Summary of the Risk Management Plan (RMP) for OGSIVEO® (Nirogacestat)

Dosage strength:	100 mg and 150 mg
Pharmaceutical Form:	Film-coated tablets
Marketing Authorisation Number:	70389
Marketing Authorisation Holder	Merck (Schweiz) AG, Chamerstrasse 174, 6300 Zug
Based on EU RMP:	Version 1.0, sign-off date: 16-Jun-2025

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ogsiveo is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ogsiveo in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ogsiveo.

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 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 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	<u>Routine risk communication:</u> 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) <u>Routine risk minimization activities recommending specific clinical measures to address the risk</u>: SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet Section 2 (What you need to know before you take Ogsiveo) <u>Other routine risk minimization measures beyond the Product Information:</u> 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