomenorrhoea, menstruation irregular, dysmenorrhoea, heavy menstrual bleeding, vulvovaginal dryness, hot flush, decreased anti-Müllerian hormone (AMH) and increased follicle-stimulating hormone (FSH).
[f] Upper respiratory tract infection (URTI) includes URTI, viral URTI, acute sinusitis, and sinusitis.
-- Represents no cases were reported.

2.6.8.12. Post marketing experience

Nirogacestat was approved in the United States on 27th November 2023 for the treatment of adult patients with progressing DT requiring systemic treatment. As of 27 May 2024, 7 patients reported an event of ovarian toxicity; the cases contained limited clinical information. No cases of testicular toxicity were reported. A pregnancy was reported in a 29-year-old patient who discontinued nirogacestat 3

years previously; during nirogacestat treatment irregular menstruation (grade 2, assessed by the investigator as not related) was reported but no OT event. The outcome of the pregnancy is presently not known.

Compassionate use program (CUP)

As of 23 Oct 2023, 249 individuals had participated in the nirogacestat CUP, with the first shipment on 19 February 2019. As of the 2023 October data cut-off, the following countries were participating in the CUP program: Australia, Belgium, Canada, Finland, France, Germany, Italy, Netherlands, New Zealand, United Kingdom, and United States.

Of these 249 patients, 144 individuals reported one or more AEs in 145 separate case reports.

The mean age of CUP patients was 35.4 years (age range was from 1 years to 83 years). A total of 25 patients were <18 years of age, 209 were aged 18<65 years, and 15 were aged ≥65 years. Females represented 63% of the patients, and 11 were receiving nirogacestat for indications other than DT: adenoid cystic carcinoma (5), adamatinomatous craniopharyngioma (2), glomus tumuor (1), non-small cell lung cancer (1), SETTLE syndrome (1), and liposarcoma (1).

When comparing the recognized safety profile of nirogacestat to AEs reported from the nirogacestat CUP, the safety data appear to be representative of the overall safety profile previously recognized for nirogacestat therapy and provide supportive evidence for this application. The reports from paediatric participants provide additional insight into the possible effects on growing bones observed in non-clinical studies.

2.6.9. Discussion on clinical safety

The clinical safety database providing data for safety assessment in the applied for indication and at the recommended dose proposed for marketing (150 mg BID) is based on 3 studies: the pivotal study NIR-DT-301, consisting of a double-blind phase and its open-label extension (OLE), and 2 supportive studies, 14-C-0007 and A8641014.

The safety assessment is mainly based on the dataset from the pivotal study NIR-DT-301.

The clinical safety database used for determination of adverse reactions consists of 88 patients who received at least 1 dose of nirogacetstat (150 mg twice daily) (hereinafter referred to as the integrated DT population).

The size of the safety database, although limited, is considered adequate, given the orphan indication.

The patient population enrolled in the pivotal study (primary analysis) was representative for patients with DT in terms of age (median age of 33 years; range 18 - 73 years), with 4% of patients aged ≥65 years, and gender distribution (64% female).

In the Primary analysis population, median treatment duration was 20.6 months (range 0.3-33.6 months) in the nirogacestat arm vs. 11.4 months (range 0.2-33 months) in the placebo arm.

Median treatment duration in the Integrated DT population was similar to the Primary analysis population, i.e., 21.5 months.

In the OLE population, median treatment duration ranged from 7.1 months (range 0.3-31.9 months) for patients switching from placebo to nirogacestat to 29.4 months (range 13.7-38.4 months) for patients continuing nirogacestat. Of the 84 patients, 71% were exposed to nirogacestat for at least 12 months and 55% for at least 24 months.

Overall safety profile

Primary analysis population

The frequency of patients with any AE was similar across study arms, 100% with nirogacestat and 96% with placebo.

The most common TEAEs (≥25%) in the nirogacestat arm (nirogacestat vs. placebo) were diarrhoea (84% vs. 35%), nausea (54% vs. 39%), fatigue (51% vs. 36%), hypophosphatemia (42% vs. 7%), rash maculo-papular (32% vs. 6%), headache (29% vs. 15%) and stomatitis (29% vs. 4%).

TEAEs of grade ≥3 were reported at a higher frequency with nirogacestat (55%) compared with placebo (17%). Common grade ≥3 TEAEs (≥5%) in the nirogacestat arm were diarrhoea (16%), folliculitis and rash maculo-papular (6%, each). In the placebo arm, no single TEAE was reported in more than 5% of patients.

In study NIR-DT-301, one on-treatment death due to a TEAE of sepsis was reported in the placebo arm. In the nirogacestat arm, a death due to multiorgan failure in the context of disease progression was reported more than 30 days after last dose; this death is assessed as not related to nirogacestat.

SAEs were reported at a higher frequency with nirogacestat (19%) compared with placebo (11%). SAEs reported in more than 1 patient in the nirogacestat arm were premature menopause (n=3; 4%) and in the placebo arm sepsis (n=3; 4%) and COVID-19 (n=2; 3%). The remaining SAEs were reported in a single patient in either treatment arm.

In the Primary analysis population, TEAEs leading to treatment discontinuation were reported at a higher frequency with nirogacestat (23%) compared with placebo (3%). TEAEs leading to treatment discontinuation reported in more than 1 patient in the nirogacestat arm were diarrhoea (n=4; 6%) and premature menopause (n=3; 4%), with 1 further patient (1%) discontinuing treatment due to ovarian failure. The remaining TEAEs leading to treatment discontinuation with nirogacestat were reported in single patients. The discontinuation rate of 23% is high, reflecting the high toxicity associated with nirogacestat treatment.

TEAEs leading to dose reduction were reported in 42% of patients on nirogacestat vs. none on placebo. TEAEs leading to dose reduction reported in more than 1 patient in the nirogacestat arm were diarrhoea (9%), stomatitis, rash maculo-papular, hypophosphatemia (4%, each), hidradenitis and folliculitis (3%, each).

Integrated DT population

In study 14-C-0007, one on-treatment death due to cerebrovascular accident was reported with a latency time of 5 years. Given the long latency time and the concurrent condition of hypertension, this death is assessed as not related to nirogacestat.

Data in the Integrated DT population were generally consistent with those in the Primary analysis population.

OLE population

No deaths due to TEAEs were reported in the OLE population.

Data in the OLE population were generally consistent with those in the Primary analysis population.

Overall, the incidence of any TEAE, grade ≥3 TEAEs, SAEs, TEAEs leading to discontinuation and TEAEs leading to dose reduction was higher in patients switching from placebo compared with patients continuing nirogacestat. This data is consistent with most TEAEs being reported during the first or second 28-day treatment cycle.

AEs of special interest

Ovarian toxicity

Primary analysis population

Ovarian toxicity (OT) (narrow search) was defined as a term encompassing four PTs: ovarian failure, premature menopause, amenorrhea, and menopause. Based on an imbalance across study arms also the following PTs are considered adverse reactions: menstruation irregular (11% vs. 4%), heavy menstrual bleeding (11% vs. 0%), dysmenorrhea (5% vs 0%), vulvovaginal dryness (3% vs. 0%), hot flush (30% vs 9%), increased FSH (16% vs 0%) and decreased AMH (7% vs 0).

OT was reported in 75% of women of child-bearing potential (WOCBP) in the nirogacestat arm vs. none in the placebo arm. There were three serious adverse reactions of ovarian toxicity, all premature menopause, representing 11% of all participants reporting ovarian toxicity. Among WOCBP, dose modification was reported as dose reduced in 7%, as dose interrupted in 7% and 4 patients (15%) discontinued nirogacestat treatment permanently.

Resolution of OT events was assessed by the investigator based on resolution of the events that triggered the reporting of the OT event (i.e. abnormal menstruation or hormone levels). At the time of the data cut-off for the primary analysis (7 April 2022), the outcome of OT was reported as recovered/resolved in 63% (17 of 27 patients) of patients with OT events and not recovered/resolved in 37% (10 of 27 patients). The outcome was reported as unknown in 1 patient (4%). As of the latest follow-up date, i.e., 24 October 2022, ovarian toxicity was reported as resolved in 1 further WOCBP. Apart from age close to the natural age of menopause, no conclusions can be drawn regarding possible reasons for non-resolution of OT events.

Off-treatment resolution

Of the 27 WOCBP with OT events, 13 patients discontinued nirogacestat for any reason. Of these, data on resolution of OT was not available in 2 patients, as both were lost to follow-up. In the remaining 11 patients, OT was reported as resolved. In 2 patients no information on the return of menstruation was available; however, hormone levels had returned to normal. The remaining 9 patients reported return of menstruation, although FSH and/or oestradiol levels had not normalised in 4 patients. Of the latter 4 patients, evaluation of resolution of OT event in terms of hormone levels was hampered in 1 patient due to peri-menopausal age (48 years) and in 1 patient due to use of combined oral contraceptive.

On-treatment resolution

Of the 14 WOCBP with OT events continuing nirogacestat treatment, OT was reported as resolved in 10 patients and as not resolved in 4 patients (as of 24 October 2022). In the 10 patients reporting return of menstruation, FSH and/or oestradiol levels had not returned to normal in 3 patients. As of the latest follow-up (2 August 2024), the OT event was ongoing in 3 patients continuing nirogacestat.

Hormone levels

The pattern of hormone levels in WOCBP reflects the ovarian toxicity observed with nirogacestat, with increased levels of FSH and LH, decreased levels of AMH, oestradiol and progesterone compared with the placebo arm.

Oestrogen suppression for >6 months was reported in 10 out of 36 WOCBP in the nirogacestat arm. Based on analysis of data for prolonged oestrogen suppression and the relatively low number of WOCBP on nirogacestat in the pivotal study, no firm conclusion can be drawn regarding the potential of nirogacestat to induce prolonged oestrogen suppression.

In the Primary Analysis and the OLE population, 4 patients had a dose reduction. In 1 patient, the event of OT was reported as resolved following dose reduction; however, a second event of ovarian failure was reported, while the patient continued to receive a reduced dose. Overall, the limited data

available regarding dose reduction for ovarian toxicity do not warrant a dose recommendation in the SmPC.

OLE population

Generally, the reporting pattern of OT events and hormone levels in the OLE population was consistent with the Primary analysis population.

Female fertility

As of the latest follow-up date (24 October 2022), resolution of OT events was reported in 21 of 27 WOCBP with OT (79%). The assessment of OT was only performed in the pivotal study in which hormones (AMH, FSH, LH, oestradiol and progesterone) were collected at baseline, C1D22, C2D28, C4, every three cycles thereafter and 90 days after the last treatment dose in women with OT and 30 days after the last dose in women without OT. ASCO recommends hormone collection at least 1-2 years after the end of treatment, so the period for hormonal assessment in the pivotal study is not sufficient for a complete characterisation of long-term safety. In addition, clinical measures (menstruation, pregnancy and livebirths) should also be collected at time points later than 2 years after the end of treatment, but in the pivotal study data on livebirth and pregnancies were not collected and only the return of menstruation was recorded via pharmacovigilance. According to the above recommendation, even women who maintain or resume menstruation may have impaired fertility potential and the risk of premature ovarian insufficiency or early menopause cannot be excluded in these patients. In addition, despite the observed non-clinical effects on epithelial degeneration and necrosis, the effects on the uterus have not been evaluated. Taking all these measures into account, it can be concluded that the assessment to identify OT is considered acceptable, but the data on long-term safety of ovarian function and the impact on fertility are lacking.

Ovarian toxicity and adverse effects on female infertility are included as important identified risk and important potential risk respectively in the RMP. The applicant has committed to perform a post-authorisation safety study (category 3 PASS) in order to determine the ovarian function recovery rate of OT events in post-pubertal and premenopausal females treated with nirogacestat for at least 12 cycles. The final CSR is anticipated in 2031.

Skin and subcutaneous tissue disorders

In the pivotal study, dermatologic reactions were reported at a higher incidence in patients receiving nirogacestat than in those receiving placebo; they included maculo-papular rash (32% vs 6%), hidradenitis (9% vs 0), and folliculitis (13% vs 0). The median time to rash events was 22 days (range 2 to 603 days). Skin and subcutaneous disorders led to dose reduction in 9% of patients receiving nirogacestat, including maculo-papular rash in 4% and hidradenitis in 3%. Maculo-papular rash led to treatment discontinuation in 1%. A warning is also included in section 4.4 of the SmPC to inform healthcare professionals that patients should be monitored for dermatologic reactions throughout the course of treatment and managed as clinically indicated. For Grade 3 dermatologic reactions, nirogacestat should be withheld until resolved to Grade ≤ 1 or baseline, then it should be restarted at a dose of 100 mg twice daily.

Hepatotoxicity

In the Primary analysis population, ALT and AST increased was reported at a higher frequency with nirogacestat (19% and 17%, respectively; grade 3: 3%, each) compared with placebo (8% and 11%, respectively; grade 3: 1%, each). None of the patients on nirogacestat in the Primary analysis population had increased AST or ALT levels of >3xULN in combination with increased total bilirubin levels of >2xULN. There were no cases of DILI or cases meeting the Hy's law criteria reported with nirogacestat in any of the patient populations.

In non-clinical studies, hepatic necrosis has been observed. Although no cases of DILI in association with nirogacestat have been observed, the sample size of the safety database may have been too small to have captured events of DILI or severe hepatoxicity. DILI has been included in the RMP as an important potential risk.

Hypersensitivity reactions

In the OLE population, a case of grade 3 anaphylactic reaction was reported on Day 10, leading to treatment discontinuation of nirogacestat. As the clinical details in this case were not supportive for a diagnosis of anaphylactic reaction, this event is not considered to be an ADR.

Other noteworthy TEAEs

Effects on mature bone and bone fractures

Bone imaging to monitor the development of osteoporosis was not performed, so the low incidence of osteoporosis in the nirogacestat group (1% in the primary and DT populations) is not surprising. However, given the effect of nirogacestat on oestrogen suppression and hypophosphatemia/renal proximal tubular dysfunction, and based on the non-clinical data, an effect on bone structure and the risk of osteopenia, osteoporosis and fractures cannot be neglected.

In the pivotal study, bone fractures occurred in 4 participants treated with nirogacestat, but not in the placebo group (6% versus 0%). All reports of bone fracture were non-serious and Grade 1 or 2. In the integrated DT 150 mg BID group, 8 of 88 patients (9%) reported fractures and in the OLE phase, one event of teeth fracture was related to nirogacestat. It is acknowledged that other risk factors (age, osteoporosis at baseline, previous therapies) were reported in these cases. Bone fracture events did not lead to dose reduction or treatment discontinuation in any patient receiving nirogacestat. The effects on bone are likely to be more pronounced with long-term use and in patients with multiple risk factors such as age, menopause, osteoporosis, previous fractures. Since treatment with nirogacestat is intended for a long period of time, it is not known how oestrogen levels will develop with continued treatment and how this would affect bone fractures. Furthermore, given the effect of nirogacestat on renal proximal tubular function and the occurrence of hypophosphatemia, osteomalacia may be expected as a complication of these conditions. Apart from an indirect effect of nirogacestat on bone metabolism, GS inhibition may exert a direct effect on bone formation through interference with Wnt/β-catenin signalling. Overall, given the imbalance in bone fracture events in the pivotal study as well as a plausible mechanism, a causal association between nirogacestat and bone fractures is considered an at least reasonable possibility. Bone fractures have been included as a common ADR in section 4.8 of the SmPC and also included as an identified important risk in the RMP. This risk will be further investigated by the category 3 PASS, a Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis.

Diarrhoea

In the pivotal study diarrhoea was reported in 84% of patients receiving nirogacestat compared to 35% in patients receiving placebo. Grade 3 events occurred in 16% and 1% of patients, respectively. Grade ≤ 2 diarrhoea resolved in 74% of patients who continued on nirogacestat treatment. The median time to first onset of diarrhoea in patients receiving nirogacestat was 9 days (range 2 to 234 days). Diarrhoea led to dose reduction in 10% of patients and treatment discontinuation in 7% receiving Nirogacestat. A warning is also included in section 4.4 of the SmPC to inform healthcare professionals that patients who experience diarrhoea during treatment with nirogacestat should be monitored and managed using anti-diarrhoeal medicinal products. For Grade 3 diarrhoea that persists for ≥ 3 days despite maximal medical therapy, nirogacestat should be withheld until diarrhoea is resolved to Grade ≤ 1 or baseline, then it should be restarted at 100 mg twice daily.

Non-melanoma skin cancers

Non-melanoma skin cancers were reported at a higher incidence in patients receiving nirogacestat than in those receiving placebo in the pivotal trial, 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 two cases of non-melanoma skin cancer were reported outside of the double-blind phase of the pivotal trial. A warning is included in section 4.4 of the SmPC to inform healthcare professionals that skin examinations should be performed prior to initiation of nirogacestat and routinely during treatment with nirogacestat. Cases should be managed according to clinical practices and patients may continue with nirogacestat treatment without dose adjustment.

Laboratory data

Primary analysis population

Median levels of eosinophils were higher in the nirogacestat arm compared with placebo. Increased levels were first observed during cycle 1 and persisted throughout the double-blind period. Shifts to grade 1 eosinophilia were observed at a higher incidence with nirogacestat (26%) compared with placebo (6%). Taking further into account the reporting of TEAEs (2% with nirogacestat vs. 0% with placebo), eosinophilia is considered an adverse reaction.

Median levels of blood urate were consistently lower with nirogacestat compared with placebo. Decreased levels were first observed during cycle 1 and persisted throughout the double-blind period.

Proteinuria and glycosuria have been included as ADRs in section 4.8 based on imbalances across study arms in the pivotal study.

The increased incidence of hypophosphatemia, hypokalaemia, glucosuria, proteinuria and low serum urate levels observed with nirogacestat is consistent with Fanconi syndrome, characterised by inadequate reabsorption in the proximal renal tubules of the kidney. In the Primary Analysis population, 1 patient (1%) in the nirogacestat arm was diagnosed with renal tubular disorder (grade 2) on Day 121, following nephrology consultation, based on findings of non-diabetic glycosuria, hypophosphataemia, hypokalaemia, and hypouricaemia. The dose of nirogacestat was reduced and the patient was treated with potassium and phosphate supplementation. As a pharmacological mechanism, gamma secretase inhibition may interfere with the homeostasis of the epithelium in the glomerulus and tubular components of the nephron by secondary inhibition of the Sox9 activation that is needed to initiate the repair of the proximal tubule epithelium and interference with replacement of injured podocytes, respectively. While the normal kidney has a low level of epithelial turnover, sustained gamma secretase inhibition could permit small foci of injury with delayed healing to accumulate and contribute to the Grade 1 proteinuria and glycosuria observed in some participants after 2 months of nirogacestat treatment. The reporting of glycosuria with a frequency very common with no concurrent elevations of blood glucose levels supports an effect of nirogacestat on renal proximal tubular function. Renal tubular disorder is included as an ADR in section 4.8 of the SmPC with a frequency common.

Although no differences in serum creatinine or creatinine clearance have been observed between the study arms in the pivotal study, the underlying mechanism for proteinuria, whether of glomerular or tubular origin, is not clear. The ADRs pertaining to renal dysfunction (i.e. glycosuria, proteinuria and renal tubular disorder) were of grade 1 or 2 severity and no SAEs have been reported. Taking into account that nirogacestat is a first in class gamma-secretase inhibitor as well as the small sample size of the safety database, severe renal toxicity is included in the RMP as an important potential risk.

For male patients, no trend over time was observed for any of the hormones (i.e. FSH, LH, progesterone, testosterone and free testosterone); no relevant differences were observed between the study arms. Data for the OLE population were consistent with those in the Primary analysis population.

No TEAEs were reported with nirogacestat regarding changes in male hormone level or reproductive disorders. In non-clinical studies, reduced testes weight and decreased sperm motility as well as a decrease in morphologically normal sperm were observed, at doses relevant for clinical use. A statement that male fertility may be impaired based on non-clinical data is included in section 4.6 of the SmPC.

In addition, based on non-clinical findings, adverse effects on male fertility is included as an important potential risk in the RMP.

Vital signs and ECGs

No clinically significant trends were identified in vital sign parameters with nirogacestat compared with placebo.

In the Primary analysis population, median change in QTcF from baseline to the highest post-baseline value was 17.0 msec for nirogacestat (range: -2 to 57 msec) vs. 9 msec for placebo (range: -7 to 45 msec). Across the analysis populations, none of the patients treated at the 150 mg BID dose, reported a QTcF interval of >500 msec or an increase in QTcF of >60 msec. Taking further into account the results of the concentration-QTc analysis, no concern regarding QTc prolongation is raised.

Safety in special populations

Given the small number of patients aged ≥65 years, and patients with renal or hepatic impairment, no firm conclusion regarding safety in these populations can be drawn.

Use during pregnancy and embryofoetal toxicity

In the embryo foetal developmental toxicity study in rats, nirogacestat induced significant embryo loss, early resorptions and decreased foetal weights in surviving embryos, at doses relevant for clinical use (see the non-clinical assessment report for further details). These findings are consistent with the Notch pathway being essential for embryo-foetal development.

In the OLE population, 1 pregnancy was reported during nirogacestat treatment, which resulted in spontaneous abortion. As contraceptive measure, the patient was using a condom with spermicide only; no hormonal contraception was used.

Embryofoetal toxicity is identified as an important potential risk in the RMP. Given the important potential risk of embryofoetal toxicity and the occurrence of desmoid tumours in patients in the fertile age range with a predominance in female patients, implementation of additional risk minimisation measures is warranted as described in the RMP. The main objective of the healthcare professional guide and patient card is to prevent pregnancy in female patients who are taking nirogacestat and in female partners of male patients who are taking nirogacestat.

Furthermore use in pregnancy and in women of child-bearing potential not using highly effective contraception is contra-indicated.

A negative pregnancy test is required before starting treatment with nirogacestat.

Since no in vivo study investigating the effects of nirogacestat on contraceptive steroids has been performed, it is not known if the efficacy of systemically acting hormonal contraceptives is affected. A recommendation regarding use of contraceptives, recommending a highly effective method (non-hormonal method or locally acting hormonal contraceptives, i.e., intrauterine device) and a barrier method, has been included in sections 4.4 and 4.6 of the SmPC.

Contraception is recommended to continue for 1 week following treatment discontinuation based on pharmacokinetic properties (terminal half-life of 23 hours and a wash-out of 5 half-lives) and taking into account that nirogacestat was found to have no genotoxic potential.

Further, a recommendation to refrain from donation of sperm or oocytes during treatment and for 1 week following discontinuation has been included in section 4.6 of the SmPC. In case of pregnancy or suspected pregnancy, a recommendation for female patients to contact their HCP and to stop taking nirogacestat has been included in sections 4.4 and 4.6.

Since no in vivo study investigating the effects of nirogacestat on contraceptive steroids has been performed, it is not known if the efficacy of systemically acting hormonal contraceptives is affected. A recommendation regarding use of contraceptives, i.e., at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method, has been included in sections 4.4 and 4.6 of the SmPC.

Use during breast feeding

Based on the overall safety profile of nirogacestat, use during breastfeeding and for 1 week after the last dose of Ogsiveo, is contra-indicated.

Adverse reactions

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Overdose

The symptoms of Ogsiveo overdose are expected to be an extension of its pharmacological actions and may include diarrhoea, nausea, vomiting, hypophosphataemia, elevated transaminases, and epistaxis.

Due to the high level of protein binding, Ogsiveo is not expected to be dialyzable in patients with normal serum protein levels. In the event of an overdosage, treatment with Ogsiveo should be stopped and general supportive measures should be initiated.

Assessment of paediatric data on clinical safety

In study ARST1921, an open-label study in paediatric patients with DT, 2 patients were reported with epiphyseal disorders: epiphysiolysis and hip fracture. Two further cases were reported from the compassionate use program: epiphyseal disorder and osteonecrosis.

Growth plate abnormalities have been observed in non-clinical studies with rats. Notch inhibition may lead to growth plate abnormalities through promotion of chondrocyte proliferation and hypertrophy and inhibition of angiogenesis.

Epiphyseal disorders in paediatric patients with open growth plates has been included as an important potential risk in the RMP.

Data on paediatric population has been adequately reflected in sections 4.2 and 4.8.

2.6.10. Conclusions on the clinical safety

While the safety database is limited for this orphan condition, the safety profile of nirogacestat is considered acceptable for the proposed use in adult patients with progressing desmoid tumours who require systemic treatment.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 70: list of safety concerns

Important identified risks	Ovarian Toxicity Non-melanoma skin cancers Bone fracture
Important potential risks	Epiphyseal disorder with off-label use in the pediatric population with open growth plates Drug induced liver injury Embryo-fetal toxicity Adverse effect on female fertility Adverse effect on male fertility Severe renal toxicity
Missing information	None

2.7.2. Pharmacovigilance plan

Table 71: On-going and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)*				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				
None				
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
Protocol Number: NIR-DT-401 A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF)	To determine the ovarian function recovery rate of OT events in post-pubertal and premenopausal females treated with nirogacestat for at least 12 cycles	Ovarian toxicity Adverse effect on female fertility Bone fracture	Database lock	31 Dec 2030
			Final Clinical Study Report	31 Dec 2031

2.7.3. Risk minimisation measures

Table 72: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
Ovarian toxicity (Important	**Routine risk minimization measures**:	**Routine pharmacovigilance**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
identified risk)	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.6 (Fertility, pregnancy and lactation) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Package leaflet Section 4 (Possible side effects) **Additional risk minimization measures**: None	**activities beyond adverse reactions reporting and signal detection:** A list of questions specific to OT will be used by Pharmacovigilance to collect information on each report of OT **Additional pharmacovigilance activities**: Protocol Number: NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF)
Non-melanoma skin cancers (Important identified risk)	**Routine risk minimization measures:** SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Package leaflet Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Bone fracture (Important identified risk)	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects) Package leaflet Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Protocol Number: NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF)
Epiphyseal disorder with off-label use in the pediatric population with open growth plates (Important potential risk)	**Routine risk minimization measures**: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.8 (Undesirable effects) Package leaflet Section 2 (What you need	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	to know before you take Ogsiveo) **Additional risk minimization measures**: None	**detection:** None **Additional pharmacovigilance activities**: None
Embryo-fetal toxicity (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) SmPC Section 4.6 (Fertility, pregnancy and lactation) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 2 (What you need to know before you take Ogsiveo) **Additional risk minimization measures:** • Healthcare Professional Guide • Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** PV follow-up form for pregnancy exposures including questions to determine root cause of pregnancy **Additional pharmacovigilance activities**: None
Drug induced liver injury (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Package leaflet Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: None
Adverse effect on female fertility (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, pregnancy and lactation) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 2 (What you need to know before you take Ogsiveo) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: Protocol number: NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Fibromatosis (DT/AF)
Adverse effect on male fertility (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, pregnancy and lactation) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 2 (What you need to know before you take Ogsiveo) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: None
Severe renal toxicity (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.8 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.11.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ogsiveo (nirogacestat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The presently considered indication is: *Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumours who require systemic treatment*.

Desmoid tumours (DT), also referred to as aggressive fibromatosis (AF), are rare, locally aggressive, slow growing soft tissue tumours that can cause severe pain, functional impairment, nerve damage, and bowel obstruction or perforation by infiltrating or exerting mass effects on vital structures (Constantinidou et al. 2012; Gounder et al. 2018; Hosalkar et al. 2006; Lewis et al. 1999; Penel et al. 2017; Quintini et al. 2012; Shinagare et al. 2011; Skubitz et al. 2017; Smith et al. 2000).

3.1.2. Available therapies and unmet medical need

Currently, there is no approved therapeutic option for DT in the EU, nor is there a universal standard of care.

Active surveillance is currently recommended as the first approach in DT (DTWG 2020). This approach includes monitoring via magnetic resonance imaging (MRI) (or computed tomography [CT] if MRI is not feasible) within 1 to 2 months of diagnosis then at 3- to 6-month intervals. As described in the DTWG recommendations, a decision towards an active treatment should be postponed until the occurrence of subsequent progression or increase of symptomatic burden, assessed with ≥2 further assessments and possibly not before one year from diagnosis in the absence of fulfilling RECIST for progressive disease (PD). Treatment may also be initiated sooner if the tumour is located near a vital structure (DTWG 2020).

Treatment options vary for each patient and outcomes depend on the size, location, and morbidity associated with the tumour (DTWG 2020; National Comprehensive Cancer Network 2020; Federman et al. 2022). Patients with advanced disease may be treated with surgery, radiotherapy, chemotherapy (e.g. anthracycline-based), or targeted therapy (e.g. imatinib, sorafenib, and pazopanib), NSAIDs, and antihormonal therapy but each modality is limited by either toxicities and/or limited efficacy and/or durability of response (DTWG 2020; National Comprehensive Cancer Network 2020).

3.1.3. Main clinical studies

Study NIR-DT-301 is a randomized (1:1), double-blind, placebo-controlled, phase 3 study of nrogacestat versus placebo in adult patients with progressing desmoid tumours/aggressive fibromatosis (DT).

Randomization was stratified by target tumour(s) location (intra-abdominal or extra-abdominal).

A total of 70 participants were included in the nirogacestat arm and 72 participants were randomised to receive placebo.

The primary endpoint was PFS. The definition of PFS was not standard insofar that this included not only death and radiological progression (RECIST v 1.1.) but also clinical progression.

The median follow-up time in the DB Phase (ITT population) was 19 months (min 0, max 31) for the nirogacestat treated participants and 11 months (min 0, max 31) for participants receiving placebo.

The data cut-off date for the clinical study report is 07 April 2022.

3.2. Favourable effects

Primary endpoint PFS

At the data cut-off date of 7th of April 2022, 49 PFS events had occurred (34.5% maturity) in the ITT population. The study met its primary endpoint with an HR of 0.29 (95% CI 0.15, 0.55), p-value < 0.001 (one-sided). K-M estimates of median PFS was NE in the nirogacestat arm vs. 15.1 in the placebo arm.

Secondary endpoints (type-1-error controlled)

ORR

The secondary endpoint ORR was 41% vs 8% in the nirogacestat arm and placebo arm, respectively (p <0.001) including 5 (7%) participants with CR compared to none in the placebo arm.

Median (range) time to objective response was 5.55 (2.6 to 19.4) months in the nirogacestat arm and 11.14 (2.8 to 16.4) months in the placebo arm.

PRO endpoints

BPI API: LS mean scores showed an improvement from baseline in the nirogacestat arm versus the placebo arm at Cycle 10 (-1.583 vs -0.241; LS mean difference = -1.342; p < 0.001).

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

The clinical safety database consists of 88 patients and is based on data derived from 3 studies: the pivotal study NIR-DT-301, consisting of a double-blind phase and its open-label extension (OLE), and 2 supportive studies, 14-C-0007 and A8641014.

Primary analysis population

The primary analysis population consisted of patients having received at least 1 dose of study treatment during the double-blind phase of study NIR-DT-301 (n=69 on nirogacestat, n=72 on placebo); data cut-off: 7 April 2022.

Median treatment duration was 20.6 months (range 0.3-33.6 months) in the nirogacestat arm vs. 11.4 months (range 0.2-33 months) in the placebo arm.

The most common TEAEs (≥25%) in the nirogacestat arm (nirogacestat vs. placebo) were diarrhoea (84% vs. 35%), nausea (54% vs. 39%), fatigue (51% vs. 36%), hypophosphatemia (42% vs. 7%), rash maculo-papular (32% vs. 6%), headache (29% vs. 15%) and stomatitis (29% vs. 4%).

TEAEs of grade ≥3 were reported at a frequency of 55% with nirogacestat compared to 17% with placebo. Common grade ≥3 TEAEs (≥5%) in the nirogacestat arm were diarrhoea (16%), folliculitis and rash maculo-papular (6%, each). In the placebo arm, no single TEAE was reported in more than 5% of patients.

No on-treatment deaths due to TEAEs were reported with nirogacestat. In the placebo arm, 1 on-treatment death due to a TEAE of sepsis was reported.

SAEs were reported at a frequency of 19% with nirogacestat compared to 11% with placebo. SAEs reported in more than 1 patient in the nirogacestat arm were premature menopause (4%) and in the placebo arm sepsis (4%) and COVID-19 (3%). The remaining SAEs were reported in a single patient in either treatment arm.

TEAEs leading to treatment discontinuation were reported at a frequency of 23% with nirogacestat compared to 3% with placebo. TEAEs leading to treatment discontinuation reported in more than 1 patient in the nirogacestat arm were diarrhoea (6%) and premature menopause (4%), with 1 further patient (1%) discontinuing treatment due to ovarian failure. The remaining TEAEs leading to treatment discontinuation with nirogacestat were reported in a single patient.

Ovarian toxicity (OT) was reported as ovarian failure, premature menopause, amenorrhoea, or menopause. OT was reported in 75% of women of child-bearing potential (WOCBP) in the nirogacestat arm vs. none in the placebo arm. Median time onset of OT was 62 days (range 1-381 days); median duration of OT was 149 days (range 11-865 days). Among WOCBP, dose modification was reported as dose reduced in 7%, as dose interrupted in 7% and treatment discontinuation in 15%. Resolution of OT events (i.e. return of menstruation or normalisation of hormone levels) was reported as recovered/resolved in 63% (data cut-off: 7 April 2022).

ALT and AST increased was reported at a frequency of 17% and 16%, respectively, (grade 3: 3%, each) with nirogacestat compared to 8% and 11%, respectively, (grade 3: 1%, each) with placebo. None of the patients on nirogacestat in the Primary analysis population had increased AST or ALT levels of >3xULN in combination with increased total bilirubin levels of >2xULN. There were no cases of DILI or cases meeting the Hy's law criteria reported with nirogacestat in any of the patient populations.

Bone fractures occurred in 6% of patients treated with nirogacestat vs. 0% in the placebo arm.

Safety data for the Integrated DT population and OLE population are consistent with the primary analysis population.

3.5. Uncertainties and limitations about unfavourable effects

As no data on hormone levels (FSH, LH, AMH and oestradiol) has been collected at 12 and 24 months post-treatment, there is no data on long-term ovarian damage in terms of the primordial follicle pool. Ovarian toxicity and adverse effects on female fertility will be further investigated in a post authorisation safety study (PASS) with a CSR expected by 31 December 2031.

In non-clinical studies, reduced testes weight and decreased sperm motility as well as a decrease in morphologically normal sperm were observed, at doses relevant for clinical use. The potential risk of testicular toxicity and the potential impact on male fertility are adequately addressed in the SmPC.

In non-clinical studies, hepatic necrosis has been observed. Although no cases of DILI in association with nirogacestat have been observed, the sample size of the safety database may have been too small to have captured events of DILI or severe hepatoxicity. DILI has been included as an important potential risk in the RMP.

Given the important potential risk of embryofoetal toxicity and the occurrence of desmoid tumours in patients in the fertile age range with a predominance in female patients, strict risk minimisation measures have been implemented in the SmPC including a contraindication for use in pregnancy and in women of child-bearing potential not using highly effective contraception. In addition, additional risk minimisation measures have been implemented.

3.6. Effects table

Table 73: Effects Table for Ogsiveo for the treatment of adult patients with desmoid tumours – Study NIR-DT-301 (DeFi); data cut-off: 07 Apr 2022.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	
Favourable Effects						
			Nirogacestat N=69	Placebo N=72		
PFS	Progression free survival (BICR)	Median, months (95% CI)	NR (NR, NR)	15.1 (8.4, NR)	0.29 (0.15, 0.55) p-value < 0.001	
ORR CR PR	Overall response rate Complete response Partial response	Proportion (%) 95% CI	29 (41) (29.8, 53.8) 5 (7) 24 (34)	6 (8) (3.1, 17.3) 0 6 (8)	p-value < 0.001	
BPI-SF	Pain score	Change from baseline	-1.583	-0.241	LS mean difference = - 1.342; p<0.001	Type 1 error protected
Unfavourable Effects						
			Nirogacestat N=69	Placebo N=72		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	
Any Grade ≥3 TEAE		%	55	17		
Any TEAE leading to discontinuation	All grade	%	3	23		
Diarrhoea	All grade Grade ≥3	%	84 16	35 1		
Nausea	All grade Grade ≥3	%	54 1	39 0		
Hypophosphatemia	All grade Grade ≥3	%	42 3	7 0		
Rash maculo-papular	All grade Grade ≥3	%	32 6	6 0		
Stomatitis	All grade Grade ≥3	%	29 4	4 0		
Ovarian toxicity[1]	All grade	%	39	0	75% of WOCBP No data on long-term fertility	
ALT	All grade Grade ≥3	%	17 3	8 1	No cases of DILI reported with nirogacestat Limited sample size	
AST	All grade Grade ≥3	%	16 3	11 1		
Bone fracture	All grade Grade ≥3	%	6 0	0 0		

Abbreviations: GODDESS (Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale), BPI (Brief Pain Inventory), DT (Desmoid Tumours); BPI-SF Average Pain Intensity (API) score, WOCBP (women of child-bearing potential)
Notes:

[1] Ovarian toxicity includes PTs ovarian failure, premature menopause, amenorrhoea, menopause and oligomenorrhoea

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy demonstration of nirogacestat 150 mg BID for the treatment of progressive DT derives from the double-blind phase of the pivotal study NIR-DT-301 (DeFi) in which a statistically significant and clinically relevant benefit has been demonstrated. The primary endpoint indicates an approximately 70% reduced risk of disease progression as per RECIST. Despite the large amount of missing data, *a* statistical robustness of the PFS analysis has been shown in sensitivity analyses.

In support of the meaningfulness of the primary outcome measure in this disease, the PRO instrument BPI-SF Average Pain Intensity (API) score (secondary endpoints [type-1 error protected]) reported a statistically significant reduction in pain for patients treated with nirogacestat as compared to patients in the control arm. Based on further sensitivity analyses in which missing PRO data were imputed, the PRO results can be considered statistically robust.

Treatment with nirogacestat comes with considerable toxicity as reflected by the high discontinuation rate of 23% due to TEAEs in the double-blind phase of study NIR-DT-301. Nevertheless, the median duration of exposure is quite long, with more than half of the patients having been exposed to nirogacestat for 2 years, suggesting that toxicity with nirogacestat is manageable with dose modifications. Overall, the extent of exposure is considered adequate to allow for assessment of long-term safety.

No on-treatment deaths due to TEAEs were reported with nirogacestat.

Qualitatively, the safety profile of nirogacestat is mostly characterised by GI symptoms (diarrhoea, nausea and stomatitis), rash and ovarian toxicity. Especially, ovarian toxicity as well as the lack of data on the impact of nirogacestat on long-term fertility, is of concern given the occurrence of desmoid tumours in a patient population with a peak age around 30 years and a predominance in female patients. Data on resolution of ovarian toxicity in terms of return of menstruation and/or normalisation of hormone levels in the majority of these patients is noted. Ovarian toxicity and adverse effects on female infertility are included as an important identified and potential risk, respectively, in the RMP and will be further investigated in a Post-authorisation safety study (PASS, cat 3).

Given the important potential risk of embryofoetal toxicity and the occurrence of desmoid tumours in patients in the fertile age range with a predominance in female patients, use in pregnancy and in women of child-bearing potential not using highly effective contraception is contra-indicated. Furthermore, strict risk minimisation measures have been implemented in the SmPC as well as additional risk minimisation measures with a healthcare guide and patient card with the main objective of preventing unwanted pregnancy.

Overall, the safety profile is considered acceptable for the treatment of adult patients with progressing desmoid tumours who require systemic treatment.

Given the nature of this non-malignant disease, as well as the emerging safety profile of nirogacestat, it is considered that the B/R would be positive only in patients with progressing DT.

Therefore, the following indication statement was agreed:

Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumours who require systemic treatment.

3.7.2. Balance of benefits and risks

A benefit in delaying tumour progression outweighs toxicities in patients with progressive DT. The risks of ovarian toxicities will be further investigated in a post-authorisation safety study and the risk of embryofoetal toxicity will be mitigated with additional risk minimisation measures.

3.7.3. Additional considerations on the benefit-risk balance

Nitrosamine impurities

During the procedure, two nitrosamine impurities were detected in the finished product above the acceptable intake limit of 1500 ng/day calculated according to the CPCA (category 5). The applicant proposed several approaches to reduce the levels of impurities below the AI, including the use of low nitrite microcrystalline cellulose (MCC) and re-formulating the product (e.g. introducing a nitrite scavenger), however, was unable to implement these changes within the legal timelines of the procedure.

The applicant proposed an interim acceptable intake limit of 20 µg/day (corresponding to 66,667 ppb/day based on a maximum daily dose of 300 mg) for the sum of ASYM-136911 and ASYM-136912, based on the less-then-lifetime multiplier from ICH M7 for products taken for between 1 and 10 years.

The non-clinical working party (NcWP) was consulted on the AI limit proposed by the applicant and concluded that the theoretical excess cancer risk (TECR) for the total NDSRI impurities(ASYM 136911 + ASYM 136912) is near or below the acceptable TECR of 1:100,000 for 7 years of treatment duration or less. The average treatment in the NIR-DT-301 study was 33.6 months, (2.8. years) with 97% of patients discontinuing nirogacestat before reaching 5 years of treatment. The unmet medical need for a severe condition with a beneficial clinical profile, the fact that both impurities are considered to have relatively low mutagenic potential, and the fact that long term treatment is unlikely, were also taken into consideration.

Therefore, the CHMP exceptionally agreed the temporary higher AI limit of 20 µg/day for the combined nitrosamine impurities.

The applicant is required to develop effective measures (i.e. optimise the formulation, manufacturing process and/or control strategy) by Q3 2027 (**Annex II.D condition**) in order to reduce the levels of the 2 nitrosamines impurities below the AI limit at release and throughout shelf-life.

3.8. Conclusions

The overall benefit/risk balance of Ogsiveo is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ogsiveo is favourable in the following indication:

Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumours who require systemic treatment.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Ogsiveo (nirogacestat) in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at minimising in utero exposure to Ogsiveo (nirogacestat) and the subsequent potential risk of embryo-fetal toxicity.

The MAH shall ensure that in each Member State where Ogsiveo (nirogacestat) is marketed, all healthcare professionals who are expected to prescribe or patients who are expected to use Ogsiveo (nirogacestat) have access to/are provided with the following educational materials:

- Physician educational material
- Patient card

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals:

The healthcare professional guide should contain the following key elements:

- Nirogacestat may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.
- Nirogacestat is contraindicated in pregnant women and in women of childbearing potential not using highly effective contraception.
- A pregnancy test must be performed and be negative before start of treatment with nirogacestat.
- Women 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.
- Nirogacestat may reduce the efficacy of hormonal contraceptives.
- Patients should be advised to use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method.
- Female patients of childbearing potential should be informed about the potential risk of embryo-foetal harm and the use of appropriate contraceptive measures before start of treatment with nirogacestat.
- Pregnancy testing during treatment with nirogacestat should be considered for women of childbearing potential experiencing amenorrhea.

- Male patients 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.
- Patients should be advised to tell their doctor immediately if they suspect that they are pregnant.
- Patients should be given the patient card.

The patient card:

The patient card should contain the following key elements:

- Nirogacestat may cause embryo-foetal harm, including foetal loss, when used during pregnancy.
- Patients who are women of childbearing potential, and male patients with female partners who are of childbearing potential, have to use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose.
- If you are a woman who can become pregnant or a man with a partner who can become pregnant, you must use at least one highly effective method of contraception (such as an intrauterine device) or two complementary forms of contraception including a barrier method.
- If you suspect that you may be pregnant during treatment with nirogacestat, contact your treating oncologist immediately. If you are pregnant, you must not take nirogacestat.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The applicant is required to develop effective measures (i.e. an optimized formulation, manufacturing process and/or control strategy) to ensure the sum of ASYM-136911 and ASYM-136912 impurities does not exceed the AI limits of 1.5 µg/day throughout shelf-life and submit the appropriate variation to implement the change(s) and tighten the release and shelf-life specification limit to NMT 1.5 µg/day in the finished product'.	Q3 2027
A Progress report should be submitted.	Q3 2026

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that nirogacestat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).