European Union (EU) Risk Management Plan (RMP) for Ogsiveo® (nirogacestat)

RMP version to be assessed as part of this application:

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Summary of significant changes in this RMP	

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Qualified Person for Pharmacovigilance (QPPV):

QPPV name	Dr. Eric Caugant, MD
QPPV signature and Date	EU QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AF	Aggressive fibromatosis
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
APC	Adenomatous polyposis coli
ATC	Anatomical therapeutic chemical code
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
BID	Twice daily
CM	Cancer monotherapy
C_{max}	Maximum concentration
CPN	Chronic progressive nephropathy
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAPT	N-S-phenyl-glycine-t-butyl ester
DB	Double-blind
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DLP	Data lock point
DT	Desmoid tumor(s)
EEA	European economic area
ECG	Electrocardiograph
EU	European Union
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FSH	Follicular stimulating hormone
GALT	Gut associated lymphoid tissue
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GS	Gamma-secretase
HCP	Healthcare Professional
HIV	Human immunodeficiency virus
HV	Healthy volunteer
IgM	Immunoglobulin M
IgD	Immunoglobulin D

Abbreviation or Term	Definition/Explanation
INN	International nonproprietary name
LOAEL	Lowest observed adverse effect level
NK	Natural killer
NOAEL	No observed adverse effect level
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
OT	Ovarian Toxicity
P-gp	P-glycoprotein
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
TNBC	Triple-negative breast cancer
mTNBC	Advanced triple receptor-negative breast cancer
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of childbearing potential

Part I: Product(s) Overview

Table Part I.1 Product Overview

Product Overview	
Active substance(s) (international nonproprietary name [INN] or common name)	Nirogacestat
Pharmacotherapeutic group(s) (anatomical therapeutic chemical [ATC] Code)	L01XX81
Marketing authorization applicant	SpringWorks Therapeutics Ireland Limited Hamilton House, 28 Fitzwilliam Place Dublin 2, D02 P283 Ireland
Medicinal Products to which this RMP refers	1 (One)
Invented name(s) in the European Economic Area (EEA)	European Union (EU): Ogsiveo®
Marketing authorization procedure	Centralised
Brief description of the product	Chemical class Gamma-secretase inhibitor
	Summary of mode of action Nirogacestat is a reversible and non-competitive inhibitor of gamma-secretase (GS) that blocks proteolytic activation of Notch receptors.
	Important information about its composition: None
Hyperlink to the product information	Ogsiveo Summary of Product Characteristics
Indication(s) in the EEA	Current: Ogsiveo as monotherapy is indicated for the treatment of adult patients with progressing desmoid tumors who require systemic treatment.
	Proposed: Not applicable
Dosage in the EEA	Current: 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.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Film-coated tablet. Ogsiveo 50 mg film-coated tablets Ogsiveo 100 mg film-coated tablets Ogsiveo 150 mg film-coated tablets
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specifications

Part II: Module SI - Epidemiology of the indication and target population

Indication

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

Incidence

In the European Union (EU), the incidence of desmoid tumor (DT) is about 3 to 5 cases per million per year in the general population (van Broekhoven 2015; Orphanet Report Series 2024).

Prevalence

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 3-7 times the incidence rate (Anneberg 2022; White 2021). Note: prevalence was calculated as the number of newly incident patients with DT plus patients with DT from the Danish Sarcoma Database who had subsequent contact at a hospital in each calendar year, divided by the total population size of Denmark as of the end of the same calendar year.

Demographics of the population in the proposed indication

Age

DT most commonly occur in individuals between the ages of 15 to 60 years, with a peak age of about 30 years (de Camargo 2010; Skubitz 2017; Anneberg 2022).

Gender

There is a 2- to 3-fold predominance in females (de Camargo 2010; Skubitz 2017; Anneberg 2022).

Racial and/or ethnic origin

Data on racial and ethnic origin are sparse because of the rarity of the disease. The limited available data on familial syndromes with a predisposition to DT (see risk factors below), concluded that differences seen were most likely due to selection of patients undergoing genetic testing, or methods of DNA mutational analyses used, rather than inherent biologic differences between the groups (Inra 2015).

Risk factors

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*) tumor suppressor gene is mutated (Skubitz 2017). Familial adenomatous polyposis-associated DT is more frequently associated with abdominal tumors, especially in the Gardner variant of FAP, which is associated with intestinal polyposis, osteomas, fibromas, and epidermal inclusion cysts (Skubitz 2017). Intra-abdominal DT are one of the leading causes of death in patients with FAP (Quintini 2012). Although common in patients with FAP, most cases of DT occur spontaneously in adults and are associated with a mutation in β-catenin (CTNNB1) (Lazar 2008; Tejpar 1999).

In addition to *APC* mutation, a study of 2260 patients with FAP in The Netherlands, France, Denmark, and Finland suggested that a family history of DT and abdominal surgery were also risk factors for the development of DT in patients with FAP (Nieuwenhuis 2011). However, a smaller study of 442 patients with FAP in France suggested that family history of DT was not a risk factor (Lefevre 2008).

Aside from FAP, other risk factors for development of DT include pregnancy, prior surgery, and trauma (Valesano 2017).

The higher incidences of DT during and after pregnancy and following exposure to oral contraceptives and reports of spontaneous tumor regression during menopause underline the potential influence of the female sex hormonal environment. The most common site for pregnancy associated tumors is the abdominal wall (Kasper 2011; Robinson 2012).

The main existing treatment options

Currently, there is no approved therapeutic option for DT in the EU, nor is there a universal standard of care. Treatment options vary for each patient and outcomes depend on the size, location, and morbidity associated with the tumor (Desmoid Tumor Working Group [DTWG] 2020; National Comprehensive Cancer Network [NCCN] 2020; Federman 2022).

DT have an unpredictable course and thus present challenges in determining a sequence of treatments. In 2024, revised consensus guidelines on the management of DT were published (Kasper 2024). Options for treatment fall into the following categories:

a) Active surveillance. Active surveillance is the current recommended primary treatment for the management of asymptomatic DT. Patients will be actively monitored with regular imaging and intervention only considered in the event of symptomatic DT.

b) Systemic therapy. In the event of progressing DT, a primary treatment option is systemic therapy for any anatomical DT location, with first-line treatment depending on the clinical scenario and expected effectiveness of treatment.

    i. Tyrosine kinase inhibitors (TKIs) (e.g., imatinib, nilotinib, sorafenib, pazopanib). Rash, fatigue, hypertension, diarrhea, nausea, vomiting, abdominal pain, and neutropenia have been reported for drugs in this class, with some events being Grade ≥3 (Riedel 2022).
    ii. Chemotherapy (e.g., methotrexate, vinblastine, vinorelbine, doxorubicin, dacarbazine, hydroxycarbamide [also known as hydroxyurea]). Well known toxicities for chemotherapy include nausea, vomiting, hematologic abnormalities, and embryo-fetal toxicity (Riedel 2022). Several mechanisms have been proposed by which chemotherapy induces ovarian damage, including direct DNA damage with or without apoptosis of primordial follicles, disruption to the ovarian vasculature and stromal tissue, and atresia of growing follicles leading to accelerated primordial follicle recruitment (Cui 2023).

c) Surgery. Surgery can be considered provided that expected surgical morbidity is limited. Surgery was historically the therapeutic option for localized, extra-abdominal, small volume DT. However, surgery is no longer regarded as the cornerstone of DT treatment. Although they do not metastasize, desmoid tumors are associated with local recurrence rates ranging from 24% to 77% after surgical resection, regardless of margin status, based on retrospective, observational data. Factors associated with local recurrence post-surgery include tumor location, age of the participant, tumor size, margin status, and prior recurrence (Easter 1989; Penel 2017; Crago 2013; Tsagozis 2017). The main risks associated with surgery are local recurrence and morbidity associated with the surgical procedure.

d) Radiotherapy (with or without surgery). Risks associated with radiotherapy include fatigue, hair loss and skin changes as well as other local effects depending upon the site of the radiotherapy, such as risk of a second malignancy (Radiation Therapy Side Effects 2022).

e) Cryoablation. Cryoablation appears to be an effective alternative treatment for local control of small to medium-sized extra-abdominal tumors. According to CRYODESMO-01, a prospective, open-label, non-randomized trial, cryoablation was effective in growing DT after 2 or more lines of medical therapy or with functional symptoms or pain (Kurtz 2021). Cryoablation is of limited utility for patients with large tumors near vital structures, is not widely available, and requires interventional radiological expertise (Kujak 2010; Schmitz 2016; Kasper 2024).

Risks associated with the specific agents mentioned above are described in their respective product information.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

DT are rare and locally aggressive monoclonal, fibroblastic proliferation characterised by a variable and often unpredictable clinical course (Kasper 2024). Although histologically benign, DT are locally invasive and associated with a high local recurrence rate despite lacking metastatic potential (Kasper 2011). The course of DT depends on tumor size, location, and vital structure involvement. Spontaneous regression, long-lasting stable disease, and disease progression can occur; however, reliable and validated predictive factors of spontaneous regression are lacking (Penel 2017). Common primary sites affected by these tumors include the abdominal wall, mesentery, and neurovascular bundle of the extremities. DT do not metastasize and in the absence of vital structure involvement can pose a low risk of death (except in Gardner's syndrome), but they confer substantial morbidity and complications. Patients may be asymptomatic or may present with severe pain, swelling, deformity, loss of range of motion, bowel obstruction or perforation, or compromise of vital structures. Additional associated complications in young adults include long-term opioid use, social isolation, insomnia, anxiety, depression, and interruption of education and employment (Gounder 2018).

Important co-morbidities

FAP is a syndrome that pre-disposes a patient to DT. Approximately 5-10% of DT arise in the context of FAP (Desmoid Tumor Working Group [DTWG] 2020).

Part II: Module SII - Nonclinical part of the safety specification

Table SII.1 Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Key issues identified from acute or repeat-dose toxicity studies In the nonclinical toxicology studies, nirogacestat was administered to mice, rats, and dogs in repeat-dose toxicology studies up to 3 months in duration followed by a 1-month recovery in the longer treatment duration studies. 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 No Observed Adverse Effect Level (NOAEL) in the 1-month mouse study was 20 mg/kg/day. In the 3-month rat study, ovarian atrophy, alterations in the oestrous cycle, decreased cellularity in gut associated lymphoid tissue (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, in the 3-month rat study, all dose levels showed chronic progressive nephropathy, pulmonary phospholipidosis, and salivary gland necrosis in a dose-dependent manner. 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, only 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.	Many of the toxicologic effects in the repeat-dose toxicology studies with nirogacestat in mice, rats, and dogs are related to 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 systemic exposures at the NOAEL or Lowest Observed Adverse Effect Level (LOAEL) are below those in humans after administration of nirogacestat at 150 mg BID, suggesting that animals are more sensitive to the adverse effects of nirogacestat.
Reproductive/developmental toxicity **Rat fertility studies** In the rat fertility studies male and female mating indices in the 5, 20, 40, and 80 mg/kg/day groups were comparable to the control group. However, lower fertility indices were observed in female rats treated with 20, 40, or 80 mg/kg/day. There were no effects on male fertility and pregnancy indices at 5 mg/kg/day. The absence of any pregnant female rats in the 40 mg/kg/day group precluded evaluation of intrauterine parameters. For the 6 pregnant female rats in the 20 mg/kg/day group, a higher mean litter proportion of pre-implantation loss resulted in a lower mean number of implantation sites and consequently	An ovarian cycle time of only 4 days in the rat means that histologic sections of an ovary reveal a dynamic picture of preovulatory and regressing follicles. The development and growth of the corpus luteum is reliant on angiogenesis from pre-existing vessels of the follicular theca layer (Woad 2016), and inhibition of angiogenesis leads to attenuated follicular growth and disrupted ovulation (Robinson 2009). The Notch and vascular endothelial growth factor (VEGF) signaling pathways (of which gamma-secretase is

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
lower mean number of live embryos. A higher mean litter proportion of pre-implantation loss was also noted in the 5 mg/kg/day group and resulted in a slightly lower mean number of implantation sites and consequently a lower mean number of live embryos. Similar findings were noted when treated female rats were paired with untreated male rats. When treated male rats were paired with untreated female rats, test material-related lower male fertility and pregnancy indices were observed in the 20 and 40 mg/kg/day groups when compared to the control group; pregnancy and fertility indices were 27.3% and 0.0% in these respective groups. These effects were considered adverse. There were no effects on male fertility and pregnancy indices at 5 mg/kg/day. Sperm motility was markedly lower at all dose levels, and mean cauda epididymal sperm concentrations were lower in the 20 and 40 mg/kg/day groups when compared to the control group. In addition, the percentages of morphologically normal sperm in the 20 and 40 mg/kg/day groups were lower than the control group. A dose-dependent increase in ovarian atrophy was noted in the 1-month and 3-month rat studies, as well as oocyte mineralization in the 3-month dog study. In rats, the changes were characterized by decreased number of follicles associated with an increased number of small hyperbasophilic corpora lutea and decreased ovarian weights. In the rat fertility studies, ovarian atrophy occurred due to decreases in corpora lutea and decreases in developing follicles, with the follicles composed of primordial and early-stage primary follicles but lacked antral follicles. Asynchrony of the estrous cycle in the rest of the reproductive tract was also seen in the rat 1- and 3-month studies, as well as the 3-month dog study. Partial recovery of this effect was evident in the 150-mg/kg/day recovery group in the 1-month study, while ovarian cysts and altered estrous cycle persisted in the recovery groups from the 3-month rat and dog studies suggesting a recovery period longer than 1 month would be required to assess reversibility. Sperm motility was markedly lower at all dose levels, and mean cauda epididymal sperm concentrations were lower in the 5, 20, 40 and 80 mg/kg/day groups when compared to the control group. In addition, the percentages of morphologically normal sperm in all dose groups were lower than the control group. No effects on the testes were noted in the 1- and 3-month pivotal rat toxicity studies or 1-month dog study. In the 3-month dog study, changes in the testes include vacuolation of Sertoli cells, degenerative	an integral part) are critically involved in angiogenesis in the ovary (Xie 2017; Boulton 2008). Ovarian effects have been observed after chronic administration of a VEGF inhibitor resulting in marked reduction in luteal area when compared to the ovaries of controls (Wedge 2005). The observations of ovarian atrophy and decreased numbers of developing follicles in the rat is consistent with nirogacestat affecting angiogenesis in the developing follicles with no impact on pre-antral follicles. The developmental and reproductive toxicities of nirogacestat are also due to GS inhibition. These negative effects on embryonic development were anticipated based on transgenic studies in mice demonstrating that the loss of Notch signaling is embryonically lethal (Donoviel 1999; Swiatek 1994). 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 oestrous cyclicity, are likely due to inhibition of Notch signaling in ovaries, as this signaling pathway is critical in the regulation of mammalian folliculogenesis (Vanorny 2017). Similar ovarian changes were observed with another GS inhibitor (Simutis 2018). In the testes, Notch signaling is critical for spermatogenesis (Murta 2016). These effects on both male and female sex organs could explain the effects on nirogacestat on fertility indices measured in both male and female rats. These findings are relevant to human use, and it can be anticipated that similar effects on female and male fertility and embryo-fetal development would be observed in humans since they were observed in animals at exposures lower than that achieved in humans. It is thus anticipated that only a transient effect on sperm quality would be observed in humans while on nirogacestat because any effect of

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
spermatids and loss of spermatocytes and germinal cells at doses of 10 mg/kg/day 50 (reduced to 20) mg/kg/day. A finding of Sertoli cell degeneration was present in the 1-month recovery group. The relationship of a finding of spermatid degeneration to nirogacestat in 1 dog in the 50 (reduced to 20) mg/kg/day dose group is unclear as similar findings have been described in peripubertal/juvenile dogs (Goedken 2008). **Rat embryo-fetal developmental toxicity Study** The embryo-fetal toxicity of nirogacestat was assessed in pregnant rats administered 0 (vehicle), or nirogacestat at 5, 20, 50, or 150 mg/kg/day (01214011) during Gestation Days 6 through 17. At 5 mg/kg/day, the Gestation Day 17 total Cmax and AUC0-24 were 202 ng/ml and 1400 ng•h/mL, respectively. These exposures are well below those achieved in humans (total AUC0-24 12860 ng•h/mL) after nirogacestat administration of 150 mg BID (Study A8641014). Decreases in epididymis and testes weights were noted in rats in the fertility and early embryonic development toxicology study. 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 corresponding with lower mean number of viable fetuses and lower mean fetal body weights were noted at 20 mg/kg/day. In the 50-mg/kg/day group, only 2 fetuses were available for fetal morphology evaluation. One of the 2 fetuses at 50 mg/kg/day and a single fetus at 20 mg/kg/day were noted with edema (entire subcutis). No other external malformations or developmental variations were noted for fetuses at 5, 20, and 50 mg/kg/day. Intrauterine growth and survival at 5 mg/kg/day were unaffected by nirogacestat administration; therefore, 5 mg/kg/day was considered the NOAEL for this study. In pregnant rats that survived to the scheduled necropsy, decreases in body weight and body weight gain occurred at ≥50 mg/kg/day that correlated with decreases in food consumption. Lower mean gravid uterine weights were noted at ≥20 mg/kg/day groups compared to the control group. The lower gravid uterine weights and body weight effects noted during the latter portion of gestation were primarily attributed to increased post-implantation loss and/or lower fetal weights noted in these groups.	nirogacestat on sperm quality would resolve after nirogacestat therapy discontinuation. Nevertheless, adverse effect on male fertility is considered an Important Potential Risk for nirogacestat. Adverse effect on female fertility is considered an Important Potential Risk for nirogacestat. Ovarian toxicity (OT) is considered an Important Identified Risk for nirogacestat. Embryo-fetal toxicity is considered an Important Potential Risk for nirogacestat.
Genotoxicity Nirogacestat was assessed *in vitro* in the bacterial mutagenicity assay (06GR106), the *in vitro* cytogenetic (human lymphocyte) assay (06GR107),	No genotoxic effects in humans are anticipated based upon non-clinical studies.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
and *in vivo* in a rat micronucleus study (01214020). Nirogacestat was negative in both *in vitro* assays, as well as the *in vivo* micronucleus study.	
Carcinogenicity The carcinogenicity of nirogacestat was assessed in a 6-month repeat dose study in transgenic rasH2 mice. There were no new neoplasms observed in this carcinogenicity study. At 10 or 30 mg/kg/day, there was no evidence of an increase in neoplasms compared to controls. At 100 mg/kg/day, there was a test article-related higher incidence of hemangiosarcoma in males and females, when compared to the sex-matched controls, with a statistically significant overall trend for hemangiosarcoma (of any tissue) in both males and females ($p < 0.05$). In this study, the incidence of hemangiosarcoma of any tissue in males was highest in 100 mg/kg/day males (32%, incidence 8/25), which exceeded the Testing Facility's historical control range, while the female incidence (16%) was below the historical control range.	Hemangiosarcoma is a common spontaneous neoplasm in mice, rats, and dogs, but rare in humans. Dose-dependent increases in the incidence of hemangiosarcomas have been observed in mice for a variety of approved drugs and chemicals that are not carcinogenic in rats or in humans (Cohen 2009). Similar to nirogacestat, these drugs and chemicals were not mutagenic or clastogenic suggesting the increase in hemangiosarcomas in mice occurs through a nongenotoxic mechanism and does not translate to other species. No carcinogenic effects in humans are anticipated based upon the non-clinical carcinogenicity study. The rat 2-year carcinogenicity study was not conducted given that that human systemic exposures exceed those that can be achieved in animal toxicology studies. In addition, nirogacestat is not genotoxic *in vitro* or *in vivo*; therefore, any finding in a 2-year rat study would occur through a non-genotoxic mechanism. Given the observed species differences in toxicity of nirogacestat with rats much more sensitive to humans, any finding in a 2-year rat study would be suspect and questionable in relation to translation given that non-genotoxic mechanism in rodents are difficult to translate to humans. In addition, the 6-month carcinogenicity study did not identify any new neoplasms and there was no evidence of skin tumors in mice, further justifying the lack of translatability of rodent carcinogenicity to human cancer risk assessment. Nevertheless, in humans, the occurrence of new neoplasms in patients receiving nirogacestat will be assessed via routine pharmacovigilance. The non-melanoma skin cancers reported from clinical trials are not believed to be due to nirogacestat directly causing new skin cancers, but rather to it changing skin homeostasis to

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	permit the growth of skin cancers emerging due to known causes.
Hematopoietic/immune In the 1- and 3-month rat and dog studies, decreases in lymphocyte counts corresponded to decreases in B and T cells, as well as natural killer (NK) cells. Changes in B-cell surface markers included decreases in IgM and IgD expression. These changes were associated with decreases in spleen and thymic weights in rats and dogs that correlated with microscopic evidence of decreased cellularity in these tissues. Decreases in circulating B and T cells were expected due to the inhibition of GS activity.	Inhibition of GS activity results in decreased Notch signaling, a signal transduction pathway known to play a major role in cellular differentiation in proliferating tissues including lymphopoietic tissues (Maillard 2005; Wong 2004; He 2003). The similarities in incidences of hematologic treatment-emergent adverse events between the nirogacestat and placebo arms of Study NIR-DT-301, along with the low value for those incidences, does not support recognizing any hematologic adverse events as identified or potential risks for nirogacestat.
Gastrointestinal effects In the 1-month and 3-month rat and dog studies, treatment-related changes in the gastrointestinal tract included hyperplasia of the mucosa that was associated with decreased food consumption and body weights in a dose-dependent manner. The microscopic findings in the intestines were characterized with increased thickening of the villi and crypt epithelium due to the increased number of enterocytes (mostly goblet cells), with greater frequency and severity in the early segments of the intestinal tract. The endogenous population of goblet cells are greater in the more distal parts of the gut, thus making the observation of goblet cell hyperplasia in later portions of the intestine more difficult (Milano 2004). Occasionally, at higher doses, this change was associated with epithelial degeneration and necrosis of the epithelial cells lining the mucosal crypts. In cases where this change was moderate-to-marked, erosion, hemorrhages, inflammation, and fibrin deposition were reported. These findings in the intestinal tract are considered mechanism-related and consistent with published effects of GS inhibitors on Notch in proliferative tissues (Fre 2005; Milano 2004; Searfoss 2003; Van Es 2005; Wong 2004).	These findings in the intestinal tract are considered mechanism-related and consistent with published effects of GS inhibitors on Notch in proliferative tissues (Fre 2005; Milano 2004; Searfoss 2003; Van Es 2005; Wong 2004). Gastro-intestinal effects, such as diarrhea and nausea, were observed at a higher rate in the nirogacestat arm compared to placebo in Study NIR-DT-301. However, this risk is not considered important for risk management as it requires no further characterization and will be followed up via routine pharmacovigilance and the risk minimization messages in the product information are adhered by prescribers as part of standard clinical practice.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Renal effects Treatment-related changes in the kidney were present in rat and dog repeat dose studies. In the 1- and 3-month rat studies, kidneys of female rats had tubule protein casts with associated increases in blood urea nitrogen and in the 3-month study, urine protein levels were elevated in both male and female rats with small amounts of blood observed in the urine in male rats. The kidney changes in the 1-month study reversed; however, in the 3-month rat study, the kidney nephropathy persisted in both male and female rats. In the dog, kidney findings were limited to the 3-month study characterized as single cell necrosis of tubular epithelial cells. These changes were not observed in the recovery dogs. The effect of nirogacestat on the kidney could be related to inhibition of Notch signaling. In addition to kidney development, Notch appears to play a key role in maintaining kidney homeostasis, and inhibition can lead to kidney cysts (Mukherjee 2019), which is what was seen in the nirogacestat rat studies.	No apparent effect of GS inhibition on the physiologic function of kidney cells has been reported in the literature (Mukherjee 2019). However, GS 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 (Stamellou 2021). While the normal kidney has a low level of epithelial turnover (Castrop 2019), sustained GS inhibition could permit small foci of injury with delayed healing to accumulate and contribute to the Grade 1 proteinuria and glucosuria observed in some participants after 2 months of nirogacestat treatment. Severe renal toxicity is considered an Important Potential Risk for nirogacestat.
Hepatic effects Treatment-related changes in the liver consisted of increased incidence and/or severity of hepatocellular vacuolation in the 1-month rat and mouse studies. These changes were characterized by multiple clear, variable-sized vacuoles present in the cytoplasm of hepatocytes mostly located in the periportal areas. Liver sections from the 1-month rat study stained positive with oil-red-O, consistent with lipid vacuoles. In the 3-month rat study, centrilobular hepatocellular necrosis occurred at 50 mg/kg/day that corresponded to increases in liver enzymes and total bilirubin. There were no hepatic changes in the recovery animals. In dogs, liver changes were considered secondary to intestinal changes leading to inflammation within the liver. In the 1-month dog study, treatment-related epithelial hyperplasia was observed in the intestinal tract of male and female dogs at 80 mg/kg/day resulting in minimal to mild inflammation within the liver due to bacterial migration to the liver from the disrupted intestinal mucosal barrier and through the hepatic portal vein (Jubb 1992). Increases in WBC parameters (increases in neutrophils, monocytes, and eosinophils), fibrinogen, liver enzymes, and globulin were associated with this inflammation. There was no recovery group in this study, but there was no	Based upon the non-clinical findings, hepatic effects may be expected in humans exposed to nirogacestat. Drug induced liver injury (DILI) is considered an Important Potential Risk for nirogacestat.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
evidence of direct hepatotoxicity. Similar effects were seen in the 3-month dog study. Hepatic inflammation and necrosis were not present in the recovery dogs.	
Musculoskeletal effects Increased retention of the hypertrophic zone of the growth plate and articular cartilage was seen in the sternum and stifle joints of rats given nirogacestat at ≥20 mg/kg/day in the 1-month and 3-month studies. This change was characterized by minimal-to-moderate thickening of the hypertrophic zone in the cartilage with pallor and slight vacuolation of the osteocytes in the primary spongiosa. There was decreased incidence and severity of this change in the recovery rats suggesting this effect is reversible. Similar findings have been observed after administration of a VEGF inhibitor (Wedge 2005). Once daily oral administration of a VEGF receptor -2 tyrosine kinase inhibitor to female rats led to hypertrophy in the bone growth plate and inhibition of endochondral ossification in the epiphyseal growth plates, a physiologic process that is highly dependent upon angiogenesis. No changes to the growth plates were noted in the 10- to 11-month-old beagle dogs used in the dog studies.	With the exception of longitudinal bone extension during growth and cyclical changes in the female reproductive tissues, angiogenesis does not typically occur in healthy adults. Growth plates are closed in adult humans and other higher species. This is most likely the reason why the bone changes were not seen in the dog studies. Thus, these roles for Notch in growth plate biology may not be an issue for treatment of adult participants. It is therefore not expected that there will be adverse musculoskeletal effects in adults. However, in the event that nirogacestat is used off label in the pediatric population, there is the potential for epiphyseal disorders due to nirogacestat. Epiphyseal disorder with off-label use in the pediatric population with open growth plates is therefore an Important Potential Risk for nirogacestat.
Cardiovascular effects The cardiovascular effects of nirogacestat were assessed in male beagle dogs implanted with telemetry devices using a single dose crossover design (Report 06GR083). 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 post-dose, 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 in humans Cmax (508 ng/mL) after administration of 150 mg BID in DT patients. Based on the outcome of this Good Laboratory Practice (GLP) study, nirogacestat does not adversely affect cardiovascular function in male dogs, but systemic exposures similar to those in humans could not be achieved.	Based upon non-clinical data, no anticipated cardiovascular effect is expected with exposure to nirogacestat in humans. The effects of nirogacestat concentration on QTc interval prolongation were evaluated using a nonlinear mixed effects model developed using data from 6 healthy participant clinical trials and 2 patient clinical trials. The 90% confidence intervals for the predicted mean change in QTcF were below 10 msec at twice the expected maximum concentration (Cmax) with moderate CYP3A4 inhibition. Therefore, no clinically significant prolongation in QTcF interval is associated with therapeutic dosing of nirogacestat alone or with moderate CYP3A4 inhibition.
Other toxicity-related information or data	
Drug-drug Interactions: CYP3A4 In vitro studies with human liver microsomes indicated that nirogacestat is primarily metabolized by CYP3A4 (85%).	Co-administration of nirogacestat with strong or moderate inhibitors of CYP3A4 may increase serum nirogacestat concentrations. Co-administration of nirogacestat with strong and moderate inducers of

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
	CYP3A4 may decrease serum nirogacestat concentrations. Nirogacestat is a weak inhibitor of CYP3A4 at therapeutic doses and may increase the exposure of drugs that are metabolized by CYP3A4.
Drug-drug Interactions: CYP2C8, CYP2C9, CYP2C19, and CYP2B6 In vitro studies showed that nirogacestat may induce CYP2C8, CYP2C9, CYP2C19, and CYP2B6 and thus there is a risk that nirogacestat can cause decreased exposure of substrates of these enzymes.	When substrates of CYP2C8, CYP2C9, CYP2C19, and CYP2B6 are administered with nirogacestat, evaluation for reduced efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.
Drug-drug Interactions: P-gp In vitro permeability studies with MDR1-transfected Madin-Darby Canine Kidney cells also indicate that nirogacestat may be a substrate of P-glycoprotein (P-gp). A nonclinical study with *Mdr1a/1b* knockout and wild-type mice also supported nirogacestat as a substrate of P-gp. In vitro, nirogacestat has been shown to be an inhibitor of P-gp.	The effect on nirogacestat observed in the clinical drug-drug interaction (DDI) study with itraconazole may be due in part to P-gp inhibition as itraconazole is known to be a weak-to-moderate inhibitor of P-gp as well. While effects from P-gp inhibition cannot be ruled out, CYP3A4 inhibition is believed to have been the dominant interaction. A single-dose drug-drug interaction study demonstrated that nirogacestat did not affect the exposure of dabigatran, a P-gp substrate, which supports the absence of clinically meaningful P-gp inhibition by nirogacestat.
Breast cancer resistance protein (BCRP) inhibitors An in vitro study showed that nirogacestat is not a substrate of BCRP.	Nirogacestat may be used with BCRP inhibitors (e.g., cyclosporine, darolutamide, fostamatinib).
Drug-drug Interactions: Gastric acid reducing agents The solubility characteristics of nirogacestat suggest that raising pH in the stomach and gastrointestinal tract may impact systemic exposure. Co-administration of nirogacestat with drugs that increase gastric pH, such as proton pump inhibitors or H2-receptor antagonists, may reduce the solubility, and thus the absorption, of nirogacestat.	The effects of acid reducing agents (i.e., H2-receptor antagonists, proton pump inhibitors, and antacids) on nirogacestat exposure have not been evaluated in a clinical study, however, co-administration of these medicinal products may reduce the bioavailability of nirogacestat. Concomitant use of nirogacestat with proton pump inhibitors and H2 blockers is not recommended. However, if concomitant use with acid reducing agents cannot be avoided, nirogacestat can be staggered with antacids by administering nirogacestat 2 hours before or 2 hours after antacid use.

AE: Adverse Event; BID: Twice a day; Cmax: Maximum concentration; DDI: Drug-drug interaction; DILI: Drug induced liver injury; EGC: Electrocardiogram; GALT: Gut associated lymphoid tissue; GLP: Good laboratory practice; GS: Gamma-secretase; NK: Natural Killer; NOAEL: No observed adverse effect level; LOAEL: Lowest observed adverse effect level; OT: Ovarian Toxicity; P-gp: P-glycoprotein; VEGF: Vascular endothelial growth factor; WOCBP: Women of childbearing potential

Table SII.2 Conclusions on Nonclinical Data

Safety Concerns	
Important identified risks	Ovarian toxicity
Important potential risks	Epiphyseal disorder with off label-use in the pediatric population with open growth plates Embryo-fetal toxicity Drug induced liver injury Severe renal toxicity Adverse effect on female fertility Adverse effect on male fertility
Missing information	None (based upon non-clinical findings)

Part II: Module SIII - Clinical trial exposure

The integrated clinical safety program of nirogacestat comprises safety data collected from all clinical studies in participants with DT (Studies A8641014, 14-C-0007, and NIR-DT-301), clinical pharmacology studies in healthy volunteers (HV) (Studies A8641001, A8641008, NIR-DT-101, NIR-DT-102, and NIR-DT-103), and studies in participants with advanced solid tumors (Studies A8641014 and A8641020, a Phase 2 monotherapy study in patients with metastatic mTNBC) utilizing doses from 20 mg to 330 mg BID, continuously.

The double-blind phase of Study NIR-DT-301 is the pivotal trial for nirogacestat since it is the only study of participants with DT to incorporate a placebo arm. Additional descriptive analyses were performed for the ongoing open-label extension (OLE) phase of Study NIR-DT-301. The OLE population includes all participants in Study NIR-DT-301 who enrolled into the OLE phase.

The studies in Table SIII.1 define the safety populations used for exposure and safety data analyses. It should be noted that there is overlap of the populations. The pivotal Phase 3 Study NIR-DT-301 (Primary Analysis Population) is the focus of the demonstration of safety for the European Union (EU) Marketing Authorisation Application (MAA) as it is the pivotal study for the application and was the only study in participants with DT conducted using a placebo comparator arm. The Integrated All DT Safety population, specifically the nirogacestat 150 mg group within this population, is being used primarily to provide an additional estimate of event incidence and incidence rate. The Integrated CM Population is not being given significant consideration in determining the safety profile of nirogacestat for the treatment of DT since doses higher than 150 mg BID were used in these studies and the patients were being treated for advanced cancer. All patients with DT treated in the Integrated CM Population studies are included in the Integrated All DT Population.

Table SIII.1 Definition of Data Populations

All DT Participants (Integrated All DT Population)		
Study No.	**Study Title**	**No. of Participants Treated with Nirogacestat**
NIR-DT-301 (double-blind phase)	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing DT	69
14-C-0007	Phase 2 Trial of the γ-secretase Inhibitor Nirogacestat (PF-03084014) in Adults with DT	17
A8641014	A Phase 1 Trial of PF-03084014 in Patients with Advanced Solid Tumor Malignancy and T-cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma	9 participants with DT (includes 2 participants treated with nirogacestat 150 mg BID)
Population Total		95 (includes 88 participants treated with nirogacestat 150 mg BID)

All Cancer Participants Treated with Monotherapy Nirogacestat (Integrated All CM Population)		
Study Number	**Study Title**	**Number of Participants Treated with Nirogacestat**
NIR-DT-301 (double-blind phase)	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing DT	69
14-C-0007	Phase 2 Trial of the γ-secretase Inhibitor Nirogacestat (PF-03084014) in Adults with DT	17
A8641014	A Phase 1 Trial of PF-03084014 in Patients with Advanced Solid Tumor Malignancy and T-cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma	Solid Tumor: 64 (includes 9 participants with DT)
A8641020	Phase 2 Study of Single-Agent PF-03084014 in Patients with Advanced TNBC With or Without Genomic Alterations in Notch Receptors	19
Population Total		177

Healthy Volunteers Treated with Single Dose (HV Population)		
Study No.	**Study Title**	**No of Participants Treated with Nirogacestat**
A8641001	A Phase 1, First-Into Human, Escalating Dose Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of PF-03084014 After Administration of Single Oral Doses to Healthy Adult Subjects	26
A8641008	A Phase 1 Investigator-And-Subject Blind Randomized Placebo-Controlled, Two-Period Crossover Study in Healthy Participants to Evaluate the Pharmacodynamic Effects of Single Oral Doses of PF-03084014 on Aβ Concentrations in Cerebrospinal Fluid Using Serial Sampling Methodology	10
NIR-DT-101	A Phase 1, Single-center, Open-label, Pharmacokinetics, Metabolism, Mass Balance, and Safety Study of [^{14}C]-PF-03084014 (Nirogacestat) Following Single Oral Dose Administration in Healthy Male Volunteers	10
NIR-DT-102	A 2 Part, Open-label Phase 1 Study to Determine the Mass Balance Recovery, Absorption, Metabolism, and Excretion of [^{14}C]-Nirogacestat and the Absolute Bioavailability of Nirogacestat Following Administration of a Single Oral Dose in Healthy Male Subjects	Part 1: 6 Part 2: 6
NIR-DT-103 [a)]	A Three-Part Study to Evaluate the Effects of Itraconazole or Rifampin on the Pharmacokinetics of Nirogacestat and the Effects of Nirogacestat on the Pharmacokinetics of Dabigatran Etexilate in Healthy Participants	Part 1: 25 Part 2: 24 Part 3: 21
Population Total		128

a) Part 1 of the NIR-DT-103 Study was terminated early after dosing with nirogacestat but prior to dosing with rifampin due to a safety concern with rifampin.

CM: cancer monotherapy; DT: desmoid tumor(s); HV: healthy volunteer; DT: Desmoid tumor; TNBC: Triple-negative breast cancer

Exposure data provided in the tables below focuses on the nirogacestat 150 mg BID treatment group in Study NIR-DT-301 (double-blind phase), NIR-DT-301 (OLE phase), Integrated All DT Population, and Integrated CM Population.

Table SIII.2 Summary of Exposure and Compliance 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
Total duration of exposure[a] (participant years)	79.9	100.0	80.9	101.1	180.1
Mean duration of exposure[b] (months)	13.312	17.400	13.482	17.583	24.560
Median duration of exposure[b] (months)	11.400	20.567	11.400	20.928	21.503
Mean relative dose intensity[c] (%)	98.847	87.397	98.803	87.305	85.410
Median relative dose intensity[c] (%)	100.000	96.104	100.000	96.104	92.293

Reference: NIR-DT-301CSR Table 14.1.3.1, Table SCS.4.3.1
BID: twice daily; DT: desmoid tumor(s); N; participants; mg: milligram
a Duration of exposure is calculated as: (Last Dose Date - First Dose Date +1)/30.4375.
b Participant Years is calculated as: (Last Dose Date - First Dose Date +1)/365.25
c Relative Dose intensity is calculated as: 100*(cumulative dose received/planned dose received). Planned dose is daily dose in mg/day * duration of exposure in days. If participants most recent dose modification is an interruption and the participant has not discontinued, days of interruption up until the data cut point are added to the denominator.

The number and percentage of participants in the Integrated All DT nirogacestat 150 mg BID treatment group within the Integrated DT Safety Population by duration of exposure category was 59 (67%) at ≥12 months, 31 (35%) at ≥24 months, and 12 (14 %) at ≥36 months or longer (Table SCS.4.3.1). The number and percentage of participants in the total nirogacestat group in the Integrated DT Safety Population by duration of exposure category was 64 (67%) at ≥12 months, 34 (36%) at ≥24 months, and 15 (16%) at ≥36 months or longer (Table SCS.4.3.1). The number and percentage of participants in the total nirogacestat group in the OLE population by duration of exposure category was 60 (71%) at ≥12 months, 46 (55%) at ≥24 months, and 7 (8%) at ≥36 months or longer (Table SCS.4.4).

Table SIII.3 Exposure by Sex 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**
Sex					
Male	25 (35%)	25 (36%)	25 (35%)	25 (36%)	29 (33%)
Female	47 (65%)	44 (64%)	47 (65%)	44 (64%)	59 (67%)

Reference: NIR-DT-301 CSR Table 14.1.2.1.1, Table SCS.3.3

Table SIII.4 Exposure by Age in Participants who Received Nirogacestat 150 mg BID and Placebo (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
Age (at time of informed consent)					
Mean (SD)	37.0(12.89)	37.3(14.48)	37.0(12.89)	37.3(14.48)	37.5(14.31)
Median	34.5	33.0	34.5	33.0	33.0
Min, Max	18, 76	18, 73	18, 76	18, 73	18, 73
<27 Years	14 (19%)	20 (29%)	14 (19%)	20 (29%)	23 (26%)
27 to <34 Years	18 (25%)	15 (22%)	18 (25%)	15 (22%)	22 (25%)
34 to <46 Years	25 (35%)	13 (19%)	25 (35%)	13 (19%)	17 (19%)
≥46 Years	15 (21%)	21 (30%)	15 (21%)	21 (30%)	26 (30%)
≥65 Years	3 (4%)	3 (4%)	3 (4%)	3 (4%)	4 (5%)
≥70 Years	2 (3%)	2 (3%)	2 (3%)	2 (3%)	2 (2%)
≥75 Years	2 (3%)	0	2 (3%)	0	0

Reference: NIR-DT-301 CSR Table 14.1.2.1.1, Table SCS.3.3

Table SIII.5 Exposure by Race and Ethnic Origin 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**
Race, n(%)					
Asian	3 (4%)	1 (1%)	3 (4%)	1 (1%)	1 (1%)
Black or African American	5 (7%)	4 (6%)	5 (7%)	4 (6%)	6 (7%)
White or Caucasian	54 (75%)	63 (91%)	54 (75%)	63 (91%)	80 (91%)
Other	10 (14%)	1 (1%)	10 (14%)	1 (1%)	1 (1%)
Ethnicity					
Hispanic or Latino	9 (13%)	1 (1%)	9 (13%)	1 (1%)	1 (1%)
Not Hispanic or Latino	55 (76%)	66 (96%)	55 (76%)	66 (96%)	68 (77%)
Unknown	3 (4%)	0	3 (4%)	0	0
Not Reported	5 (7%)	2 (3%)	5 (7%)	2 (3%)	19 (22%)

Reference: NIR-DT-301 CSR Table 14.1.2.1.1, Table SCS.3.3

Table SIII.6 Exposure by Geographic Region in Participants who Received Nirogacestat 150 mg BID and Placebo (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
Geographic region					
North America	53 (74%)	44 (64%)	53 (74%)	44 (64%)	63 (72%)
Europe	19 (26%)	25 (36%)	19 (26%)	25 (36%)	25 (28%)

Reference: NIR-DT-301 CSR Table 14.1.2.1.1, Table SCS.3.3

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Exclusion criteria:

Participant has known malabsorption syndrome or pre-existing gastrointestinal conditions that may impair 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 is not allowed.

Reason for exclusion:

Impaired absorption of oral nirogacestat would result in sub-optimal plasma levels of nirogacestat and hence would impact the efficacy results of the study.

Is it considered to be included as missing information?

No

Rationale:

The likelihood of these patients being prescribed nirogacestat, an oral medication, is small as potential prescribers will appreciate that such patients would have limited absorption of nirogacestat and will not prescribe it. Additional pharmacovigilance activities to investigate nirogacestat use in this patient population is unwarranted.

Exclusion criteria:
Participant has experienced any of the following within 6 months of signing informed consent:

- clinically significant cardiac disease (New York Heart Association Class III or IV);
- myocardial infarction
- severe/unstable angina
- coronary/peripheral artery bypass graft
- symptomatic congestive heart failure
- cerebrovascular accident
- transient ischemic attack or
- symptomatic pulmonary embolism.

Reason for exclusion:

Inclusion of these participants would confound the safety results of this study.

Is it considered to be included as missing information?

No.

Rationale:

Based upon the non-clinical findings and clinical data there is no reason to think that the safety profile of nirogacestat would differ in this patient population. Additionally, because of the rareness of the disease, it would not be feasible to undertake a specific study in this patient population as the sample size would be too small.

Exclusion criteria:

Participant has abnormal QT interval corrected by Fridericia's formula (> 450 msec for male participants, > 470 msec for female participants, or > 480 msec for participants with bundle branch

block) after electrolytes have been corrected (triplicate ECG readings, done approximately 2-3 minutes apart and averaged) at screening.

Participant is using concomitant medications that are known to prolong the QT/QTcF interval including Class Ia (e.g., quinidine, procainamide, disopromide) and Class III (e.g., dofetilide, ibutilide, sotalol) antiarrhythmics at the time of informed consent. Non-antiarrhythmic medications which may prolong the QT/QTcF interval are allowed provided the participant does not have additional risk factors for Torsades de Pointes (TdP).

Participant has congenital long QT syndrome.

Participant has a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).

Reason for exclusion:

Inclusion of these participants would confound the safety results of this study.

Is it considered to be included as missing information?

No.

Rationale:

The effects of nirogacestat concentration on QTc interval prolongation were predicted using a model based on data from several healthy participant studies and two studies in participants with cancer diagnoses. The 90% confidence intervals for the predicted mean change in QTcF were below 10 msec at twice the expected Cmax with moderate CYP3A4 inhibition. Therefore, no clinically significant prolongation in QTcF interval is associated with therapeutic dosing of nirogacestat alone or with moderate CYP3A4 inhibition. Note that this modeling had not been completed at the time of the initiation of Study-NIR-DT-301.

Exclusion criteria:

Participant has had lymphoma, leukemia, or any malignancy within the past 5 years at the time of informed consent, except for any locally recurring cancer that has been treated curatively (e.g., resected BCC or SCC, superficial bladder cancer, carcinoma in situ of the cervix or breast), with no evidence of metastatic disease for 3 years at the time of informed consent.

Reason for exclusion:

Such participants may have concurrent malignant disease which would impact the efficacy and safety endpoints of the study. Additionally, such participants may require further treatment during the duration of the study which would require withdrawal from the study.

Is it considered to be included as missing information?

No

Rationale:

Additional pharmacovigilance activities to ascertain the safety profile in patients with DT and concomitant malignancy would not be feasible.

Exclusion criteria:

Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).

Reason for exclusion:

Participants were excluded as a precautionary measure as treatment-related changes in the liver consisting of hepatocellular vacuolation (mild) were observed in the 1-month rat study and transient increases in alanine aminotransferase/aspartate aminotransferase (ALT/AST) have been observed in clinical studies.

Is it considered to be included as missing information?

No

Rationale:

Nirogacestat is not recommended for use in patients with severe hepatic impairment due to the potential risk of increased nirogacestat distribution which could result in higher exposures of nirogacestat in tissues.

Exclusion criteria:

Participant is currently using or anticipates using food or drugs that are known strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3A inducers within 14 days prior to the first dose of study treatment.

Reason for exclusion:

Nirogacestat is primarily metabolized by CYP3A4 and inclusion of these patients would impact safety and efficacy results.

Is it considered to be included as missing information?

No

Rationale:

The product label provides adequate instruction concerning use of nirogacestat with CYP3A4 inhibitors and inducers.

Exclusion criteria:

Participant has a positive human immunodeficiency virus (HIV) antibody test.

Participant has presence of Hepatitis B surface antigen at screening.

Participant has a positive Hepatitis C antibody or Hepatitis C ribonucleic acid (RNA) test result at screening or within 3 months prior to starting study treatment.

Reason for exclusion:

These patients were excluded in order to eliminate confounding factors for safety and efficacy. Additionally, they were excluded as a precautionary measure taking into account non-clinical information suggesting a possible effect on immune cells.

Is it considered to be included as missing information?

No

Rationale:

DT is a rare disease, and it would not be feasible to undertake any study in these patients with DT and who were also positive for HIV or Hepatitis B or Hepatitis C.

Exclusion criteria:

Participant with active or chronic infection at the time of informed consent and during the screening period.

Reason for exclusion:

These patients were excluded in order to eliminate confounding factors for safety and efficacy. Additionally, they were excluded as a precautionary measure taking into account non-clinical information suggesting a possible effect on immune cells.

Is it considered to be included as missing information?

No

Rationale:

DT is a rare disease, and it would not be feasible to undertake any study in these patients with DT and active or chronic infection.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

In the clinical development program of nirogacestat, 88 participants and 128 participants received 150 mg BID of nirogacestat in the Integrated DT Safety Population and Integrated CM Population, respectively. Across all doses in the Integrated All DT Safety Population, 95 participants were treated with nirogacestat. In the ongoing open label extension of Study NIR-DT-301, 45 additional participants were treated with nirogacestat 150 mg BID, while 39 participants continued on nirogacestat 150 mg BID from the DB phase. The clinical development program at the time of the primary analysis of Study NIR-DT-301 is unlikely to detect rare adverse reactions. The duration of exposure data as described in Part II: Module SIII above indicates that the current clinical trial experience is sufficiently likely, in this rare disease, to detect commonly occurring adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.3 Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pediatrics	A total of 25 patients under 18 years of age have been treated with nirogacestat in a compassionate use program as of 23 Oct 2023 (data on file). Additionally, as of 31Dec2023, 30 pediatric patients have been treated with nirogacestat in the Children's Oncology Group Study ARST 1921 which is studying nirogacestat in pediatric patients with DT (data on file).
Elderly	In the Integrated All DT Safety Population nirogacestat 150 mg BID group, there were 4 patients ≥ 65 years and in the Integrated CM Population nirogacestat 150 mg BID group there were 19 patients ≥ 65 years.
Pregnant or breastfeeding women	One patient who was not practicing effective birth control conceived while taking nirogacestat. Nirogacestat treatment was discontinued and 33 days later she experienced a spontaneous abortion.
Patients with relevant comorbidities:	

Type of Special Population	Exposure
Patients with hepatic impairment	12 patients with moderate hepatic impairment were studied in Study NIR-DT-104.
Patients with renal impairment	None
Patients with a disease severity different from inclusion criteria in clinical trials	None
Population with relevant different ethnic origin	In all the patient populations, the majority of the patients exposed to nirogacestat were non-Hispanic or Latino (69-96%), with 100% of the OLE patients continuing nirogacestat being non-Hispanic or Latino. In all the patient populations, the majority of the patients exposed to nirogacestat were white (91-92%), with 100% of the OLE patients continuing nirogacestat being white.
Subpopulations carrying relevant genetic polymorphisms	None
Other	Not applicable

BID: Twice a day; CM: Cancer monotherapy; DT: Desmoid tumor(s); OLE: Open Label extension

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

Nirogacestat (Ogsiveo) received US FDA approval on 27Nov2023. Nirogacestat is not authorized in any other territory. The estimated post-marketing exposure through the data lock point of 27Aug2024 is presented below.

SV.1.1 Method used to calculate exposure

Estimated patient exposure to Ogsiveo was calculated based on the number of patients that have been reported through specialty pharmacies, patient support programs, and medically integrated dispensing pharmacies. Estimated shipments per reporting period may vary as patients may discontinue or discontinue and restart in different reporting periods. Additionally, medication provided via channels other than those noted above are estimates based on shipment. The cumulative estimate for patient exposure is counted based on the unique number of patients exposed to date. A patient can be counted in each interval but is only counted once for the cumulative exposure.

SV.1.2 Exposure

Cumulatively from 27Nov2023 through 27Aug2024, post-marketing exposure to Ogsiveo in the USA is estimated to be 1212 patients.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no apparent potential for misuse of nirogacestat for illegal purposes.

Part II: Module SVII - Identified and potential risks

This section describes safety data from the double-blind (DB) phase of Study NIR-DT-301 based on the primary analysis data cut (07Apr2022). Safety findings from the final database lock date (30 Jun 2022) of the DB phase of NIR-DT-301 were consistent with those of the primary analysis.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

1. **Reason for not being considered important: Known risks that do not impact the risk-benefit profile:**

   a. Fatigue

   Analyses are based on the Preferred Term of fatigue.

   In Study NIR-DT-301, fatigue was reported in 35 participants (51%) in the nirogacestat arm and 26 participants (36%) in the placebo arm.

   All events of fatigue in both treatment arms were Grade 1 or 2, with the exception of 2 participants in the nirogacestat arm who reported Grade 3 fatigue.

   There were no serious events of fatigue in either arm.

   No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

   b. Epistaxis

   In Study NIR-DT-301, epistaxis was reported in 10 participants (14%) in the nirogacestat arm and 1 participant (1%) in the placebo arm.

   All events of epistaxis in both treatment arms were Grade 1, with the exception of 1 participant in the nirogacestat arm who reported Grade 2 epistaxis. There were no serious events of epistaxis in either arm.

   No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

   c. Upper Respiratory Tract Infection

   Upper respiratory tract infections (URTI) are represented by the Preferred Terms of upper respiratory tract infection, viral respiratory tract infection, acute sinusitis, and sinusitis.

   In Study NIR-DT-301, URTIs were reported by 11 participants (16%) in the nirogacestat arm and 1 participant (1%) in the placebo arm.

   There were no URTIs of Grade ≥3 and no serious URTIs.

   No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

   d. Dyspnea

   This analysis is based on the single Preferred Term of dyspnea.

   In Study NIR-DT-301, the Preferred Term of dyspnea was reported in 11 participants (16%) in the nirogacestat arm and 4 participants (6%) in the placebo arm.

   All events of dyspnea were Grade 1 or 2.

No events of dyspnea in participants in the nirogacestat arm were serious or led to drug discontinuation.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

e. Cough

This analysis is based on the single Preferred Term of cough in order to increase its specificity on cough symptoms not associated with an accompanying infection. A case level analysis was conducted, and cough was not associated with co-occurring confounding terms such as upper respiratory tract infection.

In Study NIR-DT-301, the Preferred Term of cough was reported in 11 participants (16%) in the nirogacestat arm and 3 participants (4%) in the placebo arm.

All events of cough were Grade 1 or 2.

No events of cough were serious or led to drug discontinuation.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

f. Influenza-like illness

This analysis is based on the single Preferred Term of influenza like illness in order to increase its specificity on flu-like symptoms in isolation from any accompanying infection.

The occurrence of influenza-like illness in the Study NIR-DT-301 is consistently greater in the nirogacestat 150 mg BID arm compared to the placebo arm for incidence (10% vs. 3%), EAIR (0.07 vs. 0.02 participants with event per patient-year), and EAER (0.07 vs. 0.03 events per patient-year) values.

All events of influenza-like illness were Grade 1 or 2.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

g. Headache

In Study NIR-DT-301, headache was reported in 20 (29%) of the nirogacestat treated patients and 11 (15%) of the placebo patients. Headache is a commonly experienced condition in the general population and a role for GS inhibition in its origin is not clear. However, the onset during the first two cycles of treatment suggested a causative relationship to nirogacestat.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

h. Nausea

In Study NIR-DT-301, nausea was reported in 37 participants (54%) in the nirogacestat arm and 28 participants (39%) in the placebo arm. Most nausea events were Grade 1 or 2; One participant in the nirogacestat arm reported a Grade 3 event. There were no nausea SAEs.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

i. Stomatitis

Analyses are based on the Preferred Terms of stomatitis, mouth ulceration, oral pain, and oropharyngeal pain

In Study NIR-DT-301, stomatitis was reported by 26 participants (38%) in the nirogacestat arm and 5 participants (7%) in the placebo arm.

Most events were Grade 1 or 2 events, with 3 (4%) participants in the nirogacestat arm reporting Grade 3 events. One of the Grade 3 events was an SAE.

Stomatitis led to dose interruption in 2 (8% of participants with a stomatitis event), and dose reduction in 3 (12% of participants with a stomatitis event); all dose modifications occurred in the nirogacestat arm. No participants discontinued nirogacestat due to stomatitis.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

j. Alopecia

In Study NIR-DT-301, alopecia was reported in 13 (19%) participants in the nirogacestat arm and 1 (1%) participant in the placebo arm. All events of alopecia were Grade 1, and 12 of the events in the nirogacestat arm occurred in women.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

k. Dry skin

In Study NIR-DT-301, dry skin was reported in 11 (16%) participants in the nirogacestat arm and 5 (7%) participants in the placebo arm. All events of dry skin in the nirogacestat arm were Grade 1 or Grade 2. Ten participants reported Grade 1 events, and one participant reported Grade 2. Eight of the participants who reported dry skin in the nirogacestat arm were female.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

l. Pruritus

In Study NIR-DT-301, pruritus was reported in 9 (13%) participants in the nirogacestat arm and 6 (8%) participants in the placebo arm. All events of pruritus in the nirogacestat arm were Grade 1 or Grade 2. Six participants reported Grade 1 events, and 3 participants reported Grade 2 events. Six of the participants who reported pruritus in the nirogacestat arm were female.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

m. Dizziness

In Study NIR-DT-301, dizziness was reported in 8 (12%) participants in the nirogacestat arm and 4 (6%) participants in the placebo arm. All events of dizziness in the nirogacestat arm were Grade 1 or Grade 2. Seven participants reported

Grade 1 events, and one participant reported Grade 2. Seven of the participants who reported dizziness in the nirogacestat arm were female.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

n. Dry mouth

In Study NIR-DT-301, dry mouth was reported in 8 (12%) participants in the nirogacestat arm and 3 (4%) participants in the placebo arm. All events of dry mouth in the nirogacestat arm were Grade 1. Five of the participants who reported dry mouth in the nirogacestat arm were female.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

o. Eosinophilia

In Study NIR-DT-301, eosinophilia was reported as a treatment-emergent adverse event (TEAE) in 2 (3%) participants in the nirogacestat arm and no participants in the placebo arm. All events of eosinophilia in the nirogacestat arm were Grade 1. One of the participants who reported eosinophilia in the nirogacestat arm was female.

In Study NIR-DT-301, laboratory findings of increased eosinophils were observed in 18 (26%) participants in the nirogacestat arm and 4 (6%) participants in the placebo arm. All elevations in both arms were considered Grade 1.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

2. Reason for not being considered important: Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice where the product is authorised).

a. Hidradenitis

In Study NIR-DT-301, hidradenitis was reported in 6 participants (9%) in the nirogacestat arm and none in the placebo arm. Five participants (7%) reported Grade 2 events, and 1 (1%) participant reported a Grade 3 event.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

b. Folliculitis

In Study NIR-DT-301, folliculitis was reported in 9 participants (13%) in the nirogacestat arm and none in the placebo arm. Two participants (3%) reported a Grade 2 events, and 4 (6%) participants reported Grade 3 events.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

c. Rash

In Study NIR-DT-301, 46 (67%) of participants in the nirogacestat arm reported skin rash events (narrow definition, see Annex 7 for the Preferred Terms included in the definition) compared to 13 (18%) in the placebo arm. Rash maculo-papular was reported in 22 (32%) of participants in the nirogacestat arm compared with 4 (6%) in the placebo arm. Dermatitis acneiform was reported in 15 (22%) of participants in the nirogacestat arm compared with 0 in the placebo arm. There were 4 (6%) participants in the nirogacestat arm who experienced maculopapular rash at Grade ≥ 3, compared to none in the placebo arm. No other skin rashes were reported as Grade ≥ 3.

Among participants who reported a skin rash event (narrow definition), skin rash events led to dose modification in the nirogacestat arm but not in the placebo arm; dose reduction occurred in 7 participants (15%), drug discontinuation occurred in 1 participant (1%), and dose interruption occurred in 10 participants (22%) in the nirogacestat arm.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

d. Diarrhea

In Study NIR-DT-301, diarrhea events were reported in 58 participants (84%) in the nirogacestat arm and 25 (35%) in the placebo arm.

Most diarrhea events were Grade 1 or 2; 11(16%) participants in the nirogacestat arm and 1 (1%) participant in the placebo arm had a Grade 3 diarrhea event.

There were no serious events in the nirogacestat arm.

Diarrhea led to dose interruption in 9 (16% of participants with a diarrhea event), and dose reduction in 6 (10% of participants with a diarrhea event), in participants in the nirogacestat arm. Diarrhea lead to treatment discontinuation in 4 (7% of participants with a diarrhea event) in participants in the nirogacestat arm.

Most diarrhea events resolved, although 22 participants in the nirogacestat arm and 10 participants in the placebo arm had a diarrhea event that did not resolve by the data cutoff date.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

e. Hypokalemia

In Study NIR-DT-301, hypokalemia was reported in 8 participants (12%) in the nirogacestat arm and 1 participant (1%) in the placebo.

Most events were Grade 1 to 2 events, with one Grade 3 event in the nirogacestat arm.

There were no serious events.

In Study NIR-DT-301, laboratory findings of decreased potassium were observed in 15 participants (22%). Grade 3 decreased potassium occurred in 1 participant (1.4%).

Hypokalemia can be managed via labeling to advise on monitoring and potassium supplementation, and this is within the realms of normal clinical practice.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

f. Hypophosphatemia

In Study NIR-DT-301, 29 (42%) participants in the nirogacestat arm reported hypophosphatemia compared to 5 (7%) in the placebo arm. Most participants reported Grade 1 or 2 events, with 2 participants in the nirogacestat treatment arm reported a Grade 3 event.

In Study NIR-DT-301, laboratory findings of decreased phosphate were observed in 46 participants (67%). Phosphate <2 mg/dL occurred in 20% of participants who received nirogacestat compared to 0 participants who received placebo.

Most events of hypophosphatemia were managed with replacement therapy with 72% of participants reporting an event of hypophosphatemia receiving a concomitant medication.

There were no serious events of hypophosphatemia.

Hypophosphatemia can be managed via labeling to advise on monitoring and phosphate supplementation, and this is within the realms of normal clinical practice.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

g. Proximal renal tubule effect

Glycosuria and proteinuria were observed in 52% and 46%, respectively, of participants receiving nirogacestat in the double-blind phase of study NIR-DT-301, compared with 1% and 39%, respectively, in participants receiving placebo. Median time to onset of glycosuria and proteinuria was 85 days (range: 55 to 600 days) and 72 days (range: 38 to 937 days), respectively. One participant in NIR-DT-301 reported renal tubule disorder with increased urinary excretion of uric acid, glucose and phosphate but no excess excretion of low molecular weight proteins (beta2-microglobulin) or any change in renal function. The event was managed with dose reduction.

h. Drug-drug interactions

Effect of moderate and strong CYP3A4 inhibitors

- In a clinical study, co-administration of itraconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) increased nirogacestat Cmax by 2.5-fold and AUC by 8.2-fold. Co-administration with moderate CYP3A4 inhibitors is expected to result in clinically relevant increases in exposure.
- Concomitant use with strong inhibitors of CYP3A4 (e.g., clarithromycin, oral ketoconazole, itraconazole) and moderate inhibitors of CYP3A4 (e.g., erythromycin and fluconazole) should therefore be avoided.
- Alternative concomitant medicinal products with no or minimal CYP3A4 inhibition should be considered. If therapeutic alternatives are not

available, nirogacestat should be immediately interrupted for the period of time in which a strong or moderate CYP3A4 inhibitor is given.

- Patients should avoid consuming grapefruit and grapefruit juice when taking nirogacestat since they include inhibitors of CYP3A4.

Effect of strong or moderate CYP3A4 inducers

- The effects of CYP3A4 inducers on nirogacestat exposure have not been evaluated in a clinical study. Moderate and strong inducers are expected to result in clinically relevant decreases in exposure of nirogacestat that could lead to reduced efficacy.
- Concomitant treatment with strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampicin, phenobarbital and St. John's wort) and moderate CYP3A inducers (e.g., efavirenz and etravirine) should therefore be avoided. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected.

Effect of acid-reducing agents

- Nirogacestat has pH-dependent solubility, with substantially reduced solubility at pH greater than 6.0. The effects of acid reducing agents (i.e., H2-receptor antagonists, proton pump inhibitors and antacids) on nirogacestat exposure have not been evaluated in a clinical study, however, co-administration of these medicinal products may reduce the bioavailability of nirogacestat. Concomitant use of nirogacestat with proton pump inhibitors and H2 blockers is not recommended. However, if concomitant use with acid reducing agents cannot be avoided, nirogacestat can be staggered with antacids by administering nirogacestat 2 hours before or 2 hours after antacid use.

Effects of nirogacestat on the pharmacokinetics of other medicinal products: CYP substrates

- A drug-drug interaction study in healthy volunteers investigating the effects of multiple doses of nirogacestat at a dose of 95 mg once daily on the exposure of midazolam, a sensitive CYP3A4 substrate, resulted in a 1.3-fold increase in midazolam Cmax and a 1.6-fold increase in midazolam AUC. The effect of the clinical dose of nirogacestat (150 mg twice daily) on midazolam exposure has not been studied and may be different. Nirogacestat should not be used with concomitant administration of CYP3A4 substrates that have narrow therapeutic indices (e.g., cyclosporine, tacrolimus, digitoxin, warfarin, carbamazepine).
- In vitro studies showed that nirogacestat may induce CYP2C8, CYP2C9, CYP2C19, and CYP2B6 and thus there is a risk that nirogacestat can cause decreased exposure of substrates of these enzymes. When substrates of CYP2C8, CYP2C9, CYP2C19, and CYP2B6 are administered with nirogacestat, evaluation for reduced efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

- Since no study has been performed investigating the effect of nirogacestat on systemic contraceptive steroid exposure, it is unknown whether nirogacestat reduces the effectiveness of systemically acting hormonal contraceptives. Women of childbearing potential should use highly effective contraceptive methods.

Drug transporter systems

- A single-dose drug-drug interaction study demonstrated that nirogacestat did not affect the exposure of dabigatran, a P-gp substrate, which supports the absence of clinically meaningful P-gp inhibition by nirogacestat.

Oncologists treating patients with DT will be familiar with drugs that have the potential for drug-drug interactions as part of their normal clinical and prescribing practices.

No additional pharmacovigilance or risk minimization activities beyond routine pharmacovigilance or risk minimization measures are required for this risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Ovarian Toxicity	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study and multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study. **Clinical** In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo. OT was reported to resolve in WOCBP both while continuing nirogacestat and after stopping nirogacestat. Ovarian toxicity has been reported to resolve in 79% of women of childbearing potential during treatment and in all women who discontinued nirogacestat for any reason and for whom follow-up information is available (2 patients lost to follow up).
Risk-benefit impact	In view of the seriousness of progressing DT and the need for treatment, the risk of OT does not outweigh the benefits of treatment with nirogacestat. Further characterization of this risk will include the additional pharmacovigilance activity of Study NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Important Identified Risk: Non-Melanoma Skin Cancers	
Scientific evidence for risk to be added in the safety specification	**Non-Clinical** There was no increase in neoplasms compared to controls in the 6-month mouse carcinogenicity studies, and specifically no test-article related proliferative findings were noted in the scheduled sacrifice animals. In the 3-month rat toxicology study, facial pustules were observed in 2 females dosed at 50 mg/kg/day, which correlated with follicular cysts observed microscopically. **Clinical** In the double-blind phase of Study NIR-DT-301, among participants who received nirogacestat, 2 participants (3%) in the nirogacestat 150 mg BID arm reported non-melanoma skin cancer events. One of these participants also reported a second event of BCC in close temporal relationship to the report of SCC. No participants who were given placebo reported a non-melanoma skin cancer. In the on-going open-label extension phase of Study NIR-DT-301, a report of BCC has been received after the closure of the double-blind phase from a participant who had continued into the OLE from the nirogacestat arm. In the ongoing14-C-0007 Study, 1 (6%) report of SCC has been received. In the ongoing Study (NIR-OGT-201), a phase 2 trial of nirogacestat in patients with recurrent ovarian granulosa cell tumors, 1 report of SCC has been received. An additional report of BCC has been received from a partner study. Of note, there are no reports of malignant melanoma from participants in the nirogacestat development program. No participants reporting a non-melanoma skin cancer have reported the development of a second skin cancer during their follow-up period as of the data cut-off date for this summary of safety. Review of the details of each report show that each reporting participant had confounding factors for the development of non-melanoma skin cancers such as age older than 60, fair skin, or a history of sunburns or sunbathing without the use of sunblock. An increased occurrence of non-melanoma skin cancers has been observed in clinical trials with the gamma-secretase inhibitors semagacestat and avagacestat (Doody 2013; Henley 2014; Coric 2012).
Risk-benefit impact	In view of the seriousness of DT and the need for treatment, the results from the clinical development program to date do not suggest that the identified risk of non-melanoma skin cancers would outweigh the benefits of treatment with nirogacestat, particularly since non-melanoma skin cancers can be readily diagnosed and managed with regular skin examinations and excision of observed lesions.

Important Identified Risk: Bone fracture	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** Non-clinical toxicology studies did not observe decreased bone mineralization in the animal species tested in the timeframes studied. **Clinical** In Study NIR-DT-301, numerically more participants reported a bone fracture in the nirogacestat arm than in the placebo arm (4

Important Identified Risk: Bone fracture	
	[6%]and 0, respectively). The fractures were reported on treatment days 1, 86, 163, and after 2 years of treatment respectively. All reports of fracture were from post-menopausal females ≥50 years of age. The participant who reported a fracture after 2 years of treatment did not have abnormal low phosphate values at any time during the study prior to her fracture, but she had low oestradiol values throughout the study, including at baseline. The smaller number of participants in the Study NIR-DT-301 placebo arm treated for ≥12 months (34 [47%]) or ≥24 months (8 [11%]) compared with those in the nirogacestat arm treated for ≥12 months (45 [65%]) or ≥24 months (19 [28%]) limits the ability of the 2 arms to detect late-onset events.
Risk-benefit impact	In view of the seriousness of progressing DT and the need for treatment, the risk of bone fracture does not outweigh the benefits of treatment with nirogacestat. Further characterization of this risk will include the additional pharmacovigilance activity of Study NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Important Potential Risk: Epiphyseal Disorder with Off-label Use in the Pediatric Population with Open Growth Plates	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** Increased retention of the hypertrophic zone of the growth plate and articular cartilage was seen in the sternum and stifle joints of rats given nirogacestat in the 1-month and 3-month studies. This change was characterized by minimal-to-moderate thickening of the hypertrophic zone in the cartilage with pallor and slight vacuolation of the osteocytes in the primary spongiosa. **Clinical** Four cases involving pediatric patients from the ongoing pediatric clinical Study ARST1921, and the nirogacestat compassionate use program (PTs of Epiphysiolysis, Hip fracture, Epiphyseal disorder, and Osteonecrosis), provide insufficient information to fully assess the effect of nirogacestat on the growing bones of these children. The cases are few in number, some lack information concerning the radiographic appearance of the growth plates, and each patient had been previously treated with chemotherapeutic agents with a known negative impact on bone development.
Risk-benefit impact	As nirogacestat is indicated only in the adult population, the risk-benefit of the product remains positive.

Important Potential Risk: Drug induced liver injury	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** In the 3-month study with 1-month recovery in dogs, hepatic inflammation and necrosis with associated elevations in liver enzymes were observed at doses ≥10 mg/kg/day. These hepatic findings resolved in the recovery phase. The inflammation was associated with necrosis resulting from endotoxemia originating from the disrupted intestinal mucosal barrier. In the 1-month study in dogs, hepatic inflammation, correlating with disrupted intestinal mucosal barrier, was observed at 80 mg/kg/day. In the 3-month rat study, elevations in ALT, AST, ALP, GGT and total bilirubin were observed in female rats receiving 50 mg/kg/day of nirogacestat. Exclusively in moribund rats or rats found dead at 50 mg/kg/day, microscopic findings consistent with centrilobular hepatic necrosis were observed. At doses ≥20 mg/kg/day, centrilobular hepatocellular hypertrophy was observed. At doses ≥5 mg/kg/day, periportal lipid vacuolation was observed. In the 1-month rat study receiving ≥20 mg/kg/day, hepatic treatment-related changes were observed in the liver consisting of an increase in the incidence and severity of hepatocellular lipid vacuolation in the periportal areas. **Clinical** In Study NIR-DT-301, there was an increased incidence of elevated transaminases in the nirogacestat 150 mg BID arm compared to the placebo arm, and the time to first onset for most participants reporting an event was during the first 3 cycles. Two participants in the nirogacestat arm reported Grade 3 events. There was no report of DILI.
Risk-benefit impact	The potential for drug induced liver injury can be managed with labeling which advises that liver function tests should be monitored regularly during treatment with nirogacestat, and that dose interruptions, dose modifications, or treatment discontinuation may be required to manage the risk. In view of the seriousness of progressing DT and the need for treatment, the potential risk of DILI does not outweigh the benefits of treatment with nirogacestat.

Important Potential Risk: Embryo-fetal Toxicity	
Scientific evidence for risk to be added in the safety specification	**Non-Clinical** The embryo-fetal toxicity of nirogacestat was assessed in pregnant rats administered 0 (vehicle), or nirogacestat at 5, 20, 50, or 150 mg/kg/day (01214011) during Gestation Days 6 through 17. At 5 mg/kg/day, the Gestation Day 17 total Cmax and AUC0-24 were 202 ng/ml and 1400 ng•h/mL, respectively. These exposures are well below those achieved in humans (total AUC0-24 12860 ng•h/mL) after nirogacestat administration of 150 mg BID (Study A8641014). 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 corresponding with lower mean number of viable fetuses and lower mean fetal body weights were noted at 20 mg/kg/day. In the 50-mg/kg/day group, only 2 fetuses were available for fetal morphology evaluation. One of the 2 fetuses at 50 mg/kg/day and a single fetus at 20 mg/kg/day were noted with edema (entire subcutis). No other external malformations or developmental variations were noted for fetuses at 5, 20, and 50 mg/kg/day. Intrauterine growth and survival at 5 mg/kg/day were unaffected by nirogacestat administration; therefore, 5 mg/kg/day was considered the NOAEL for this study. In pregnant rats that survived to the scheduled necropsy, decreases in body weight and body weight gain occurred at ≥50 mg/kg/day that correlated with decreases in food consumption. Lower mean gravid uterine weights were noted at ≥20 mg/kg/day groups compared to the control group. The lower gravid uterine weights and body weight effects noted during the latter portion of gestation were primarily attributed to increased post-implantation loss and/or lower fetal weights noted in these groups. **Clinical** One participant who was not practicing effective birth control conceived while taking nirogacestat. Nirogacestat treatment was discontinued and 33 days later she experienced a spontaneous abortion.
Risk-benefit impact	With routine risk minimization of labeling advising on the use of contraception and additional risk minimization measures of a Healthcare Professional Guide and Patient Card, the risk-benefit of the product remains positive.

Important Potential Risk: Adverse Effect on Female Fertility	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study. Multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study.

Important Potential Risk: Adverse Effect on Female Fertility	
	In the rat reproductive toxicity study, of the 22 female rats in each of the 20 and 40 mg/kg/day groups there were 18 (82%) and 22 (100%), respectively, that were determined to not be pregnant compared to 3 of the 22 (14%) females in the control group. No test material-related effects were noted on female reproductive performance (mating, fertility, or pregnancy) in the 5 mg/kg/day group. All females in this group had evidence of mating and were pregnant. **Clinical** Anti-Mullerian hormone (AMH), which is produced by developing ovarian follicles and is considered to be a marker of ovarian reserve, was decreased in women of childbearing potential while receiving nirogacestat (reflecting the interference with follicular development) and mean values were returning toward baseline at the final follow-up visit in the double-blind phase and OLE of Study NIR-DT-301. In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo. One female participant in Study NIR-DT-301 reported a pregnancy while receiving nirogacestat, although the pregnancy ended in a spontaneous abortion. As of 25Nov2024, 2 post-marketing events of women who became pregnant after being prescribed nirogacestat have been reported to SpringWorks, one approximately 1 month and the other approximately 5 months after stopping nirogacestat. The outcomes of these pregnancies are not yet known. As of 25Nov2024, 1 event has been reported to SpringWorks Pharmacovigilance of a participant who received nirogacestat in Study NIR-DT-301 and who conceived approximately 2 years after stopping nirogacestat to start a family. The outcome of this pregnancy is not yet known.
Risk-benefit impact	In view of the seriousness of progressing DT and the need for treatment, the potential risk of an adverse effect on female fertility does not outweigh the benefits of treatment with nirogacestat. Further characterization of this potential risk will include the additional pharmacovigilance activity of study NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Important Potential Risk: Adverse Effect on Male Fertility	
Scientific evidence for risk to be added in the safety specification	**Nonclinical** No effect on male mating indices was noted at any dose of nirogacestat tested. Decreases in epididymis and testes weights were noted in rats in the fertility and early embryonic development toxicology study. No changes in testes weights were noted in dogs or rats in either the 1- or 3-month pivotal toxicology studies. Changes in sperm motility and morphology were noted in rats at doses ≥20 mg/kg/day. These changes in sperm in rats did not lead to embryotoxicity, but rather decreased fertility while on treatment. In the 1- and 3-month repeat-dose rat studies, there were no microscopic change in the testes at doses as high as 50 mg/kg/day. Therefore, these effects appear to be limited to spermatogenesis with a low severity that did not induce microscopic changes in rats. It is unknown if these effects occur in humans. Microscopic findings of vacuolation of Sertoli cells were noted in the 10- to 11-month-old peripubertal beagle dogs used in the 3-month dog study. However, the relationship to treatment of this finding is unclear since similar findings have been described in peripubertal dogs (Goedken 2008). In addition, to demonstrate reversibility in dogs a recovery period longer than 28 days is required given that the total spermatogenesis cycle in dogs can take over 60 days (Soares 2009). **Clinical** In the Integrated DT Safety Population and the DB phase of Study NIR-DT-301, there were no events within the fertility disorders SMQ (narrow) that were reported in male participants. In the OLE phase of Study NIR-DT-301, a male participant reported 1 event of hypogonadism. This 18-year-old Asian male who transitioned from placebo to nirogacestat 150 mg BID, had a TEAE of hypogonadism reported on Day 603 of nirogacestat treatment. The participant's free testosterone level was normal throughout the OLE phase, except for a single low value of 2.88 pg/mL (normal range: 51.92 to 204.78 pg/mL) on Day 505, which returned to 129.79 on Day 603. No action was taken with nirogacestat treatment, he was treated with transdermal testosterone starting on day 603, and the outcome of this event is still listed as ongoing. The single, very low value of testosterone and free testosterone during nirogacestat treatment (Day 505) was not confirmed by a repeat assay in real time, as would be appropriate given the variability in test results reported for testosterone assays (Herati 2016). One participant in Study NIR-DT-301, who received placebo in the DB phase and received nirogacestat for 256 days in the OLE phase, fathered 2 children after stopping his study participation to start a family. The children were born approximately 1 year and 2 ½ years after his last dose of nirogacestat. There were no complications during both pregnancies and no reported

Important Potential Risk: Adverse Effect on Male Fertility	
	congenital anomalies in either child.
Risk-benefit impact	In view of the seriousness of progressing DT and the need for treatment, the potential risk of an effect on male fertility does not outweigh the benefits of treatment with nirogacestat.

Important Potential Risk: Severe Renal Toxicity	
Scientific evidence for risk to be added in the safety specification	**Non-clinical** In the 3-month dog study there were no treatment-related urinalysis findings or microscopic findings involving the kidney in the dosing or 1-month recovery phases. In the 3-month rat study, findings were elevated urine protein in males and females at ≥20 mg/kg/day, elevated specific gravity along with small amounts of blood in male rats at 50 mg/kg/day, and small to large amounts of blood and formed elements (casts) in the urine of female rats at 50 mg/kg/day. Absolute and relative (kidney/brain) mean kidney weights were increased (1.15x-1.21x control mean) in males at ≥20 mg/kg/day and females at 20 mg/kg/day. Kidney weights remained elevated (1.22x–1.28x control mean) in recovery males and females at 50 mg/kg/day. The elevated weight correlated with the increased incidence of chronic progressive nephropathy (CPN) in both males and females. Microscopic findings in the kidney comprised an increased incidence and severity of CPN in males at ≥5 mg/kg/day and females at ≥20 mg/kg/day, and glomerulonephropathy characterized by expanded mesangial matrix with sporadic deposition of hyaline protein droplets in males and females at ≥20 mg/kg/day. In addition, there were sporadic tubular casts, and the tubular epithelium associated with the casts was foamy and contained hyaline droplets. Changes of CPN were present in recovery males and females at ≥20 mg/kg/day. Males and females at 50 mg/kg/day (primarily those that were found dead or sacrificed moribund) had abundant pigment (strongly positive for iron with Perl's iron stain) within tubular epithelial cells. The pigment was hemoglobin from breakdown of red blood cells in the circulation. **Clinical** In the nirogacestat integrated DT population and the OLE phase of Study NIR-DT-301 there were no TEAEs of chronic kidney disease reported. In the double-blind phase of Study NIR-DT-301, 32 of 69 (46%) participants in the nirogacestat arm and 28 of 72 (39%) participants in the placebo arm had laboratory observations of proteinuria. TEAEs of proteinuria were reported by 1% of participants in the nirogacestat arm and 3% of participants in the placebo arm. In addition, 36 of 69 (52%) participants in the nirogacestat arm and 1 of 72 (1%) participants in the placebo arm had laboratory observations of glycosuria. TEAEs of

Important Potential Risk: Severe Renal Toxicity	
	glycosuria were reported by 6% of participants in the nirogacestat arm and no participants in the placebo arm.
Risk-benefit impact	In view of the seriousness of progressing DT and the need for treatment, a potential risk of severe renal toxicity does not outweigh the benefits of treatment with nirogacestat.

Missing Information
None

AF: Aggressive Fibromatosis; BID: Twice a day; CM: Cancer monotherapy; DILI: Drug induced liver injury; DT: Desmoid tumor; OT: Ovarian toxicity OLE: Open Label extension; WOCBP: Women of child-bearing potential

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Ovarian Toxicity	
Potential mechanisms	Inhibition of the Notch pathway may disrupt ovarian function by interference with angiogenesis and the cell-to-cell signaling needed to support and control luteal development (Woad 2016; Robinson 2009; Vanorny 2017). Nirogacestat inhibits Notch signaling which may therefore result in OT.
Evidence source(s) and strength of evidence	**Non-clinical** Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study and multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study. **Clinical** In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo.
Characterization of risk: Frequency	**Clinical** Given prior studies did not collect information from investigators concerning childbearing status or measure reproductive hormone levels, the focus of this discussion of OT is based upon data from Study 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 lab abnormality). OT was reported to resolve in WOCBP both while continuing nirogacestat and after stopping nirogacestat. Ovarian toxicity has been reported to resolve in 79% of women of childbearing potential during treatment and in all women who discontinued nirogacestat for any reason and for whom follow-up information is available (2 patients lost to follow up). Of the 27 WOCBP who reported OT, 20 (74%) were reported in women < 34 years of age. The large majority (23/27; 85%) of WOCBP with reported OT events were either refractory to prior therapy or had recurrent disease while only 4 (15%) were treatment naïve. Geographical location, race or ethnicity did not influence the incidence of OT in nirogacestat treated patients. The median time to first onset of ovarian toxicity was 8.9 weeks (1 day to 54 weeks), and the overall median duration was 18.9 weeks (11 days to 215 weeks). The median time to resolution after discontinuing nirogacestat was 10.9 weeks (4 to 18 weeks). Among the 27 WOCBP who reported an event of OT, only 4 received a hormonal contraceptive (n = 3), an anticonvulsant (n = 1), and/or a selective

Important Identified Risk: Ovarian Toxicity	
	serotonin-norepinephrine reuptake inhibitor (n = 1) to manage symptoms of their OT.
Seriousness	OT events were reported as serious due to investigator assessment as medically important in 4 WOCBP in the nirogacestat arm and none in the placebo group. This included 3 events of premature menopause and one event of ovarian failure (representing 11% of all participants reporting ovarian toxicity); all were reported as serious due to investigator assessment as medically important SAEs prior to the implementation of Study NIR-DT-301 Protocol Amendment 3.
Severity	All events were Grade 1 or 2 in severity.
Risk factors and risk groups	A logistic regression analysis of OT in WOCBP who received nirogacestat found no apparent risk factors in the development of OT. The extent of ovarian reserve prior to exposure to nirogacestat may theoretically impact the potential for reversibility of OT, with those with lower reserve being less likely to experience reversibility of OT. Older patients or patients who have had prior therapy with drugs affecting ovarian function are likely to have lower reserves.
Preventability	There is no known method to prevent OT in WOCBP who are treated with nirogacestat. The risk of OT should be discussed with patients who are WOCBP prior to prescribing nirogacestat. Product labeling includes advice that WOCBP should be advised about the risk of ovarian toxicity before initiating treatment with nirogacestat.
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, the risk of OT does not outweigh the benefits of treatment with nirogacestat. Further characterization of this risk will include the additional pharmacovigilance activity of Study NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF).
Public health impact	There is no significant public health impact of OT associated with use of nirogacestat.

AF: Aggressive fibromatosis; BID: Twice a day; CM: Cancer monotherapy; DT: Desmoid tumor; OT: Ovarian Toxicity OLE: Open Label extension; PT: Preferred Term; WOCBP: Women of child-bearing potential

Important Identified Risk: Non-Melanoma Skin Cancers	
Potential mechanisms	Notch plays a crucial role in maintaining the homeostasis of cutaneous epithelial cells (Nowell 2013) by regulating and maintaining skin homeostasis, orchestrating keratinocyte differentiation at the level of inter-follicular epidermis and hair follicles, and finally working in epithelial barrier formation (Condorelli 2021). Notch signaling also affects inflammatory processes in the skin. Loss of Notch activity leads to release of the proinflammatory cytokine thymic stromal lymphopoietin, which results in chronic inflammation, a condition related to atopic dermatitis (Siebel 2017).
Evidence source(s) and strength of evidence	In the double-blind phase of Study NIR-DT-301, among participants who received nirogacestat, 2 participants (3%) in the nirogacestat 150 mg BID arm reported non-melanoma skin cancer events. One of these participants also reported a second event of BCC in close temporal relationship to the report of SCC. No participants who were given placebo reported a non-melanoma skin cancer. In the on-going open-label extension phase of Study NIR-DT-301, a report of BCC has been received after the closure of the double-blind phase from a participant who had continued into the OLE from the nirogacestat arm. In the ongoing 14-C-0007 Study, 1 (6%) report of SCC has been received. In the ongoing Study (NIR-OGT-201), a phase 2 trial of nirogacestat in patients with recurrent ovarian granulosa cell tumors, 1 report of SCC has been received. An additional report of BCC has been received from a partner study. Of note, there are no reports of malignant melanoma from participants in the nirogacestat development program. No participants reporting a non-melanoma skin cancer have reported the development of a second skin cancer during their follow-up period as of the data cut-off date for this summary of safety. Review of the details of each report show that each reporting participant had confounding factors for the development of non-melanoma skin cancers such as age older than 60, fair skin, or a history of sunburns or sunbathing without the use of sunblock. An increased occurrence of non-melanoma skin cancers has also been observed in clinical trials with the gamma-secretase inhibitors semagacestat and avagacestat (Doody 2013; Henley 2014; Coric 2012).
Characterization of risk: Frequency	The observed incidence of SCC of the skin in the Primary Analysis Population is 3% for the duration of the study, which had a median duration of exposure for the nirogacestat 150 mg BID arm of 20.6 months (compared to 11.4 months for the placebo arm). The exposure adjusted incidence rate for SCC of the skin for the nirogacestat 150 mg BID arm in the Primary Analysis Population is 0.02 participants with the event per patient-year and the EAER is 0.02 events per patient-year.
Seriousness	One (1) of the four (4) reports of non-melanoma skin cancers was a serious adverse event (from Study 14-C-0007).
Severity	One event of BCC was Grade 3 (from NIR-DT-301 OLE); all other reported non-melanoma skin cancer events were Grade 2.
Risk factors and risk groups	The primary risk factor common to development of both BCC and SCC is cumulative ultraviolet (UV) exposure from sunlight or tanning beds, which leads to UV-induced alterations in skin protein expression. Increased age is also a risk factor, likely due to increased accumulation of UV exposure. The other most common risk factor is Fitzpatrick skin types I and II, which are

Important Identified Risk: Non-Melanoma Skin Cancers	
	characterized by light skin which burns easily. There does not appear to be a strong link between *APC* loss of function mutations and SCC or BCC (Niu 2020). Immunosuppression is also an important risk factor for the development of cutaneous malignancies.
Preventability	It is commonly known that non-melanoma skin cancers can be prevented by avoiding prolonged exposure to the sun, or by using protective clothing or sunblock or sunscreen. Early detection of SCC, with subsequent excision, can reduce the risk of metastasis. The product label includes advice that skin examinations should be performed prior to initiation of nirogacestat and routinely during treatment with nirogacestat.
Impact on the risk-benefit balance of the product	In view of the seriousness of DT and the need for treatment, the results from the clinical development program to date do not suggest that the identified risk of non-melanoma skin cancers would outweigh the benefits of treatment with nirogacestat, particularly since non-melanoma skin cancers can be readily diagnosed and managed with regular skin examinations and excision of observed lesions.
Public health impact	There is no significant public health impact of non-melanoma skin cancers associated with use of nirogacestat.

Important Identified Risk: Bone fracture	
Potential mechanisms	Gamma-secretase inhibition associated with nirogacestat administration has been recognized to affect ovarian function and proximal renal tubule function. Hypophosphatemia is also a recognized risk for nirogacestat, as is diarrhoea (which may contribute to hypophosphatemia). Prolonged decreased oestrogen levels (Recker 2000), and prolonged hypophosphatemia (Aljuraibah 2022), may contribute to a decrease in bone mineralization, which may decrease bone strength and increase the risk for bone fracture.

Important Identified Risk: Bone fracture	
Evidence source(s) and strength of evidence	Non-clinical toxicology studies did not observe decreased bone mineralization in the animal species tested in the timeframes studied. In Study NIR-DT-301, 20 (29%) participants had abnormal low phosphate values that consecutively spanned 90 days or more. None of these participants reported a bone fracture. In Study NIR-DT-301 the mean and median estradiol values in the nirogacestat arm of the DB phase decreased at Cycle 2, Day 28, but showed a return towards the baseline range from Cycle 7, Day 1, onwards. A decrease in oestrogen for a few months is unlikely to have a clinically meaningful effect on bone strength since a longitudinal study found little change in bone mineral density or bone strength index in the first 2 years after natural menopause (Ahlborg 2003). In Study NIR-DT-301, numerically more participants reported a bone fracture in the nirogacestat arm than in the placebo arm (4 [6%] and 0, respectively). The fractures were reported on treatment days 1, 86, 163, and after 2 years of treatment respectively. All reports of fracture were from post-menopausal females ≥50 years of age. The participant who reported a fracture after 2 years of treatment did not have abnormal low phosphate values at any time during the study prior to her fracture, but she had low oestradiol values throughout the study, including at baseline. The smaller number of participants in the Study NIR-DT-301 placebo arm treated for ≥12 months (34 [47%]) or ≥24 months (8 [11%]) compared with those in the nirogacestat arm treated for ≥12 months (45 [65%]) or ≥24 months (19 [28%]) limits the ability of the 2 arms to detect late-onset events.
Characterization of risk: Frequency	There were 4 participants (6%) in the nirogacestat arm of Study NIR-DT-301 who reported a bone fracture, compared to none in the placebo arm (0%).
Seriousness	None of the reports of bone fracture in the DB phase of Study NIR-DT-301 were serious.
Severity	None of the reports of bone fracture in the DB phase of Study NIR-DT-301 were Grade ≥3.
Risk factors and risk groups	All reports of bone fracture were from post-menopausal females ≥50 years of age.
Preventability	Calcium and vitamin D supplementation are frequently recommended to prevent osteoporosis and bone fracture in post-menopausal women.
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, the risk of bone fracture does not outweigh the benefits of treatment with nirogacestat.
Public health impact	There is no significant public health impact of bone fracture associated with the use of nirogacestat.

Important Potential Risk: Epiphyseal Disorder with Off-label Use in the Pediatric Population with Open Growth Plates	
Potential mechanisms	Notch inhibition has an inhibitory effect on angiogenesis which results in growth plate changes. In adults, growth plates are closed. However, in pediatric patients with open growth plates, this may have an adverse effect on epiphyseal development.
Evidence source(s) and strength of evidence	Increased retention of the hypertrophic zone of the growth plate and articular cartilage was seen in the sternum and stifle joints of rats given nirogacestat in the 1-month and 3-month studies. This change was characterized by minimal-to-moderate thickening of the hypertrophic zone in the cartilage with pallor and slight vacuolation of the osteocytes in the primary spongiosa. Four cases involving pediatric patients from the ongoing pediatric clinical Study ARST1921, and the nirogacestat compassionate use program, (PTs of Epiphysiolysis, Hip fracture, Epiphyseal disorder, and Osteonecrosis) provide insufficient information to fully assess the effect of nirogacestat on the growing bones of these children. The cases are few in number, some lack information concerning the radiographic appearance of the growth plates, and each patient had been previously treated with chemotherapeutic agents with a known negative impact on bone development.
Characterization of risk: Frequency	No pediatric patients were included in clinical Study NIR-DT-301. Epiphyseal disorder is only a risk if nirogacestat is administered to pediatric patients with open growth plates. The proposed indication is for the treatment of adult patients with DT.
Seriousness	All four (4) reports were serious.
Severity	Two (2) of the reports were Grade 3.
Risk factors and risk groups	Pediatric patients whose growth plates are not closed are at risk.
Preventability	The product label stipulates that nirogacestat is indicated for the treatment of adult patients and also includes a description of the observations of widening of the epiphyseal growth plate in paediatric patients with open growth plates treated with nirogacestat.
Impact on the risk-benefit balance of the product	As nirogacestat is indicated only in the adult population, the risk-benefit of the product remains positive.
Public health impact	There is no impact on public health.

Important Potential Risk: Embryo-fetal Toxicity	
Potential mechanisms	Gamma-secretase, acting through other substrates in addition to Notch, plays a major role in normal embryonic development (Jurisch-Yaksi 2013). Knock-out mice lacking the presenilin component of gamma-secretase exhibit severely abnormal development of various tissues, consisting of a neuronal migration disorder, midline defects of the body wall and defective somitogenesis (Jurisch-Yaksi 2013).
Evidence source(s) and strength of evidence	In animal reproduction studies, administration of nirogacestat to rats during organogenesis resulted in embryo loss, resorption and decreased fetal weights in surviving embryos, while administration of nirogacestat to rats prior to conception resulted in decreased early embryo-fetal implantation and early embryonic loss. These effects occurred at exposures below those occurring clinically at the recommended dose. Transgenic studies in mice demonstrated that the loss of Notch signaling is embryonically lethal (Donoviel 1999, Swiatek 1994). A publication by (Wang 2023) provides insights into the possible mechanism of action driving the observations of embryo-fetal toxicity in nonclinical studies with nirogacestat. In ovo injection with glycolysis inhibitor or gamma-secretase inhibitor both decreased the hepatic glycolysis level and impaired goose embryonic development. The blockade of Notch signaling was also accompanied by the inhibition of PI3K/Akt signaling in the embryonic primary hepatocytes and embryonic liver. The decreased glycolysis and impaired embryonic growth induced by the blockade of Notch signaling were restored by activation of PI3K/Akt signaling. In a rat embryo-fetal development study with avagacestat, (Sivaraman 2023) found dose-related increased fetal mortality, decreased fetal growth, and increased fetal malformations. Reductions in female fecundity were attributed to impaired ovarian follicular development that was reflected in dose-dependent reductions in implantation sites, litter size, and gravid uterine weights. This article provides support for gamma-secretase inhibition being the mechanism for the observations of embryo-fetal toxicity in non-clinical studies with nirogacestat.
Characterization of risk: Frequency	Studies in pregnant rats noted complete or nearly complete resorptions of litters at doses of 50 and 150 mg/kg/day. There is limited clinical data available to use to estimate the frequency of the occurrence of embryo-fetal toxicity in humans. One participant who was not practicing effective birth control conceived while on nirogacestat. Nirogacestat treatment was discontinued and 33 days later she experienced a spontaneous abortion.
Seriousness	A report of a loss of pregnancy or miscarriage would be considered serious.
Severity	A report of a loss of pregnancy is Grade 4 per CTCAE 5.0.
Risk factors and risk groups	There are no known risk factors that would predispose a pregnant woman to have a loss of pregnancy due to treatment with nirogacestat.
Preventability	Preventing pregnancy by means of contraception is the intervention required to prevent embryo-fetal toxicity and the loss of pregnancy. Product labeling advises that nirogacestat may cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. The pregnancy status of WOCBP should be verified prior to initiating treatment with nirogacestat. WOCBP and men with female partners of childbearing potential should be advised to avoid pregnancy while on nirogacestat. WOCBP must use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of

Important Potential Risk: Embryo-fetal Toxicity	
	nirogacestat. It is unknown whether nirogacestat reduces the effectiveness of systemically acting 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 during treatment with Ogsiveo and for 1 week after the last dose of Ogsiveo. WOCBP should be advised to inform their healthcare provider immediately of a known or suspected pregnancy, and that nirogacestat should not be taken if they are pregnant. Women of childbearing potential should not donate eggs (oocytes) during treatment with nirogacestat and for 1 week after receiving the last dose of nirogacestat. Male patients with female partners of childbearing potential must use highly effective contraceptive methods during treatment with nirogacestat and for 1 week after the last dose of nirogacestat. Male patients should not donate sperm during treatment with nirogacestat and for 1 week after the last dose of nirogacestat. Additional risk minimization materials for this important potential risk include a Healthcare Professional Guide and a Patient Card.
Impact on the risk-benefit balance of the product	With routine risk minimization of labeling advising on the use of contraception and additional risk minimization measures of a Healthcare Professional Guide and Patient Card, the risk-benefit of the product remains positive.
Public health impact	There is no significant public health impact of the embryo-fetal toxicity associated with the use of nirogacestat.

Important Potential Risk: Drug Induced Liver Injury	
Potential mechanisms	Hepatic necrosis observed in dog studies was associated with systemic inflammation due to endotoxemia.
Evidence source(s) and strength of evidence	**Non-clinical:** In the 3-month study with 1-month recovery in dogs, hepatic inflammation and necrosis with associated elevations in liver enzymes were observed at doses ≥10 mg/kg/day. These hepatic findings resolved in the recovery phase. The inflammation was associated with necrosis resulting from endotoxemia originating from the disrupted intestinal mucosal barrier. In the 1-month study in dogs, hepatic inflammation, correlating with disrupted intestinal mucosal barrier, was observed at 80 mg/kg/day. In the 3-month rat study, elevations in ALT, AST, ALP, GGT and total bilirubin were observed in female rats receiving 50 mg/kg/day of nirogacestat. Exclusively in moribund rats or rats found dead at 50 mg/kg/day, microscopic findings consistent with centrilobular hepatic necrosis were observed. At doses ≥20 mg/kg/day, centrilobular hepatocellular hypertrophy was observed. At doses ≥5 mg/kg/day, periportal lipid vacuolation was observed. In the 1-month rat study receiving ≥20 mg/kg/day, hepatic treatment-related changes were observed in the liver consisting of an increase in the incidence and severity of hepatocellular lipid vacuolation in the periportal areas. **Clinical:** In Study NIR-DT-301, there was an increased incidence of elevated transaminases in the nirogacestat 150 mg BID arm compared to the placebo arm, and the time to first onset for most participants reporting an event was during the first 3 cycles. Two participants in the nirogacestat arm reported Grade 3 events. There was no report of DILI.
Characterization of risk: Frequency	In Study NIR-DT-301, 12 participants (17%) in the nirogacestat arm reported 17 events of ALT increased and 6 participants (8%) reported 11 events in the placebo arm. Eleven participants (16%) in the nirogacestat arm reported 16 events of AST increased and 8 participants (11%) reported 12 events in the placebo arm. The majority of participants reporting ALT and AST elevations had their first onset of the event in the first 3 cycles of treatment. There was no report of DILI.
Seriousness	There were no serious DILI events in participants treated with nirogacestat monotherapy.
Severity	In Study NIR-DT-301, of the 12 participants receiving nirogacestat who experienced ALT elevations, 2 experienced Grade 3 events, and the rest were Grade 1 or 2. Of the 8 participants who experienced AST elevations, 2 experienced Grade 3 events and the rest were Grade 1 and 2.
Risk factors and risk groups	None identified.
Preventability	The potential for drug induced liver injury can be managed with labelling which advises that liver function tests should be monitored regularly during treatment with nirogacestat, and that dose interruptions, dose modifications, or treatment discontinuation may be required to manage the risk. With these measures the risk-benefit balance of the product remains positive.

Important Potential Risk: Drug Induced Liver Injury	
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, the potential risk of DILI does not outweigh the benefits of treatment with nirogacestat.
Public health impact	There is no significant public health impact of potential DILI associated with the use of nirogacestat.

Important Potential Risk: Adverse Effect on Female Fertility	
Potential mechanisms	Effects of nirogacestat on female fertility in humans are unknown. An exposure-response relationship was identified between nirogacestat and serum follicular stimulating hormone (FSH) levels, with FSH increasing linearly with increasing serum concentrations of nirogacestat. Inhibition of the Notch pathway may disrupt ovarian function by interference with angiogenesis and the cell-to-cell signaling needed to support and control luteal development (Woad 2016; Robinson 2009; Vanorny 2017). Nirogacestat inhibits Notch signaling which may therefore result in OT. Disruption of the luteal cycle may impair female fertility while the woman is taking nirogacestat. Disruption of the luteal cycle should cease after stopping nirogacestat.
Evidence source(s) and strength of evidence	**Non-clinical** Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study. Multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study. In the rat reproductive toxicity study, of the 22 female rats in each of the 20 and 40 mg/kg/day groups, there were 18 (82%) and 22 (100%), respectively, that were determined to not be pregnant compared to 3 of the 22 (14%) females in the control group. No test material-related effects were noted on female reproductive performance (mating, fertility, or pregnancy) in the 5 mg/kg/day group. All females in this group had evidence of mating and were pregnant. **Clinical** Anti-Mullerian hormone (AMH), which is produced by developing ovarian follicles and is considered to be a marker of ovarian reserve, was decreased in women of childbearing potential while receiving nirogacestat (reflecting the interference with follicular development) and mean values were returning toward baseline at the final follow-up visit in the double-blind phase and OLE of Study NIR-DT-301. In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo. One female participant in Study NIR-DT-301 reported a pregnancy while receiving nirogacestat, although the pregnancy ended in a spontaneous abortion. As of 25Nov2024, 2 post-marketing events of women who became pregnant after being prescribed nirogacestat have been reported to SpringWorks: one approximately 1 month, and the other approximately 5 months after stopping nirogacestat. The outcomes of these pregnancies are not yet known. As of 25Nov2024, 1 event has been reported to SpringWorks Pharmacovigilance of a participant who received nirogacestat in Study NIR-DT-301 and who conceived approximately 2 years after stopping nirogacestat to start a family. The outcome of this pregnancy is not yet known.

Important Potential Risk: Adverse Effect on Female Fertility	
Characterization of risk: Frequency	Data are not available to estimate the frequency of infertility in women of childbearing potential being treated with nirogacestat, although the 75% who reported ovarian toxicity in the double-blind-phase of Study NIR-DT-301 may serve as a conservative proxy for the upper limit. An estimate of the frequency of fertility effects is precluded by the protocol instruction to use effective contraception continuously prior to the first nirogacestat dose and through the drug washout after permanent discontinuation. Of the 63 women of childbearing potential treated with nirogacestat in either the double-blind phase or OLE of Study NIR-DT-301, 1 (1.6%) reported a pregnancy while receiving nirogacestat, which along with the 2 post-marketing reports of pregnancy in women receiving nirogacestat, indicates that infertility does not occur in all women receiving nirogacestat. Data are also not available to estimate the frequency of infertility in women of childbearing potential who desire to become pregnant after stopping treatment with nirogacestat. The 3 reports of pregnancies in women who had stopped taking nirogacestat suggests that any effect on fertility that may occur while receiving nirogacestat does not persist after inhibition of gamma-secretase is no longer present. The return toward normal values for AMH after stopping nirogacestat suggests there is not a sustained marked effect on ovarian reserve associated with nirogacestat treatment.
Seriousness	Not applicable
Severity	Not applicable
Risk factors and risk groups	Women of childbearing potential are the only group that is at risk for effect on female fertility.
Preventability	Any risk for an effect on female fertility can only be prevented by choosing not to take nirogacestat. A decision to store oocytes prior to starting nirogacestat can mitigate the impact of the risk.
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, the potential risk of an adverse effect on female fertility does not outweigh the benefits of treatment with nirogacestat. Further characterization of this potential risk will include the additional pharmacovigilance activity of Study NIR-DT-401: A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF).
Public health impact	There is no significant public health impact of a potential risk for an effect on female fertility associated with use of nirogacestat.

Important Potential Risk: Adverse Effect on Male Fertility	
Potential mechanisms	Gamma-secretase inhibition by N-S-phenyl-glycine-t-butyl ester (DAPT) in an adult CD1 mouse model found that in vivo Notch blockade disrupted expression patterns of Notch components in the testis, increased germ cell apoptosis (mainly in the last stages of the spermatogenic cycle), and increased morphological defects in spermatozoa in the epididymis. Plasma testosterone concentrations were not affected by DAPT treatment (Murta 2014).

Important Potential Risk: Adverse Effect on Male Fertility	
Evidence source(s) and strength of evidence	**Nonclinical** No effect on male mating indices was noted at any dose of nirogacestat tested. Decreases in epididymis and testes weights were noted in rats in the fertility and early embryonic development toxicology study. No changes in testes weights were noted in dogs or rats in either the 1- or 3-month pivotal toxicology studies. Changes in sperm motility and morphology were noted in rats at doses ≥20 mg/kg/day. These changes in sperm in rats did not lead to embryotoxicity, but rather decreased fertility while on treatment. In the 1- and 3-month repeat-dose rat studies, there were no microscopic changes in the testes at doses as high as 50 mg/kg/day. Therefore, these effects appear to be limited to spermatogenesis with a low severity that did not induce microscopic changes in rats. It is unknown if these effects occur in humans. Microscopic findings of vacuolation of Sertoli cells were noted in the 10- to 11-month-old peripubertal beagle dogs used in the 3-month dog study. However, the relationship to treatment of this finding is unclear since similar findings have been described in peripubertal dogs (Goedken 2008). In addition, to demonstrate reversibility in dogs, a recovery period longer than 28 days is required given that the total spermatogenesis cycle in dogs can take over 60 days (Soares 2009). **Clinical** In the Integrated DT Safety Population and the DB phase of Study NIR-DT-301, there were no events within the Fertility disorders Standardised MedDRA Query (SMQ) (narrow) that were reported in male participants. In the OLE phase of Study NIR-DT-301, a male participant reported 1 event of hypogonadism; This 18-year-old Asian male who transitioned from placebo to nirogacestat 150 mg BID, had a TEAE of hypogonadism reported on Day 603 of nirogacestat treatment. The participant's free testosterone level was normal throughout the OLE phase, except for a single low value of 2.88 pg/mL (normal range: 51.92 to 204.78 pg/mL) on Day 505, which returned to 129.79 on Day 603. No action was taken with nirogacestat treatment, he was treated with transdermal testosterone starting on day 603, and the outcome of this event is still listed as ongoing. The single, very low, value of testosterone and free testosterone during nirogacestat treatment (Day 505) was not confirmed by a repeat assay in real time, as would be appropriate given the variability in test results reported for testosterone assays (Herati 2016). A participant in Study NIR-DT-301, who received placebo in the DB phase and received nirogacestat for 256 days in the OLE phase, fathered 2 children after stopping his study participation to start a family. The children were born approximately 1 year and 2½ years after his last dose of nirogacestat. There were no complications during both pregnancies and no reported congenital anomalies in either child.

Important Potential Risk: Adverse Effect on Male Fertility	
Characterization of risk: Frequency	Of the 25 males exposed to nirogacestat in the Study NIR-DT-301 double-blind phase, and the 13 males newly exposed to nirogacestat in the OLE, 1 (3%) participant reported an event associated with an effect on the testes; Grade 1 hypogonadism, based on a single, unconfirmed abnormal low testosterone value. Data are limited to estimate the frequency of infertility in men who desire to father a child after stopping treatment with nirogacestat. Of the total 38 males exposed to nirogacestat in Study NIR-DT-301, 1 (3%) has reported fathering children after stopping nirogacestat.
Seriousness	There were no reports of infertility in men in the clinical trial database. The event of hypogonadism was non-serious Grade 1.
Severity	There were no reports of infertility in men in the clinical trial database. The event of hypogonadism was non-serious Grade 1.
Risk factors and risk groups	Men are the only group that is at risk for effect on male fertility. Since there were no reports of infertility in men in the clinical trial database, no additional insights are available concerning additional risk factors for this potential risk. The single report of unconfirmed hypogonadism in a male does not provide sufficient data to draw inferences concerning risk factors.
Preventability	Any risk for an effect on male fertility can only be prevented by choosing not to take nirogacestat. A decision to store sperm prior to starting nirogacestat can mitigate the impact of the risk.
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, the potential risk of an effect on male fertility does not outweigh the benefits of treatment with nirogacestat.
Public health impact	There is no significant public health impact of a potential risk of an effect on male fertility associated with use of nirogacestat.

Important Potential Risk: Severe Renal Toxicity	
Potential mechanisms	Nirogacestat affects some proximal renal tubule transporters. Clinical manifestations include glycosuria and proteinuria, but not excess excretion of low molecular weight proteins or acute changes in laboratory markers of renal function. All instances of shifts in laboratory values of proteinuria in participants in the nirogacestat arm of Study NIR-DT-301 were Grade 1 (≥ upper limit of normal but <1.0 g/24 hr, per CTCAE v5.0), which is unlikely to lead to severe renal toxicity according to observations in the Ramipril Efficacy In Nephropathy (REIN) study, in which patients with a baseline urinary protein excretion rate ≤1.9 g/24 hr had a rate of glomerular filtration rate (GFR) decline to kidney failure of 4.3% over 3 years of follow-up, compared to 15.7% in patients with protein excretion of 2.0 to 3.8 g/24 hr, and 32.5% in patients with protein excretion of ≥3.9 g/24 hr (Ruggenenti 1998).
Evidence source(s) and strength of evidence	**Non-clinical** In the 3-month dog study there were no treatment-related urinalysis findings or microscopic findings involving the kidney in the dosing or 1-month recovery phases. In the 3-month rat study, findings were elevated urine protein in males and females at ≥20 mg/kg/day, elevated specific gravity along with small amounts of blood in male rats at 50 mg/kg/day, and small to large amounts of blood and formed elements (casts) in the urine of female rats at 50 mg/kg/day. Absolute and relative (kidney/brain) mean kidney weights were increased (1.15x to 1.21x control mean) in males at ≥20 mg/kg/day and females at 20 mg/kg/day. Kidney weights remained elevated (1.22x to 1.28x control mean) in recovery males and females at 50 mg/kg/day. The elevated weight correlated with the increased incidence of chronic progressive nephropathy (CPN) in both males and females. Microscopic findings in the kidney comprised an increased incidence and severity of CPN in males at ≥5 mg/kg/day and females at ≥20 mg/kg/day, and glomerulonephropathy characterized by expanded mesangial matrix with sporadic deposition of hyaline protein droplets in males and females at ≥20 mg/kg/day. In addition, there were sporadic tubular casts and the tubular epithelium associated with the casts was foamy and contained hyaline droplets. Changes of CPN were present in recovery males and females at ≥20 mg/kg/day. Males and females at 50 mg/kg/day (primarily those that were found dead or sacrificed moribund) had abundant pigment (strongly positive for iron with Perl's iron stain) within tubular epithelial cells. The pigment was hemoglobin from breakdown of red blood cells in the circulation. **Clinical** In the nirogacestat integrated DT population and the OLE phase of Study NIR-DT-301, there were no TEAEs of chronic kidney disease reported. In the double-blind phase of Study NIR-DT-301, 32 of 69 (46%) participants in the nirogacestat arm and 28 of 72 (39%) participants in the placebo arm had laboratory observations of proteinuria. TEAEs of proteinuria were reported by 1% of participants in the nirogacestat arm and 3% of participants in the placebo arm. In addition, 36 of 69 (52%) participants in the nirogacestat arm and 1 of 72 (1%) participants in the placebo arm had laboratory observations of glycosuria. TEAEs of glycosuria were reported by 6% of participants in the nirogacestat arm and no participants in the placebo arm.

Important Potential Risk: Severe Renal Toxicity	
Characterization of risk:	In the nirogacestat integrated DT population and the OLE phase of Study NIR-DT-301, there were no TEAEs of chronic kidney disease reported.
Frequency	In the double-blind phase of Study NIR-DT-301, 32 of 69 (46%) participants in the nirogacestat arm and 28 of 72 (39%) participants in the placebo had laboratory observations of proteinuria. TEAEs of proteinuria were reported by 1% of participants in the nirogacestat arm and 3% of participants in the placebo arm. In addition, 36 of 69 (52%) participants in the nirogacestat arm and 1 of 72 (1%) participants in the placebo arm had laboratory observations of glycosuria. TEAEs of glycosuria were reported by 6% of participants in the nirogacestat arm and no participants in the placebo arm.
Seriousness	In the nirogacestat integrated DT population and the OLE phase of Study NIR-DT-301, there were no SAEs of glycosuria, proteinuria, or chronic kidney disease.
Severity	CTCAE v5.0 grades the presence of any glycosuria as Grade 1, with no other grades. CTCAE v5.0 grades proteinuria according to both a qualitative scale and quantitative excretion of protein per 24 hours. Grade 1 is 1+ proteinuria or ≥ULN to <1.0 g protein/24 hours; Grade 2 is 2+ and 3+ proteinuria or 1.0 to <3.5 g protein/24 hours; Grade 3 is 4+ proteinuria or ≥3.5 g protein/24 hours; there are no criteria for Grades 4 or 5. In the Study NIR-DT-301 double-blind and OLE phases, all instances of observed glycosuria were Grade 1. In the Study NIR-DT-301 double-blind and OLE phases, all instances of observed proteinuria were Grade 1, except for 4 observed Grade 2 values in the OLE phase.
Risk factors and risk groups	Given there are no reports of chronic kidney disease in the nirogacestat clinical trial data, there are no known risk factors or contributing factors.
Preventability	In view of the absence of known risk factors or contributing factors, the only available method of preventing the occurrence of this important potential risk would be to reduce the dose or discontinue nirogacestat upon the observation of glycosuria or proteinuria. There are no data to inform the value of either dose modification since no reported events of glycosuria or proteinuria led to dose modification. In addition, there is little increased risk of severe renal toxicity to prevent since the level of proteinuria present in the nirogacestat data was not associated with increased risk of progression to decreased GFR and renal failure in the REIN study (Ruggenenti 1998).
Impact on the risk-benefit balance of the product	In view of the seriousness of progressing DT and the need for treatment, a potential risk of severe renal toxicity does not outweigh the benefits of treatment with nirogacestat.
Public health impact	There is no significant public health impact of a potential risk of severe renal toxicity associated with use of nirogacestat.

SVII.3.2. Presentation of the missing information

Missing information
None

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1 Summary 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

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities consisting of adverse reaction collection and reporting, and signal detection, will be employed as per all appropriate local pharmacovigilance requirements.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for ovarian toxicity: A list of questions specific to OT will be used by Pharmacovigilance to collect information on each report of ovarian toxicity. See Annex 4 for the specific follow-up questions that will be used.

Pharmacovigilance follow-up for embryo-fetal toxicity: A list of questions specific to pregnancy exposures, including the failures of risk minimization measures leading to the pregnancy, will be used by Pharmacovigilance to collect information on each report, and to support the evaluation of the effectiveness of the risk minimization measures. See Annex 4 for the specific follow-up questions that will be used.

Other forms of routine pharmacovigilance activities

Not applicable

III.2 Additional pharmacovigilance activities

To address the Important Identified Risks of ovarian toxicity, bone fracture and the Important Potential Risk of the adverse effect on female fertility, SpringWorks plans to conduct a Category 3 Phase 4 prospective, open label, single arm, interventional clinical trial to evaluate the incidence and ovarian function recovery rates in post-pubertal and premenopausal females with desmoid tumors treated with nirogacestat (Study NIR-DT-401). This study was developed in response to the post-marketing requirements from the United States Food and Drug Administration (FDA) to further characterize onset and resolution of ovarian toxicity in adult premenopausal females with DT. This study has been agreed with the FDA with the final protocol submitted to the FDA in Oct 2024.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1 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	To determine the ovarian function	Ovarian toxicity	Study initiation	31 Dec 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A Single-arm, Open-label Phase 4 Study of Nirogacestat in Adult Premenopausal Females with Desmoid Tumors/Aggressive Fibromatosis (DT/AF)	recovery rate of OT events in post-pubertal and premenopausal females treated with nirogacestat for at least 12 cycles	Adverse effect on female fertility Bone fracture	Database lock	31 Dec 2030
			Final Clinical Study Report	31 Dec 2031

Part IV: Plans for post-authorization efficacy studies

Table Part IV.1 Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations.

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
	None			
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
	None			

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

V.1. Routine Risk Minimization Measures

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Ovarian Toxicity (Important identified risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.6 (Fertility, pregnancy and lactation) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Non-melanoma skin cancers (Important identified risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Bone fracture (Important identified risk)	Routine risk communication: SmPC Section 4.8 (Undesirable effects) Package leaflet Section 4 (Possible side effects) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product

Safety Concern	Routine Risk Minimization Activities
	Information: None
Epiphyseal disorder with off label-use in the pediatric population with open growth plates (Important potential risk)	Routine risk communication: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.8 (Undesirable effects) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Routine risk minimization activities recommending specific clinical measures to address the risk: Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Embryo-fetal toxicity (Important potential risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: 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) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Drug induced liver injury (Important potential risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet Section 2 (What you need to know before you take

Safety Concern	Routine Risk Minimization Activities
	Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Adverse effect on female fertility (Important potential risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Adverse effect on male fertility (Important potential risk)	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Severe renal toxicity (Important potential risk)	Routine risk communication: SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 4 (Possible side effects) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

SmPC: Summary of product characteristics

V.2. Additional Risk Minimization Measures

Table Part V.2. Additional Risk Minimization Measures

Additional Measure	Objective Safety Concern	Rationale	Target Audience	Plans to Evaluate Effectiveness
Healthcare Professional (HCP) Guide Patient Card	Embryo-fetal toxicity	Minimize in utero exposure to nirogacestat and the subsequent potential risk of embryo-fetal toxicity	Healthcare professionals Male and female patients	Periodic Safety Update Report (PSUR) evaluation of the following: Pregnancy reports (failures of risk minimization) Gap analysis of risk minimization measure failures Review of pregnancy outcomes

Healthcare Professional Guide

Objective

The objective of this additional risk minimization activity is to prevent pregnancy in patients who are taking nirogacestat, and in partners of male patients who are taking nirogacestat. This will be accomplished by informing HCPs about the Key Risk Minimization Messages for the Important Potential Risk of embryo-fetal toxicity (see Annex 6) and encourage the reporting of nirogacestat pregnancy exposures to SpringWorks via local routine pharmacovigilance systems.

Rationale for additional risk minimization activity

In animal reproduction studies, administration of nirogacestat to rats during organogenesis resulted in embryo loss, resorption and decreased fetal weights in surviving embryos, while administration of nirogacestat to rats prior to conception resulted in decreased early embryo-fetal implantation and early embryonic loss.

Target audience and planned distribution path

The target audience is healthcare professionals in specialist centers which treat patients with desmoid tumors. The distribution path of the Healthcare Professional Guide will be determined and agreed with the relevant National Competent Authorities.

Patient Card

Objective

The objective of this additional risk minimization activity is to prevent pregnancy in female patients who are taking nirogacestat and in female partners of male patients who are taking nirogacestat. This will be accomplished by informing patients about the key risk minimization elements for the Important Potential Risk of embryo-fetal toxicity (see Annex 6) and encourage the reporting of nirogacestat pregnancy exposures to SpringWorks via local routine pharmacovigilance systems.

Rationale for additional risk minimization activity

In animal reproduction studies, administration of nirogacestat to rats during organogenesis resulted in embryo loss, resorption, and decreased fetal weights in surviving embryos, while administration of nirogacestat to rats prior to conception resulted in decreased early embryo-fetal implantation and early embryonic loss.

Target audience and planned distribution path

The target audience will be female patients of childbearing potential or male patients with a female partner of childbearing potential who are commencing treatment with nirogacestat for desmoid tumors. The Patient Card will be provided to the patient via the Healthcare Professional.

HCP Guide and Patient Card plans to assess the effectiveness of the interventions and criteria for success.

Healthcare Professionals and patients will be encouraged to report any occurrence of pregnancy to SpringWorks Pharmacovigilance Department. Whilst in an ideal world, no reports of pregnancy should be received, realistically it is recognized that this may not be achievable. In the event that a pregnancy is reported, a targeted follow up questionnaire will be utilized to determine the root cause of the failure of the risk minimization activity in addition to following the pregnancy until outcome. The root cause investigation will determine the following:

- Whether the patient received the Patient Card
- Whether the patient understood the content of the Patient Card
- Method of contraception practiced
- Reason for contraception failure

V.3. Summary of Risk Minimization Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ovarian toxicity (Important identified risk)	**Routine risk minimization measures**: 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	**Routine pharmacovigilance 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,

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		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 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
Embryo-fetal toxicity (Important potential risk)	**Routine risk minimization measures:** SmPC Section 4.4 (Special warnings	**Routine pharmacovigilance**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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	**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 Fibromatosis (DT/AF)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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

Part VI: Summary of the risk management plan

Summary of the risk management plan for Ogsiveo

This is a summary of the risk management plan (RMP) for Ogsiveo. The RMP details important risks of Ogsiveo, how these risks can be minimized, and how more information will be obtained about Ogsiveo's risks and uncertainties (missing information).

Ogsiveo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ogsiveo should be used.

This summary of the RMP for Ogsiveo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ogsiveo RMP.

I. The medicine and what it is used for

Ogsiveo is authorized for the treatment of adult patients with Desmoid Tumors.

It contains nirogacestat (as nirogacestat dihydrobromide) as the active substances and it is taken by mouth.

Further information about the evaluation of Ogsiveo's benefits can be found in the Ogsiveo EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ogsiveo, together with measures to minimize such risks and the proposed studies for learning more about the risks associated with Ogsiveo, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Ogsiveo is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of Ogsiveo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ogsiveo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

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 Embryo-fetal toxicity Drug induced liver injury Severe renal toxicity Adverse effect on female fertility Adverse effect on male fertility
Missing information	None

II.B Summary of important risks

Important Identified Risk: Ovarian Toxicity	
Evidence for linking the risk	**Non-clinical**

Important Identified Risk: Ovarian Toxicity	
to the medicine	Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study and multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study. **Clinical** In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo. OT was reported to resolve in WOCBP both while continuing nirogacestat and after stopping nirogacestat. Ovarian toxicity has been reported to resolve in 79% of women of childbearing potential during treatment and in 100% of women who discontinued nirogacestat for any reason and for whom follow-up information is available (2 patients lost to follow up).
Risk factors and risk groups	A logistic regression analysis of OT in WOCBP who received nirogacestat found no apparent risk factors in the development of OT. The extent of ovarian reserve prior to exposure to nirogacestat may theoretically impact the potential for reversibility of OT, with those with lower reserve being less likely to experience reversibility of OT. Older patients or patients who have had prior therapy with drugs affecting ovarian function are likely to have lower reserves.

Important Identified Risk: Ovarian Toxicity	
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.6 (Fertility, pregnancy and lactation) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None
Additional pharmacovigilance activity	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)

Important Identified Risk: Non-melanoma Skin Cancers	
Evidence for linking the risk to the medicine	In the double-blind phase of Study NIR-DT-301, among participants who received nirogacestat, 2 participants (3%) in the nirogacestat 150 mg BID arm reported non-melanoma skin cancer events. One of these participants also reported a second event of BCC of the skin in close temporal relationship to the report of SCC. No participants who were given placebo reported a non-melanoma skin cancer. In the on-going open-label extension phase of Study NIR-DT-301, a report of BCC has been received after the closure of the double-blind phase from a participant who had continued into the OLE from the nirogacestat arm. In the ongoing 14-C-0007 Study, 1 (6%) report of SCC has been received. In the ongoing Study (NIR-OGT-201), a phase 2 trial of nirogacestat in patients with recurrent ovarian granulosa cell tumors, 1 report of SCC has been received. An additional report of BCC has been received from a partner study. Of note, there are no reports of malignant melanoma from participants in the nirogacestat development program. No participants reporting a non-melanoma skin cancer have reported the development of a second skin cancer during their follow-up period as of the data cut-off date for this summary of safety. Review of the details of each report show that each reporting participant had confounding factors for the development of non-melanoma skin cancers such as age older than 60, fair skin, or a history of sunburns or sunbathing without the use of sunblock.

Important Identified Risk: Non-melanoma Skin Cancers	
	An increased occurrence of non-melanoma skin cancers has been observed in clinical trials with the gamma-secretase inhibitors semagacestat and avagacestat (Doody 2013, Henley 2014, Coric 2012).
Risk factors and risk groups	The primary risk factor common to development of both BCC and SCC is cumulative ultraviolet (UV) exposure from sunlight or tanning beds, which leads to UV-induced alterations in skin protein expression. Increased age is also a risk factor, likely due to increased accumulation of UV exposure. The other most common risk factor is Fitzpatrick skin types I and II, which are characterized by light skin which burns easily. There does not appear to be a strong link between APC loss of function mutations and SCC or BCC (Niu 2020). Immunosuppression is also an important risk factor for the development of cutaneous malignancies.
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None

Important Identified Risk: Bone fracture	
Evidence for linking the risk to the medicine	Non-clinical toxicology studies did not observe decreased bone mineralization in the animal species tested in the timeframes studied. In Study NIR-DT-301, 20 (29%) participants had abnormal low phosphate values that consecutively spanned 90 days or more. None of these participants reported a bone fracture. In Study NIR-DT-301 the mean and median estradiol values in the nirogacestat arm of the DB phase decreased at Cycle 2, Day 28, but showed a return towards the baseline range from Cycle 7, Day 1, onwards. A decrease in oestrogen for a few months is unlikely to have a clinically meaningful effect on bone strength since a longitudinal study found little change in bone mineral density or bone strength index in the first 2 years after natural menopause (Ahlborg 2003).

Important Identified Risk: Bone fracture	
	In Study NIR-DT-301, numerically more participants reported a bone fracture in the nirogacestat arm than in the placebo arm (4 [6%] and 0, respectively). The fractures were reported on treatment days 1, 86, 163, and after 2 years of treatment respectively. All reports of fracture were from post-menopausal females ≥50 years of age. The participant who reported a fracture after 2 years of treatment did not have abnormal low phosphate values at any time during the study prior to her fracture, but she had low oestradiol values throughout the study, including at baseline. The smaller number of participants in the Study NIR-DT-301 placebo arm treated for ≥12 months (34 [47%]) or ≥24 months (8 [11%]) compared with those in the nirogacestat arm treated for ≥12 months (45 [65%]) or ≥24 months (19 [28%]) limits the ability of the 2 arms to detect late-onset events.
Risk factors and risk groups	All reports of bone fracture were from post-menopausal females ≥50 years of age.
Risk minimization measures	Routine risk communication: SmPC Section 4.8 (Undesirable effects) Package leaflet Section 4 (Possible side effects) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Additional pharmacovigilance activity	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)

Important Potential Risk: Epiphyseal Disorder with Off-label Use in the Pediatric Population with Open Growth Plates	
Evidence for linking the risk to the medicine	Increased retention of the hypertrophic zone of the growth plate and articular cartilage was seen in the sternum and stifle joints of rats given nirogacestat in the 1-month and 3-month studies. This change was characterized by minimal-to-moderate thickening of the hypertrophic zone in the cartilage with pallor and slight vacuolation of the osteocytes in the primary spongiosa. Four cases involving pediatric patients from the ongoing pediatric clinical Study ARST1921, and the nirogacestat compassionate use program, (PTs of Epiphysiolysis, Hip fracture, Epiphyseal disorder, and Osteonecrosis) provide insufficient information to fully assess the effect of nirogacestat on the growing bones of these children. The cases are few in number, some lack information concerning the radiographic

Important Potential Risk: Epiphyseal Disorder with Off-label Use in the Pediatric Population with Open Growth Plates	
	appearance of the growth plates, and each patient had been previously treated with chemotherapeutic agents with a known negative impact on bone development.
Risk factors and risk groups	Pediatric patients whose growth plates are not closed are at risk.
Risk minimization measures	Routine risk communication: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.8 (Undesirable effects) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Routine risk minimization activities recommending specific clinical measures to address the risk: Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None

Important Potential Risk: Embryo-fetal Toxicity	
Evidence for linking the risk to the medicine	In animal reproduction studies, administration of nirogacestat to rats during organogenesis resulted in embryo loss, resorption and decreased fetal weights in surviving embryos, while administration of nirogacestat to rats prior to conception resulted in decreased early embryo-fetal implantation and early embryonic loss. These effects occurred at exposures below those occurring clinically at the recommended dose. Transgenic studies in mice demonstrated that the loss of Notch signaling is embryonically lethal (Donoviel 1999, Swiatek 1994). A publication by (Wang 2023) provides insights into the possible mechanism of action driving the observations of embryo-fetal toxicity in nonclinical studies with nirogacestat. In ovo injection with glycolysis inhibitor or gamma-secretase inhibitor both decreased the hepatic glycolysis level and impaired goose embryonic development. The blockade of Notch signaling was also accompanied by the inhibition of PI3K/Akt signaling in the embryonic primary hepatocytes and embryonic liver. The decreased glycolysis and impaired embryonic growth induced by the blockade of Notch signaling were restored by activation of PI3K/Akt signaling. In a rat embryo-fetal development study with avagacestat, (Sivaraman 2023) found dose-related increased fetal mortality, decreased fetal growth, and increased fetal malformations. Reductions in female fecundity were attributed to impaired ovarian follicular development that was reflected in dose-dependent reductions in implantation sites, litter size, and gravid uterine weights. This article provides support for gamma-secretase inhibition being the mechanism for the observations of embryo-fetal toxicity in non-clinical studies with nirogacestat.

Important Potential Risk: Embryo-fetal Toxicity	
	One participant who was not practicing effective birth control conceived while on nirogacestat. Nirogacestat treatment was discontinued and 33 days later she experienced a spontaneous abortion.
Risk factors and risk groups	There are no known risk factors that would predispose a pregnant woman to have a loss of pregnancy due to treatment with nirogacestat.
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: 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) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None Additional risk minimization measures: Healthcare Professional Guide Patient Card

Important Potential Risk: Drug Induced Liver Injury	
Evidence for linking the risk to the medicine	**Non-clinical** In animal studies, hepatic necrosis associated with systemic inflammation due to endotoxemia observed in dog studies. In a 3-month study with 1-month recovery in dogs, hepatic inflammation and necrosis with associated elevations in liver enzymes were observed at doses ≥10 mg/kg/day. These hepatic findings resolved in the recovery phase. The inflammation was associated with necrosis resulting from endotoxemia originating from the disrupted intestinal mucosal barrier. In a 1-month study in dogs, hepatic inflammation, correlating with disrupted intestinal mucosal barrier, was observed at 80 mg/kg/day. In a 3-month rat study, elevations in ALT, AST, ALP, GGT and total bilirubin were observed in female rats receiving 50 mg/kg/day of nirogacestat. Exclusively in moribund rats or rats found dead at 50 mg/kg/day, microscopic findings consistent with centrilobular hepatic necrosis were observed. At doses ≥20 mg/kg/day, centrilobular hepatocellular hypertrophy was observed. At doses ≥5 mg/kg/day, periportal lipid vacuolation was observed. In a 1-month rat study receiving ≥20 mg/kg/day, hepatic treatment-related changes were observed in the liver consisting of an increase in the incidence and severity of hepatocellular lipid vacuolation in the periportal areas. **Clinical** In Study NIR-DT-301, there was an increased incidence of elevated transaminases in the nirogacestat 150 mg BID arm compared to the placebo arm, and the time to first onset for most participants reporting an event was during the first 3 cycles. Two participants in the nirogacestat arm reported Grade 3 events. There was no report of DILI.
Risk factors and risk groups	None identified

Important Potential Risk: Drug Induced Liver Injury	
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet Section 2 (What you need to know before you take Ogsiveo) Other routine risk minimization measures beyond the Product Information: None

Important Potential Risk: Severe Renal Toxicity	
Evidence for linking the risk to the medicine	**Non-clinical** In the 3-month dog study, there were no treatment-related urinalysis findings or microscopic findings involving the kidney in the dosing or 1-month recovery phases. In the 3-month rat study, findings were elevated urine protein in males and females at ≥20 mg/kg/day, elevated specific gravity along with small amounts of blood in male rats at 50 mg/kg/day, and small to large amounts of blood and formed elements (casts) in the urine of female rats at 50 mg/kg/day. Absolute and relative (kidney/brain) mean kidney weights were increased (1.15x to 1.21x control mean) in males at ≥20 mg/kg/day and females at 20 mg/kg/day. Kidney weights remained elevated (1.22x to 1.28x control mean) in recovery males and females at 50 mg/kg/day. The elevated weight correlated with the increased incidence of CPN in both males and females. Microscopic findings in the kidney comprised an increased incidence and severity of CPN in males at ≥5 mg/kg/day and females at ≥20 mg/kg/day, and glomerulonephropathy characterized by expanded mesangial matrix with sporadic deposition of hyaline protein droplets in males and females at ≥20 mg/kg/day. In addition, there were sporadic tubular casts, and the tubular epithelium associated with the casts was foamy and contained hyaline droplets. Changes of CPN were present in recovery males and females at ≥20 mg/kg/day. Males and females at 50 mg/kg/day (primarily those that were found dead or sacrificed moribund) had abundant pigment (strongly positive for iron with Perl's iron stain) within tubular epithelial cells. The pigment was hemoglobin from breakdown of red blood cells in the circulation.

Important Potential Risk: Severe Renal Toxicity	
	Clinical In the nirogacestat integrated DT population and the OLE phase of Study NIR-DT-301, there were no TEAEs of chronic kidney disease reported. In the double-blind phase of Study NIR-DT-301, 32 of 69 (46%) participants in the nirogacestat arm and 28 of 72 (39%) participants in the placebo arm had laboratory observations of proteinuria. TEAEs of proteinuria were reported by 1% of participants in the nirogacestat arm and 3% of participants in the placebo arm. In addition, 36 of 69 (52%) participants in the nirogacestat arm and 1 of 72 (1%) participants in the placebo arm had laboratory observations of glycosuria. TEAEs of glycosuria were reported by 6% of participants in the nirogacestat arm and no participants in the placebo arm.
Risk factors and risk groups	Given there are no reports of chronic kidney disease in the nirogacestat clinical trial data, there are no known risk factors or contributing factors.
Risk minimization measures	Routine risk communication: SmPC Section 4.8 (Undesirable effects) SmPC Section 5.3 (Preclinical safety data) Package leaflet Section 4 (Possible side effects) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

Important Potential Risk: Adverse Effect on Female Fertility	
Evidence for linking the risk to the medicine	**Non-clinical** Ovarian atrophy with decreased or no corpora lutea or follicular development was observed in the 1- and 3-month rat studies, with recovery of microscopic findings noted in the 1-month study. Multifocal ovarian follicular cysts were present in recovery females at doses of ≥20 mg/kg/day in the 3-month study. No ovarian findings were noted in the 1-month dog study. Mineralization of oocytes was noted in the 3-month dog study in all females at doses ≥2 mg/kg/day in both the dosing and recovery phase of the study. In the rat reproductive toxicity study, of the 22 female rats in each of the 20 and 40 mg/kg/day groups, there were 18 (82%) and 22 (100%) rats, respectively, that were determined to not be pregnant compared to 3 of the 22 (14%) females in the control group. No test material-related effects were noted on female reproductive performance (mating, fertility, or pregnancy) in the 5 mg/kg/day group. All females in this group had evidence of mating and were pregnant.

Important Potential Risk: Adverse Effect on Female Fertility	
	Clinical AMH, which is produced by developing ovarian follicles and is considered to be a marker of ovarian reserve, was decreased in women of childbearing potential while receiving nirogacestat (reflecting the interference with follicular development) and mean values were returning toward baseline at the final follow-up visit in the double-blind phase and OLE of Study NIR-DT-301. In the double-blind phase of Study NIR-DT-301, 27 (75%) women of childbearing potential receiving nirogacestat reported ovarian toxicity (defined as ovarian failure, premature menopause, amenorrhea, oligomenorrhea, and menopause) compared to no women receiving placebo. One female participant in Study NIR-DT-301 reported a pregnancy while receiving nirogacestat, although the pregnancy ended in a spontaneous abortion. As of 25Nov2024, 2 events of women who became pregnant after being prescribed nirogacestat have been reported to SpringWorks: one approximately 1 month, and the other approximately 5 months after stopping nirogacestat. The outcomes of these pregnancies are not yet known. As of 25Nov2024, one event has been reported to SpringWorks Pharmacovigilance of a participant who received nirogacestat in Study NIR-DT-301 and who conceived approximately 2 years after stopping nirogacestat to start a family. The outcome of this pregnancy is not yet known.
Risk factors and risk groups	Women of childbearing potential are the only group that is at risk for effect on female fertility.
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None
Additional pharmacovigilance activity	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)

Important Potential Risk: Adverse Effect on Male Fertility	
Evidence for linking the risk to the medicine	**Nonclinical** No effect on male mating indices was noted at any dose of nirogacestat tested. Decreases in epididymis and testes weights were noted in rats in the fertility and early embryonic

Important Potential Risk: Adverse Effect on Male Fertility	
	development toxicology study. No changes in testes weights were noted in dogs or rats in either the 1- or 3-month pivotal toxicology studies. Changes in sperm motility and morphology were noted in rats at doses ≥20 mg/kg/day. These changes in sperm in rats did not lead to embryotoxicity, but rather decreased fertility while on treatment. In the 1- and 3-month repeat-dose rat studies, there were no microscopic changes in the testes at doses as high as 50 mg/kg/day. Therefore, these effects appear to be limited to spermatogenesis with a low severity that did not induce microscopic changes in rats. It is unknown if these effects occur in humans. Microscopic findings of vacuolation of Sertoli cells were noted in the 10- to 11-month-old peripubertal beagle dogs used in the 3-month dog study. However, the relationship to treatment of this finding is unclear since similar findings have been described in peripubertal dogs (Goedken 2008). In addition, to demonstrate reversibility in dogs, a recovery period longer than 28 days is required given that the total spermatogenesis cycle in dogs can take over 60 days (Soares 2009). **Clinical** In the Integrated DT Safety Population and the DB phase of Study NIR-DT-301, there were no events within the Fertility disorders SMQ (narrow) that were reported in male participants. In the OLE phase of Study NIR-DT-301, a male participant reported 1 event of hypogonadism. This 18-year-old Asian male who transitioned from placebo to nirogacestat 150 mg BID, had a TEAE of hypogonadism reported on Day 603 of nirogacestat treatment. The participant's free testosterone level was normal throughout the OLE phase, except for a single low value of 2.88 pg/mL (normal range: 51.92 to 204.78 pg/mL) on Day 505, which returned to 129.79 on Day 603. No action was taken with nirogacestat treatment, he was treated with transdermal testosterone starting on day 603, and the outcome of this event is still listed as ongoing. The single, very low value of testosterone and free testosterone during nirogacestat treatment (Day 505) was not confirmed by a repeat assay in real time, as would be appropriate given the variability in test results reported for testosterone assays (Herati 2016). One participant in Study NIR-DT-301, who received placebo in the DB phase and received nirogacestat for 256 days in the OLE phase, fathered 2 children after stopping his study participation to start a family. The children were born approximately 1 year and 2 ½ years after his last dose of nirogacestat. There were no complications during both pregnancies and no reported congenital anomalies in either child.
Risk factors and risk groups	Men are the only group that is at risk for effect on male fertility. Since there were no reports of infertility in men in the clinical trial database, no additional insights are available concerning

Important Potential Risk: Adverse Effect on Male Fertility	
	additional risk factors for this potential risk. The single report of unconfirmed hypogonadism in a male does not provide sufficient data to draw inferences concerning risk factors.
Risk minimization measures	Routine risk communication: 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) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

To be determined.

II.C.2 Other studies in post-authorisation development plan

None

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Ovarian Toxicity Follow up Form

1. Please provide the date of the first dose of nirogacestat.

   Date:_____

2. Please provide the date of the last dose of nirogacestat prior to the onset of the event.

   Date:_____

3. Please provide the start date of the patient's last menstrual cycle before the start of the ovarian toxicity event.

   Date:_____

4. What is the typical interval between the start of the menstrual cycles for the patient?

   Days:_____

5. Did the patient have a prior history of menopause, premature menopause, irregular menses, amenorrhea, polycystic ovary syndrome (PCOS), infertility, or in-vitro fertilization (IVF)? If yes, please describe below.

   _____Yes _____No
   Comment / Description:
6. Has the patient been previously treated with any of the following therapies? Please complete the table below.

Prior Treatment	Yes	No	Unknown	Date(s) (if known)
Tyrosine kinase inhibitor (please specify):				
Anthracycline chemotherapy (please specify):				
Other chemotherapy (please specify):				
Antihormonal therapy (please specify):				
Local ablative treatment (please specify):				
Radiotherapy (please specify location):				

7. Did the patient have symptoms related to ovarian toxicity prior to or following administration of nirogacestat? Please complete both sections corresponding to pre- and post- nirogacestat of the table below.

Clinical observations	**Pre-Nirogacestat treatment**			**New Onset or Ongoing since starting Nirogacestat treatment**			**Worsening Post-Nirogacestat treatment**		
	Yes	**No**	**Unknown**	**Yes**	**No**	**Unknown**	**Yes**	**No**	**Unknown**
Amenorrhea									
Irregular menstruation									
Hot flashes									
Night sweats									
Vaginal dryness									
Dyspareunia									
Decreased libido									
Irritability									
Mood swings									
Other (please specify):									

8. Please provide reproductive hormone laboratory values and units, along with reference ranges, in the table below. Please provide all results available. You may also provide the laboratory report(s) as an attachment to this questionnaire.

Date (please specify)	**Reproductive Hormone Value and Units**			
	Anti-mullerian hormone	**Follicle stimulating hormone**	**Luteinizing hormone**	**Estradiol**

Please provide laboratory reference ranges:

- AMH:
- FSH:
- LH:
- Estradiol:

9. Was the nirogacestat dose modified as a result of the ovarian toxicity observation(s)?
    a. ____Yes ____No ____Unknown

i. If unknown, please fill in comment below.

b. Please complete the table below. Please use one row for each dose modification (reducing, stopping, resuming).

Date	Dose Reduced without Stopping Drug		Dosing Stopped (Interrupted or Discontinued)		Dosing Resumed at Same Dose after Stopping		Dosing Resumed at Reduced Dose after Stopping		Outcome*		
	Yes	No	Yes	No	Yes	No	Yes	No	A	B	C

*Outcome Selections to choose:

A. Not recovered/Not resolved
B. Recovered/Resolved: normal menses have resumed and all symptoms have resolved
C. Recovered/Resolved with sequelae: normal menses have resumed but some symptoms are continuing, such as the symptoms listed in the table in question 7

Comment / Description:

10. Is the patient taking, or has the patient taken while on nirogacestat, hormonal contraceptives? If so, please provide the dates and medication used below.
    a. ____Yes ____No
    b. Medication:
    c. Date(s):
11. Is the patient using an IUD?
    a. ____Yes ____No
    b. Name of IUD:
    c. Date(s):
12. Did the patient require any medications for the treatment of ovarian toxicity? Please complete the table below.

	Yes	No	Unknown	Dose	Date(s)	Ovarian Toxicity Outcome*		
						A	B	C
Hormone replacement therapy (please specify):								
SSRI/SNRI (please specify):								
Topical hormone therapy (please specify):								
Gabapentin								
Clonidine								
Other:								

*Outcome Selections to choose:

A. Not recovered/Not resolved
B. Recovered/Resolved: normal menses have resumed and all symptoms have resolved
C. Recovered/Resolved with sequelae: normal menses have resumed but some symptoms are continuing, such as the symptoms listed in the table in question 7

13. Did the patient permanently discontinue nirogacestat therapy? Please describe why and provide the date below.
    a. ____Yes ____No ____Unknown
    b. Reason:
    c. Date:
14. What is the current status of your ovarian toxicity? Please select one option below:
    a. _____Not recovered/Not resolved
    b. _____Recovered/Resolved: normal menses have resumed and all symptoms have resolved
    c. _____Recovered/Resolved with sequelae: normal menses have resumed but some symptoms are continuing, such as the symptoms listed in the table in question 8

Ogsiveo Post-Marketing Targeted Questionnaire for Pregnancy

Appendix D9b

SpringWorks THERAPEUTICS	Ogsiveo Post-Marketing Targeted Questionnaire for Pregnancy Argus Case <SW-00XXXX>

PLEASE FORWARD ALL PAGES TO:
Email Recipient: PV@springworkstx.com
Fax number: +1-866-750-4514

Date of this report: |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y) ☐ **Initial** ☐ **Follow-up #**_____

I. MATERNAL INFORMATION

☐ Not applicable *(Mother not administered product, complete Paternal section only)*

Initials_____	**Date of birth:** |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)	**Height:** |__|__|__| **cm** ☐ Not known **Weight:** |__|__|__| . |__| **kg** ☐ Not known

Date on which pregnancy diagnosed: |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)

Diagnosis of pregnancy confirmed by: ☐ Lab ☐ Ultrasound ☐ Other

Please specify: .....

First day of last menstrual period: |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)

Expected date of delivery: |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)

II. MEDICAL HISTORY

Obstetric history:

Number of pregnancies: |__|__| (including the current one)

Number of live births: |__|__|

Number of abortions:

- Spontaneous: |__|__|
- Therapeutic: |__|__|

Has the patient experienced adverse events in earlier pregnancies? ☐ No ☐ Yes ☐ Not applicable

If yes, please specify:

.....
.....
.....
.....

Other personal medical history including use of illicit drugs, smoking or drinking habits during pregnancy, etc.:

.....
.....
.....

Relevant Family History:

.....
.....
.....
.....

Appendix D9b

SpringWorks THERAPEUTICS	Ogsiveo Post-Marketing Targeted Questionnaire for Pregnancy Argus Case <SW-00XXXX>

Pre-Natal Information:

Did this pregnancy occur following natural conception (even if under treatment with fertility drugs)? ☐ No ☐ Yes

Did this pregnancy follow *in-vitro* fertilization? ☐ No ☐ Yes

Has the patient experienced adverse events in the current pregnancy? ☐ No ☐ Yes *(please specify)*

.....

.....

Is there any evidence of a birth defect from a prenatal test? ☐ No ☐ Yes *(please specify)*

.....

.....

Relevant Tests and Laboratory Findings:

TEST	TEST DATE (dd / mmm / yyyy)	RESULTS/UNITS	NORMAL RANGE

III. Ogsiveo Product Details

Indication for Use:	Lot # Exp. Date:	Dose:	Route: ☐ Oral
Start date: |__|__|/|__|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)		Stop date: |__|__|/|__|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)	

IV. Relevant Concomitant Medications

Drug name	Total daily dose	Route	Start date (dd / mmm / yyyy)	Stop date (dd / mmm / yyyy)	Indication

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V. PATERNAL DETAILS

☐ Not applicable *(father not administered product, complete Maternal section only)*

(If route of exposure to drug was via the father, please additionally complete the following section)

Initials_____	**Date of birth:** |__|__|/|__|__|__|/|__|__|__|__| (d d / m m m / y y y y)	**Height:** |__|__|__| **cm** ☐ Not known **Weight:** |__|__|__| . |__| **kg** ☐ Not known

Paternal Medical Exposure (in addition to Ogsiveo therapy)

Drug name	Total daily dose	Route	Start date (dd / mmm / yyyy)	Stop date (dd / mmm / yyyy)	Indication

VI. NEONATAL INFORMATION

Date of delivery or termination of pregnancy:
\|__\|__\|/\|__\|__\|__\|/\|__\|__\|__\|__\|
(d d / m m m / y y y y)

☐ **Live birth**
- **Number of neonates:** _____
- **Method of delivery:**
  ☐ Normal Vaginal ☐ Forceps ☐ Caesarean
- **Other (Specify):** _____

☐ **Not a live birth** *(clarify below)*
- ☐ Spontaneous Abortion
- ☐ Stillbirth
- ☐ Elective termination

Gestational age: \|__\|__\| **weeks**
Weight at birth: \|__\|__\|__\|__\| **g**
Length at birth: \|__\|__\| **cm**
Apgar scores:
- At 1 minute: _____
- At 5 minutes: _____

Gestational age: \|__\|__\| **weeks**
Weight at birth: \|__\|__\|__\|__\| **g**
Length at birth: \|__\|__\| **cm**
Apgar scores:
- At 1 minute: _____
- At 5 minutes: _____

** If more than 2 neonates, please enter the above information for the other babies in section IX.*

Did any complications/problem during pregnancy occur? ☐ No ☐ Yes *(if yes, provide details below)*

.....

.....

.....

Were any congenital anomalies present? ☐ No ☐ Yes *(if yes, provide details below)*

.....

.....

.....

Was the baby's hospitalization prolonged? ☐ No ☐ Yes *(if yes, provide details below)*

.....

.....

Did the baby receive any special treatment? ☐ No ☐ Yes *(if yes, provide details below)*

.....

.....

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SpringWorks THERAPEUTICS	**Ogsiveo Post-Marketing Targeted Questionnaire for Pregnancy** **Argus Case <SW-00XXXX>**

VII. Causality Assessment

In case of abnormal pregnancy outcome, was any relationship suspected between the abnormal pregnancy outcome and the use of the Ogsiveo

☐ UNRELATED / NOT SUSPECTED

☐ RELATED / SUSPECTED

Please state reason for causality assessment:

.....

.....

.....

VIII. Root Cause of Contraceptive Failure

Did the patient receive the Patient Card (*only applicable in Europe*)? ☐ N/A (outside Europe) ☐ No ☐ Yes (if Yes, see question below)

Was Patient Card understood by the patient (*only applicable in Europe)*? ☐ N/A (outside Europe) ☐ No ☐ Yes

Was the patient informed about the potential risk of embryo-foetal harm and appropriate contraceptive measures before the start of treatment with nirogacestat? ☐ No ☐ Yes

Was the patient considered to be a woman of childbearing potential at the time nirogacestat was prescribed? ☐ No ☐ Yes

Was a pregnancy test performed before the start of treatment with nirogacestat? ☐ No ☐ Yes

Was she advised to use highly effective contraception during treatment with nirogacestat and for 1 week after the last dose of nirogacestat? ☐ No ☐ Yes

Was she informed that nirogacestat may reduce the efficacy of hormonal contraceptives and therefore, a nonhormonal contraceptive method should be used or have their male partner use a condom? ☐ No ☐ Yes

Was she advised that pregnancy testing during treatment with nirogacestat should be considered for women of childbearing potential experiencing amenorrhea? ☐ No ☐ Yes

If the patient is a male with a female partner of childbearing potential, was he advised to use highly effective contraception during treatment with nirogacestat and for 1 week after the last dose of nirogacestat. ☐ No ☐ Yes

Was the patient / partner using a contraceptive method(s) when the pregnancy occurred? ☐ No ☐ Yes

If Yes, please specify the contraceptive methods from the list below:

Tubal ligation ☐ No ☐ Yes

Intrauterine device ☐ No ☐ Yes

Hormonal birth control ☐ No ☐ Yes

Partner's vasectomy ☐ No ☐ Yes

Male latex or synthetic condom ☐ No ☐ Yes

Diaphragm ☐ No ☐ Yes

Cervical cap or shield ☐ No ☐ Yes

Spermicide or sponge ☐ No ☐ Yes

Withdrawal ☐ No ☐ Yes

Abstinence ☐ No ☐ Yes

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VIII. ROOT CAUSE OF CONTRACEPTIVE FAILURE (CONTINUED)

If No, why did the patient and/or partner interrupt or stop using contraception?

Wanted a child ☐ No ☐ Yes

Partner disapproved ☐ No ☐ Yes

Side effects ☐ No ☐ Yes

Health concerns ☐ No ☐ Yes

Inconvenience ☐ No ☐ Yes

Forgot ☐ No ☐ Yes

Other, specify_____

IX. NARRATIVE AND ADDITIONAL INFORMATION

Please indicate the section to which the additional information refers.

X. REPORTER'S INFORMATION

Reporter' name: _____

Reporter's signature: _____

Date: |__|__|/|__|__|__|/|__|__|__|__|
(d d / m m m / y y y y)

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

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-fetal harm, including fetal 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-fetal 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-fetal harm, including fetal 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.