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RESEARCH**

APPLICATION NUMBER:

217677Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA MULTI-DISCIPLINARY REVIEW AND EVALUATION

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Application Type	505(b)(1) New Drug Application (New Molecular Entity) with major amendment
Application Number(s)	NDA 217677
Priority or Standard	Priority
Submit Date(s)	December 24, 2022
Received Date(s)	December 27, 2022
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Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	Refer to electronic stamp date
Established Name	Nirogacestat
(Proposed) Trade Name	OGSIVEO
Pharmacologic Class	Gamma secretase inhibitor
Code name	PF-03084014
Applicant	SpringWorks Therapeutics, Inc.
Formulation(s)	Tablet
Dosing Regimen	150 mg orally twice daily
Applicant Proposed Indication(s)/Population(s)	For the treatment of adults with desmoid tumors.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with progressing desmoid tumors who require systemic treatment

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OPQ = Office of Pharmaceutical Quality
 OPDP = Office of Prescription Drug Promotion
 OSI = Office of Scientific Investigations
 OSIS = Office of Study Integrity and Surveillance
 OSE = Office of Surveillance and Epidemiology
 DEPI = Division of Epidemiology
 DMEPA = Division of Medication Error Prevention and Analysis
 DRM = Division of Risk Management

NDA/IND Multi-disciplinary Review and Evaluation NDA 217677
Nirogacestat (PF-03084014)

DVP = Division of Pharmacovigilance

DUOG = Division of Urology, Obstetrics, and Gynecology

DGE = Division of General Endocrinology

DCOA = Division of Clinical Outcome Assessment

PFSS = Patient-Focused Statistical Scientists

Glossary

AAG	human α 1-acid glycoprotein
A β	amyloid β
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
AF	aggressive fibromatosis
ALT	alanine aminotransferase
AMH	anti-müllerian hormone
APC	adenomatous polyposis coli
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC ₀₋₂₄	area under the curve from 0 to 24 hours
AUC _{inf}	area under the curve from time 0 to infinity
AUC _{tau}	area under the curve over the dosing interval
BC	breast cancer
BDC	bile duct cannulated
BOR	best overall response
BID	twice daily
BMI	body mass index
BPI	Brief Pain Inventory
BTB	Breakthrough Therapy Designation
CFR	Code of Federal Regulations
CI	confidence interval
C _{avg}	average concentration
CL	clearance
CL/F	apparent clearance
CL _p	systemic plasma clearance
C _{max}	maximum observed concentration
C _{min}	minimum observed concentration
CNS	central nervous system
COG	Children's Oncology Group
COVID-19	coronavirus disease 2019
cQT	concentration QT
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSF	cerebrospinal fluid

CSR	clinical study report
CT	computed tomography
CTNNB1	catenin β 1
CV	coefficient of variation
CYP	cytochrome
CYP3A4	cytochrome P450 3A4
d	day
DB	double-blind
DCR	disease control rate
DDI	drug-drug interaction
DELFI	dissociation-enhanced lanthanide fluorescence immunoassay
DO	Division of Oncology
DOP	Division of Oncology Products
DOR	duration of response
DoSD	duration of stable disease
DT	desmoid tumors
DTIS	GOunder/DTRF DEsmoid Symptom/Impact Scale Impact Scale
DTRF	Desmoid Tumor Research Foundation
DTSS	GOunder/DTRF DEsmoid Symptom/Impact Scale Total Symptom Scale
DTWG	Desmoid Tumor Working Group
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFD	embryonic-fetal development
ERR	exposure-response relationship
F	female
F (%)	absolute oral bioavailability
FAP	familial adenomatous polyposis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
fu	fraction unbound
GALT	gut-associated lymphoid tissue
GCP	good clinical practice
GIST	gastrointestinal stroma
GLP	good laboratory practice
GODDESS	GOunder/DTRF DEsmoid Symptom/Impact Scale
GOF	goodness of fit
GS	gamma secretase
GSI	gamma secretase inhibitor
h	hour
HEK	human embryonic kidney
HERG	human ether-à-go-go related gene

HPB-ALL	human peripheral blood-acute lymphoid leukemia
HR	hazard ratio
HRQoL	health-related quality of life
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IndMax	maximum induction rate
IRB	Independent Review Board
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
ka	absorption rate constant
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LH	luteinizing hormone
LS	least squares
M	male
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NE	not estimable
NICD	Notch intracellular domain
NK	natural killer
NME	new molecular entity
N/No	number
NOAEL	no-observed-adverse effect level
NR	not reported
NS	not significant
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OD	ovarian dysfunction
ODWG	Organ Dysfunction Working Group
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality

OR	objective response
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiological-based pharmacokinetic(s)
PD	progressive disease
PDx	pharmacodynamic(s)
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PK/PDx	pharmacokinetic/pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population pharmacokinetics
PP	per protocol
PPND	pre- and post-natal development
PR	partial response
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
REMS	risk evaluation and mitigation strategy
RT-PCR	reverse transcription polymerase chain reaction
RTOR	Real-Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCM	stepwise covariate modeling
SCS	Summary of Clinical Safety
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
StD	standard deviation
t _{1/2}	apparent terminal elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
TK	toxicokinetic
TKI	tyrosine kinase inhibitor

T _{max}	median time of occurrence of maximum serum concentration
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
URTI	upper respiratory tract infection
V _c	central volume of distribution
V _{p1}	peripheral volume of distribution – shallow compartment
V _{p2}	peripheral volume of distribution – deep compartment
VPC	visual predictive check
vs	versus
V _{ss}	apparent volume of distribution at steady state
WOCBP	women of childbearing potential
WOE	weight of evidence

1 EXECUTIVE SUMMARY

1.1. Product Introduction

Nirogacestat (OGSIVEO®) is an oral, small molecule γ -secretase inhibitor. At the time of the New Drug Application (NDA) submission on December 23, 2022, nirogacestat was not approved for any indication in the United States or elsewhere. The Applicant's proposed indication at the time of the NDA submission was:

OGSIVEO is a gamma secretase inhibitor indicated for the treatment of adults with desmoid tumors.

The proposed dosing regimen is 150 mg (3 × 50 mg tablets) administered orally twice daily (BID).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for **traditional approval** of nirogacestat in patients with desmoid tumors (DT) is based on the results of the NIR-DT-301 study, an international, multicenter, randomized, double-blind, placebo-controlled study in 142 adult patients with progressing DTs which demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and objective response rate (ORR) in patients treated with nirogacestat over placebo including supportive patient-reported outcome data for pain.

Substantial evidence of effectiveness was established with one adequate and well controlled investigation (i.e., Study NIR-DT-301), with highly persuasive results, that is considered to be the scientific equivalent of two clinical investigations.

Patients (n = 142) in Study NIR-DT-301 were randomized 1:1 to receive nirogacestat or placebo until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons. Cross-over from placebo to nirogacestat was allowed at the time of radiographic disease progression (patients remained blinded without allowing for cross over for clinical progression events). Cross-over was also permitted following the primary PFS analysis.

The primary efficacy endpoint was PFS determined by

- Blinded Independent Central Imaging Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or
- The onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.

The key secondary endpoints were objective response rate by central review; and the following patient-reported outcomes (PROs) measures:

- Brief Pain Inventory (BPI) short form,
- GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS),
- Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks, and
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30 (EORTC QLQ-C30).

Additional secondary endpoints or objectives included duration of response, comparing change in tumor volume measured by magnetic resonance imaging (MRI), and safety.

During the development of nirogacestat, FDA expressed concerns regarding the inclusion of clinical progression as a PFS-defining event (e.g., the potential for bias exists in classifying a patient). Although bias may have been mitigated via the double-blind design, toxicities related to nirogacestat (e.g., GI toxicity, dermatological toxicities, ovarian suppression, or hypophosphatemia) may have allowed patients or clinicians to determine treatment assignment.

The data submitted by the Applicant of an adequate and well-controlled trial provided substantial evidence for the effectiveness of nirogacestat administered at 150 mg BID versus placebo for the treatment of adult patients with progressing DTs who require systemic treatment and supports traditional the approval for the proposed indication. This conclusion is based on results from the NIR-DT-301 study which demonstrated a clinically and statistically significant improvement in PFS in patients who received nirogacestat compared to placebo with a hazard ratio (HR) of 0.29 (95% confidence interval [CI]: 0.15, 0.55], $p < 0.001$).

Concerns with respect to the inclusion of clinical progression events were mitigated via the following factors:

- Nirogacestat demonstrated improved PFS in a sensitivity analysis based on radiographic assessment alone compared to placebo with a hazard ratio of 0.31 (95% CI: 0.16, 0.62). Notably most events observed in the trial were radiographic progression and not clinical progression.

Category of PFS event	Nirogacestat N=70	Placebo N=72
Radiographic progression	11 (16%)	30 (42%)
Qualified clinical progression	1 (1%)	6 (8%)
Death before progression	0	1 (1%)

- The assessment of tumor shrinkage (i.e., response rate per RECIST) favored the nirogacestat arm with an ORR of 41% (29.8, 53.8) for patients treated with nirogacestat versus 8% (3.1, 17.3) in patients who received placebo (note, the 95% CIs are based on FDA's analysis which differ slightly from the Applicant's).
- A key component of the quality of life for patients with DT is improvement in pain. Results from the BPI short form data were used as supportive evidence of the results of PFS. FDA conducted analyses on patients with clinical responses at various thresholds, and results were consistent in showing that more patients in the nirogacestat arm experienced pain improvement. Although other PRO results were also generally supportive of the nirogacestat treatment effect, missing PRO data precluded FDA from determining that specific PRO treatment effect sizes were accurate.

In summary, although FDA had concerns regarding the inclusion of clinical progression events, overall, the totality of the data were highly persuasive with respect to benefit following nirogacestat treatment (in patients with DT who need systemic therapy).

DT is a rare, serious condition that has significant morbidity and mortality, and has a high unmet medical need. A single randomized trial to support the approval of nirogacestat is acceptable in the context of the unmet medical need in the indicated population and the robustness of the efficacy results. Therefore, the review team recommends granting traditional approval to nirogacestat for the treatment of adult patients with progressing desmoid tumors who require systemic treatment.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Desmoid tumors (DTs) are a rare subtype of soft tissue sarcoma (STS) that are locally aggressive and characterized by infiltrative growth which can affect surrounding vital organs causing significant impairment in the daily life of a patient due to chronic pain, functional deficits, psychological problems and decrease in quality of life (Kasper 2020). DTs have also been known to spontaneously regress. DTs have been reported to account for approximately 0.03% of all tumors (Reitamo 1982). They occur between the age of 15 and 60 years and with a peak age of about 30 years (Kasper 2011) and are twice as common in females as in males (Mishra). DTs are characterized by variable clinical behavior. Although most grow progressively larger over time, growth is usually indolent, and periods of growth arrest/spontaneous regression are not uncommon (Bonvalot 2013). The largest patient registry for DTs is the Desmoid Tumor Research Foundation Patient Registry and Natural History Study. In the first 15 months the registry was launched the ethnicity of 329 patients in the registry with DT was 92% White, 1.6% Black or African American, 1.6% Asian, 0.3% American Indian or Alaskan native, and 5% other. There have been two published DT studies that included the race and/or ethnicity. A COG clinical trial of sulindac and tamoxifen recruited 80% non-Hispanic (NH) or Latino, 14% Hispanic/Latino, 4% unknown ethnicity, 73% White, 16% Black or African American, 2.9% Asian, 1.4% Native Hawaiian or other Pacific Islander, and 7.1% unknown race (Mercier 2019). On the molecular level, DT's are characterized by mutations in the β -catenin gene, CTNNB1, or the adenomatous polyposis coli gene, APC (Kasper 2011). Most DTs arise sporadically, although between 5-15% are associated with familial adenomatous polyposis (FAP) caused by mutations in the APC gene. According to a retrospective review published in the American Society of Clinical Oncology, 96% of patients with DTs are alive 5 years after diagnosis, 92% after 10 years, and 87% after 15 years. The survival rates for patients with desmoid tumor vary based on several factors. These include the size of tumor, a patient's age and general health, and how well the treatment plan works. Other factors that can affect outcomes include where the tumor is located and how quickly the tumor grows. Intra-abdominal desmoid tumors are the most likely to cause potentially life-threatening complications, such as intestinal obstruction. DTs in the head and neck region can also be life-threatening (Ballo 2016).

Diagnosis can be challenging as the clinical course can be unpredictable and typically requires a multidisciplinary team with expertise in treating DTs. There is no treatment approved by the FDA for DT; however, treatment guidelines reference available options, such as active surveillance, surgery, systemic therapy, and locoregional therapy. Choice of active treatment may depend on tumor location, symptoms, and risk of morbidity (e.g., Bektas 2023 and NCCN guidelines 1.2023). Until recently, surgery had

been the mainstay of treatment; however, emerging data suggest a “wait and see” approach is reasonable for some patients. One of the most compelling pieces of data supporting observation for patients with DT comes from the published report of the placebo-controlled trial of sorafenib, in which the placebo arm had a 20% response rate, suggesting the importance of observation, especially in patients where symptoms are mild or absent (Gounder 2018). Surgery is offered to some patients who have potentially resectable extra-abdominal (extremity, trunk, breast) or abdominal wall DTs if they are medically able to tolerate surgery and if resection can be accomplished without major functional or cosmetic deficit. For the patients treated with surgery, recurrence rates have ranged from 19% to 77% with various factors affecting the rate of recurrence (Wang 2015). Primary radiation therapy (RT) is an appropriate option for patients who need local treatment but are not good surgical candidates, those who decline surgery, and those for whom surgical morbidity would be excessive. Systemic treatment is an alternative approach in these patients, especially if they are young and there are concerns about the potential for late toxicity from RT including but not limited to radiation-associated malignancies. Although a number of systemic therapies have activity against DTs there is no standard of care. There have been few prospective studies and most data from systemic treatment have come from case series or retrospective analyses (Gounder 2018). Systemic treatments described in the literature have included NSAIDs, hormonal therapy, conventional chemotherapy, and targeted therapy with tyrosine kinase inhibitors (e.g., Napolitano 2020 and NCCN v1.2023).

The data submitted by the Applicant to support the efficacy of nirogacestat in patients with DT come from the NIR-DT-301 study, an international, multicenter, randomized, double-blind, placebo-controlled study in 142 adult patients with progressing DTs and forms the primary basis on which the Applicant is seeking approval of nirogacestat in the proposed indication. The major efficacy endpoint was progression-free survival assessed by BICR via RECIST v1.1. Median PFS in patients who received nirogacestat compared to placebo was non-evaluable (NE, 95% CI: NE, NE) for patients on nirogacestat and 15.1 months (95% CI: 8.4, NE) for patients on placebo with a hazard ratio (HR) of 0.29 (95% confidence interval [CI]: 0.15, 0.55], $p < 0.001$). To support an overall favorable risk:benefit based on the effect on PFS, FDA conducted analyses on patient reported outcomes for improvement in pain, and results were consistent in showing that more patients in the nirogacestat arm experienced pain improvement over the placebo arm. Although a number of issues precluded FDA’s ability to rely on the prespecified and tested PRO results, the overall results and the additional analyses for pain demonstrated that nirogacestat had an effect on pain in those who had pain at baseline.

Safety data supporting the proposed indication reflected exposure to nirogacestat in patients enrolled on the NIR-DT-301 study (69 patients exposed to nirogacestat and 72 patients exposed to placebo), and additional supporting safety data from 17 patients

from Study 14-C-0007 (an NCI-sponsored study), 9 patients from Study A8641014, and 19 patients from study A8641020 (refer to the clinical results section of this review for details on these supportive studies). The primary analysis of safety was based on 141 patients enrolled in the NIR-DT-301 study who received either nirogacestat or placebo. An important identified risk of nirogacestat is ovarian toxicity. Reports of primary ovarian toxicity (composite terms ovarian failure, premature menopause, amenorrhea, and menopause) were noted prior to the implementation of Amendment 3 (January 27, 2020) of NIR-DT-301. In Amendment 3, the Applicant included a requirement to ask women about their menstrual history and added monitoring of hormone levels in men and women. For women of childbearing potential experiencing one of the composite terms for ovarian toxicity, 75% experienced this adverse event (AE) versus 0% in the placebo arm. Although additional information was collected following Amendment 3 regarding ovarian toxicity, this information was not sufficient to fully characterize ovarian toxicity, resolution, and sequelae. In general, nirogacestat was well tolerated with most AEs reported as mild to moderate in severity. Diarrhea and gastrointestinal toxicity were the most common AEs. Diarrhea occurred in 84% of the safety population receiving nirogacestat versus 35% of patients receiving placebo. Diarrhea is a toxicity that oncologists are well-trained to manage and are acceptable for a population with a serious and life-threatening condition

During the course of the review of the application, a major amendment was issued to the Applicant based in part on findings during the Office of Scientific Investigation (OSI). FDA inspection revealed discrepancies in the Applicant's reporting of sum of target tumor measurements for 7 patients; and deficiencies in the financial disclosure, and conflict of interest provided by the Applicant. Inspections of the clinical investigators revealed no discrepancies or regulatory violations. After a thorough review of the updated data, FDA did not find any significant discrepancies that would alter the positive risk:benefit for the treatment of patients with DT with nirogacestat.

The review team recommends granting traditional approval to nirogacestat for the treatment of adult patients with progressing desmoid tumors who require systemic treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- DTs are rare, locally aggressive and invasive tumors, but do not metastasize. - DTs are diagnosed in approximately 900-1500 patients in the US annually. - Although extremity desmoids can also occur, most patients develop abdominal tumors, one-half of which are intra-abdominal, the remainder involving the abdominal wall leading to symptoms of pain and impaired mobility that can negatively impact their quality of life. - The 5-year survival of patients is dependent upon site of tumor, size, proximity to vital structures. For all patients with DT, nearly 96% of patients with DTs are alive 5 years after diagnosis, 92% after 10 years, and 87% after 15 years.	DT is a rare soft tissue sarcoma that is locally aggressive, causing significant morbidity and (less commonly) mortality and represents a population with a high unmet medical need that include early and accurate diagnosis and approved treatments.
<u>Current Treatment Options</u>	- There are no FDA therapies approved for DT - Published treatment guidelines describe use of surgery, radiation, cytotoxic chemotherapy, or other targeted therapies. - Radiation may be an appropriate treatment but is reserved for patients who cannot tolerate systemic therapy and where surgery would be too morbid. Many factors play into the role of the use of surgery.	There is an unmet medical need for new effective systemic treatments for patients with DTs. There are no FDA-approved therapies. Due to the nature of desmoid tumors, complete surgical resection is often challenging and the risk of recurrence is variable and has been reported to be as high as 70%. Radiation therapy in combination with surgery may reduce the recurrence rate but given the high-rate of abdominal tumors, side effects may be a deterrent. For systemic therapies, there has been no consensus on standard of care.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	- The mPFS in patients who received nirogacestat compared to placebo was non-evaluable (NE, 95% CI: NE, NE) and 15.1 months (95%CI: 8.4, NE), respectively. The HR was 0.29 (5% CI: 0.15, 0.55). The results were both clinically and statistically significant. - PRO data was collected during the conduct of the study to assess PRO measures from baseline over time. Due to missing data, FDA was not able to confirm the accuracy of PRO results submitted by the applicant, and therefore, the results were considered exploratory. A significant effect on patients is pain. Pain can be debilitating, require narcotic medication to properly control, and affect one's ability to perform daily functions of life. FDA performed additional analysis on the BPI short form and noted that nirogacestat had an effect on pain in those who had pain at baseline versus those who received placebo.	For progressing DTs who require systemic therapy there is no consensus on standard of care treatment for these patients in which the tumor may have debilitating effects on day to day living, significantly affecting their quality of life. Improvements demonstrated in PFS and ORR were supported by favorable findings from patient-reported pain. Reducing a patient's pain is an important component in improving a patient's quality of life. The results of the study meet the evidentiary standards for granting traditional approval in the proposed patient population.
<u>Risk and Risk Management</u>	- Toxicity profile includes diarrhea and gastrointestinal toxicities, dermatological toxicities, and wasting of electrolytes (phosphorus and potassium). Toxicities were generally manageable with supportive care or dose interruption; dose modifications, and discontinuations. - Treatment with nirogacestat confers a risk of ovarian toxicity.	A PMR will be issued to capture appropriate data on women of child bearing potential to characterize ovarian toxicity in this patient population with potential labeling updates in the future for nirogacestat for ovarian toxicity.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
X	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	X Patient-reported outcome (PRO)	Section 8.1.1.2 and 8.1.3.2
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	See DCOA review for full discussion on qualitative studies
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

Patient-reported outcomes was a secondary endpoint that was used to assess the overall clinical benefit in support of the marketing application. The following PRO measurements were used:

- GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Symptom/Impact Scale (GODDESS);

NDA/IND Multi-disciplinary Review and Evaluation NDA 217677
Nirogacestat (PF-03084014)

- Brief Pain Inventory short form;
- Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks; and
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30.

(Refer to Efficacy Results – Secondary or exploratory COA (PRO) endpoints for details)

X

Leslie Doros

Cross-Disciplinary Team Leader

2 THERAPEUTIC CONTEXT

2.1. Analysis of Condition

The Applicant's Position:

Desmoid tumors (DT), also referred to as aggressive fibromatosis (AF), are rare, locally invasive, slow growing soft tissue tumors that can cause severe pain and functional impairment by infiltrating or exerting mass effects on vital structures.

DT arise in the deep soft tissue and are characterized by infiltrative growth and a tendency toward local recurrence ([Kasper et al. 2011](#)). DT cause significant morbidity by infiltrating or exerting mass effects on vital structures, which can lead to severe pain, functional impairment, and rarely, life-threatening complications ([Lewis et al. 1999](#); [Penel et al. 2017](#); [Smith & Kransdorf 2000](#)). The most common primary tumor sites include abdominal walls, limbs, girdles, and mesenteric areas. Despite an inability to metastasize, they can behave aggressively, causing significant morbidity, with elevated rates of local recurrence following surgery (as high as 70%) despite wide excisions ([Penel et al. 2017](#)). Mortality is occasionally observed owing to the local aggressive nature and vital structure involvement of some DT ([Smith & Kransdorf 2000](#)).

DT most commonly occur in individuals between the ages of 15 to 60 years, with a peak age of about 30 years, and a 2- to 3-fold predominance in females ([de Camargo et al. 2010](#); [Skubitz 2017](#); [Anneberg et al. 2022](#)). The global incidence of DT is about 3 to 5 cases per million per year in the general population with approximately 1,000 to 1,650 cases diagnosed in the United States per year ([van Broekhoven et al. 2015](#); [Prevalence of Rare Diseases: Bibliographic Data, 2020](#)).

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](#)). FAP-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 et al 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*) ([Bo et al. 2012](#); [Lazar et al. 2008](#); [Tejpar et al. 1999](#)). β -catenin is an integral component of the Wnt/ β -catenin/T-cell transcription factor signaling pathway, which is frequently dysregulated in

cancer. Patients with DT carrying β -catenin mutations have a lower 5-year recurrence-free survival rate than patients with wild-type tumors ([Kummar et al. 2017](#)).

The clinical course of DT may be unusual and heterogeneous, characterized not only by tumor growth, proliferation, and disease progression, but also by stabilization and spontaneous remission ([Desmoid Tumor Working Group \[DTWG\] 2020](#); [Kasper et al. 2011](#)). Compression of vital structures by DT can result in severe pain, functional impairment, nerve damage, and bowel obstruction or perforation ([Constantinidou et al. 2012](#); [Gounder et al. 2020](#); [Hosalkar et al. 2006](#); [Penel et al. 2017](#); [Quintini et al. 2012](#); [Shinagare et al. 2011](#); [Skubitz 2017](#)). Additionally, DT-specific morbidities can negatively impact school, work, and psychosocial functioning ([Hosalkar et al. 2006](#); [Schut et al. 2022](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of DT. It is a rare tumor with an incidence of 2-4 cases per million per year in the United States (U.S.) and has been reported to comprise approximately 0.03% of all cancers (or tumors), and <3% of all soft tissue sarcomas (Hosalkar et al., 2006). Ethnicity of 329 patients from the Desmoid Tumor Research Foundation Patient Registry noted the majority of patients with DT in the US to be 92% White, 1.6% Black or African American, 1.6% Asian, 0.3% American Indian or Alaskan native, and 5% other. DTs may occur during and after pregnancy, and regress during menopause, so hormones may play a role in the pathophysiology of DTs, and most DTs express low levels of nuclear estrogen receptor- β (Janinis et al., 2003). As stated by the Applicant, most DTs occur spontaneously, and approximately 85% are associated with a mutation in the CTNNB1 gene (most commonly in exon 3) (Skubitz et al., 2017). Approximately 10% of DTs are associated with an APC gene mutation, which is a tumor suppressor gene involved in β -catenin degradation. Five to 15% of DTs are associated with FAP (de Camargo et al., 2010; Skubitz et al., 2017). Somatic mutations in CTNNB1 and germline mutations in APC genes are probably mutually exclusive in DT (Penel et al., 2017). Although DT is rarely fatal, intra-abdominal tumors which account for 5% of spontaneous DTs are one of the leading causes of mortality. DTs associated with FAPs account for a small proportion of DTs, 80% are intra-abdominal, particularly in the Gardner variant of FAP (Quintini et al., 2012).

2.2. Analysis of Current Treatment Options

There is no Food and Drug Administration (FDA)-approved therapeutic option for the treatment of DT, nor is there a universal standard of care for patients with advanced progressing tumors. Treatment options vary for each patient depending on the size, location, and morbidity associated with the tumor.

Active surveillance is currently recommended as the first approach in DT (DTWG 2020). This approach includes continuous monitoring via magnetic resonance imaging (MRI) (or computed tomography [CT] if MRI is not feasible) within 1 to 2 months of diagnosis then at 3- to 6-month

intervals. A decision regarding active treatment should be postponed until the occurrence of subsequent progression or increase of symptomatic burden, assessed with ≥ 2 further assessments and possibly not before 1 year from diagnosis in the absence of fulfilling Response Evaluation Criteria in Solid Tumors (RECIST) progressive disease (PD; [DTWG 2020](#)).

Historically, surgery was the therapeutic option of choice for localized, extra-abdominal, small volume DT; however, surgery is no longer regarded as the cornerstone of DT treatment given the associated morbidity and high rate of relapse after surgery ($> 70\%$) ([Penel et al. 2017](#)).

Radiotherapy has been used both in the adjuvant setting after surgery and in the primary setting, mainly for extra-abdominal tumors. Radiotherapy after surgery is an independent positive prognostic factor for local recurrence and overall survival, and radiotherapy alone or in combination with surgery led to significantly lower recurrence rates ([Kasper et al. 2011](#)).

Various systemic therapies have been studied in patients with relapsed or recurrent DT, patients with DT that are not amenable to surgery or radiotherapy, or patients for whom surgery is potentially mutilating.

Traditional chemotherapy may be considered in patients requiring systemic therapy for DT. Kasper et al. provided an overview of chemotherapy regimens that have been studied in patients with advanced disease ([Kasper et al. 2011](#)). A combination of methotrexate and vinblastine was one of the first chemotherapy regimens widely used for DT, with response rates ranging from 30% to 50%. Low-dose vinblastine-methotrexate combination has demonstrated disease stabilization and long-term tolerance in pediatric patients with progressive DT ([Azzarelli et al. 2001](#); [Fortunati et al. 2020](#); [Penel et al. 2020](#); [Skapek et al. 2007](#)). Because this regimen does have considerable toxicity, vinorelbine has largely replaced vinblastine in this regimen. However, due to the toxicity of a prolonged course using either combination, this regimen is not well tolerated by adults long-term ([Skubitz, 2017](#)). It should be noted that these studies were small and uncontrolled, and the most effective chemotherapeutic regimen has not been established.

As a standard-dose chemotherapy, anthracycline-based chemotherapy (doxorubicin plus dacarbazine) may be used in cases requiring rapid tumor response, e.g., intra-abdominal and head and neck tumors. The response rate is usually around 50% (Garbay et al. 2012), but it usually occurs as late as [several months after](#) the start of therapy. Shrinkage can continue even after treatment withdrawal and long-term disease control is achieved in up to 50% to 70% of the patients ([DWTG, 2020](#)).

Tyrosine kinase inhibitors (TKIs) have been investigated and demonstrated some benefit in studies of adults with DT. Meaningful responses have been observed with TKIs, such as imatinib, sorafenib, and pazopanib ([DTWG 2020](#); [Gounder et al. 2018](#); [Kasper et al. 2017](#); [Toulmonde et al. 2019](#)), although sorafenib is the only agent to have been studied in a

randomized, double-blind (DB), placebo-controlled clinical trial in patients with DT and despite a positive Phase 3 study (hazard ratio [HR] for progression or death = 0.13; 95% CI, 0.05 to 0.31; $p < 0.001$) in 87 patients with progressive, symptomatic, or recurrent DT, it is not FDA-approved for this indication ([Gounder et al. 2018](#)).

A benefit in both tumor response and patient-reported outcomes (PROs) would be beneficial and clinically meaningful to patients with DT particularly given the significant unmet need as there are currently no FDA approved therapies for DT ([DTWG 2020](#)).

The Applicant's Position:

DT are rare, locally-aggressive, and invasive soft-tissue tumors that can cause substantial morbidity including severe pain, functional impairment, and disfigurement affecting everyday activities. There is currently no accepted standard of care and no FDA approved therapies for the treatment of DT (DTWG, [2020](#); [National Comprehensive Cancer Network, 2020](#)). Nirogacestat has the potential to address a significant unmet medical need for this indication.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the current treatments offered in clinical practice for DTs. A multidisciplinary approach to diagnosis and treatment is warranted given the rarity and heterogenous presentation of patients with DT.

Due to the high recurrence rate after surgery as previously described by the Applicant, the DTWG 2020 consensus guidelines recommend initial active surveillance for patients who do not need immediate treatment (e.g., vital organ involvement, and intolerable symptoms). Data from retrospective studies are conflicting regarding whether adding post-operative radiotherapy decreases the recurrence rate, and because surgical management is less frequent in current practice, the combination of surgery and radiation is rarely done (DTWG 2020, NCCN 2.2023). Furthermore, a retrospective study in 142 patients with treatment-naïve ($n=74$) or previously treated ($n=68$) DT reported that 5-year progression-free survival was similar between patients who were underwent observation (47%) to patients who were treated with systemic therapy (54%, $p=0.07$); both patients with progressing and stable DTs were included in this retrospective study (Fiore et al., 2009). NCCN consensus guidelines state that surgery is the primary treatment for patients with resectable DTs, but that observation is an option for selected patients with resectable tumors. NCCN concludes that patients with DT "can be managed appropriately with a careful 'wait and see' approach if their tumors are asymptomatic and are not located in an area that could lead to functional limitations if the tumor increases in size" (NCCN 2.2023).

For patients with DT who do need to initiate treatment, management is heterogenous, but a more conservative approach with systemic therapy is preferred in some patients over local therapy, such as surgery or radiotherapy (DTWG 2020).

3 REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nirogacestat was studied under IND (b) (4) by Pfizer. On 10 January 2018, Pfizer submitted a transfer of ownership for nirogacestat IND (b) (4) to SpringWorks Therapeutics (SpringWorks). Per 21 Code of Federal Regulations (CFR) 312.50, SpringWorks submitted an acknowledgement of the sponsor transfer change for IND (b) (4) on 19 January 2018.

(b) (4) SpringWorks then filed an administrative split from IND (b) (4) for a new IND 138207 under the review jurisdiction of Division of Oncology 2 (DO2, formerly known as Division of Oncology Products 2 [DOP2]). The review jurisdiction for nirogacestat IND 138207 (DT) changed from DOP2 to DOP3 at the start of 2021. Refer to [Table 1](#) for a summary of key regulatory activities.

The following regulatory designations were granted to nirogacestat:

- Orphan Drug: 07 June 2018
- Fast Track: 01 November 2018
- Breakthrough Therapy Designation (BTD): 28 August 2019
- Nirogacestat was also accepted into Real-Time Oncology Review (RTOR) by the Oncology Center of Excellence (OCE) (03 June 2022).

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the U.S. FDA regulatory actions for nirogacestat. An initial Pediatric Study Plan (iPSP) was agreed upon between FDA and SpringWorks on April 25, 2022, for a partial waiver of PREA requirements for patients 0-<2 years of age and a deferral in older pediatric patients awaiting the results of Children's Oncology Group (COG) Study ARST1921, which will be submitted post-approval. ARST1921 is an ongoing Phase 2 study evaluating the safety, pharmacokinetics, and efficacy of nirogacestat in pediatric patients >1 to <18 years-old with progressive, surgically unresectable DT. Study ARST1921 was activated in September 2020 and was expected to take approximately 3 years to accrue; per clinicaltrials.gov, updated on 11/22/2023, this study is active but no longer accruing patients. Patients are being followed for 2 years to evaluate outcomes including safety.

Although Study ARST1921 allowed for the enrollment of patients above one year of age (rather than 2 years as described in the Waiver of the PREA requirement for patients ages 0-<2), FDA agreed with the waiver for children under age 2 years given the following:

- Recent research and guidelines espousing a conservative strategy for desmoid-type fibromatosis in children (Orbach D et al. 2017, DTWG Guidelines 2020);
- COG study requirements for non-resectable tumors, progressing tumors, and previous systemic treatment;
- Observed risk of widening of growth plates, and theoretical risk on organ maturation (however, this risk would be solely based on non-clinical embryonic studies of the NOTCH pathway and not on data observed in patients); and
- Age distribution of 59 patients (over 63 months) in prior COG trial ARST0321 (Skapek SX, et al, 2013) with 78% of 59 patients being 10 years of age or older (additionally ARST0321 did not require previous systemic treatment).

Given the above factors, enrollment of a sufficient number of patients younger than 24 months of age would be highly impracticable for this rare disease.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

[Table 1](#) summarizes the key regulatory history for the nirogacestat development program under IND 138207 for DT.

Table 1: Key Regulatory History from Nirogacestat IND 138207

Date	Communication Type	Summary
21Mar2018	Pre-IND/EOP2 Meeting with DOP2	Meeting objectives: - To obtain feedback on adequacy of current nonclinical data package to support conducting Phase 3 pivotal clinical trial and submission of NDA - To obtain feedback regarding proposed study design of planned Phase 3 protocol, including primary and secondary endpoints, use of new DT-specific PRO tool, tumor volume assessment by MRI, and cardiovascular safety monitoring - To obtain concurrence on size of anticipated safety database to support NDA submission - To obtain feedback on eligibility of nirogacestat for fast-track designation
07Jun2018	Orphan Drug Designation Granted letter from Office of Orphan Products Development	Orphan drug designation granted for treatment of DT (aggressive fibromatosis)
23Oct2018	“Study May Proceed” letter from DOP2	Study NIR-DT-301
26Oct2018	Type C Meeting with DOP2 and Clinical Outcome Assessment (COA)	Meeting objectives: - Discuss ongoing development and use of two desmoid-tumor patient-reported outcome (PRO) instruments: Desmoid Tumor Symptom Scale (DTSS) and Desmoid Tumor Impact Scale (DTIS), as fit-for-purpose tools to potentially support labeling, including: - To obtain feedback on qualitative evidence for DTSS and DTIS to measure key concepts important to patients with DT - To obtain feedback on proposed plan to develop quantitative evidence for psychometric properties and scoring of DTSS and DTIS
01Nov2018	“Grant Fast Track” letter from DOP2	Treatment of adult participants with progressive, unresectable, recurrent or refractory DT or deep fibromatosis, to demonstrate a statistically robust and clinically meaningful effect on progression-free survival (PFS) as assessed by blinded independent review, in a randomized, placebo-controlled trial(s)

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Date	Communication Type	Summary
24Apr2019	Type C Meeting with DOP2	Meeting objectives: - Discuss a planned interim analysis for Phase 3 pivotal study (NIR-DT-301) Key outputs: - No interim analysis was conducted - Agency shared constructive and comprehensive feedback on the planned Patient-Reported Outcomes for Study NIR-DT-301
28Aug2019	“Grant BTB” letter from DOP2	Treatment of adult participants with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis
13Jul2020	Type B (Clinical Pharmacology) Meeting with DO2	Meeting objectives included feedback on: - Completed nonclinical ADME studies - Results of human ADME studies (NIR-DT-101 and NIR-DT-102), conducted to determine primary routes of elimination and metabolic pathways, regarding safety and clinical pharmacology implications - Physiological-based pharmacokinetic (PBPK) model addressing risk of nirogacestat as inhibitor of CYP3A4 - Proposed drug-drug interaction (DDI) clinical study (NIR-DT-103) designed to investigate effects of CYP3A4 inhibition and induction on nirogacestat pharmacokinetics and effect of nirogacestat on inhibition and induction of P-glycoprotein - Proposed QT assessments included in DDI clinical study (NIR-DT-103) - Overall clinical pharmacology package for nirogacestat NDA
18Sep2020	Agency-Requested Telecon	Protocol Amendment 4 added clinical progression to the definition of PFS. Clinical progression occurs when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status.
13Nov2020	Type B (BTB) Meeting with DO2	Meeting objectives: Multidisciplinary comprehensive discussion of nirogacestat development program, including planned clinical trials and plans for expediting manufacturing development strategy

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Date	Communication Type	Summary
22Jan2021	Type B (Clinical) Meeting with DO2 and DOP3	Meeting objectives: Gain alignment on proposed amendment to Protocol NIR-DT-301 (DeFi), Statistical Analysis Plan (SAP), and the Psychometric Analysis Plan)
09Apr2021	IND 138207	Based on the severity of the embryo-fetal development (EFD) effects of nirogacestat observed in the dose-range finding study in rats (Study 01214026) and the importance of the gamma-secretase pathway in embryo implantation and development, SpringWorks requested a waiver for conducting the definitive EFD study in rat, the range finding and definitive EFD studies in rabbits, as well as the pre- and post-natal development (PPND) study in rats.
24May2021	Memo	A definitive EFD study in rat, the range finding and definitive EFD studies in rabbits, and the PPND study in rats do not appear warranted to support an NDA. SpringWorks should submit an integrated summary with the NDA using a weight-of-evidence (WOE) approach for reproductive risk assessment. The WOE risk assessment may not rely on product-specific literature for which SpringWorks does not have right-to-reference. A final determination of the acceptability of the nonclinical package will be a review issue.
15Jun2021	IND 138207	In the 6-month carcinogenicity study (Study 20174162), a significant increase in hemangiosarcomas was noted in both male and female transgenic mice with the incidence above historical control values of the test facility. Therefore, SpringWorks requested a waiver for the 2-year carcinogenicity study in rats and requested the Agency's confirmation that this study is unnecessary to support the NDA.
02Aug2021	Type B (Clinical/Clinical Pharmacology) Meeting (WRO) with DO3	Meeting objectives including discussion of topics in anticipation of NDA, including: - Study NIR-DT-301 (DeFi) Statistical Analysis Plan (SAP) - Population pharmacokinetics (PopPK) Analysis Plan - Exposure response Analysis Plan - Concentration-QT (C-QT) Analysis Plan
10Nov2021	Email	Whether Study NIR-DT-104 is sufficient to evaluate varying degrees of hepatic impairment will be a review issue. The need for severe hepatic impairment study will be determined at the NDA review. FDA agreed with plan to proceed with Child-Pugh evaluation with an interim PK report in the NDA, followed by a full CSR upon completion of NCI criteria-based enrollment.

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Date	Communication Type	Summary
11Jan2022	Email	FDA review of Study No. 20174162, titled “A GLP 26-week Carcinogenicity Study of Nirogacestat Dihydrobromide by Oral Gavage in cByB6F1/Tg rasH2 Hemizygous Mice”, concluded the following: • 26-week carcinogenicity study in Tg rasH2 mice was adequate in both male and female mice • There was a numerical increase in whole body hemangiosarcomas in male mice that exceeded the historical control incidence, however, it was determined not to be statistically significant. • The 26-week carcinogenicity study in Tg rasH2 mice was negative for drug-related neoplasms in female mice. Considering these conclusions, FDA recommends submitting an updated justification if SpringWorks proposes to not conduct a 2-year rat carcinogenicity study. The justification could address duration and exposure, carcinogenic potential, genotoxicity, indication and participant population, general toxicology study findings (e.g., histopathology), the findings in the 26-week mouse carcinogenicity study, and/or other relevant factors.
10Mar2022	Proprietary Name Request Conditionally Acceptable	Brand name: OGSIVEO
25Apr2022	Agreed Initial Pediatric Study Plan – Agreement letter from OCEPeRC	Agreed iPSP
03Jun2022	Email	RTOR granted by OCE

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Date	Communication Type	Summary
23Aug2022	Type B (Pre-NDA) Meeting with DO3	Meeting outcomes included: • Agency agreed on the RTOR schedule, format, and content of the NDA • Agency agreed that the pivotal study and accompanying supportive studies will be sufficient to review the NDA • Agency agreed that a REMS will not be required • Recommended to develop a proposal to further study ovarian dysfunction in the post-market setting, and that this proposal should be submitted with the original NDA submission for review • Agency requested data supporting clinical pharmacology

Abbreviations: ADME: absorption, distribution, metabolism, excretion; AF: aggressive fibromatosis; BTM: Breakthrough Therapy Designation; CMC: chemistry, manufacturing, and controls; COA: clinical outcome assessment; C-QT: concentration QT; DDI: drug-drug interaction; DOP: Division of Oncology Products; DT: desmoid tumors; DTIS: Desmoid Tumor Impact Scale; DTRF: Desmoid Tumor Research Foundation; DTSS: Desmoid Tumor Symptom Scale; EFD: embryo-fetal development; EOP: End of Phase; IND: Investigational New Drug; iPSP: Initial Pediatric Study Plan; MRI: magnetic resonance imaging; NDA: New Drug Application; OPQ: Office of Pharmaceutical Outcomes; PBPK: physiologically-based pharmacokinetic(s); PFS: progression-free survival; PopPK: population pharmacokinetics; PPND: pre- and post-natal development; PRO: patient-report outcomes; REMS: Risk Evaluation and Mitigation Strategy; RT: Real Time Oncology Review; SAP: statistical analysis plan; WOE: weight of evidence; WRO: written request only.

The FDA's Assessment:

The Applicant has outlined the key regulatory interactions between the Applicant and FDA. Refer to Section 8 below (Study Design) for FDA's position and comments regarding the change in study design to allow for clinical progression events in the definition of progression free survival.

In addition, the following interactions took place:

- September 17, 2019: Executive Carcinogenicity Assessment Committee (ECAC). Recommendations provided by the ECAC were contingent on the results of the final report not being notably different from those in the draft report.
- April 14, 2020, May 1, 2020, May 15, 2020, and June 4, 2020: Requests for FDA feedback. The Applicant submitted dissolution data and requested feedback from FDA on the acceptability of the proposed dissolution method.
- November 21, 2019: Type C meeting to obtain guidance on several aspects of the CMC development plan for nirogacestat.
- December 4, 2020: FDA provided comments for the pivotal study NIR-DT-103.

- April 4, 2022: Advice Letter requesting a revised PRO SAP, version 5.0 for NIR-DT-301.

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations (OSI)

Nirogacestat is a New Molecular Entity, so FDA inspected the Applicant (SpringWorks Therapeutics, Inc), the imaging contract research organization (b) (4) and 3 domestic clinical sites that enrolled large number of patients and/or where most of the patients received the active drug, nirogacestat. The investigators at the clinical sites were Drs. Brian Van Tine (site #06), Mrinal Gounder (site #17), and Priscilla Merriam (site #22), and each site enrolled 5 to 14 patients. FDA has not previously inspected the Applicant or Dr. Merriam, and FDA had previously inspected (b) (4), and the other 2 investigators.

FDA inspection revealed discrepancies in the Applicant's reporting of sum of target tumor measurements for 7 patients; and potential deficiencies in the financial disclosure, and conflict of interest provided by the Applicant. Inspections of the clinical investigators revealed no discrepancies or regulatory violations.

FDA inspection of (b) (4) revealed discrepancies for 5 patients in the sum of target tumor measurements between the blinded, independent reads and the data listings submitted to the FDA by the Applicant. The inspection revealed that the discrepancies occurred at the Applicant, prior to the submission to FDA. FDA asked the Applicant to address this discrepancy, and the Applicant initiated an internal investigation. The Applicant's internal investigation found 2 additional patients who had discrepancies in the sum of target tumors, and the Applicant determined that the root cause of discrepancies was a programming error by the CRO responsible for the statistical analysis and development of SDTM and ADaM datasets for Study NIR-DT-301 (b) (4). The programming error added measurements of new lesions into the sum of target tumors, which error resulted in incorrect sum of target tumor measurements for 7 out of 142 patients enrolled in Study NIR-DT-301. The Applicant subsequently submitted a corrective and preventative action (CAPA) plan, as well as an Amendment to the CSR with the corrections in the sum of target tumor measurements for these 7 patients, and the associated efficacy tables, listings, figures, and datasets. FDA reviewed the datasets submitted on May 5, 2023, and was able to replicate the relevant tables and figures in the Amendment to the CSR.

FDA inspection also observed deficiencies in financial disclosure and conflict of interest reporting by the Applicant. Three investigators (b) (6) and were paid: (b) (6) (site # (b) (6)), (b) (6) (site # (b) (6)), and (b) (6) (site # (b) (6)). However, only (b) (6) disclosed that she received >\$25,000 on

her financial disclosure form (FDF) and the other investigators listed no monetary stipend on their FDF. The Applicant reported no financial disclosures for any investigator or sub-investigator involved in Study NIR-DT-301 on their Form FDA 3454. (b) (6) (site # (b) (6)) disclosed (b) (6) (receiving <\$25,000), and this service was not disclosed by the Applicant.

FDA inspection also revealed that the Applicant did not have a procedure in place for evaluation of conflict of interest. The Applicant responded that they will consider expanding their existing financial disclosure procedure to include capturing conflict of interest and updating their financial disclosure process.

In light of this report from OSI, the FDA clinical reviewer requested the Applicant to resubmit the financial disclosures forms and to provide the details of the disclosable financial arrangements or interest the Applicant had with clinical investigators. The Applicant responded that the financial disclosure forms they submitted were accurate with “no reportable financial conflicts of interest for all principal/sub-investigators (including (b) (6)) for Study NIR-DT-301.” The Applicant provided further details regarding (b) (6) and (b) (6) financial disclosures based on comments these investigators had provided in their financial disclosure forms. The Applicant stated that (b) (6), which were independent of her work related to Study NIR-DT-301. (b) (6), for which she did not receive cumulative payments $\geq$ \$25,000. (b) (6) which were independent of his work related to Study NIR-DT-301 and for which (b) (6) was compensated <\$25,000. (b) (6) also disclosed that (b) (6) a (b) (6) monetary value of \$25,000.” The Applicant states that (b) (6).

Based on the Applicant’s response to FDA clinical reviewer’s request regarding the financial disclosure, it appears that (b) (6) and (b) (6) received compensation for (b) (6) that were not related to NIR-DT-301. (b) (6) did receive compensation related to NIR-DT-301, i.e., compensation for (b) (6), but the compensation was not more than \$25,000. Thus, FDA agrees that the financial disclosure forms submitted by the Applicant were accurate and that the investigators did not have financial interests or arrangements as defined by 21CFR54.2. Furthermore, the financial arrangements are unlikely to impact the efficacy outcome of the trial given that the primary efficacy measure of NIR-DT-301 was determined by blinded, central review. Although there was a limited number of clinical progression events in the study, the overall results were supported by an analysis limited to an assessment of radiographs alone (as well as blinded assessment of ORR and PRO assessments).

The Applicant also stated that they audited 8 clinical sites (including (b) (6)) during the trial and used data analytics software (b) (4) to programmatically perform surveillance for data irregularities.

Based on the inspections, NIR-DT-301 appears to have been conducted adequately, and the data generated by the inspected clinical investigators and the imaging CRO appear adequate for review. Based on the review of the Amendment to CSR and datasets submitted to on May 5, 2023, the data submitted to support NIR-DT-301 are adequate for review.

Lastly, errors in datasets that affected up to 16 tables and 6 figures for laboratory summary and shift tables, and one table for concomitant medications were identified. These updated, corrected tables and figures were received on May 5, 2023.

4.2. Product Quality

The FDA CMC review team determined the application to be acceptable from a product quality review team. The review entered into FDA's DAARTS system on May 24, 2023, with a revision on June 5, 2023.

The CMC team concluded (below copied from the CMC memos):

- The assessment of DS was adequate. Nirogacestat hydrobromide is the USAN name for the drug substance (DS). Nirogacestat hydrobromide is a white to off-white powder and a crystalline substance. Nirogacestat hydrobromide drug substance is a salt containing two hydrogen bromide molecules.
- Nirogacestat hydrobromide is manufactured (b) (4)
(b) (4)
- The DP s composed of compendial excipients, manufactured from conventional manufacturing processes, stored in standard presentations for solid oral dosage forms, and stored at controlled room temperature. No product quality issues related to identity, assay, purity, or quality were identified during review.
- The manufacturing process is (b) (4)
(b) (4) The intended commercial manufacturing batch size is identical to exhibit batches. The manufacturing equipment proposed for commercial batches are of same size and operating principle as of the exhibit batches. All clinical studies were conducted using drug product

manufactured at the commercial manufacturing site (b) (4). No changes in manufacturing process and formulation are identified from clinical to registration and proposed commercial batches.

- All manufacturing facilities including testing and packaging sites proposed for the commercial manufacturing of nirogacestat tablets 50 mg were found acceptable based on GMP compliance and firm's prior experience in performing the proposed responsibilities. No preapproval inspection was recommended for any facility. The primary drug product manufacturing site is (b) (4). The drug substance manufacturing site is (b) (4).
- The application is recommended for approval with a 48-month shelf life for (b) (4) 180-count configurations when stored "at 20°C-25°C (68°F-77°F). Excursions are permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature."

4.3. Clinical Microbiology

The CMC review indicated that "production scale batches of nirogacestat hydrobromide drug substance were tested for TAMC, TYMC, and absence of E. Coli. The highest TAMC level observed was 20 CFU/g and no TYMC levels have been observed above 10 CFU/g. Batch history appears to indicate a low risk of microbial contamination or viability for the drug substance. This and the fact that the DS is not hygroscopic justifies no controls in the release specification for microbial limits."

CMC also found that the microbial limit testing for DP at release and on stability to be acceptable. The microbiology laboratory at SGS France had been covered in a previous GMP inspection. Overall the Application was acceptable from a microbiological (manufacturing perspective).

4.4. Devices and Companion Diagnostic Issues

No devices or companion diagnostics were used to support this NDA.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

The established pharmacologic class of nirogacestat is gamma secretase inhibitor. By inhibiting the activity of gamma secretase, nirogacestat blocks the proteolytic activation of Notch, which has a role in cellular proliferation, differentiation, survival, and oncogenesis.

Nirogacestat inhibited the activity of gamma secretase in vitro with an IC₅₀ of 6.2 nM. In a cellular assay using human embryonic kidney (HEK) 293 cells that express a constitutively active NΔE mutant of Notch, nirogacestat inhibited the activity of Notch intracellular domain (NICD) with an IC₅₀ of 7.7 nM. In human peripheral blood-acute lymphoid leukemia (HPB-ALL) cells that harbor Notch mutations, nirogacestat inhibited the activity of NICD with an IC₅₀ of 41 nM and induced growth inhibition with an IC₅₀ of 32 nM. Nirogacestat also demonstrated growth inhibition in various Notch expressing patient-derived desmoid tumor cell lines in vitro with IC₅₀s of 4-160 μM. Nirogacestat exhibited anti-tumor activity in numerous Notch-driven tumor xenograft models in mice but did not induce tumor growth inhibition in a non-Notch-driven tumor xenograft model.

SpringWorks conducted stand-alone GLP-compliant safety pharmacology studies in rats and dogs to assess the effect of nirogacestat on the central nervous system, pulmonary function, and the cardiovascular system. There were no nirogacestat-related adverse effects on the central nervous system, pulmonary function, or the cardiovascular system at single doses up to 500 mg/kg. Nirogacestat blocked the hERG channel with an IC₅₀ of 1 μM; however, this IC₅₀ is greater than 100 times the free C_{max} in humans at the 150 mg BID dose. Consistent with these findings, nirogacestat did not have effects on QT prolongation clinically or in in vivo nonclinical studies.

The toxicity of nirogacestat was assessed in GLP-compliant 3-month repeated-dose toxicity studies in rats and dogs. Shorter duration repeated-dose toxicity studies were also conducted with nirogacestat and the findings were generally consistent with 3-month repeated-dose toxicity studies. Rats received up to 25 mg/kg (50 mg/kg/day) oral nirogacestat, twice per day, for 3 months, resulting in mean exposure levels (AUC) up to 3.4 times the AUC of 6740 ng.h/mL in patients with desmoid tumors at the 150 mg BID dose. Dogs received up to 5 mg/kg (10 mg/kg/day) oral nirogacestat, twice per day, for 3 months, resulting in mean exposure levels (AUC) up to 0.46 times the AUC of 6740 ng.h/mL in patients with desmoid tumors at the 150 mg BID dose. Toxicity was generally consistent across species and consisted of intestinal

hyperplasia, fibrinoid necrosis of blood vessels, lymphoid depletion, nephropathy, liver toxicity, and reproductive organ toxicity. Additional toxicities that only occurred in rats consisted of thickening of the hypertrophic cartilage zone, fibrosis/necrosis in the heart, and epidermal cysts. Male reproductive organ toxicity consisted of seminiferous tubule abnormalities, Sertoli cell degeneration, and epididymal oligospermia. Female reproductive organ toxicity consisted of ovarian degeneration/necrosis/atrophy, oocyte mineralization, and mammary acinar hyperplasia.

In humans, nirogacestat can cause diarrhea, stomatitis, and ovarian dysfunction at the recommended 150 mg BID dose. Loose stool and intestinal hyperplasia occurred in rats and dogs administered nirogacestat. Intestinal hyperplasia was associated with epithelial inflammation and necrosis in dogs. Consistent with these adverse intestinal findings, Notch has been reported to regulate intestinal cell differentiation and inhibition of Notch drives goblet cell proliferation (Fre, et al., 2005; Milano, et al., 2004; Van Es, et al., 2005; Wong, et al., 2004). Notch also reportedly regulates gastric cell differentiation (Demitrack and Samuelson, 2016) which may contribute to stomatitis in humans. Regarding ovarian dysfunction in humans, ovarian degeneration/necrosis/atrophy and oocyte mineralization occurred in animals administered nirogacestat and was consistent with Notch regulation of mammalian folliculogenesis (Vanorny and Mayo, 2014).

SpringWorks evaluated the effect of nirogacestat on male and female fertility in a dedicated GLP-compliant study. Male rats received up to 40 mg/kg/day of oral nirogacestat for 65 days including 28 days prior to mating with untreated female rats. Female rats received up to 40 mg/kg/day of oral nirogacestat for 35 days including 14 days prior to mating with untreated male rats and through Gestation Day 7. Nirogacestat resulted in reduced fertility when administered to male rats at ≥ 5 mg/kg/day (approximately 0.16 times the 150 mg BID dose based on body surface area (BSA)) or female rats at ≥ 20 mg/kg/day (approximately 0.65 times the 150 mg BID dose based on BSA). Nirogacestat resulted in a lack of fertility when administered to male or female rats at ≥ 40 mg/kg/day (approximately 1.3 times the 150 mg BID dose based on BSA). In pregnant female rats, nirogacestat increased pre-implantation loss at ≥ 20 mg/kg/day (approximately 0.65 times the 150 mg BID dose based on BSA).

To address the potential for nirogacestat-mediated reproductive activity, SpringWorks conducted a preliminary embryo-fetal development study with nirogacestat in rats. Daily oral administration of nirogacestat to pregnant rats resulted in decreased fetal body weights, post-implantation loss, and fetal subcutis edema at doses ≥ 20 mg/kg/day (approximately 0.85 times the exposure in patients with desmoid tumors based on AUC at the 150 mg BID dose). Based on

these adverse findings, the team recommends a warning for embryo-fetal toxicity in Section 5 of the labeling. Because of the potential for embryo-fetal toxicity, a recommendation for females and males of reproductive potential to use contraception during treatment with nirogacestat and, based on a half-life of 25 hours, for 1 week after the last dose is included in Section 8.3 of the labeling. Lactating women are advised not to breastfeed during treatment with nirogacestat and, based on a half-life of 25 hours, for 1 week after the last dose.

Nirogacestat was not considered genotoxic since it was not mutagenic in a bacterial reverse mutation (Ames) assay and was not clastogenic in an in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay.

To support continuous daily oral dosing of nirogacestat, SpringWorks conducted a 26-week oral carcinogenicity study with nirogacestat in transgenic rasH2 mice. Mice received up to 100 mg/kg/day of oral nirogacestat, resulting in mean exposure levels (AUC) less than those in humans at the 150 mg BID dose. The results showed an increased incidence of whole body hemangiosarcomas in 100 mg/kg/day males that was above the historical control value for the test facility but did not reach statistical significance for trend and pairwise comparisons. The study was negative for drug-related neoplasms in female mice. Overall, the result of the transgenic mouse carcinogenicity study was concluded to be negative.

Although activation of Notch signaling is associated with various cancers, literature reports that Notch signaling may paradoxically suppress tumorigenesis in certain tumor types including squamous cell carcinoma (SCC) and neuroendocrine tumors (Zhou, et al., 2022). Inhibition of Notch signaling has been associated with an increased incidence of skin cancers in humans (Coric, et al., 2012; Doody, et al., 2013; Penninkilampi, et al., 2016), and administration of nirogacestat to patients with desmoid tumors resulted in cutaneous squamous cell carcinoma and/or basal cell carcinoma in five patients, with no malignancies occurring in the placebo arm. Based on these adverse clinical findings, the clinical team recommends a warning and precaution for cutaneous malignancies in the nirogacestat label. No additional nonclinical studies to assess the tumorigenic potential of nirogacestat in animals are warranted based on the inclusion of the malignancy warning in the label.

Nirogacestat is not expected to demonstrate phototoxicity given that it does not absorb light in the ultraviolet A and B (UVA-UVB)/visible range from 290 to 700 nm.

There are no approvability issues from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for nirogacestat.

5.3. Pharmacology

Primary Pharmacology

The Applicant's Position:

Nonclinical pharmacology characterized the effects of nirogacestat in cell-free assays, cell culture experiments, and animal models of human disease. Early nonclinical and clinical investigations were conducted with nirogacestat to evaluate potential therapeutic use in the treatment of Alzheimer's disease due to the involvement of gamma-secretase (GS) in the cleavage of the amyloid β peptide ($A\beta$); [REDACTED] (b) (4)
in Study A8641002 [REDACTED] (b) (4)

[REDACTED] Therefore, nirogacestat was evaluated in a variety of Notch-driven tumor models including T-cell acute lymphoblastic leukemia (T-ALL), breast cancer, colorectal cancer (CRC), pancreatic cancer, liver cancer, and prostate cancer. Results of early studies in participants with solid tumors demonstrated evidence of therapeutic activity in participants with DT, which led to the selection of this indication for further clinical development.

In Vitro Pharmacology

In vitro evaluation of enzyme kinetics was completed with cell-free assays using the human isoform of GS extracted from HeLa cells and a recombinant human APP-C100-FLAG peptide purified in *E. coli* (PF-03084014-Pharm-001). Cellular assays were also conducted using the human embryonic kidney (HEK) 293 stable cell line that expresses NΔE construct (containing aa1727-2813 of NOTCH1). Nirogacestat displayed potent activity with IC₅₀ of 7.7 nM (0.34 nM free) for NICD inhibition (PF-03084014-Pharm-001). In human peripheral blood-acute lymphoid leukemia (HPB-ALL) cells that harbor *NOTCH1* mutations, the effects of nirogacestat on growth and NICD inhibition were assessed with the key biochemical and cellular properties provided in [Table 2](#). For comparison to observed human serum values at steady state after a 150 mg BID dosing regimen, free mean maximum observed concentration (C_{max}) and minimum observed concentration (C_{min}) are estimated at 10.2 nM and 2.2 nM, respectively.

Table 2: Summary of Key Pharmacologic Properties of Nirogacestat

Assay	Free Nirogacestat IC50	
	nM	ng/mL
Biochemical Activity		
Biochemical A β assay ^a	6.2	3.0
Kinetic analysis of A β assay ^a	--	--
Cellular Activity		
HEK293 NICD DELFIA assay ^b	0.34	0.17
HPB-ALL NICD inhibition ^c	1.82	0.89
HPB-ALL growth inhibition ^c	1.40	0.69
In Vivo Pharmacodynamics		
Plasma IC50 by PK/PDx analysis ^d	0.42	0.21

Abbreviations: A β : amyloid β peptide; DELFIA: Dissociation-enhanced lanthanide fluorescence immunoassay; fu: unbound fraction; GS: gamma-secretase; HPB-ALL: human peripheral blood-acute lymphoid leukemia; IC50: half-maximal inhibitory concentration; NICD: Notch intracellular domain; PK: pharmacokinetics; PDx: pharmacodynamics.

^a Biochemical inhibition of GS was determined using detergent-solubilized membranes from HeLa cells as an enzyme source and affinity-purified recombinant human APP-C100-FLAG peptide produced in *E. coli* as a substrate. The GS cleavage product A β ₁₋₄₀ was detected using a DELFIA-based immunoassay.

^b IC50 values were determined using NICD levels after exposure of HEK293 cells to nirogacestat. NICD was detected using a DELFIA-based immunoassay and are reported with correction for fu.

^c IC50 values were determined after exposure of HPB-ALL cells to serial dilutions of nirogacestat. IC50 for NICD was determined by Western blot analysis for cell lysates and IC50 for growth inhibition was determined using a resazurin assay.

^d IC50 values were determined by PK/PDx modeling using an indirect response model, with NICD as the PDx endpoint, and based on naïve pooling of individual observed PK and tumor PDx data. The model used data from HPB-ALL xenograft tumor models in mice and IC50 values are reported with correction for fu.

Nirogacestat and Notch Signaling in Desmoid Tumors

Nirogacestat was evaluated for antitumor effects in 7 patient-derived DT cell lines ([Shang et al. 2015](#)). *NOTCH1*, *JAG1*, and *HES1* were shown to be present in all patient lines, with high levels of nuclear localization of NICD confirming active Notch signaling. Dose-dependent decreases in NICD and *HES1* were confirmed by Western blot in 2 of the cell lines and a varying degree of growth inhibition was determined using cell proliferation assays in 5 of the cell lines at concentrations ranging from 0.01 to 10 μ M over a 27-day treatment period. For these patient-derived cells, the IC50 for growth inhibition ranged from 4.19 μ M in the most sensitive line to 158.8 μ M in the most resistant line. Cell migration and invasion assays were conducted with 5 of the patient-derived cell lines and all showed significant reductions in migration and invasion after 7 days treatment with 10 μ M nirogacestat. The IC50 values for growth inhibition

and the migration reduction observed at 10 μ M are higher than the total and free maximum serum concentrations observed at steady state in Study A8641014 (geometric mean: 2.54 μ M and 10.2 nM, respectively). However, 4 of the 5 evaluated cell lines showed statistically significant growth inhibition at 1 μ M, with 3 of the 5 showing statistically significant growth inhibition at 0.01 μ M. Therefore, while the migration experiments may not conclusively support expected effects of nirogacestat at therapeutically relevant exposures, the effects on Notch-target expression and growth inhibition do support a role for GSI-mediated inhibition of Notch signaling as a potential mechanism for nirogacestat in the treatment of DT.

In Vivo Pharmacology

The antitumor activity of nirogacestat in a range of Notch-driven tumor models (T-ALL) and a non-Notch-driven tumor model (GTL-16) is provided in [Table 3](#).

Table 3: Antitumor Activity of Nirogacestat in Notch-Driven Models

Tumor Model	Tumor Type	Notch Mutation	Dose (mg/kg)	Schedule	%TGI ^a (Day ^b)	p-Values Treated vs Control (Final Day)	Free AUC ^c (ng·h/mL)
SupT1	T-ALL	Activating <i>NOTCH1</i> translocation	17	BID	0 (13)	NS	15
			50	BID	49 (13)	NS	19
			150	BID	91 (13)	< 0.05	63
HPB-ALL	T-ALL	Activating <i>NOTCH1</i> mutation	17	BID	63 (14)	< 0.01	2
			50	BID	43 (14)	NS	14
			150	BID	109 (14)	< 0.01	103
MDA-MB-231	BC	<i>NUMB</i> deletion	50	BID	58 (14)	< 0.05	32
			100	BID	49 (14)	NS	80
			150	BID	70 (14)	< 0.01	148
DLD1	CRC	Activating <i>KRAS</i> mutation	17	BID	0 (18)	NS	1
			50	BID	57 (18)	NS	22
			150	BID	83 (18)	< 0.05	88
BxPC3	Pancreatic	Activating <i>NOTCH1</i> signaling	200	QD	80 (29)	< 0.01	NR
A2780	Ovarian	<i>NOTCH3</i> gene amplification	150	BID	46 (14)	NS	NR
GTL-16	GIST	None	200	BID	0 (15)	NA	NR

Abbreviations: AUC: area under the curve; BC: breast cancer; BID: twice daily; CRC: colorectal cancer; GIST: gastrointestinal stromal; HPB-ALL: human peripheral blood-acute lymphoid leukemia; NA: not applicable; NR: not reported; NS: not significant, QD: once daily; TGI: tumor growth inhibition.

^a Percent (%) values shown are the % of TGI measured by calipers on last day for drug-treated compared to vehicle-treated mice and are calculated as: $100 * \{1 - [(Treated_{Day\ last} - Treated_{Day\ 1st}) / (Control_{Day\ last} - Control_{Day\ 1st})]\}$.

^b Study duration in days.

^c AUC was determined using plasma samples collected at 1, 4, 24 h for SupT1, HPB-ALL, and MDA-MB-231 models; 1, 4, 7 h for DLD1 model on the last day of the TGI studies.

Antitumor Efficacy and Association with NICD Inhibition After Oral Administration

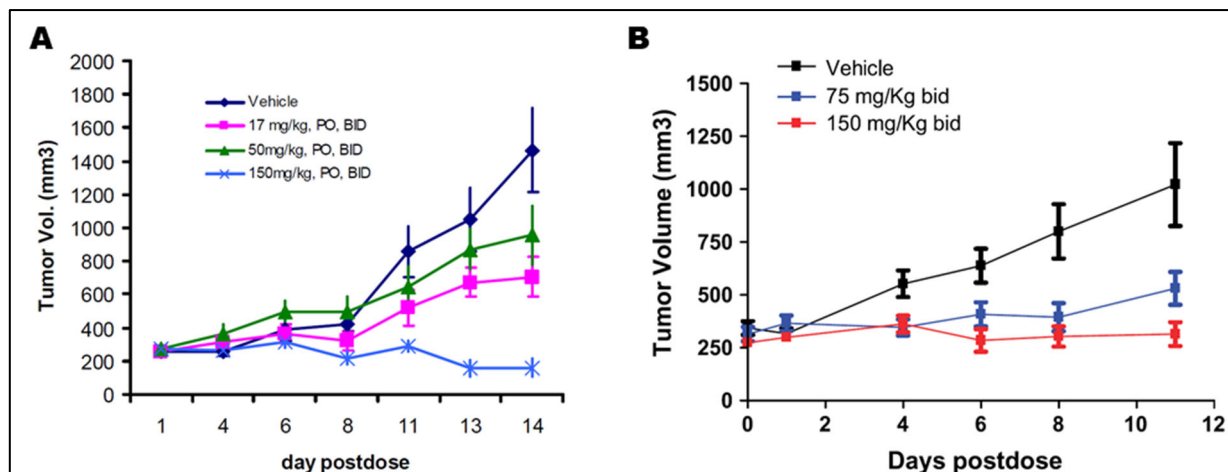
A series of experiments were performed with nirogacestat in human tumor xenograft models in athymic nu/nu mice to evaluate its ability to reduce NICD levels in tumors and establish a PK/PDx relationship for NICD reduction to plasma concentration of nirogacestat. In addition, the ability of nirogacestat to inhibit tumor growth or exhibit cytoreductive activity in mouse models and the relationship of antitumor efficacy to plasma concentration were also assessed.

PK/PDx relationships for NICD inhibition were assessed exclusively in the HPB-ALL xenograft model due to the robust and consistent level of NICD inhibition observed in this model. To evaluate the NICD pharmacodynamic (PDx) response to nirogacestat, HPB-ALL tumors were harvested at several time points after oral administration at 2 dose levels (50 and 200 mg/kg) in single-dose studies. NICD levels in tumors were quantitated by Western blot analysis using an antibody against NICD. At 50 mg/kg, > 50% reduction in NICD was observed by 4 hours and approximately 70% reduction in NICD was obtained at 24 hours postdose. The 200-mg/kg dose level was observed for up to 72 hours and achieved maximal NICD inhibition of approximately 80%, with the duration of NICD inhibition remaining greater than 40% for up to 48 hours. Similar results were also observed in the SupT1 T-ALL xenograft model.

The HPB-ALL xenograft model was utilized to evaluate the relationship of TGI to time, dose-dependent inhibition of NICD, and plasma exposure of nirogacestat. To assess antitumor efficacy in HPB-ALL model, initial repeat dose studies were performed at 3 dose levels (17, 50, and 150 mg/kg BID for 14 days; PF-03084014-Pharm-001). Tumor volume was measured utilizing electronic Vernier calipers. Nirogacestat demonstrated robust antitumor activity in this model after 14 days of treatment in tumor-bearing mice ([Figure 1A](#)). Maximum TGI (> 100%) by nirogacestat occurred at 150 mg/kg, with tumor regression observed in 6 out of 8 animals. A similar repeat dose study in the HPB-ALL xenograft using doses of 75 and 150 mg/kg BID was reported for up to 11 days ([Wei et al. 2010](#)). Maximal median reduction in tumor volume of approximately 75% and 92% was observed at the 75- and 150-mg/kg dose levels by Day 11, respectively ([Figure 1B](#)). Nirogacestat was well tolerated as no significant weight loss, morbidity, or mortality was observed at doses up to 100 mg/kg BID. At 150 mg/kg, slight body weight loss (10%–15%) was observed sporadically and this occurred usually after ~10 days of dosing. Dosing holidays were given to mice that lost > 10% body weight until the body weight returned to normal. Additional immunohistochemical and gene expression assays in these studies supported the inhibition of Notch signaling and induction of apoptosis as associated effects of nirogacestat administration ([Wei et al. 2010](#)). Tumor samples at Day 7 of 150 mg/kg BID treatment showed significant reduction of NICD by Western blot relative to vehicle controls

and notable reduction of expression in Notch-target genes *HES1* and *C-MYC* by reverse transcription polymerase chain reaction (RT-PCR) evaluation. Day 7 samples from the same treatment also exhibited a notable reduction of Ki67 staining and an increase in activated caspase-3 levels.

Figure 1: Tumor Volume Reduction in Notch-driven HPB-ALL Xenograft Models



The robustness of the HPB-ALL models suggests the mechanism of TGI is partly mediated through cell growth inhibition by nirogacestat. Tumor volume reduction was largely dose- and drug exposure-dependent with an exception at the lower dose levels (17 or 50 mg/kg). The exact reason for this observation is unclear although it is likely due to the high variability in tumor size of this model.

Key conclusions:

- At 150 mg/kg, inhibition of NICD between ~40%-80% was required to achieve complete inhibition of tumor growth (109% TGI at 150 mg/kg BID × 14d).
- At 50 mg/kg, less NICD inhibition (20%-40%) was consistent with partial inhibition of tumor growth (43% TGI at 50 mg/kg BID × 14d).
- Continuous NICD inhibition for the duration of the administration schedule at either dose level is necessary to achieve corresponding TGI.

PK/PDx Modeling

The PK/PDx data used for the modeling were based on 2 different studies with testing dose levels of 50 and 200 mg/kg over a 72-hour period (PF-03084014-Pharm-001). Based on this PK/PDx modeling, the plasma free IC₅₀ for NICD inhibition in vivo was estimated at 0.42 nM, which is consistent with free cellular potency determined in HEK293 cells (Table 2). Single-dose PDx analysis revealed that the 50-mg/kg dose level yielded ~40%-50% NICD reduction, which correlates with ~50% TGI upon continuous BID dosing at this dose level. At 50 mg/kg, the free plasma area under the plasma concentration-time curve from 0 to 24 hours (AUC₀₋₂₄) was 56

ng·h/mL and free plasma steady-state average concentration (C_{avg}) was 2.3 ng/mL (4.8 nM). Taking into consideration protein binding differences between mouse and human, this target free plasma C_{avg} of 2.3 ng/mL equates to a total human plasma C_{avg} of 575 ng/mL, and this free plasma AUC_{0-24} of 56 ng·h/mL equates to a total human plasma AUC_{0-24} of 14,000 ng·h/mL. These predicted efficacious exposures are most comparable to the daily AUC of 12,860 ng·h/mL observed at steady state in participants receiving 150 mg BID in Study A8641014.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Note that the steady state $AUC_{0-\tau}$ (where $\tau=12$ hrs) in patients with desmoid tumors was 3370 ng·hr/mL after administration of nirogacestat at 150 mg BID.

Secondary Pharmacology

The Applicant's Position:

Nirogacestat was evaluated for interaction with a number of other proteases, receptors, ion channels, and kinases. Activity (IC_{50}) in a broad panel of common receptors was $> 1 \mu M$ in all assays (757060). The IC_{50} was determined for all receptors where inhibition was greater than 50% at the screening concentration of 10 mM. Testing at other aspartic proteases (pepsin A, BACE 1 and cathepsin D) or serine proteases (chymotrypsin A, trypsin) showed negligible inhibition at 20 mM (PF-03084014-Pharm-001). Nirogacestat also showed less than 25% inhibition at 10 mM in a panel of 10 kinase enzymes, including ABL, CK1d, GSK3 β , IKK2, IKKi, LCK, MK2, P38, PKA, PKCzeta (PF-03084014-Pharm-001). By comparison, the human serum free C_{max} observed at steady-state in Study A8641014 was 4.98 ng/mL (10.2 nM) after oral administration of 150 mg BID. Therefore, these off-target hits pose a minimal risk at the current therapeutic dose.

The FDA's Assessment:

FDA generally agrees with the Applicant's position; however, FDA notes the units in the Applicant's position that are in mM should be μM based on the study report.

Safety Pharmacology

The Applicant's Position:

The safety pharmacology of nirogacestat was evaluated in vitro and in vivo as outlined in [Table 4](#). In vitro, nirogacestat and metabolite M283 (PF-03015273) were assessed for binding to the human ether-à-go-go related gene (hERG) to assess the risk of QT prolongation. The $1.0 \mu M$ hERG IC_{50} is 98-fold over the human free geometric mean C_{max} of 4.98 ng/mL (10.2 nM) after administration of 150 mg BID as observed in Study A8641014. For the in vivo studies, a respiratory and neurobehavior study were conducted in rats, while a stand-alone

cardiovascular study was conducted in telemetered dogs. There were no hazards identified in the safety pharmacology studies that would pose a risk in humans.

Table 4: Safety Pharmacology

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses or Concentration	Gender and No. per Group	Noteworthy Findings	GLP	Study No.
Neurological Function	Rat/Sprague-Dawley	Oral Gavage	0, 5, 20, or 500 mg/kg	M/6	No adverse findings	Yes	06GR112
Pulmonary Function	Rat/Sprague-Dawley	Oral Gavage	0, 5, 20, or 500 mg/kg	M/6	Non-adverse increase in respiration at 500 mg/kg group	Yes	06GR115
Cardiovascular Function	Dog/Beagle	Oral Gavage	0, 2, 80, and 500 mg/kg	M/4 (1 per dose per period)	No significant changes to heart rate, blood pressure, or ECG parameters.	Yes	06GR083
hERG Potassium Channel	hERG-transfected HEK293 cells	In vitro	0.3, 1, 3, and 10 μ M	NA	The IC ₅₀ was 1.0 μ M	Yes	181008.TQV

Abbreviations: Admin: administration; ECG: electrocardiogram; GLP: good laboratory practice; hERG: human Ether-á-go-go Related Gene; IC₅₀: half maximal inhibitory concentration; M: Male; NA: Not applicable; No: number.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. In a non-GLP study, the in vitro effect of the M283 metabolite (PF-03015273) on the hERG channel current expressed in HEK293 cells was > 30 μ M.

5.4. ADME/PK

The Applicant's Position:

The in vitro and in vivo nonclinical pharmacokinetic (PK) studies were designed to characterize the absorption, distribution, metabolism, and excretion (ADME) properties of nirogacestat. These studies enabled thorough evaluation of its pharmacological and toxicological profiles in preclinical animal models. Toxicokinetic (TK) data for nirogacestat were derived from Good

Laboratory Practice (GLP) studies using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods validated under GLP conditions. Plasma protein binding and blood-to-plasma ratio were determined in mouse, rat, dog, and human. Brain penetration was evaluated in mouse and tissue distribution and excretion was evaluated in rat and dog. Initial in vitro metabolite profiling was performed across species to support selection of toxicology species. The in vitro cytochrome P450 (CYP) inhibition and induction potential of nirogacestat was also evaluated and nirogacestat was examined for effects on drug transporters in cell lines expressing specific hepatic and renal transporters to guide drug interaction risk assessments. Pharmacokinetic/pharmacodynamic (PK/PDx) modeling was performed on nirogacestat-mediated inhibition of NICD levels in tumors as a biomarker for inhibition of tumor growth. The ADME characterization of nirogacestat is sufficient to support the NDA.

Absorption										
Nirogacestat exhibits moderate permeability in Madin-Darby canine kidney (MDCK) cells (19SPRWP7), and at a pH range of 1.2 to 6.0 a 150 mg dose will be 100% dissolved; solubility decreases at pH $\geq$ 6.5 (19SPRWP12). PK parameters of nirogacestat following oral and intravenous (IV) administration of nirogacestat to male Sprague-Dawley rats (Report DM2006-03084014-018) and male and female Beagle dogs (Report DM2006-03084014-023) is provided in Table 5.										
Table 5: Mean ($\pm$ StD) PK Parameter Values of Nirogacestat in Rats and Dogs Following Single-Dose Administration										
Species (Strain)	Sex/n	Dose (mg/kg)	Route	C_{max} (ng/mL)	T_{max} (h)	t_{1/2} (h)	CLp^a (mL/min/kg)	V_{ss} (L/kg)	AUC_{inf} (ng*h/mL)	F (%)
Rat (Sprague-Dawley)	M/4	5.0	Oral	25.3 $\pm$ 19.6	1.0 $\pm$ 0.0	NA	NA	NA	106 $\pm$ 56	3.32 $\pm$ 1.74
	M/3	2.0	IV	NA	NA	11.7 $\pm$ 2.6	26.9 $\pm$ 6.3	17.4 $\pm$ 5.5	1280 $\pm$ 270	NA
Dog (Beagle)	M+F/3	4.0	Oral	280 $\pm$ 32	1.2 $\pm$ 0.8	NA	NA	NA	1400 $\pm$ 380	14.9 $\pm$ 4.0
	M+F/3	0.1	IV	NA	NA	12.4 $\pm$ 3.2	7.91 $\pm$ 3.29	4.66 $\pm$ 1.11	236 $\pm$ 95	NA
Abbreviations: AUC_{inf}: area under plasma concentration-time curve from time 0 to infinity; CLp: systemic plasma clearance; C_{max}: maximum observed concentration; F: female; F (%): absolute oral bioavailability; h: hour; IV: intravenous; M: male; NA: not applicable; T_{max}: time to reach C_{max}; StD: standard deviation; t_{1/2}: apparent terminal elimination half-life; V_{ss}: apparent volume of distribution at steady state. ^a Plasma clearances shown are based on blood-to-plasma ratios in the rat and dog (0.514 and 0.387, respectively), the corresponding blood clearances were 52.3 and 20.4 mL/min/kg in the rat and dog.										
Absolute/Relative Bioavailability			In nonclinical species, rats and dogs, oral bioavailability was 3% and 15%, respectively.							
T_{max}			In toxicology studies, T _{max} ranged from 0.5 to 7 hours.							

Distribution	
Volume of Distribution	Estimates of apparent volume of distribution at steady state for nirogacestat were greater than total body water in rats and dogs, suggesting that nirogacestat readily distributes to tissues in these species.
Protein Binding	Initial plasma protein binding was reported in DM2006-03084014-020; however, the human plasma unbound fraction from that study was later found to be erroneously high. Serum protein binding was re-evaluated (191159, 135033, and 21SPRWP4) for mouse (CD1), rat (Sprague-Dawley), and dog (Beagle) with unbound free fractions of 0.2% for all three species. The fraction unbound of 0.4% was determined for human plasma and serum in confirmatory studies (2103037-03 and 21SPRWP2).
Tissue Distribution	A whole-body autoradiography study showed that radioactivity derived from [¹⁴ C] nirogacestat is widely distributed throughout the body as early as 30 minutes postdose (8299694). CNS exposure may be possible; however, radioactivity was primarily concentrated in non-circumventricular tissues. The extensive metabolism observed in mass-balance studies conducted in rat (8299694), dog (SPW/02), and human (NIR-DT-101 and NIR-DT-102) may also limit the interpretation of the autoradiography study with regard to tissue distribution of unchanged nirogacestat. A CNS distribution study (DM2006-03084014-017) showed that the brain-to-plasma AUC ratio was approximately 6-fold higher in mdr1a/1b(-/-) knockout mice compared with wild type, suggesting that P-gp efflux may serve to prevent accumulation of nirogacestat in the brain.
Metabolism	
Metabolite Profile	In vitro metabolism of nirogacestat is consistent across nonclinical species and humans. All circulating metabolites observed in humans were present in microsomal incubations of one or more of the evaluated nonclinical species. In vitro, CYP3A4 was the major enzyme responsible for the metabolism of nirogacestat. This observation was supported by a healthy volunteer clinical DDI study (NIR-DT-103) where itraconazole-mediated CYP3A4 inhibition increased the serum AUC of nirogacestat by 8.23-fold. In vivo mass-balance studies in rat and dog both identified M283 (PF-03015273) as the most abundant major metabolite, though human studies (NIR-DT-101 and NIR-DT-102) found this metabolite to represent less than 10% of radioactivity recovered in serum. In all mass-balance studies, the largest fraction of recovered radioactivity is recovered in serum and was consistently unretained in high-performance liquid chromatography systems. As such, the resulting metabolites were not identified, but it is believed that they represent polar, low molecular weight compounds that are the result of extensive metabolism of the radiolabel into endogenous biomolecules.
CYP Induction and Inhibition	Nirogacestat induced CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 in human hepatocytes. Nirogacestat also reversibly inhibited CYP3A. Nirogacestat was determined to be a time-dependent inhibitor of CYP3A. Nirogacestat did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and demonstrated little to no time-dependent inhibitory potency for these enzymes. In a healthy volunteer clinical DDI study (A8641002), the net

	effect of nirogacestat-mediated CYP3A4 interaction increased the serum AUC of midazolam by 58.9%.	
Excretion		
Transporters	Nirogacestat is unlikely to be a substrate or inhibitor of MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 at clinically relevant concentrations (092718 and 19SPRWP5). Nirogacestat had an efflux ratio of 1.4 in BCRP-MDCK cells and is not likely to be a substrate of BCRP (14PFIZP1S1PF37P). Nirogacestat did not reach an IC50 for BCRP inhibition in MDCKII-LE cells at concentrations up to 120 µM (163120). Metabolite M283 (PF-03015273) exhibited poor permeability across MDR1-MDCK cells and was determined to be a substrate (efflux ratio 4.75) but not an inhibitor of P-gp (2003103 and 2003104). An observed efflux ratio of 4.6 in MDR1-transfected MDCK cells suggests that nirogacestat is a substrate of P-gp (13PFIZP4S2-PF-8). Nirogacestat also inhibited P-gp-mediated efflux of digoxin in vitro with an IC50 of 2.3 µM. However, in a healthy volunteer clinical DDI study (NIR-DT-103), nirogacestat-mediated P-gp inhibition had no effect on the exposure of dabigatran etexilate.	
Excretion Route	In nonclinical studies, the primary route of excretion was the feces with more than 70% of the radiolabeled dose recovered in feces in both rats and dogs. In bile duct cannulated (BDC) rats, the primary elimination pathway following oral administration is hepatic clearance and biliary excretion with more than 46% of radioactivity recovered in the feces and between 28 to 31% excretion of radioactivity via biliary excretion. Mean urinary excretion in mass-balance studies was 5.2% and 3.1% in rats and dogs, respectively. A mean of 7.0% of radiolabel was recovered in expired air in rats. In non-radiolabeled rat studies where nirogacestat was administered orally or intravenously, < 1% of unchanged nirogacestat was recovered in bile, urine, or feces.	

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Additional notable findings are described below.

Tissue distribution: Excluding excreta, the highest Cmax levels of radiolabeled [14C] nirogacestat were uveal tract, liver, adrenal gland, spleen, and pituitary gland. Radiolabeled [14C] nirogacestat exhibited an affinity for pigmented ocular tissues containing melanin. Although low concentrations of [14C] nirogacestat-derived radioactivity were present in non-circumventricular central nervous system (CNS) tissues, radioactivity was higher in the choroid plexus than in the blood (approximately 7.5-fold higher AUC and 4.4-fold higher Cmax), which may suggest that nirogacestat crosses the blood-cerebrospinal fluid barrier. At 672 hours postdose, radioactivity concentrations persisted in thirteen tissues (adrenal gland, bone marrow, exorbital lacrimal gland, eyes, lymph nodes, meninges, pituitary gland, spleen, stomach mucosa, thymus, thyroid, uveal tract, and vitreous humor), most notably the uveal

tract with concentrations that were at least 10-fold higher than those observed for all other non-ocular tissues.

Metabolism: The percent contribution of the major cytochrome P450 (CYP) isoforms contributing to nirogacestat metabolism were CYP3A4 (85.7%), 2C9 (6.24%), 2C19 (10.5%), and 2D6 (5.03%).

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Nirogacestat was assessed in a series of nonclinical toxicology studies in alignment with applicable ICH guidance documents. The oral route of exposure was selected for these studies since the oral route is the intended clinical route of administration. The rat and dog were selected as the toxicology species based on nirogacestat PK and metabolism properties compared across species. The definitive studies were performed in the United States in accordance with the United States Department of Health and Human Services, FDA, United States Code of Federal Regulations, Title 21, Part 58: GLP for Nonclinical Laboratory Studies.

Nirogacestat was administered to rats and dogs in repeat dose general toxicology studies up to 3 months in duration followed by a 1-month recovery. A 1-month mouse study was conducted to support a 6-month carcinogenicity study in transgenic mice. Many of the Nirogacestat-related toxicities were attributed to GS inhibition and disruption of the Notch signaling pathway. 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 estrous cycle and 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, all dose levels evaluated in the rat study showed chronic progressive nephropathy, pulmonary phospholipidosis, and salivary gland necrosis in a dose-dependent manner. In the dog study, 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 dog study, a NOAEL was not identified.

The exposures at the NOAEL or lowest observed adverse effect level in the 1 and 3-month studies were below the human steady state exposures after administration of nirogacestat at 150 mg BID. Conduct of additional general toxicology studies were not required based on FDA feedback received at the end-of-Phase 1 meeting; therefore, the 6-month rat and 9-month dog studies with nirogacestat were not conducted. See [Table 14](#) for safety margin calculations.

Table 6: 5- and 28-Day Mouse Study

Study Number: 20174161									
Study Title: A 5-day and 28-day Range-Finding Study of PF-03084014 by Oral Gavage in cByB6F1 Hybrid Mice									
Key Drug-related Adverse Findings:									
- Target organ effects were noted in the small intestine (duodenum, jejunum, and ileum), liver, femoral physis, sternal cartilage, and thymus. - Microscopic changes in the testes and ovary were also noted. - No Observed Adverse Effect Level: 20 mg/kg/day									
GLP compliance: Yes									
Dose and frequency of dosing:			0, 20, 100, 300/200 mg/kg/day (10, 50, and 150 mg/kg/dose twice daily) for 28 days						
Route of administration:			Oral						
Formulation/Vehicle:			0.5% (w/v) methylcellulose in water/suspension						
Species/Strain:			Mouse/cByB6F1 Hybrid						
Number/Sex/Group:			10 in main study, 36 in TK treatment groups, 6 TK control group						
Age:			7 weeks						
Satellite groups:			Toxicokinetic group						
Toxicokinetics									
Daily Dose (mg/kg)		0 (Control)		5		150		300	
Number of TK Animals		M:6	F:6	M:36	F:36	M:36	F:36	M:36	F:36
C _{max} (ng/mL) Day 28		NA	NA	29.4	30.8	1010	1030	1340	1370
AUC ₀₋₂₄ (ng·h/mL) Day 28		NA	NA	43.9	41.9	2250	2590	5980	5700
Findings									
Died or Sacrificed Moribund		One high dose female							

Body Weight and Food Consumption	Body weight and body weight gain were decreased in rats treated with 300 mg/kg/day corresponding to a decrease in food consumption. The effect on body weight was more pronounced in male rats.
No Noteworthy Findings	Clinical chemistry, coagulation, ophthalmology, and urinalysis
Clinical Observations	Dehydration, hunched posture, thin or ungroomed fur in the high-dose group. Due to these findings, the high dose was suspended from Days 9 through 13 and reinitiated on Day 14 at a lower dose of 200 mg/kg/day.
Hematology	Elevations in white blood cell parameters in high dose male mice
Organ Weight	Organ to body weight ratio changes compared to control mice included increases in liver (high dose mice), spleen (high and mid-dose mice), thymus (high dose mice) and epididymis (high dose males), ovary (high and mid-dose females).
Microscopic Observations	• Increase bone and thickness of the physis in males and females at 300/200 mg/kg/day • Epididymis with cellular debris at ≥ 100 mg/kg/day • Cellular depletion in mandibular salivary gland in males at ≥ 5 mg/kg/day • Liver necrosis in one high dose female and vacuolation at ≥ 100 mg/kg/day • Ovarian epithelial degeneration and necrosis at ≥ 100 mg/kg/day • Small intestine goblet cell metaplasia and/or Paneth cell hyperplasia at ≥ 5 mg/kg/day • Decreased cellularity in the spleen at ≥ 100 mg/kg/day • Seminiferous tubules with atypical residual bodies at ≥ 100 mg/kg/day • Thymus lymphoid depletion at 300/200 mg/kg/day • Uterus epithelial degeneration and necrosis at ≥ 100 mg/kg/day

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; M: male; GLP: Good Laboratory Practice; NA: not applicable; -: no noteworthy findings or data.

The FDA's Assessment:

FDA disagreed with or had edits to the following parts of the Applicant's position. FDA noted the daily dose information in the table was incorrect based on the study report.

Dose and frequency of dosing:	0, 20, 100, 300/200 mg/kg/day (10, 50, and 150/100 mg/kg/dose twice daily) for 28 days			
Daily Dose (mg/kg/day)	0 (Control)	20	100	300/200

Findings																																																																																																																																																																																																																																															
Died or Sacrificed Moribund	One high dose female was found dead on Day 8.																																																																																																																																																																																																																																														
Body Weight and Food Consumption	Results were unremarkable. No changes in body weight, body weight gain, or food consumption.																																																																																																																																																																																																																																														
No Noteworthy Findings	Coagulation, ophthalmology, and urinalysis were not assessed.																																																																																																																																																																																																																																														
Hematology	Elevations in white blood cell parameters in males and females at ≥ 100 mg/kg/day.																																																																																																																																																																																																																																														
Organ Weight	Organ to body weight ratio changes compared to control mice were decreases in spleen (high and mid-dose mice), thymus (high dose mice), epididymis (high dose males), and ovary (high and mid-dose females).																																																																																																																																																																																																																																														
Microscopic Observations	<table><tr><th colspan="2" rowspan="2"># of animals examined</th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th>10</th><th>10</th><th>10</th><th>10</th><th>10</th><th>9</th></tr><tr><th>Findings</th><th>Grade*</th><th>20 mg/kg</th><th>100 mg/kg</th><th>300/200 mg/kg</th><th>20 mg/kg</th><th>100 mg/kg</th><th>300/200 mg/kg</th></tr><tr><td>Bone (femur)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- increased thickness, physis</td><td>1</td><td>0</td><td>0</td><td>10</td><td>0</td><td>0</td><td>9</td></tr><tr><td>- increased bone</td><td>1</td><td>0</td><td>0</td><td>10</td><td>0</td><td>0</td><td>9</td></tr><tr><td>Bone (sternum)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- increased thickness, cartilage</td><td>1</td><td>0</td><td>0</td><td>10</td><td>0</td><td>0</td><td>7</td></tr><tr><td>Liver</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- vacuolation</td><td>1-3</td><td>0</td><td>3</td><td>5</td><td>0</td><td>0</td><td>2</td></tr><tr><td>Salivary gland, mandibular</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- depletion</td><td>2-4</td><td>10</td><td>10</td><td>10</td><td>0</td><td>0</td><td>0</td></tr><tr><td>- degeneration</td><td>1</td><td>10</td><td>10</td><td>10</td><td>0</td><td>0</td><td>0</td></tr><tr><td>Spleen</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- decreased cellularity</td><td>1</td><td>0</td><td>2</td><td>6</td><td>0</td><td>3</td><td>6</td></tr><tr><td>Small intestine, duodenum</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- hyperplasia, paneth cell</td><td>1</td><td>0</td><td>2</td><td>9</td><td>0</td><td>0</td><td>8</td></tr><tr><td>- metaplasia, goblet cell</td><td>1-3</td><td>0</td><td>5</td><td>10</td><td>1</td><td>4</td><td>9</td></tr><tr><td>Small intestine, ileum</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- hyperplasia, paneth cell</td><td>1-2</td><td>0</td><td>4</td><td>10</td><td>1</td><td>5</td><td>8</td></tr><tr><td>Thymus</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- lymphoid depletion</td><td>1</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td><td>2</td></tr><tr><td>Epididymides</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- cellular debris</td><td>1</td><td>0</td><td>1</td><td>8</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Testes</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- atypical residual bodies, seminiferous tubules</td><td>1-2</td><td>0</td><td>8</td><td>8</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>Ovary</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- follicle depletion</td><td>2-4</td><td>NA</td><td>NA</td><td>NA</td><td>0</td><td>10</td><td>9</td></tr><tr><td>Uterus</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>- atrophy</td><td>1-2</td><td>NA</td><td>NA</td><td>NA</td><td>0</td><td>8</td><td>9</td></tr></table> *Severity of findings was generally dose-dependent. Grades 1, 2, 3, and 4 refer to minimal, mild, moderate, and marked, respectively. NA denotes not applicable.	# of animals examined		Males			Females			10	10	10	10	10	9	Findings	Grade*	20 mg/kg	100 mg/kg	300/200 mg/kg	20 mg/kg	100 mg/kg	300/200 mg/kg	Bone (femur)								- increased thickness, physis	1	0	0	10	0	0	9	- increased bone	1	0	0	10	0	0	9	Bone (sternum)								- increased thickness, cartilage	1	0	0	10	0	0	7	Liver								- vacuolation	1-3	0	3	5	0	0	2	Salivary gland, mandibular								- depletion	2-4	10	10	10	0	0	0	- degeneration	1	10	10	10	0	0	0	Spleen								- decreased cellularity	1	0	2	6	0	3	6	Small intestine, duodenum								- hyperplasia, paneth cell	1	0	2	9	0	0	8	- metaplasia, goblet cell	1-3	0	5	10	1	4	9	Small intestine, ileum								- hyperplasia, paneth cell	1-2	0	4	10	1	5	8	Thymus								- lymphoid depletion	1	0	0	2	0	0	2	Epididymides								- cellular debris	1	0	1	8	NA	NA	NA	Testes								- atypical residual bodies, seminiferous tubules	1-2	0	8	8	NA	NA	NA	Ovary								- follicle depletion	2-4	NA	NA	NA	0	10	9	Uterus								- atrophy	1-2	NA	NA	NA	0	8	9
# of animals examined				Males			Females																																																																																																																																																																																																																																								
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- depletion	2-4	10	10	10	0	0	0																																																																																																																																																																																																																																								
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The Applicant's Position:

Table 7: 1-Month Rat Study

Study Number: 06GR067 Study Title: 1-Month Oral Toxicity Study of PF-03084014-04 in Rats Key Drug-related Adverse Findings: - Target organ effects were noted in the small intestine (duodenum, jejunum, and ileum), liver, femoral physis, sternal cartilage, and thymus. - Microscopic changes in the testes and ovary were also noted. - No Observed Adverse Effect Level: 5 mg/kg/day GLP compliance: Yes								
Dose and frequency of dosing:			0, 5, 20, 150 mg/kg/day once daily for 28 days					
Route of administration:			Oral					
Formulation/Vehicle:			0.5% (w/v) methylcellulose in water/suspension					
Species/Strain:			Rat/Sprague Dawley					
Number/Sex/Group:			10 in main study, 20 in TK group					
Age:			8-9 weeks					
Satellite groups:			Toxicokinetic group					
Daily Dose (mg/kg)		0 (Control)		5		20		150
Number of Animals		M:10	F:10	M:10	F:10	M:10	F:10	M:10 F:10
Toxicokinetics								
C _{max} (ng/mL)								
Day 30		NA	NA	19.3	42.7	328	414	NA NA
AUC ₀₋₂₄ (ng·h/mL)								
Day 30		NA	NA	50.7	137	993	2400	NA NA
Findings								
Died or Sacrificed Moribund		Two females were euthanized on Day 10 and 1 female on Day 11. Due to continued adverse clinical signs and decreased body weight and food consumption, dosing was terminated in the 150 mg/kg dose group, randomly selected animals (5 M and 3 F) were euthanized on Day 11/12 (F/M).						
Body Weight and Food Consumption		Body weight and body weight gain were decreased in rats treated with 150 mg/kg/day corresponding to a decrease in food consumption.						
No Noteworthy Findings		Coagulation, ophthalmology, and urinalysis						
Clinical Observations		Limited to the high dose group and consisted of decreased activity, hunched posture, rough and stained fur, salivation and loose stools.						

Hematology and Flow Cytometry	Decrease in total lymphocyte count was observed at 150 mg/kg/day, along with a decrease in T-cell population at 20 mg/kg/day, and a decrease in natural killer (NK) and B cells was observed at 150 mg/kg/day. IgD expression was decreased in B cells at ≥ 20 mg/kg/day, while IgM expression was decreased in female rats at 5 and 20 mg/kg/day
Clinical Chemistry	Slight increase in γ -glutamyl transferase at 150 mg/kg/day
Organ Weight	Meaningful organ to body weight ratio change compared to control was limited to decreases in ovarian weight at > 20 mg/kg/day.
Microscopic Observations	- Hypertrophic retention of bone in the sternum and joint at ≥ 20 mg/kg/day - Ovarian atrophy and vaginal asynchrony at ≥ 20 mg/kg/day - Lymphoid depletion in spleen, thymus, lymph nodes in 20 mg/kg/day females - Hepatocellular vacuolation consisting of lipid in the cytoplasm of periportal hepatocytes was noted in a few individual rats at ≥ 20 mg/kg/day
Post-Dose Observations	Effects on body weights and food consumption recovered after cessation of dosing at 150 mg/kg/day. Partial reversibility of microscopic changes in the ovary and bone in the 150-mg/kg/day group.

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; M: male; GLP: Good Laboratory Practice; NA: not applicable; -: no noteworthy findings or data.

The FDA's Assessment:

FDA had additions or edits to the following parts of the Applicant's position.

Key Drug-related Adverse Findings:	
Microscopic changes in the ovary were also noted.	
GLP compliance: Yes	
Dose and frequency of dosing:	0, 5, 20, 150 mg/kg/day once daily for 30 days
Findings	
Died or Sacrificed Moribund	The two females euthanized on Day 10 and 1 female on Day 11 were in the high dose group.
Clinical Observations	High dose group findings also included alopecia and chromodacryorrhea.
Clinical Chemistry	Increased blood urea nitrogen (1.7-2.3x control mean) at 150 mg/kg/day. Decreased total protein (0.93-0.83x control mean) and calcium (0.98-0.91x control mean) at 150 mg/kg/day.
Organ Weight	Meaningful organ to body weight ratio change compared to control was limited to decreases in thymic and/or ovarian weights at > 20 mg/kg/day.

Microscopic Observations		Males			Females		
# of animals examined		10	10	10	10	10	10
Findings	Grade*	5 mg/kg	20 mg/kg	150 mg/kg	5 mg/kg	20 mg/kg	150 mg/kg
Bone (sternum)							
- retention of hypertrophic zone	1-3	0	0	5	0	6	3
Joint							
- retention of hypertrophic zone	1-3	0	3	7	0	7	6
Liver							
- hepatocellular vacuolation	1-2	2	5	1	2	5	2
Lymph Node (mesenteric)							
- lymphoid depletion	1-4	0	0	5	0	8	6
Lymph Node (inguinal)							
- lymphoid depletion	1-4	0	0	4	0	1	6
Small intestines							
- hyperplasia	1-3	0	0	5	0	0	5
- erosion / ulcer	1-3	0	0	3	0	0	0
Spleen							
- lymphoid depletion	1-4	0	0	5	0	8	6
Stomach							
- erosion / ulcer	1-3	0	0	2	0	0	4
Thymus							
- lymphoid depletion	1-4	0	0	5	0	10	6
Ovary							
- atrophy	1-2	NA	NA	NA	0	10	4
Vagina							
- asynchrony	present	NA	NA	NA	0	4	5

*Severity of findings was generally dose-dependent.

Small intestines consist of duodenum, jejunum, and ileum; highest incidence presented.

Grades 1, 2, 3, and 4 refer to minimal, mild, moderate, and marked, respectively.

NA denotes not applicable.

The Applicant's Position:

Table 8: 3-Month Rat Study

Study Number: 06GR493	
Study Title: 3-Month Oral Toxicity Study of PF-03084014-04 in Rats with a 1-Month Recovery	
Key Drug-related Adverse Findings:	
- Lymphoid depletion, hypertrophic zone of the growth plate, ovarian atrophy, epidermal cysts, myofibrosis, and mammary hyperplasia all appear related to direct or indirect pharmacologic activity of nirogacestat. - No Observed Adverse Effect Level: not determined; the Lowest Observed Adverse Effect Level was 2 mg/kg/day.	
GLP compliance: Yes	
Dose and frequency of dosing:	0, 5, 20, 50 mg/kg/day (2.5, 10, or 25 mg/kg/dose 6 hours apart) for 28 days

Route of administration:	Oral							
Formulation/Vehicle:	0.5% (w/v) methylcellulose in water/suspension							
Species/Strain:	Rat/Sprague Dawley							
Number/Sex/Group:	10 in main study, 5 in control, 20 and 50 mg/kg/day for recovery							
Age:	8-9 weeks							
Satellite groups:	Toxicokinetic group (3/sex in control, 4/sex in treatment groups)							
Daily Dose (mg/kg)	0 (Control)		5		20		50	
Number of Animals	M:15	F:15	M:10	F:10	M:15	F:15	M:15 ^a	F:15 ^a
Toxicokinetics								
C _{max} (ng/mL) Day 30	NA	NA	19.6	56.7	232	372	1550	NA
AUC ₀₋₂₄ (ng·h/mL) Day 30	NA	NA	223	680	2230	4520	23100	NA
Findings								
Died or Sacrificed Moribund	Moribund animals were euthanized early on Days 84 and 89 in the high dose females. Due to mortality and adverse clinical signs in female rats at the 50-mg/kg/day dose level, dose administration was terminated for female rats at this dose level after 88 consecutive days. Two remaining female toxicokinetic animals at this dose level were incorporated into the main study on Day 88 and a cohort of 50-mg/kg/day female rats were necropsied on Day 89, while the remaining female rats in this dose level continued on study to assess recovery.							
Body Weight and Food Consumption	On Day 64 for male rats and Day 57 for female rats, decreases in mean body weight gain were observed at 50 mg/kg/day, secondary to significant decreases in food consumption in most female rats.							
No Noteworthy Findings	Ophthalmology and urinalysis							
Clinical Observations	Limited to the high dose group and consisted of decreased activity, hunched posture, pallor, rough and stained fur, and chromodacryorrhea.							
Hematology and Flow Cytometry	Decrease red blood cell parameters and lymphocytes at ≥ 20 mg/kg/day; increases in neutrophils at ≥ 20 mg/kg/day. Decreases in all T-cell subsets and decreased IgD expression on B cells, and increased NK cells at ≥ 20 mg/kg/day.							
Clinical Chemistry	Increased alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, blood urea nitrogen, creatinine, and total bilirubin in females at 50 mg/kg/day. Slight increases in alanine aminotransferase, aspartate aminotransferase, and cholesterol were elevated in mid-dose females and high dose males.							

Organ Weight	Meaningful organ to body weight ratio changes compared to controls included increases in kidney and liver weights; decreases in thymus and ovarian weights at ≥ 20 mg/kg/day.
Microscopic Observations	- Hypertrophic retention of bone in the tibia, femur, sternum, and growth plate at ≥ 20 mg/kg/day - Ovarian atrophy and estrous asynchrony at ≥ 5 mg/kg/day - Seminiferous tubule giant cell in 2 high dose males - Lymphoid depletion in spleen, thymus, and lymph nodes in ≥ 20 mg/kg/day in males and/or females - Lung foamy macrophage at ≥ 5 mg/kg/day - Hepatocellular hypertrophy at ≥ 5 mg/kg/day - Progressive nephropathy in male rats at ≥ 5 mg/kg/day - Hyperplasia of the small intestinal epithelium - Adrenal vacuolation and necrosis at ≥ 20 mg/kg/day - Myonecrosis/fibrosis in the heart in females ≥ 20 mg/kg/day and 2 male rats at 50 mg/kg/day
Post-Dose Observations	During the recovery phase, decreases in mean body weight gain were observed at ≥ 20 mg/kg/day. Increases in food consumption were observed in female rats at 50 mg/kg/day during the recovery phase. Increased metaphyseal bone and epidermal cysts in male and female rats, cardiomyopathy in male rats, and ovarian follicular cysts, disruption of the estrous cycle, decreased ovarian weights, increased liver weights, myonecrosis/myofibrosis, and hyperplasia of the mammary gland in female rats were still present after the recovery period.

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable.

^a One control female rat was euthanized on Day 43 for humane reasons. In the 50-mg/kg/day group 4 males and 8 females died or were euthanized in extremis beginning on Day 58. Due to morbidity and mortality in the 50 mg/kg/day group females, the surviving females were euthanized early on Days 88. A total of 4 remaining female rats were placed into recovery on Day 89. One high-dose female died during the recovery phase.

The FDA's Assessment:

FDA disagreed with or had edits to the following parts of the Applicant's position. FDA noted the day of TK sampling in the table was incorrect based on the study report.

Study Number: 08GR493
No Observed Adverse Effect Level: not determined; the Lowest Observed Adverse Effect Level was 5 mg/kg/day.
Toxicokinetics

C _{max} (ng/mL) Day 90	NA	NA	19.6	56.7	232	372	1550	NA
AUC ₀₋₂₄ (ng·h/mL) Day 90	NA	NA	223	680	2230	4520	23100	NA
Findings								
Hematology and Flow Cytometry	Decreased red blood cell parameters (89-96% of control) and lymphocytes (64–71% of control) at ≥ 20 mg/kg/day; increases in neutrophils (2.27-5.22x control) at ≥ 20 mg/kg/day. Decreases in all T cell subsets (18-39% of control) and decreased IgD expression on B cells (29-76% of control), and increased NK cells (270-318%) at ≥ 20 mg/kg/day.							
Clinical Chemistry	On Day 92, minor increases in AST (1.16x control) and chloride (1.03x control) and decreases in total protein and albumin (91-93% of control mean) were observed in 50 mg/kg/day males compared to controls. In 20 mg/kg/day females, increases in ALT (2.15x control), total protein (1.09x control), and cholesterol (1.37x control) and decreases in sodium (98% of control) were observed compared to controls.							

Microscopic Observations	# of animals examined		Males			Females		
			10	10	11	10	10	13
			5	20	50	5	20	50
Findings	Grade*	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Adrenal Gland								
- hypertrophy	1-2	0	0	0	0	1	7	
- vacuolation	1-3	0	0	4	0	3	8	
- necrosis	1-3	0	0	1	0	1	5	
Heart								
- myonecrosis / myofibrosis	1-2	0	0	2	0	2	11	
Joint								
- deposition of woven bone	2-4	0	0	9	0	1	12	
- hypertrophic zone retention	1-4	0	4	9	0	10	12	
Kidney								
- hyperplasia	1-2	1	1	7	0	1	6	
- nephropathy	1-3	4	9	11	0	2	8	
Liver								
- hepatocellular hypertrophy	1-3	0	0	1	0	5	8	
Lung								
- fibrinoid necrosis of artery	1-3	0	0	4	0	0	11	
- foamy macrophages	1-3	0	5	6	1	3	11	
Lymph Node (mesenteric)								
- lymphoid depletion	1-3	1	6	10	1	8	12	
Lymph Node (inguinal)								
- lymphoid depletion	1-3	0	4	9	1	8	11	
Mammary Gland								
- acinar hyperplasia	1-2	0	0	0	1	5	7	
Skin								
- epidermal cyst	1	0	0	6	0	0	9	
Small intestines								
- hyperplasia	1-3	0	0	11	0	0	11	
Spleen								
- lymphoid depletion	1-3	0	5	7	0	0	12	
Sternum								
- deposition of woven bone	1-3	0	0	0	0	0	6	
- hypertrophic zone retention	1-2	0	2	9	0	4	12	
Stomach								
- erosion / ulcer	1-2	0	0	1	0	1	6	
Testes								
- seminiferous tubule giant cell	1	0	0	2	NA	NA	NA	
Thymus								
- lymphoid depletion	1-3	0	2	11	0	3	12	
Ovary								
- atrophy	1-3	NA	NA	NA	1	10	12	
Vagina								
- asynchrony	present	NA	NA	NA	1	10	2	

*Severity of findings was generally dose-dependent.

Small intestines consist of duodenum, jejunum, and ileum; highest incidence presented.

Grades 1, 2, 3, and 4 refer to minimal, mild, moderate, and marked, respectively.

NA denotes not applicable.

The Applicant's Position:

Table 9: 1-Month Dog Study

Study Number: 06GR066				
Study Title: 1-Month Oral Toxicity Study of PF-03084014-04 in Dogs				
Key Drug-related Adverse Findings:				
- Intestinal hyperplasia that led to increased inflammation in the liver at 80 mg/kg/day - Splenic extramedullary hematopoiesis at 80 mg/kg/day - No Observed Adverse Effect Level: 10 mg/kg/day				
GLP compliance: Yes				
Dose and frequency of dosing:		0, 2, 10, 80 mg/kg/day once daily for 28 days		
Route of administration:		Oral		
Formulation/Vehicle:		0.5% (w/v) methylcellulose in water/suspension		
Species/Strain:		Dog/Beagle		
Number/Sex/Group:		3		
Age:		~9 months		
Satellite groups:		None		
Toxicokinetics (no sex differences in exposures; therefore, sex combined mean values are provided)				
Daily Dose (mg/kg)	0 (Control)	2	10	80
C _{max} (ng/mL)				
Day 30	NA	72.1	448	517
AUC ₀₋₂₄ (ng·h/mL)				
Day 30	NA	242	1920	2890
Findings				
Died or Sacrificed Moribund	Two dogs in the 80-mg/kg/day group were euthanized in extremis on Days 10 and 11 due to gavage trauma.			
Body Weight and Food Consumption	Slight decrease in body weights in high-dose females that corresponded with a decrease in food consumption.			
No Noteworthy Findings	Ophthalmology and urinalysis			
Clinical Observations	Emesis and loose/liquid stools were observed at ≥ 2 mg/kg/day with increased incidence at 80 mg/kg/day. Salivation and discolored feces/liquid stools were also seen at 80 mg/kg/day.			
Hematology and Flow Cytometry	Increases in white blood cell counts, fibrinogen and globulin were associated with inflammation due to bacterial embolism in the liver at 80 mg/kg/day. Decreases in B cells and T cells at ≥ 10 mg/kg/day were observed in the peripheral blood.			

Clinical Chemistry	Increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and globulin at 80 mg/kg/day.
Organ Weight	Meaningful organ to body weight ratio changes compared to controls included increases in liver weights in high dose males and decreases in thymus and spleen weights at ≥ 10 mg/kg/day.
Microscopic Observations	- Intestinal hyperplasia at 80 mg/kg/day - Extramedullary hematopoiesis in the spleen at 80 mg/kg/day - Bacterial embolism to the liver from the disrupted intestinal mucosal barrier led to increases in liver inflammation.

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; eCTD: electronic Common Technical Document; GLP: Good Laboratory Practice; NA: not applicable.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The dosing was once daily for 30 days. FDA had additions to the following parts of the Applicant's position.

Findings								
Hematology and Flow Cytometry	Increases in white blood cell counts (1.3-2.4x pre-dose values) and fibrinogen (1.3-4.5x pre-dose values) correlated microscopically with inflammation in the liver at 80 mg/kg/day.							
Clinical Chemistry	Increased liver transaminases (2.2-3.8x pre-dose values) and globulin (1.2-1.5x pre-dose values) at 80 mg/kg/day.							
Microscopic Observations	# of animals examined		Males			Females		
			3	3	3	3	3	3
			2	10	80	2	10	80
	Findings	Grade*	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
	Liver							
	- inflammation	1	0	0	1	0	0	2
	Intestinal Tract							
	- hyperplasia	1-3	0	0	3	0	0	3
	Spleen							
	- extramedullary hematopoiesis	1	0	0	1	0	0	2
*Severity of findings was generally dose-dependent. Intestinal tract consists of duodenum, jejunum, ileum, cecum, and/or colon; highest incidence presented. Grades 1, 2, and 3 refer to minimal, mild, and moderate, respectively.								

The Applicant's Position:

Table 10: 3-Month Dog Study

Study Number:	06GR495
Study Title:	3-Month Oral Toxicity Study of PF-03084014-04 in Dogs with a 1-Month Recovery

Key Drug-related Adverse Findings: - Inflammation in multiple organs and decreased cellularity in lymphoid organs - Goblet cell hyperplasia within the intestine - Sertoli degeneration in testes and oocyte mineralization in the ovary - No Observed Adverse Effect Level: not defined; the Lowest Observed Adverse Effect Level: 2 mg/kg/day GLP compliance: Yes				
Dose and frequency of dosing:	0, 2, 10, 50/20 mg/kg/day (2.5, 10, or 25/10 mg/kg/dose 6 hours apart) for 91 days			
Route of administration:	Oral			
Formulation/Vehicle:	0.5% (w/v) methylcellulose in water/suspension			
Species/Strain:	Dog/Beagle			
Number/Sex/Group:	4 in main study, 2 extra in control, and 2 extra in 20 and 50 mg/kg/day for recovery			
Age:	10-11 months			
Satellite groups:	none			
Toxicokinetics (no sex differences in exposures; therefore, sex combined mean values are provided)				
Daily Dose (mg/kg)	0 (Control)	2	10	50/20
C _{max} (ng/mL) Day 30	NA	44.1	254	503
AUC ₀₋₂₄ (ng·h/mL) Day 30	NA	481	3130	6280
Findings				
Died or Sacrificed Moribund	Two high-dose dogs and 1 mid-dose dog were euthanized early for humane reasons due to adverse clinical signs. Due to these effects in the high dose group after 5 to 7 days of administration, dosing was suspended for 26 days, and the dose was lowered to 20 (10 BID) mg/kg/day for the remainder of the study. Animals in the 50/20 (25/10 BID)-mg/kg/day group were dosed a total of 65 days.			
Body Weight and Food Consumption	Decreased food consumption was noted in male and female dogs at 50 mg/kg/day near the end of Week 1 and generally remained decreased throughout the main study period. This led to a slight decrease in body weight gain.			
No Noteworthy Findings	Ophthalmology, urinalysis, electrocardiogram			
Clinical Observations	Clinical signs in moribund animals observed before euthanasia included decreased activity, watery/discolored stools, inappetence, weight loss, and overall poor condition. Animals that survived clinical signs included emesis and decreased activity at ≥ 10 mg/kg/day.			

Hematology and Flow Cytometry	Decreased red blood cell parameters were noted in high-dose males and increases in white blood cell parameters in high-dose male and female dogs. Fibrinogen was also elevated. Decreases in B cell numbers were evident on Days 36 and 85 in male dogs treated at ≥ 2 mg/kg/day and in female dogs treated at ≥ 10 mg/kg/day.
Clinical Chemistry	Increased alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase was observed in both high dose males and females. Blood urea nitrogen was elevated in females at ≥ 10 mg/kg/day, and globulin was increased in males and females at ≥ 10 mg/kg/day.
Organ Weight	Meaningful organ to body weight ratio change compared to control was limited to increased thymus weights in high dose male dogs.
Microscopic Observations	• Mononuclear cell infiltrates in multiple organs including liver, kidney, and intestine • Intestinal goblet cell hyperplasia at ≥ 10 mg/kg/day • Pancreatic acinar degeneration/fibrosis at ≥ 10 mg/kg/day • Lymphoid depletion in spleen, thymus, and lymph nodes at ≥ 10 mg/kg/day • Sertoli degeneration and epididymal oligospermia at ≥ 10 mg/kg/day • Oocyte mineralization at ≥ 2 mg/kg/day
Post-Dose Observations	Duodenal inflammation/necrosis and colonic goblet cell hyperplasia of minimal severity, lymphocyte depletion in the spleen and lymph nodes, Sertoli cell degeneration in the testis, and oocyte mineralization in the ovaries were still present after the recovery period.

Abbreviations: AUC: area under the curve; C_{max}: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable.

The FDA's Assessment:

FDA had additions or edits to the following parts of the Applicant's position.

Study Number: 08GR495				
• Sertoli cell degeneration in testes and oocyte mineralization in the ovary.				
Dose and frequency of dosing:		0, 2, 10, 50/20 mg/kg/day (1, 5, or 25/10 mg/kg/dose 6 hours apart) for 91 days		
Number/Sex/Group:		4 in main study, 2 extra in control, and 2 extra in 10 and 50 mg/kg/day for recovery		
Toxicokinetics (no sex differences in exposures; therefore, sex combined mean values are provided)				
Daily Dose (mg/kg)	0 (Control)	2	10	50/20
C _{max} (ng/mL)				
Day 91	NA	44.1	254	503

AUC ₀₋₂₄ (ng·h/mL) Day 91	NA	481	3130	6280
Findings				
Hematology and Flow Cytometry	Decreased red blood cell parameters (1.32-1.10x pre-dose values) were noted in high-dose males and increases in white blood cell parameters (1.28-2.17x pre-dose values) were noted in high-dose male and female dogs. Fibrinogen (1.37-2.27x pre-dose values) was also elevated. Decreases in B cell numbers were evident on Days 36 and 85 in male dogs treated at ≥ 2 mg/kg/day (0.88-0.51x pre-dose values) and in female dogs treated at ≥ 10 mg/kg/day (0.96-0.56x pre-dose values).			
Clinical Chemistry	Increased alanine aminotransferase (2-21.21x pre-dose values), aspartate aminotransferase (1.94-5.08x pre-dose values), and alkaline phosphatase (1.53-5.04x pre-dose values) occurred in high-dose males and females. Blood urea nitrogen (1.54-2.45x pre-dose values) was elevated in females at ≥ 10 mg/kg/day, and globulin (1.04-1.29x pre-dose values) was increased in males and females at ≥ 10 mg/kg/day.			

Microscopic Observations	# of animals examined		Males			Females		
			4	4	5	4	5	4
	Findings	Grade*	2 mg/kg	10 mg/kg	50/20 mg/kg	2 mg/kg	10 mg/kg	50/20 mg/kg
	Gallbladder							
	- fibrinoid necrosis of blood vessel	3-4	0	0	1	0	1	0
	Heart							
	- mononuclear cell infiltration	1	3	1	1	2	1	0
	Intestinal Tract							
	- goblet cell hyperplasia	1-3	0	3	5	0	2	2
	- inflammation / necrosis	1-4	2	4	5	0	4	2
	Kidney							
	- mononuclear cell infiltration	1	2	4	4	1	5	3
	Liver							
	- inflammation	1-3	0	3	4	0	4	4
	Lymph Node (mesenteric)							
	- decreased lymphocytes	1-3	1	3	5	0	4	4
	- neutrophil infiltrate	1-2	0	2	2	0	0	1
	Lymph Node (popliteal)							
	- decreased lymphocytes	1-3	1	3	4	0	4	1
	- neutrophil infiltrate	1	0	3	2	0	0	1
	Pancreas							
	- acinar degeneration / fibrosis	1-2	0	1	3	0	1	0
	Spleen							
	- decreased lymphocytes	1-3	0	4	5	0	4	4
	- neutrophil infiltrate	1-2	2	0	2	1	1	1
	- extramedullary hematopoiesis	1	1	3	4	2	1	1
	Trachea							
	- neutrophil infiltrate	1-3	0	0	4	1	1	3
	Epididymis							
	- oligospermia	1-3	0	2	1	NA	NA	NA
	Prostate							
	- mononuclear cell infiltration	1	1	2	1	NA	NA	NA
	Testes							
	- Sertoli cell degeneration	1-3	0	2	2	NA	NA	NA
	Ovary							
	- oocyte mineralization	1	NA	NA	NA	4	5	4

*Severity of findings was generally dose-dependent.

Intestinal tract consists of duodenum, jejunum, ileum, cecum, and/or colon; highest incidence presented.

Grades 1, 2, 3, and 4 refer to minimal, mild, moderate, and marked, respectively.

NA denotes not applicable.

5.5.2. Genetic Toxicology

The Applicant's Position:

The genotoxicity of nirogacestat was assessed in a battery of genotoxicity studies in alignment with ICH S2(R1) guidance. Nirogacestat was assessed in vitro in the bacterial mutagenicity assay (06GR106), the in vitro cytogenetic (human lymphocyte) assay (06GR107), and in vivo in a rat micronucleus study (01214020). These in vitro tests were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity or insolubility, while in vivo nirogacestat was dosed up to the limit dose of 2000 mg/kg/day.

Nirogacestat was negative in both in vitro assays, as well as the in vivo micronucleus study as summarized in Table 11.

Table 11: GLP Genotoxicity Studies Conducted with Nirogacestat

Type of Test	Lot Number	Test System	Metabolic Activation ^a	Dose/Concentration	Results
Bacterial mutagenicity assay	109191-83-8F	<i>Salmonella typhimurium</i> TA1535, TA1537, TA100 and <i>Escherichia coli</i> WP2uvrA pkM101	Without and with	0.010-5.00 mg/plate	(-)
		<i>S. typhimurium</i> TA98	Without and with	0.015-5.00 mg/plate	(-)
Cytogenetics assay	109191-83-8F	Human lymphocyte 3-hour	Without	16.8, 26.2, 41.0 mg/mL	(-)
		24-hour	Without	11.7, 17.9, 19.9 mg/mL	(-)
		3-hour	With	27.3, 41.5, 46.1 mg/mL	(-)
In vivo micronucleus	01214020	Sprague Dawley Rat	NA	0, 500, 1000, 2000 mg/kg/day	(-)

Abbreviations: (-): Negative; NA: not applicable.

^a Aroclor-induced rat liver S-9 fraction from male Sprague-Dawley rats.

Nirogacestat was negative in the complete battery of genotoxicity studies as outlined in ICH S2(R1) guidance.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. FDA noted the dose/concentration units in the table were incorrect based on the study report for the cytogenetics assay.

Type of Test	Lot Number	Test System	Metabolic Activation ^a	Dose/Concentration	Results
Cytogenetics assay	109191-83-8F	Human lymphocyte 3-hour	Without	16.8, 26.2, 41.0 µg/mL	(-)
		24-hour	Without	11.7, 17.9, 19.9 µg/mL	(-)
		3-hour	With	27.3, 41.5, 46.1 µg/mL	(-)

5.5.3. Carcinogenicity

The Applicant's Position:

The carcinogenicity of nirogacestat was assessed in a 6-month repeat dose study in transgenic rasH2 mice (20174162). Nirogacestat was administered orally BID (approximately 10 hours apart) for a minimum of 26 weeks to cByB6F1/Tg rasH2 hemizygous mice at dose levels of 5, 15, and 50 mg/kg/dose (10, 30, and 100 mg/kg/day).

Survival at 10 or 30 mg/kg/day nirogacestat ranged from 92% to 96% in males and from 96 to 100% in females and was comparable to controls, whereas survival at 100 mg/kg/day was reduced to 76% in males and females at study termination. Although there were no statistically significant effects on mortality when pairwise comparisons were made between the control group and 100 mg/kg/day males or females, there was a statistically significant dose-related trend of increased mortality in the females.

Administration of nirogacestat BID by oral gavage to Tg RasH2 mice for 26 weeks at 10 or 30 mg/kg/day resulted in no effects on survival or tumor formation. At 100 mg/kg/day, administration of nirogacestat resulted in an increase in the frequency of spontaneous hemangiosarcoma in males and females. There were no significant increases in new neoplasms associated with nirogacestat administration at doses up to 100 mg/kg/day. The systemic exposures in mice at this dose level are below those in humans administered nirogacestat at 150 mg BID.

Based on the Agency's feedback for Study 20174162 provided by email on 11 January 2022, SpringWorks submitted an updated waiver request for its proposal that a 2-year rat carcinogenicity study was not required. As requested by the Agency, the updated justification addressed duration and exposure, carcinogenic potential, genotoxicity, indication and participant population, general toxicology study findings (e.g., histopathology, findings from the 26-week mouse carcinogenicity study, and other relevant factors). See [Table 14](#) for safety margin calculations.

Table 12: 6-Month Mouse Carcinogenicity Study

Study Number: 20174162	
Study Title: A GLP 26-week Carcinogenicity Study of Nirogacestat Dihydrobromide by Oral Gavage in cByB6F1/Tg rasH2 Hemizygous Mice	
Key Drug-related Adverse Findings: - No significant increases in mortality or new neoplasms at the highest dose tested (100 mg/kg/day). - Slight increase in frequency in background incidence of hemangiosarcoma at 100 mg/kg/day.	
GLP compliance: Yes	
Dose and frequency of dosing:	0, 10, 30, 100 mg/kg/day (5, 15, or 50 mg/kg/dose 10 hours apart) for 26 weeks
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/v) methylcellulose in water/suspension
Species/Strain:	Mouse/cByB6F1/Tg rasH2 hemizygous
Number/Sex/Group:	25 in main study
Age:	7 weeks

Satellite groups:		Positive control (NMU, 15/sex); TK satellite group with 12/sex in control and 36/sex in nirogacestat treated groups.						
Daily Dose (mg/kg)	0 (Control)		10		30		100	
Number of Animals	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Toxicokinetics								
C _{max} (ng/mL) Day 180	NA	NA	7.32	7.66	73.5	83.0	637	794
AUC ₀₋₁₀ (ng·h/mL) Day 180	NA	NA	7.96	6.32	145	148	1970	2430
Findings								
Died or Sacrificed Moribund	Survival at 10 or 30 mg/kg/day nirogacestat ranged from 92% to 96% in males and from 96% to 100% in females and was comparable to controls, whereas survival at 100 mg/kg/day was reduced to 76% in males and females at study termination.							
Body Weight and Food Consumption	Nirogacestat had no remarkable effects on body weight or food consumption.							
Clinical Observations	Clinical signs included hunched posture, ungroomed fur, and thin appearance in the 100-mg/kg/day group.							
Neoplastic Changes	- Incidences of hemangiosarcoma in were 3/25, 4/25, 1/25, and 8/25 in the 0, 10, 30, and 100 mg/kg/day males, respectively, and 1/25, 1/25, 1/25, and 4/25 in the 0, 10, 30, and 100 mg/kg/day females, respectively. - No new neoplasms were observed with nirogacestat administration at doses up to 100 mg/kg/day. - The NMU positive control group exhibited the expected higher incidence of neoplastic findings thereby validating the cByB6F1/Tg rasH2 hemizygous mouse model used in this study							

Abbreviations: AUC: area under the curve; C_{max}: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. FDA notes the 6-month report eCTD location is 4.2.3.4.1.

The study design for the transgenic rasH2 mouse carcinogenicity study (20174162) was reviewed by the Executive Carcinogenicity Assessment Committee (ECAC) and deemed adequate.

The incidence of whole body hemangiosarcomas in 100 mg/kg/day males was above the historical control value for the test facility, but the finding did not reach statistical significance for trend and pairwise comparisons. The study was negative for drug-related neoplasms in

female mice. Overall, the result of the transgenic mouse carcinogenicity study was concluded to be negative by the ECAC.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

The developmental and reproductive toxicology assessment of nirogacestat consisted of two separate fertility studies in male and female rats and a preliminary embryo-fetal developmental (EFD) toxicity study in pregnant rats. The first fertility study was conducted by simultaneous treatment of male and female rats before mating (01214013). The second fertility study was conducted by treating male rats with nirogacestat then mating with untreated female rats, along with treated female rats mated with untreated known breeding male rats (01214026). Only Study 0124026 is tabulated below.

Nirogacestat produced embryo toxicity when administered to pregnant rats, and impaired fertility in both male and female rats. In the EFD study in rats, nirogacestat induced significant embryo loss, early resorptions, and decreased fetal weights in surviving embryos. 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 et al. 1999](#); [Swiatek et al. 1994](#)). The changes in sex organs in nirogacestat-treated male and female rats were also anticipated based on the known role of the Notch pathway in the ovary and testes. The ovarian changes in rats and dogs, along with altered estrous cyclicity, are likely due to inhibition of Notch signaling in ovaries, as this signaling pathway is critical in the regulation of mammalian folliculogenesis ([Vanorny et al. 2017](#)). Similar ovarian changes were observed with another GS inhibitor ([Simutis et al. 2018](#)). In the testes, the Notch signaling is critical for spermatogenesis ([Murta et al. 2016](#)). These effects on both male and female sex organs could explain the effects of nirogacestat on fertility indices measured in both male and female rats.

Based on the severity of the embryo-fetal toxicities, and the known requirement for the Notch pathway for normal embryo implantation and development, the weight of evidence provides justification for not conducting the definitive embryo-fetal toxicity studies in rats and in rabbits, as well as not conducting the rat peri- and post-natal development study. As shown by [Donoviel et al \(1999\)](#), mice lacking Notch activity by inactivation of presenilin 1 and 2 (upstream of Notch and required for GS activity), leads to perinatal lethality due to multiple early developmental effects. This finding supports earlier studies in mice where a loss of Notch1 is embryonically lethal ([Swiatek et al, 1994](#)). In addition, incubating zebrafish embryos with a GS inhibitor led to impaired somite segmentation ([Geling et al 2002](#)), which is similar to other lethal effects seen in the embryos of mice with altered Notch activity. The embryonic loss in the

rat embryo-fetal development study, and the early embryonic loss in the fertility studies align with the known requirement of Notch for embryonic development. In addition, the exposures at which these effects occur in rat are below (≤ 0.1 -fold) the human systemic exposure based on AUC (12860 ng·hr/mL) after administration of 150 mg of nirogacestat BID. See Table 14 for safety margin calculations.

Table 13: Fertility and Early Embryonic Development in Male and Female Rats

Study Number: 01214026	
Study Title: An Oral (Gavage) BID-Dose Study of the Effects of PF-03084014 on Fertility and Early Embryonic Development to Implantation in Rats	
Key Drug-related Adverse Findings:	
- Decreased male and female fertility - No Observed Adverse Effect Level: F₀ Males: Not determined; F₀ Females: 5 mg/kg/day; F₁ Litters: 5 mg/kg/day	
GLP compliance: Yes	
Dose and frequency of dosing:	0, 5, 20, 40 mg/kg/day (2.5, 10 and 20 mg/kg/dose 6 hours apart)
Dosing period	M Days 0-65 and F Days 1-14 through Gestation Day 7
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/v) methylcellulose in water/suspension
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	22
Age:	9-11 weeks
Day of C-Section	Gestation Day 13
Toxicokinetics (not assessed in this study)	
Treated Male Findings (treated males mated with untreated females)	
Died or Sacrificed Moribund	One male rat each in the 20- and 40-mg/kg/day groups was euthanized on Study Day 42 or 34, respectively. The causes of death were not related to nirogacestat treatment.
Body Weight and Food Consumption	Slight decrease in body weights at 40 mg/kg/day and no adverse effects on food consumption.
Clinical Observations	Fur staining, sunken eyes at ≥ 20 mg/kg/day
Males Fertility Indices	No effect on number of mating males; however, fertile males was 22, 20, 6 and 0 in the 0, 5, 20 and 40 mg/kg/day, respectively, with decreased fertility index at ≥ 20 mg/kg/day. Decreased sperm motility at ≥ 5 mg/kg/day, and decreased sperm concentration and morphology at ≥ 20 mg/kg/day.
Untreated Female Findings	No pregnant females at 40 mg/kg/day, implantation loss observed at ≥ 5 mg/kg/day, and loss of viable embryos at ≥ 20 mg/kg/day.

Sperm Analysis	Decreased sperm motility at ≥ 5 mg/kg/day, and decreased concentration and decreases normal morphology at ≥ 20 mg/kg/day.
Microscopic Observations	Minimal cellular debris in epididymis at ≥ 20 mg/kg/day.
Treated Female Findings (treated females mated with untreated males)	
Died or Sacrificed Moribund	No unscheduled deaths
Body Weight and Food Consumption	No effect on pre-mating body weight and slight decrease in Gestation Day 13 body weight at 20 mg/kg/day. At 40 mg/kg/day, none of the females were pregnant so post-gestation weights were not determined.
Clinical Observations	No remarkable clinical signs
Female Estrous Cycle	No effect on mean number of estrous cycles, estrous length, or precoital intervals.
Female Fertility Indices	The fertility index and pregnancy index were reduced at 20 mg/kg/day and down to 0 at 40 mg/kg/day given the early embryo loss.
Microscopic Observations	Decreased ovarian corpora lutea and number of follicles at ≥ 20 mg/kg/day with severity ranging from mild to severe. Vaginal mucosal hypertrophy/hyperplasia and mucosal mucification also observed at ≥ 20 mg/kg/day.
Uterine Findings	At 40 mg/kg/day, no females were pregnant; therefore, uterine findings were not assessed. At 20 mg/kg/day, decreased number of corpora lutea, implantations, pre-implantation loss and viable embryos were observed.

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Treated male rats received oral nirogacestat for 65 days including 28 days prior to mating with untreated female rats. Treated female rats received oral nirogacestat for 35 days including 14 days prior to mating with untreated male rats and through Gestation Day 7.

FDA had the following clarifications in the table.

Males Fertility Indices	Fertile male incidence was 22, 20, 6 and 0 in the 0, 5, 20 and 40 mg/kg/day, respectively, with decreased fertility index at ≥ 20 mg/kg/day. Decreased sperm motility at ≥ 5 mg/kg/day, and decreased sperm concentration and normal morphology at ≥ 20 mg/kg/day.
Untreated Female Findings	No pregnant females at 40 mg/kg/day, increased pre-implantation loss observed at ≥ 5 mg/kg/day, and loss of viable embryos at ≥ 20 mg/kg/day.
Sperm Analysis	Decreased sperm motility at ≥ 5 mg/kg/day, and decreased sperm concentration and decreased normal morphology at ≥ 20 mg/kg/day.

Uterine Findings	At 20 mg/kg/day, decreased number of corpora lutea and increased pre-implantation loss resulted in a decreased number of implantations and viable embryos.

The Applicant's Position:

5.5.4.1 Embryo Fetal Development Study in Rats

Study Number: 1214011						
Study Title: An oral (gavage) dose range-finding study of the effects of PF-03084014 on embryo/fetal development in rats						
Key Drug-related Adverse Findings:						
- Dose dependent post-implantation loss; 100% loss at 150 mg/kg/day - Lower number of viable fetuses and lower mean fetal body weights at ≥ 20 mg/kg/day - Subcutis edema was the only fetal morphological change at ≥ 20 mg/kg/day - No Observed Adverse Effect Level: 5 mg/kg/day						
GLP compliance: No						
Dose and frequency of dosing:		0, 5, 20, 50, 150 mg/kg/day once daily during GD 6 through 17				
Route of administration:		Oral				
Formulation/Vehicle:		0.5% (w/v) methylcellulose in water/suspension				
Species/Strain:		Rat/Sprague Dawley				
Number/Group:		8 pregnant females				
Age:		10-12 weeks				
Satellite groups:		Toxicokinetic group consisting of 4 control and 8 in treated groups				
Toxicokinetics						
Daily Dose (mg/kg)	0 (Control)	5	20	50	150	
C _{max} (ng/mL)						
GD 17	NA	202	670	979	2260	
AUC _{0-t} (ng·h/mL)						
GD 17	NA	1400	5760	11400	26500	
Findings						
Died or Sacrificed Moribund		Five moribund females euthanized during GD 13-18 in the 150 mg/kg/day group.				
Body Weight and Food Consumption		Decreased body weight and food consumption was noted in the 150 mg/kg/day group through the entire dosing period. At 50 mg/kg/day, lower body weight gains occurred during GD 14-21, and at 20 mg/kg/day body weight gains were lower during GD 18-21. Lower mean gravid uterine weights at ≥ 20 mg/kg/day				

Clinical Observations	Clinical signs in moribund animals observed before euthanasia included thin body, hunched posture, thin/wet and stained fur.				
Ovarian/Uterine Exams					
Daily Dose (mg/kg)	0 (Control)	5	20	50	150
Live fetuses (%)	100	100	87.5	25.0*	0.0*
Resorptions (mean)	1.3	0.9	5.4	11.5*	13.0*
Number of fetuses (mean)	12.6	11.7	9.6	1.0	-
Number of live fetuses (mean)	12.6	11.7	8.4	0.3*	0.0*
Post-implantation loss (%)	9.11	6.94	37.72	98.21*	100*
Mean fetal weight (g)	6.11	5.90	5.15*	4.65	-

Abbreviations: AUC: area under the curve; C_{max}: maximum plasma concentration; eCTD: electronic Common Technical Document; GD: Gestation Day; GLP: Good Laboratory Practice; NA: not applicable; - no data due to lack of fetuses. *Statistically significant at $p \leq 0.05$.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Five deaths at 150 mg/kg/day indicates that this dose was maternally toxic.

5.5.5. Other Toxicology Studies

5.5.6. Phototoxicity

The Applicant's Position:

In alignment with ICH S10, no phototoxicity studies have been conducted as nirogacestat does not absorb in the ultraviolet A and B (UVA-UVB)/visible range from 290 to 700 nm.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

5.5.7. Studies on Impurities

The Applicant's Position:

A GLP 28-day repeat dose toxicity study was conducted in Sprague Dawley rats to qualify impurities (b) (4) at (b) (4)% for a nirogacestat dose of 300 mg (91103-19-529). The impurities were combined into one dosing formulation such that the dose level for each impurity was (b) (4) mg/kg/day. Rats (5/sex/group) received either the vehicle control (0.5% methylcellulose) or the impurity mixture once daily (QD) for 28 days.

There were no treatment-related adverse effects in clinical signs, body weights, clinical pathology, or after macro- and microscopic examinations. Slight decreases in adrenal weights were observed that were associated with vacuolation in 3 out of the 5 male rats. These minor changes were not considered adverse. Therefore, the NOAEL for this study was (b) (4) mg/kg/day.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

5.5.8. Safety Margins

The Applicant's Position:

The calculated safety margins for the definitive repeat dose toxicity studies with nirogacestat were calculated by dividing the total AUC₀₋₂₄ from the respective toxicology study at the NOAEL or LOAEL with the human total steady state AUC₀₋₂₄ (12860 ng·hr/mL) dosed at 150 mg BID (Table 14). The margins were based on exposures that were available at the end of the dosing period for the toxicity study. Because of the sex difference in rats, the margins were determined for both sexes, while for dogs and mice, margins were based on sex combined group mean values. Total exposures were used given that nirogacestat is highly protein bound in mouse, rat, dog and human plasma with fraction unbound of 0.2%, 0.2%, 0.2%, and 0.4%, respectively.

Table 14: Calculated Safety Margins from Definitive Repeat Dose Toxicity Studies

Study Type (Study Number)	Dose ^a (mg/kg/day)	AUC ₍₀₋₂₄₎ ^b (ng·h/mL)	C _{max} ^b (ng/mL)	Exposure Margins ^c
Repeat Dose Studies				
1-month study in mice (20174161)	20	42.9	30.1	0.003
1-month study in rats (06GR067)	5	50.7 (M) 137 (F)	19.3 (M) 42.7 (F)	0.004 0.01

3-month study in rats (08GR493)	5	223 (M) 680 (F)	19.6 (M) 56.7 (F)	0.02 0.05
1-month study in dogs (06GR066)	10	1920	448	0.1
3-month study in dogs (08GR495)	2	481	44.1	0.04
Carcinogenicity Study				
6-month study in TgRasH2 mice (20174162)	100 ^d	2200	716	0.2
Reproductive Toxicity Studies				
Fertility and early embryonic development in rats (01214013)	5 ^e	50.7 (M) 137 (F)	19.3 (M) 42.7 (F)	0.004 0.01
Fertility and early embryonic development in rats (01214026)	5 ^f	223 (M) 680 (F)	19.6 (M) 56.7 (F)	0.02 0.05
Embryo-fetal development in pregnant rats (01214011)	5	1400	202	0.1

Abbreviations: AUC: area under the concentration time curve; C_{max}: maximum concentration; F: Female; M: Male.

^a Dose is either the NOAEL or LOAEL for the study.

^b Total exposure derived from the end of the study.

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

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

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

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

The FDA's Assessment:

FDA disagrees with the Applicant's approach to the margin calculations in the table. The human exposure margins in Table 14 were calculated using a total human steady state AUC of 12860 ng·hr/mL after administration of nirogacestat at 150 mg BID. Note that the steady state AUC_{0-tau} (based on a dosing interval of 12 hours) in patients with desmoid tumors was 3370 ng·hr/mL (or approximately 6740 ng·hr/mL for comparison with animal AUC₀₋₂₄ data) after administration of nirogacestat at 150 mg BID.

X

X

Primary Reviewer

Supervisor

6 CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:

Nirogacestat is a gamma secretase (GS) inhibitor that blocks proteolytic activation of the Notch receptor. When dysregulated, Notch can activate pathways that contribute to tumor growth. The proposed recommended dosage of nirogacestat is 150 mg BID with or without food.

The clinical pharmacology review focused on the evaluation of appropriateness of the proposed dosage, administration of nirogacestat with food, use in patients with hepatic impairment (HI), and potential drug-drug interactions (DDI).

The proposed dosage of nirogacestat 150 mg BID with dose reduction to 100 mg BID for selected adverse reactions is generally acceptable based on the integrated analysis of PK, PD, efficacy and safety. The clinical effectiveness was demonstrated in pivotal Study NIR-DT-301 (*See Section 8 for details*). The overall safety of nirogacestat is considered acceptable and clinically manageable with a relative high dose intensity (87%). In addition, exposure-response analysis supported that patients who underwent dose reductions had similar best overall response (BOR) rate and duration of response (DoR) than those without dose reduction.

The review team agrees with the Applicant's proposal of administering nirogacestat without regard to food as the sub-study of food effect in the EXPAND-S phase of Study A8641014 showed that a high-fat meal had no clinically significant effect on nirogacestat exposure.

The review team assesses that no contraindication of nirogacestat for hepatic impairment (HI) is necessary based on the clinical AE evaluation on liver toxicity and the results from the HI study. The review team recommends that no dosage adjustment is necessary in patients with mild or moderate HI as the change in nirogacestat exposure in patients with moderate HI is not considered clinically meaningful compared to healthy subjects in the HI study NIR-DT-104. Insufficient data are available to characterize nirogacestat PK in patients with severe HI as

clinical data was only available in one patient with severe HI. However, the review team also does not recommend a dosage adjustment in patients with severe HI.

The review team recommends a PMC to conduct a clinical PK study to assess the effect of a proton pump inhibitor (PPI) on the PK of a single dose of nirogacestat as the in vitro study demonstrated that the solubility of nirogacestat was reduced by more than 87% at pH values of 6.0 and above. However, the effect of coadministration of acid-reducing agents (ARAs) with nirogacestat on its PK, efficacy, and safety has not been characterized in clinical studies. In addition, the review team recommends that concomitant use of PPIs and H2 receptor antagonists should be avoided, and that administration of antacids be staggered relative to the administration of nirogacestat.

The review team agrees with the Applicant's position that (1) the concomitant use of nirogacestat with strong or moderate CYP3A inhibitors and inducers should be avoided based on the results of the dedicated DDI study NIR-DT-103 and PBPK simulations and (2) the concomitant use with certain CYP3A4 and CYP2C19 substrates should be avoided where minimal concentration changes may lead to serious adverse reactions (CYP3A4 substrates) or significant decreases in efficacy (CYP2C19 substrates) based on the PBPK simulations.

6.1.1 Recommendations:

This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in Table 15 below.

Table 15: Key Review Issues with Specific Recommendations and Comments

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	Study NIR-DT-301 showed a statistically significant improvement in PFS for nirogacestat 150 mg BID compared to that of placebo. The clinical pharmacology (e.g., exposure-response analyses for efficacy, tumor size and safety) program provides supportive evidence of effectiveness.
General dosing instructions	The proposed recommended dosage of 150 mg BID taken with or without food is acceptable based on the following: • This proposed dosage has been demonstrated to be efficacious in the pivotal Study NIR-DT-301. • The safety profile of nirogacestat is considered acceptable and manageable. • Administration of nirogacestat without regard to food is supported by the results of the sub-study of food effect in

	Study A8641014 showing that a high-fat meal had no clinically significant effect on nirogacestat exposure.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Based on clinical PK data, PBPK, and exposure-response analyses, the following dosage adjustments are recommended: • Avoid concomitant use with strong and moderate CYP3A inhibitors and inducers. • Avoid concomitant use with PPIs and H2 receptor antagonists. Stagger administration with that of antacids. • Avoid concomitant use with certain CYP3A4 and CYP2C19 substrates where minimal concentration changes may lead to serious adverse reactions. • No dosage adjustment is recommended for patients with mild, moderate, or severe HI. Insufficient data are available to characterize nirogacestat PK in patients with severe HI. • No dosage adjustment is recommended for patients with renal impairment (RI).
Bioavailability between the uncoated and film-coated tablets used in clinical studies	Relative BA study between uncoated and film-coated tablet (to-be-market formulation) is not necessary as the dissolution profiles between uncoated and film-coated tablets are nearly identical at pH conditions of 1.2, 4.5 and 6.8. Refer to CMC review for additional details.
Labeling	Following are the key changes to the Applicant's proposed labeling: •  (b) (4) • Concomitant use of PPIs and H2 receptor antagonists should be avoided and the administration of antacids should be staggered relative to the administration of nirogacestat • PK parameters and characteristics of nirogacestat in Table 6 are updated.

6.1.2 Post-Marketing Requirements and Commitments

A PMC is proposed to evaluate if proton pump inhibitors alter the bioavailability of nirogacestat and to determine appropriate dosing recommendations for nirogacestat with regard to use of concomitant gastric acid reducing agents. Refer to Section below describing PMCs/PMRs.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Nirogacestat PK has been studied in 6 completed Phase 1 clinical studies conducted in healthy adult human participants (Studies A8641001, A8641002, A8641008, NIR-DT-101, NIR-DT-102, and NIR-DT-103). An additional Phase 1 study (NIR-DT-104) in participants with hepatic impairment is ongoing; an interim PK analysis has been completed and included in this review. In these studies, single oral doses of nirogacestat up to 150 mg and multiple doses up to 95 mg (Study A8641002) QD for up to 14 days have been administered. Nirogacestat was studied in participants with advanced cancers as a monotherapy in Study A8641014 utilizing doses ranging from 20 mg to 330 mg twice daily (BID), continuously. Additional investigations as monotherapy and in combination with other agents in breast cancer and pancreatic cancer were conducted; however, data were limited with regard to understanding the PK and PDx of nirogacestat. In addition, PK samples were collected in a Phase 3 study (Study NIR-DT-301; see [Section 8.1.1](#)) that was conducted using nirogacestat 150 mg BID in adult participants with progressing DT/AF. A pediatric study sponsored by the Children's Oncology Group (COG) is currently ongoing in participants aged > 12 months to < 18 years of age; data from this ongoing study is not included in this NDA.

Evaluation of the nirogacestat PK characteristics in healthy participants and participants with cancer diagnoses indicated that the compound was rapidly absorbed, with median time of occurrence of maximum serum concentration (C_{max}) (T_{max}) values of 0.5 to 1 hour generally observed. Nirogacestat exposure increased with escalating single and repeat doses, with greater than dose proportional increases observed across the dose range evaluated in single and multiple ascending dose studies. The terminal elimination half-life ($t_{1/2}$) of nirogacestat was approximately 19 hours after single doses and 26 hours after multiple doses. Nirogacestat is highly bound to both proteins, but with a greater affinity for serum human α 1-acid glycoprotein (AAG) than for serum albumin. In vitro studies indicated that nirogacestat is primarily metabolized by cytochrome P450 3A4 (CYP3A4). The impact of CYP3A4 metabolism on nirogacestat bioavailability and elimination was confirmed in a drug interaction study with itraconazole, leading to the conclusion that nirogacestat is a sensitive substrate for CYP3A4.

Two human mass balance studies (NIR-DT-101 and NIR-DT-102) were conducted to examine routes of excretion and identify potentially active metabolites. The primary route of excretion was through feces and very little unchanged nirogacestat recovered in feces, urine, or expired air. No major circulating metabolites were identified.

The PK of nirogacestat in pediatric populations has not been fully evaluated at this time. An Agreed Initial Pediatric Study Plan (iPSP) is in place to inform use in children. Studies have not been performed specifically in geriatric populations; however, age was a covariate in the Population PK (PopPK) model and no significant effect of age was found on nirogacestat PK. Because renal elimination is not the primary clearance pathway, studies have not been performed for a renally impaired population. A study is currently ongoing to evaluate nirogacestat in participants with hepatic impairment (Study-NIR-DT-104); interim PK data from this study establish that the PK of nirogacestat is altered by hepatic function. Specifically, participants that met the moderate impairment criteria by Child-Pugh but did not have total bilirubin levels $> 1.5 \times$ upper limit of normal (ULN) (National Cancer Institute – Organ Dysfunction Working Group [NCI-ODWG] moderate severity Group C) did not show significantly altered nirogacestat PK. Therefore, it is reasonable to conclude that patients with mild or moderate hepatic impairment and total bilirubin levels $\leq 1.5 \times$ ULN (NCI-ODWG normal or mild) can be treated with nirogacestat without dose modification. (b) (4)

Study A8641014 evaluated participants for a food effect on PK and reported that the geometric means were similar in the fed versus fasted condition for both C_{max} and the area under the plasma concentration-time curve over the dosing interval (AUC_{tau}); however, significant variability was observed for both PK parameters. Given the observed efficacy and safety parameters from Study NIR-DT-301 combined with reasonable variability from the food effect assessment in Study A8641014 relative to other assessments of nirogacestat PK, nirogacestat is recommended for administration without regard to food.

Nirogacestat also demonstrated evidence for both reversible and time-dependent inhibition of CYP3A4. A clinical drug interaction study (NIR-DT-103) evaluating the effects of nirogacestat on midazolam identified a weak inhibition effect on CYP3A4. In vitro studies indicated that nirogacestat inhibited the efflux transporter P-glycoprotein (P-gp) at clinically relevant concentrations; however, exposure of total dabigatran was not affected by nirogacestat administration in a clinical drug interaction study, supporting the absence of clinically meaningful P-gp inhibition by nirogacestat. A physiologically based pharmacokinetic model (PBPK) was developed based on in vitro and clinical data for nirogacestat and the effects of CYP3A induction on nirogacestat, as well as potential for nirogacestat to induce several CYP enzymes, were predicted using this model. Nirogacestat was predicted to have a potential

induction effect on CYP2C19 in a sensitivity analysis using (b) (4) times the maximum induction rate (IndMax) identified through in vitro evaluations; however, a minimal effect was predicted at the IndMax. The PBPK model was also applied to simulate the effects of various dose modification strategies in the event of a need to prescribe strong or moderate inhibitors of CYP3A4.

A population PK (PopPK) analysis was conducted using studies from 6 healthy participant studies (A8641001, A8641002, A8641008, NIR-DT-101, NIR-DT-102, and NIR-DT-103), a Phase 1 study in participants with advanced solid tumors (A8641014), and the Phase 3 study in participants with DT (NIR-DT-301). A three-compartment structural model, with two peripheral distribution compartments, first-order absorption with lag time, and central clearance was selected to describe nirogacestat PK. Notable covariates included itraconazole administration on bioavailability and clearance, participant population on clearance, and weight on the volume of distribution for the 2 peripheral compartments. Clearance was reduced approximately 44% in the advanced solid tumor and T-ALL/lymphoblastic lymphoma (LBL) population relative to healthy participants and participants with DT, suggesting that PK in participants with DT is more similar to healthy participants than participants with advanced malignancies.

The Applicant's Position:

Nirogacestat is rapidly absorbed, highly protein bound, and extensively metabolized by CYP3A4. No major circulating metabolites with activity against GS are known to occur and very little unchanged nirogacestat is recovered in feces, urine, or expired air. A PopPK analysis using several healthy participant and participant studies found that nirogacestat PK in participants with DT is more similar to PK observed in healthy participants than to PK observed in participants with advanced malignancies. Given the observed efficacy and safety parameters from Study NIR-DT-301 combined with reasonable variability from the food effect assessment in Study A8641014 relative to other assessments of nirogacestat PK, nirogacestat is recommended for administration without regard to food. The clinical PK of nirogacestat has been well characterized.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the available PK data. However, FDA notes that there is a significant difference in PK of nirogacestat administered to patients with DT and nirogacestat administered to patients with other solid tumor malignancies. Thus, the listed PK parameters such as, C_{max} , AUC_{tau} , and terminal elimination half-life of nirogacestat at steady state following 150 mg BID in patients from Study A8641014 may not be representative of patients with DT. Section 12 in the nirogacestat USPI reflects PK data from patients with DT. FDA agrees with the Applicant's position that the concomitant use of nirogacestat with strong or moderate CYP3A inhibitors and inducers should be avoided. FDA also agrees with the

Applicant's position that concomitant use with certain CYP3A4 and CYP2C19 substrates should be avoided where minimal concentration changes may lead to serious adverse reactions.

(b) (4)
See
FDA's assessment in Sections 6.3.1 and 6.3.2.4 below for details. (b) (4)

(See Therapeutic Individualization Section below).

FDA verified the population PK model and agreed with the Applicant's position that the population PK model described the observed data reasonably well and was considered adequate to predict individual PK estimates for subsequent PK/PD and E-R analysis.

6.2.2. General Dosing and Therapeutic Individualization

6.2.3. General Dosing

Applicant's Position:

The selection of 150 mg BID as the RP2D was made using the totality of evidence from Study A8641014, a Phase 1 dose-finding study of nirogacestat in participants with advanced solid tumors (see [Section 8.1.7](#)). This included the identification of the maximum tolerated dose (MTD) at 220 mg BID and data from PK and PDx measurements, as well as review of objective responses among a broad range of solid tumor types. The high response rate in the participants with DT (objective response rate [ORR]: 71.4%) led to the initiation of a Phase 2 investigator-initiated study that was conducted at 150 mg BID (Study 14-C-0007; [Kummar et al. 2017](#)). The rate of response for participants with DT in these two studies (ORR: 71.4% [Study A8641014] and 31% [Study 14-C-0007]), and the relative tolerability of the 150 mg BID dose level compared to the 220 mg BID dose level were primary factors in selection of the 150 mg BID dose in Study NIR-DT-301. For selected toxicities, dosing was interrupted and/or reduced to 100 mg BID.

The FDA's Assessment:

See FDA's assessment in the section 6.3.2.2 below for details.

6.2.4. Therapeutic Individualization

The Applicant's Position:

As described in [Section 6.2.3](#), dosing will be interrupted and/or reduced to 100 mg BID for patients who experience selected toxicities or for patients who experience life-threatening adverse reactions.

Nirogacestat PK has been characterized based on extrinsic and intrinsic factors. No therapeutic individualization is needed in the proposed indication based on demographic factors. As renal elimination of nirogacestat does not appear to be a primary clearance pathway, no dose adjustments are required in patients with renal impairment.

(b) (4)

The FDA's Assessment:

(b) (4)

FDA recommends that no dosage adjustment is recommended in patients with mild, moderate, or severe HI. See FDA's assessment in Section 6.3.2.3 below for details.

6.2.5. Outstanding Issues

The Applicant's Position:

As discussed during the Pre-NDA meeting, the Phase 1 study NIR-DT-104 evaluating the effects of hepatic impairment on the PK of nirogacestat is ongoing. An interim PK analysis was submitted in the NDA.

As described in Section 6.2.1 and Section 10, the pediatric study, ARST1921, is currently ongoing. As stated in the Agreed iPSP letter, SpringWorks has requested a deferral of pediatric studies in the NDA.

The FDA's Assessment:

The Applicant submitted an interim PPK report, which was sufficient to evaluate the effect of hepatic impairment on nirogacestat PK; thus, hepatic impairment is no longer an outstanding issue.

The review team will issue a PMC to evaluate the effects of a proton pump inhibitor (PPI) on the PK of nirogacestat.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Drug-drug interaction (DDI) risks are summarized in Section 6.2.4. Clinical pharmacology and an overview of ADME properties are provided below.

Clinical Pharmacology: Study A8641001 demonstrated that, following single oral doses of nirogacestat in healthy participants, mean exposures as measured by AUC and C_{max} increased proportionally up to the 5-mg dose group, with greater than dose proportional increases observed from 10 to 40 mg. A less than proportional increase in AUC and C_{max} was noted between the 40 mg and 65 mg doses and a slightly greater than dose proportional increase was observed during the final dose escalation from 65 mg to 120 mg. In Study A8641002, nirogacestat exposures (AUC and C_{max}) in healthy participants increased with increasing dose over the 7 mg BID to 95 mg QD dose range following repeat administration for 14 days. Nirogacestat systemic exposures were slightly greater than dose proportional across all dose groups. In Study A8641014, nirogacestat exhibited generally dose proportional behavior (AUC_{tau} and C_{max}) over the dose range tested in participants with advanced solid tumor. In summary, nirogacestat has a tendency toward slightly greater than dose proportional increases in exposure below 100 mg and somewhat dose proportional increases between 100 mg and 220 mg.

PK parameters tend to have substantial inter-subject variability as most coefficient of variation (CV) values were > 30% and even approached 100% in some cases. The geometric mean for C_{max} was 612 ng/mL in Part 3 of Study NIR-DT-103 and 534 ng/mL in Part 2 of Study NIR-DT-102 but ranged from 822 to 943 ng/mL in the other studies. Similar patterns are observed with these studies for other parameters as well, with AUC_{inf} being lower and apparent clearance (CL/F) higher than in other studies. While these deviations from the other studies are notable, the geometric mean values from these study parts are within the range of variability observed in all studies. The median T_{max} was approximately 1 hour across studies. In general, the central tendency and large inter-subject variability for single-dose PK parameters for nirogacestat at 150 mg have been consistent across studies. Rich PK sampling in multiple dose studies using doses at or greater than 100 mg BID has only been conducted in Study A8641014. Therefore, the generalized values for C_{max} (1246 ng/mL) and AUC_{tau} (6430 ng·h/mL) at steady-state are taken from the 150 mg BID evaluation at C1D21 in Study A8641014.

In Study A8641002, the median accumulation ratio at Day 14 for healthy participants was 1.12, 1.35, and 1.73 for regimens of 95 mg QD, 40 mg QD, and 7 mg BID, respectively. In Study A8641014, the median accumulation ratio at Day 21 for participants with advanced solid tumors ranged from 1.18 to 1.6 between 20 mg BID and 80 mg BID and ranged from 1.98 to 2.84 between 100 mg BID and 220 mg BID.

Absorption: Nirogacestat is rapidly absorbed, with median T_{max} observed approximately 1 hour following administration across all studies. Comparison of exposures from an intravenous dose of radiolabeled nirogacestat and orally administered nirogacestat in Study NIR-DT-102 determined a mean absolute bioavailability of 19.2% (range: 16.2% to 24.3%). Based on the high

level of radiolabel recovery in the mass balance assessments from this study and the increase in bioavailability observed when concomitantly administered with itraconazole in Study NIR-DT-103, it is likely that the absolute bioavailability of nirogacestat is limited by a strong first pass metabolism effect in the gastrointestinal tract.

Distribution: Data suggest that the distribution of nirogacestat may be limited by serum AAG levels and that nirogacestat may be more widely distributed when AAG is low. The potential for wide distribution is also supported by the results of the PopPK analysis. Observations of low exposure in the central nervous system (CNS) may be due to low bioavailability of free nirogacestat and insufficient distribution throughout the body after a single dose.

Metabolism: Nirogacestat is primarily metabolized by CYP3A4. Nirogacestat is extensively metabolized and leaves no major structural metabolites that would be active against GS. No major circulating active metabolites are believed to be active against GS.

Excretion: Nirogacestat is extensively metabolized in the gastrointestinal tract and by hepatic metabolism. Feces is the primary route of excretion for drug-related material. While renal excretion is an insignificant route of elimination for unchanged nirogacestat, renal clearance may be an important route of elimination for some metabolites of nirogacestat.

The Applicant's Position:

Nirogacestat is rapidly absorbed with the potential for wide distribution. Nirogacestat is extensively metabolized, and the primary route of excretion is through feces, with very little unchanged nirogacestat recovered in feces or urine. No major circulating metabolites were identified.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment.

FDA emphasizes that the reported PK parameters may not be directly applicable to patients with DT. The population PK model reported that clearance was more than two-fold higher in patients with DT (9.1 L/hr) compared to that of patients with other diseases (solid tumor, T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma, 4.4L/hr).

The review team does not agree with PK parameters based on all PK samples in patients with DT because certain PK samples were analyzed outside of the established long-term stability (LTS) window of 520 days (refer to OSIS review below). Therefore, these PK samples from 4 patients - (subject ID: [REDACTED] (b) (6)) were excluded. The updated PK parameters reflecting patients with DT and excluding samples outside of the stability window are shown in Table 16. Section 12 in the nirogacestat USPI reflects PK data

from patients with DT excluding the patients whose samples were analyzed outside of the LTS window.

Table 16: Updated PK parameters in patients with DT With Samples Analyzed within Established Window for LTS for Study NIR-DT-301

PK Parameters Geometric Mean (% CV)	Patients with DT (N=90)	
	Single Dose	Steady State
T _{max} (h)*	1.5 (0.5,6.5)	1.5 (0.5,4)
C _{max} (ng/mL)	373 (70)	508 (62)
AUC _{tau} (ng*h/mL)	2,110 (59)	3,370 (58)
Predicted Vz/F (L)	1,430 (65)	1,440 (65)
CL _{ss} /F (L/h)		44.5 (58)
Terminal Elimination Half-life (h)	22.5 (37)	
Time to Steady State		Approx 6 Days
Accumulation Ratio (AUC)		1.6 (18)
*Note: T _{max} is expressed as median (min, max).		

(Data Source: Table 1 on page 2 in the Applicant's response to FDA IR submitted on 8/2/2023)

FDA agrees with the Applicant to report the nirogacestat excretion results in Part 1 of Study NIR-DT-102 in the labeling given the excretion pathway is not affected by the dosage forms and formulation (see drug formulation information in Table 17). Following oral administration of 5 µCi of [¹⁴C]-nirogacestat, the mean cumulative recovery in urine and feces combined was 55%, with 17% being excreted in urine and 38% in feces. Only a small fraction (0.07%) of the dose was recovered unchanged in urine. The results of recovery in feces and urine were similar to what was observed in Study NIR-DT-101 in which 44% and 18% was recovered in the feces and urine, respectively. In addition, radioactivity collected in expired air trapping solutions contributed a further 9.7% for a total cumulative recovery of 65% over the course of 312 hours post-dose, while in Part 2 of Study NIR-DT-102, radioactivity collected in expired air trapping

solutions contributed a further 25% for a total cumulative recovery of 79% following an IV administration of nirogacestat. These results indicated that ^{14}C -labeled nirogacestat was released as a result of extensive metabolism and was ultimately eliminated as $^{14}\text{CO}_2$. Of note, Studies NIR-DT-101 and NIR-DT-102 were both designed as mass balance studies following a single oral dose of [^{14}C]-nirogacestat, however, Study NIR-DR-102 also included radioactivity data collected in expired air and PK data following IV administration of [^{14}C]-nirogacestat. Therefore, Study NIR-DR-102 was chosen to report the data in full expansion of nirogacestat excretion and absolute bioavailability.

Drug Formulation

Multiple drug formulations were used during clinical development, including powder in bottle (PiB), citrate buffer solution (CBS), and tablets (uncoated and film-coated). The film-coated tablets are the proposed to-be-market formulation, which were only used in the open-label extension (OLE) phase in Study NIR-DT-301. Table 17 lists drug formulations in each trial.

Table 17: Summary of Dosage Form and Formulation used in Clinical Studies

Study	Design	Population	Formulation	N	PK
A8641001	First in human, dose escalation	HS	Powder in bottle (PiB) oral solution	26	Rich
A8641002	Multiple doses, DDI			42	
A8641008	PD			10	
A8641014	First in patient, dose finding	DT and advanced malignancies	Uncoated Tablet	71	
NIR-DT-101	PK, Mass Balance	HS	Citrate buffer solution (CBS)	10	
NIR-DT-102	Mass Balance, ADME and Absolute BA		Part 1: CBS Part 2: IV and uncoated tablet	6	

NIR-DT-103	DDI		Uncoated tablet	70	
NIR-DT-104	Moderate HI	HS		12	
		HI patients		12	
NIR-DT-301	Efficacy and safety	Patients with DT	Uncoated and film-coated tablet	94	C _{max} and C _{trough}
Note: HS=healthy subject; HI=hepatic impairment; BA=bioavailability					

(Data Source: Table 2 on page 24 in the summary of biopharmaceutical studies and associated analytical methods)

Although the Applicant did not conduct a relative bioavailability study between PiB, CBS and tablets, sufficient data were submitted to support using all of the data collected for these formulations in PK evaluation. PK data from the studies in which PIB and CBS were administered were useful to inform the population PK modeling and describe the absorption information at the lower end of the dose range.

Relative BA between uncoated tablet and film-coated tablets is not necessary as the dissolution profiles between uncoated and film-coated tablets are nearly identical at pH conditions of 1.2, 4.5 and 6.8 (refer to CMC review for details). Therefore, the absolute BA of nirogacestat (19%) in Part 2 of Study NIR-DT-102 following oral administration of 150 mg in uncoated tablets is included in the labeling. Generally, PK parameters of the film-coated tablets should be that of the PK parameters estimated for the uncoated tablets.

6.3.2. Clinical Pharmacology Questions

6.3.3. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The effectiveness of nirogacestat 150 mg BID in participants with DT was demonstrated by the statistically significant improvement in progression-free survival (PFS) (HR = 0.22; 95% CI: 0.11, 0.42; one-sided p < 0.001) and response rates of 31% in Study 14-C-0007 and 41% vs 8% for nirogacestat vs placebo in Study NIR-DT-301 and the relative tolerability.

Exposure-response relationships were explored for several efficacy and safety endpoints using data from Studies A8641014 and NIR-DT-301, and the final model from the PopPK analysis. An exposure-response plateau was achieved within the predicted exposure ranges (AUC_{tau} and

C_{min}) for the ≥ 100 mg to 150 mg dose range. Reduction in tumor size was independent of nirogacestat exposure within the evaluated dose range, whether it was determined by volumetric MRI (NIR-DT-301 only) or using RECIST (by CT or MRI). Similarly, there was a treatment effect relationship with PFS that was independent of exposure within the evaluated dose ranges. Additional analyses were conducted to explore if a relationship between nirogacestat exposure and objective response could be described; however, exposure was not found to be a significant predictor of duration of response due to low number of participants with loss of response.

The exposure-response data support a recommended starting dose of 150 mg for all patients with allowance for dose modification based on tolerability to ensure optimal exposure for each individual.

The FDA's Assessment:

Yes, FDA agrees that the clinical pharmacology program provides supportive evidence of effectiveness by exposure-response (E-R) analyses for efficacy and tumor size.

E-R analyses were performed between nirogacestat exposure and progression-free survival (PFS) based on clinical data in Study A8641014 and Study NIR-DT-301. The PFS probability for all tumors was not associated with nirogacestat exposures at the evaluated dose range. Higher exposure appeared to correlate with a longer response, though no exposure response relationship was observed for the duration of response which could be due to small exposure range for a single dose level. Nirogacestat-mediated treatment effect on tumor size was independent of nirogacestat exposure at the evaluated dose range in participants with DT and non-DT solid tumors. Predicted change in tumor size following treatment with nirogacestat at doses ≥ 100 mg BID after 24 months was -22% (RECIST sum of longest diameter) and -55% (tumor volume), respectively. In addition, the PK/PD model for tumor size summarized by real time dose in Study NIR-DT-301 indicated comparable slope of tumor size decrease between patients with and without dose reduction. Refer to the pharmacometrics review in appendix 19.4.3 for details.

6.3.4. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed dose of 150 mg BID is effective for patients with DT, with a positive benefit:risk. Subgroup analyses did not reveal the need for different doses based on sex, race, age, or weight. In the PopPK analyses, no demographic categories were selected as covariates

that may alter PK. Most AEs were effectively managed with dose interruptions until recovery, dose reduction to 100 mg BID, and/or supportive care.

Exposure-response relationships were explored for several efficacy and safety endpoints using data from Studies A8641014 and NIR-DT-301, and the final model from the Population PK Analysis. Exposure-response relationships were explored between nirogacestat exposure and Grade ≥ 3 diarrhea, Grade ≥ 3 rash, treatment-related TEAEs, SAEs, and TEAEs leading to discontinuation. No significant relationships were found with these endpoints.

A statistically significant relationship was found between nirogacestat exposure and Grade ≥ 3 hypophosphatemia. Compared to treatment, $C_{\max}$ was found to be the best predictor of Grade ≥ 3 hypophosphatemia. Based on PopPK predicted median steady-state $C_{\max}$ values for participants with DT, this exposure-response model predicts a 6.3% probability of experiencing a Grade ≥ 3 hypophosphatemia event at the 100 mg dose and a 7.2% probability at the 150 mg dose. This implies that the 150 mg dose carries a 0.9% absolute increased risk of Grade ≥ 3 hypophosphatemia compared to the 100 mg dose.

Additional analyses were performed for ovarian dysfunction (OD) and follicle-stimulating hormone (FSH). No exposure-response relationship could be identified with OD at the evaluated dose ranges, but a linear relationship between nirogacestat concentration and FSH levels in women of childbearing potential (WOCBP) was established. FSH increased linearly with increasing nirogacestat serum concentrations; however, high variability in the drug effect, presumably due to menstrual cycle oscillation and sparse sampling, made precise estimation of drug effects difficult.

A statistically significant relationship was found between exposure and dose modifications. Participants with higher predicted exposures (AUC_{τ} and $C_{\min}$) at steady-state were more likely to have had dose modifications than those with lower steady-state exposures. Given that the majority of dose modifications were due to TEAEs, this relationship may suggest that participants with lower nirogacestat clearance were more likely to experience TEAEs that required a dose modification.

The exposure-response data support a recommended starting dose of 150 mg for all patients with allowance for dose modification based on tolerability to ensure optimal exposure for each individual.

The FDA's Assessment:

Clinical pharmacology data support the proposed recommended dosage of 150 mg BID with reduction to 100 mg BID for selected adverse reactions based on the following evidence.

- A statistically significant improvement in the primary endpoint of PFS was observed for nirogacestat 150 mg BID compared placebo, with a 71% reduction in the risk of disease progression (HR = 0.29 [95% CI: 0.15, 0.55]; $p < 0.001$) in the pivotal clinical study NIR-DT-301 (*refer to clinical review section 8 for details*).
- ORR, as one of the secondary endpoints, was statistically significantly higher ($p < 0.001$) in the nirogacestat arm (41%) versus the placebo arm (8%) in Study NIR-DT-301.
- PRO assessments evaluated as part of the secondary endpoints at the prespecified timepoint of Cycle 10 generally favored the nirogacestat arm.
- The overall safety profile of nirogacestat is considered acceptable and clinically manageable. Most frequently (> 30%) reported TEAEs in Study NIR-DT-301 and all patients with DT were diarrhea, nausea, fatigue, hypophosphatemia event, and rash maculopapular, which are expected with GS inhibition.
- Despite high rate of dose interruption and reduction (65%) in the nirogacestat arm, the relative dose intensity is high (87%) indicating the duration of dosage interruption was likely short.
- E-R analysis showed that BOR rate and DoR were similar between patients with DT with dose reductions and those w/o dose reduction.
- PK/PD model for tumor size summarized by real time dose in Study NIR-DT-301 indicated comparable tumor shrinkage between patients with and without dose reduction.
- Ovarian dysfunction (OD) is a known risk for GS inhibitors based on animal study and is one of the adverse events of special interest. The Applicant reported OD in 27 of the 36 women of childbearing potential (WOCBP, 75%) in the nirogacestat arm and none in the 37 WOCBP in the placebo arm in Study NIR-DT-301. However, there is uncertainty regarding the characterization of ovarian toxicity, including reversibility. The clinical team issued a PMR of ovarian toxicity to better characterize this toxicity and clinical outcome (*refer to clinical review section 8 for more details*).
- PK/PD analyses based on nonclinical and clinical data indicated that 100 mg BID may have a similar effect in tumor reduction as 150 mg BID, but the sample size for patients who received 100 mg BID is limited.
- E-R analyses showed positive relationships between nirogacestat exposure and decreases in serum phosphate, Grade 3+ TEAE and dosage modification as well as a positive trend between nirogacestat exposure and FSH/ovary dysfunction; however, the dose range used in the E-R analysis is narrow and the sample size of patients who

received a dosage < 150 mg BID is limited (*refer to pharmacometrics review in appendix 19.4.3 for details.*)

The proposed recommended dosage of 150 mg BID was chosen as the RP2D based on the comparison in the safety profile between dose cohorts of 150 mg and 200 mg BID and the observed clinical response in 7 patients with DT in Study A8641014. Given insufficient data are available at nirogacestat at dose levels <150 mg and no integrated approach inclusive of PK, PD, dose-response or exposure-response relationship, it is not known if a lower dose could provide clinically meaningful efficacy with less toxicity.

Collectively, the proposed recommended dosage of 150 mg BID demonstrated a clinical meaningful efficacy in patients DT compared to that of placebo. Dosage modifications for selected AEs are included in the approved labeling to manage adverse reactions.

6.3.5. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No alternative dosing regimen or management strategy is required for subpopulations based on intrinsic patient factors in the PopPK analyses.

As described in [Section 6.2.4](#),

(b) (4)

Renal Impairment: Renal elimination of nirogacestat does not appear to be a primary clearance pathway as supported by the PK characteristics of nirogacestat. No dose adjustments are required for renal impairment.

Age: No age-specific differences in TEAEs among adults were observed that would require a dosing management strategy. Nirogacestat PK has not been evaluated in pediatric populations to date. A clinical study of nirogacestat in pediatric participants with DT aged > 12 months to < 18 years of age is ongoing in collaboration with the COG (Study ARST1921). It is generally assumed that the mechanistic basis for nirogacestat in DT is the same between adults and children. Age was evaluated as a covariate in the PopPK analysis, which included 25 participants aged 65 years or older. No significant effect of age on PK was identified.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that no alternative dosing regimen is required for subpopulations regarding age, sex, race and renal function based on the updated population PK analysis (*refer to the pharmacometrics review in appendix 19.4.2 for details*).

Hepatic Impairment

(b) (4)

Instead, FDA recommends that no dosage adjustment is recommended for patients with mild, moderate, or severe HI.

Study NIR-DT-104 evaluated nirogacestat PK in patients with impaired hepatic function. Severity of HI was determined using both the Child-Pugh Classification system and the NCI-ODWG criteria for liver dysfunction. Patients with Child-Pugh Class A (mild) HI or NCI-ODWG Group D (severe) HI were not included in the PK analysis. In total, 11 patients had Child-Pugh Class B (moderate) HI and 1 patient Child-Pugh Class C (severe) HI. Of note, 5, 2, and 4 out of 11 patients in the group of Child-Pugh Class B (moderate HI) were classified as NCI-ODWG Group A (normal hepatic function), Group B (mild HI) and Group C (moderate HI), respectively. The one patient in the group of Child-Pugh Class C (severe HI) was classified as NCI-ODWG Group C (moderate HI). Table 18 lists the geometric mean ratio [GMR (90% CI)] of nirogacestat exposure following a single dose of 100 mg in patients with moderate HI by either Child-Pugh Classification or NCI-ODWG criteria compared to that of 12 subjects with normal hepatic function. Overall, C_{max} is lower in patients with moderate HI by either Child-Pugh Classification or NCI-ODWG criteria comparing to healthy subjects.

Table 18: Geometric Mean Ratio [GMR, 90% Confidence Interval (CI)] of Nirogacestat Exposure in Patients with Moderate HI vs. Healthy Subjects

GMR (90% CI)	Child-Pugh Class B (N=11)	NCI-ODWG Group C (N=5)
AUC _{inf}	107% (87 – 131%)	116% (85 – 160%)
AUC _{last}	100% (82 – 121%)	96% (74 – 125%)

C _{max}	72% (58 – 90%)	61% (47 – 80%)

(Data source: Table 3 on page 10 in Study NIR-DT-104 interim PK report addendum 01)

Safety data from Study NIR-DT-104 were also assessed. Only 1 TEAE was reported in a patient, who had moderate HI by Child-Pugh and mild HI by NCI-ODWG criteria. This adverse reaction was assessed by the investigator as Grade 1 in severity, and the patient recovered the same day with no intervention. No Grade 3 or 4 adverse reactions were reported. In addition, no clinically significant shifts in clinical laboratory values or vital signs were noted following administration of nirogacestat. Although data are limited to a single dose, moderate hepatic impairment did not appear to significantly increase toxicity.

In addition, per the communication with clinical team, the liver toxicity (AST or ALT elevation) caused by nirogacestat was considered mild as most AEs were low grade and can be reversed by dosage modifications.

Despite limited clinical data in patients with severe HI (only one patient per NCI-ODWG criteria), the review team does not recommend a dosage adjustment in patients with severe HI. A large increase in nirogacestat exposure is not expected in patients with severe HI because there was no significant change in patients with mild or moderate HI. The proposed dosage modifications (e.g., down to 100 mg BID) are expected to be sufficient to manage any emerging toxicity. A PMR for a severe HI study was not issued due to feasibility concerns and because severe HI is not expected to be common in the indicated patient population.

Therefore, combining the clinical AE evaluation on liver toxicity and the results of Study NIR-DT-104, dosage adjustments do not appear to be necessary for patients with mild or moderate HI classified using either Child-Pugh or NCI-ODWG criteria and a contraindication for HI is not justified given the lack of data in patients with severe HI.

CTNNB1 mutations and treatment efficacy

In study NIR-DT-301, genetic mutations (germline and somatic) in the *CTNNB1* and *APC* genes were centrally evaluated using blood sample and tumor biopsy collected at baseline. T41A (34.3%) and S45F (18.6%) were the most frequently observed mutations. Similar frequencies for mutations were observed in treatment arms and placebo arms. Among the 105 participants with evaluable tumor samples (of 142 enrolled), 85 participants (81%) had a *CTNNB1* mutation

and 22 participants (21%) had an *APC* mutation. FDA explored the nirogacestat efficacy in subgroups with different *CTNNB1* mutations. Responses to nirogacestat treatment were observed across *CTNNB1* mutations (Table 19). The point estimate for the PFS HR was slightly lower in the subgroup of patients whose tumors had the S45F mutation (HR=0.18, 95% CI: 0.02-1.46, ORR=62%), compared to patient with T41A mutations (HR= 0.38, 95% CI: 0.13-1.10, ORR = 33%). The results suggested nirogacestat treatment is effective across *CTNNB1* mutations. The lack of differences in clinical response is consistent with the mechanism of action. However, there were absent of *in vitro*/animal pharmacology studies on different mutations in *CTNNB1* genes. See section 8.1.3.2 for additional clinical efficacy results stratified by mutation status.

Table 19: ORR Results by CTNNB1 Mutations in Patients in Study NIR-DT-301

<i>CTNNB1</i> Mutation	Best Overall Response (BOR) in Nirogacestat n/N (%) (N= 70)	Best Overall Response (BOR) in Placebo n/N (%) (N=72)
T41A	8/24 (33)	1/21 (5)
S45F	8/13(62)	0/17 (0)
S45P	3/5 (60)	1/2 (50)
S45N	0/1 (0)	0/0
S45F/T41A	0/0 (0)	1/1 (100)
S45_G48delinsR	0/0 (0)	0/1 (0)
No mutation	10/27 (37)	3/30 (10)
Total	29/70(41)	6/72 (8)

Data Source: Reviewer's Table. Abbreviations: ORR: objective response rate; n: number of patients with BOR; N: total number of patients

6.3.6. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Due to strong dependency on CYP3A4 for elimination of nirogacestat, concomitant administration with strong or moderate inhibitors of CYP3A4 should be avoided. If a strong or

moderate inhibitor of CYP3A4 must be prescribed, a patient should cease administration of nirogacestat for the duration of use of the interacting drug. (b) (4)

There is no expectation of clinical benefit from nirogacestat if taken concomitantly with strong CYP3A4 inducers. Exposure to nirogacestat is predicted to be greatly reduced when administered concomitantly with moderate CYP3A4 inducers, but it is unknown if therapeutic benefit from nirogacestat could be expected. The effects of P-gp inhibition on nirogacestat were not evaluated in a clinical study, however any clinical effect is believed to be less important than the effect of first-pass metabolism by CYP3A4.

Nirogacestat is a weak inhibitor of CYP3A4 with clinical usage. Concomitant usage of nirogacestat with CYP3A4 substrates that have a narrow therapeutic window should be avoided as nirogacestat may increase the exposure to a CYP3A4 substrate. Nirogacestat may cause weak-to-moderate induction of CYP2C19 in some cases. In a clinical evaluation with dabigatran etexilate, nirogacestat showed no meaningful effect on P-gp inhibition.

The solubility of nirogacestat is substantially reduced at pH greater than 6.0, thus gastric acid reducing agents may reduce the bioavailability of nirogacestat. (b) (4)

In an evaluation of food effects on nirogacestat PK in Study A8641014, C_{max} and AUC_{tau} were similar between fed and fasted states but carried significant variability. In Study NIR-DT-301, nirogacestat was dosed without regard to food. Given the observed efficacy and safety parameters from Study NIR-DT-301, nirogacestat is recommended for administration without regard to food.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the labeling recommendation for the concomitant use of nirogacestat with strong or moderate CYP3A inhibitors and inducers and drugs that are substrates of CYP3A4 and CYP2C19. However, FDA does not agree with the Applicant's position regarding the labeling recommendation for the concomitant use of nirogacestat with gastric acid-reducing agents (ARAs). FDA's rationale and supportive data are summarized below.

Effect of Concomitant Medications on Nirogacestat

- a. Strong and moderate CYP3A4 inhibitors

The effects of a strong CYP3A4 strong inhibitor increased AUC_{last} , AUC_{inf} and C_{max} of a single dose 100 mg of nirogacestat by approximately 6-, 8- and 2.5-fold, respectively.

The Applicant developed a PBPK model to predict the potential DDI of nirogacestat under various scenarios following a single and multiple doses (100 mg or 150 mg) when co-administered with inhibitors of CYP3A4 in healthy subjects and patients. These simulations included the effect of coadministration of strong inhibitors (itraconazole, ketoconazole and clarithromycin), moderate inhibitors (fluconazole and erythromycin), and a weak inhibitor (cimetidine). Nirogacestat AUC is predicted to increase by 3.5 to 6.3 fold following coadministration of multiple doses of nirogacestat (150 mg BID) with strong inhibitors and increase by 2.7 to 3.2 folds with moderate CYP3A inhibitors (*Refer to the PBPK review in appendix 19.4.4 for details*).

Considering the magnitude of the increase in AUCs of nirogacestat when co-administered with strong and moderate CYP3A4 inhibitors and the positive relationship between nirogacestat exposure and adverse reactions in the E-R analysis, FDA generally agrees with the Applicant's position that concomitant use with strong or moderate CYP3A4 inhibitors should be avoided. However, FDA does not agree with the proposed labeling language; (b) (4)

FDA revised the labeling to avoid co-administration of strong or moderate CYP3A4 inhibitors or inducers with nirogacestat.

b. Strong and moderate CYP3A4 inducers

A PBPK model was used to predict the potential DDI between nirogacestat and a strong inducer (rifampicin) or a moderate inducer (efavirenz) following a single dose and multiple doses (100 mg or 150 mg BID) in healthy subjects and patients. The AUC of nirogacestat was predicted to decrease by 85% when co-administered with rifampicin and by 67% when co-administered with efavirenz with multiple doses of nirogacestat at 150 mg BID (*Refer to PBPK review in appendix 19.4.4 for details*).

FDA generally agrees with the Applicant's position to avoid the coadministration of strong or moderate CYP3A4 inducers with nirogacestat. However, FDA does not agree with the proposed labeling language; (b) (4)

FDA revised the labeling to avoid concomitant use of nirogacestat with strong or moderate CYP3A4 inducers.

c. P-gp inhibitors

The effect of concomitant use of itraconazole (a strong CYP3A4 inhibitor and a P-gp inhibitor) on nirogacestat PK was evaluated. The mean C_{max} of a single dose 100 mg of nirogacestat following multiple doses of itraconazole days was increased by approximately 2.5-fold and median T_{max} was delayed from 1 to 1.5 hours. The mass balance study revealed the absence of unchanged parent drug in feces after oral administration of 150 mg nirogacestat. Additionally, the nirogacestat PK exhibited linearity across the dosage range of 1-120 mg (SD) and 20-220 mg (BID) following oral administration. These findings indicated that the observed DDI with itraconazole was most likely a result of nirogacestat mediated CYP3A4 inhibition rather than the inhibition of P-gp. FDA agrees with the applicant that a P-gp inhibitor is unlikely to have a clinically meaningful effect of nirogacestat exposure.

d. Gastric pH-altering agents

Nirogacestat demonstrates pH-dependent solubility. The Applicant did not conduct clinical studies to evaluate the effects of gastric acid-reducing agents (ARAs), but the Applicant evaluated the effect of ARAs in the population PK model; the effect was inconclusive due to the low number of patients on ARAs. Therefore, a clinical pharmacology PMC is issued to evaluate the impact of concomitant use of a proton pump inhibitor on nirogacestat PK. Proton pump inhibitors were selected to best describe the worst-case scenario as they are the ARA with the strongest effect on pH relative to antacids and H2 receptor antagonists.

FDA does not agree with the Applicant's proposed recommendations. FDA recommends:

- Avoiding concomitant use with proton pump inhibitors and H2 receptor antagonists.
- Staggering administration of antacids (e.g., administer nirogacestat 2 hours before or 2 hours after antacid use).

Effect of Nirogacestat on Concomitant Medication

a. Substrates of CYP3A4

Co-administration of nirogacestat with oral midazolam, a sensitive probe CYP3A substrate, increased midazolam plasma AUC by 59%, indicating that a nirogacestat-is a weak CYP3A inhibitor.

The PBPK model was used to predict the magnitude of interaction between nirogacestat and midazolam following multiple doses of nirogacestat of 150 mg BID. The C_{max} and AUC of midazolam was predicted to increase by 1.8 and 2.1 folds, respectively, suggesting that nirogacestat is a weak inhibitor of CYP3A4 at the proposed recommended dosage.

Taken together, FDA agrees with the Applicant's labeling proposal that concomitant use with certain CYP3A4 substrates should be avoided where minimal concentration changes may lead to serious adverse reactions.

b. Substrates of CYP2B6, 2C8, 2C9 and 2C19

The Applicant did not conduct any clinical studies to evaluate the effects of nirogacestat-mediated induction of CYP2B6, CYP2C8, CYP2C9, and CYP2C19. No meaningful induction was predicted for nirogacestat on substrates of CYP2B6, CYP2C8, or CYP2C9 based on in vitro data and PBPK simulation. A moderate interaction was predicted for S-mephenytoin (a sensitive CYP2C19 substrate) when co-administering with nirogacestat at 100 mg and 150 mg BID using a 10-fold increase in maximum fold induction to assess a worst-case scenario, although the in vitro study indicated that the risk of DDI between nirogacestat and CYP2C19 substrates is low. Therefore, the potential induction of nirogacestat on certain CYP2C19 substrates cannot be ruled out.

Taken together, FDA agrees with the Applicant's labeling proposal that concomitant use with certain CYP2C19 substrates should be avoided where minimal concentration changes may lead to significant decreases in efficacy.

c. Substrates of P-gp

The results of Study NIR-DT-103 showed that nirogacestat is unlikely to inhibit P-gp. The C_{max} and AUC for total dabigatran was similar when administered alone ($C_{max} = 76$ ng/mL and $AUC_{inf} = 600$ h*ng/mL) or with a single dose of nirogacestat at 150 mg ($C_{max} = 73$ ng/mL and $AUC_{inf} = 587$ h*ng/mL). Labeling states that exposure to dabigatran (P-gp substrate) C_{max} and AUC were not affected by concomitant use with nirogacestat.

Food Effect

FDA agrees with the Applicant's position that a high fat and high calorie meal had no clinical meaningful effect on nirogacestat PK based on the results from the food-effect sub-study in the EXPAND-S phase of Study A8641014. Briefly, dose normalized mean C_{max} (n=13) and AUC_{tau} (n=11) were similar in the fed (5.2 ng/mL and 22.5 ng*hr/mL, respectively) and fasted condition (6.6 ng/mL and 23.7 ng*hr/mL, respectively) following 150 mg and 220 mg BID (Table 20). Considering the magnitude of the change in nirogacestat exposure and the range of 90%

confidence interval (CI), the overall changes in AUC_{tau} and C_{max} in the fed condition are not expected to be clinically meaningful.

Table 20: Geometric Least Squares Mean Ratio (GMR) of Nirogacestat Exposure in Food Effect Group

	Geometric least squares mean ratio (GMR) (90% CI: lower, Upper)	
	Food Effect Group	Food Effect Group without 2 Outliers
Dose-normalized AUC _{tau}	91% (60%, 140%)	114% (76%, 171%)
Dose -normalized C _{max}	71% (40%, 127%)	93% (54%, 162%)

(Data source: Table 12 on page 47 in the summary of clinical pharmacology studies)

Therefore, FDA agrees with the Applicant's proposed recommendation that nirogacestat be administered without regard to food.

X

X

Primary Reviewer

Team Leader

7 SOURCES OF CLINICAL DATA TABLE OF CLINICAL STUDIES

7.1. Table of Clinical Studies

Data

Safety and efficacy studies relevant to this NDA are in [the table below](#).

Table 21: Listing of Clinical Trials Relevant to this NDA

Study identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	No. of Participants	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report	No. of Centers and Countries
Efficacy and Safety								
NIR-DT-301 NCT03785964	Efficacy (defined by progression free survival), Safety, Tolerability, Overall Response Rate	Randomized, double-blind, placebo controlled, Phase 3	Tablet, 150 mg BID, Oral	69 ^a	Participants with progressing DT/AF	28-day cycles, continuously	Completed / Full	42 centers in 7 countries

NDA/IND Multi-disciplinary Review and Evaluation NDA 217677
Nirogacestat (PF-03084014)

Study identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	No. of Participants	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report	No. of Centers and Countries
A8641014 NCT00878189	Maximum Tolerated Dose, Safety and Tolerability, Characterize single-dose and multiple dose PK, PDx	Open-label, non-randomized, dose-finding study	Tablet Solid tumors: 20 mg, 40 mg, 80 mg, 100 mg, 130 mg; 150 mg, 220 mg, 330 mg all BID T-ALL/LBL: 150 mg BID Oral	Solid tumors: 64 T-ALL/LBL ^b : 8	Participants with advanced solid tumor malignancies and participants with relapsed or refractory T-ALL/LBL	Solid tumors: 21-day cycles, continuously ^c T-ALL/LBL: 21-day cycles, continuously ^c	Completed / Interim and Supplemental ^d	6 centers in 2 countries
A8641020 NCT02299635	Preliminary anti-tumor activity, Safety, PK, and PDx	Open-label, single-arm, Phase 2	Tablet, 150 mg BID, Oral	19	Patients with advanced mTNBC harboring genomic alterations in Notch receptor (NA+), and in a smaller subset of patients who test negative for genomic alterations in Notch receptors	21-day cycles, continuously	Completed / Synopsis	22 centers in 6 countries

NDA/IND Multi-disciplinary Review and Evaluation NDA 217677
 Nirogacestat (PF-03084014)

Study identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	No. of Participants	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report	No. of Centers and Countries
14-C-0007 NCT01981551	Determine response rate (Complete Response [CR] + Partial Response [PR])	Open-label, single-center, Phase 2	Tablet, 150 mg BID	17	Participants with Desmoid Tumors / Aggressive Fibromatosis	21-day cycles, continuously	Ongoing (Closed to Enrollment) / Interim	1 center in 1 country
A8641016 NCT01876251	Safety, Tolerability	Open-label, dose-finding, and expansion	PF-03084014 100 mg BID/docetaxel 75 mg/m ² PF-03084014 100 mg BID/docetaxel 100 mg/m ² PF-03084014 150 mg BID/docetaxel 75 mg/m ²	29	Patients with Metastatic or Locally Recurrent / Advanced Triple Negative Breast Cancer	21-day cycles, continuously	Completed / Abbreviated	21 centers in 4 countries
A8641019 NCT02109445	Safety, Tolerability	Phase 1: Open-label Phase 2: Randomized, active-control	PF-03084014 100 mg BID/nab-paclitaxel 125 mg/m ² /gemcitabine 1,000 mg/m ²	3	Patients with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma	28-day cycles, continuously	Completed / Synopsis	8 centers in 1 country

NDA/IND Multi-disciplinary Review and Evaluation NDA 217677
Nirogacestat (PF-03084014)

BID: Twice a day; CSF: Cerebrospinal fluid; CSR: clinical study report; DT: Desmoid Tumor; IV: intravenous; mTNBC: advanced Triple receptor negative breast cancer; NCI: National Cancer Institute; QD: once a day; PDx: pharmacodynamic(s); PK: pharmacokinetics; T-ALL/LBLL: T- cell acute lymphoblastic leukemia/lymphoblastic lymphoma.

- ^a Total number of participant exposure to nirogacestat assumes minimum exposure in the double-blind phase of the study and does not account for additional participants randomized to placebo in the double-blind phase who may go on to receive nirogacestat as part of the planned open-label extension phase of the study.
- ^b As agreed upon at the Pre-NDA meeting, participants with T-ALL/LBL were excluded from the integrated safety analyses as these hematologic malignancies were anticipated to be sufficiently different from DT to preclude any comparisons regarding safety data.
- ^c In Cycle 1 only, participants received nirogacestat for 21 days followed by 7 days off treatment for the purpose of PK assessments.
- ^d Pfizer only completed an interim report; therefore, a final report is not available. A supplemental CSR discusses the further efficacy and safety of the participants with DT.

The Applicant's Position:

The clinical studies summarized in Table 21 provide the totality of data to support an NDA submission for nirogacestat in the treatment of adult patients with DT.

The FDA's Assessment:

Table 21 accurately describes the 6 clinical trials relevant to this NDA. However, the Applicant did not include Study NIR-OGT-201, which is investigating nirogacestat in patients with recurrent ovarian granulosa cell tumors; as of October 23, 2022, 1 patient has been dosed in this trial (source: Development Safety Update Report #12, reporting period October 24, 2021, through October 23, 2022).

Not including patients who received nirogacestat at cross-over in NIR-DT-301, a total of 95 patients with DT received nirogacestat (n=69 in NIR-DT-301, n=9 in Study A8641014, and n=17 in Study 14-C-0007).

8 STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Studies A8641014, 14-C-0007, and NIR-DT-301 are the relevant studies used to support efficacy.

8.1.1. Study NIR-DT-301

8.1.2. Study Design

The Applicant's Description:

Study NIR-DT-301 was a randomized, double-blind, placebo controlled, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with RECIST v1.1 progressing DT. This study consisted of 2 phases: a DB phase and an optional open-label extension (OLE) phase. Nirogacestat was administered orally at a dose of 150 mg BID continuously, in 28-day cycles.

In the DB phase, participants were randomized (stratified by target tumor(s) location [intra-abdominal or extra-abdominal]) to study treatment (nirogacestat 150 mg BID or placebo) in a 1:1 ratio. Participants were stratified based on target lesion locations at Baseline (intra-abdominal versus extra-abdominal) as participants with intra-abdominal tumors have been found to have a less favorable outcome as compared to extra-abdominal tumors ([Howard & Pollock 2016](#)). If the participant had multiple target tumors located in both the

intra- and extra-abdominal locations, the tumor was classified as intra-abdominal. Participants remained in the DB phase until death, disease progression, discontinuation from study treatment for any reason, or the estimated number of progression events were observed and the primary PFS analysis was completed. The primary efficacy endpoint was PFS, which was defined as the time from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Progression was determined radiographically by independent, blinded Central Imaging Review using RECIST v1.1 on target tumors identified by the investigator at Screening or clinically as assessed by the investigator and confirmed by blinded independent central review.

Participants were eligible to enter the optional OLE phase if they were enrolled in the DB phase when the primary PFS analysis was completed, or they met the criteria of PD as defined by RECIST v1.1 (confirmed by central radiological review). During the OLE phase, all participants received nirogacestat 150 mg BID and remained on study until death, radiographic PD per RECIST v1.1, clinical progression, premature discontinuation, end of study, qualification for Continued Access Plan, or nirogacestat becomes commercially available. The DB phase of the study has been completed; however, the OLE phase is ongoing.

The FDA's Assessment:

FDA agrees with the description of the trial design for Study NIR-DT-301. FDA adds that patients who experienced clinical progression were not eligible to enroll in the OLE phase of the trial, and these patients were not unblinded. Patients who enrolled into the OLE phase were unblinded. Cycle 1 Day 1 (C1D1) visit for the OLE phase was within 24 hours of the end of treatment (EOT) visit for the DB phase of the trial, and assessments and determination of causality of all ongoing AEs and SAEs that occurred during the DB phase were conducted during the EOT visit prior to unblinding the patient. A longer window between the EOT and C1D1 visit of OLE was allowed with medical monitor approval.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria for the DB phase included:

- Participants ≥ 18 years of age with histologically confirmed DT (by local pathologist prior to informed consent) that progressed by $\geq 20\%$ as measured by RECIST v1.1 within 12 months of the screening visit scan.
- Were treatment naïve or recurrent or refractory to treatment with measurably progressing DT.
- Had ECOG performance status ≤ 2 .

- Had a DT tumor where continued PD did not result in immediate significant risk to the participant and had adequate organ and bone marrow function.

The FDA's Assessment:

The Applicant highlighted the key inclusion criteria. The following are additional important aspects of Study NIR-DT-301's eligibility criteria:

- Eligibility for enrollment was not dependent on central review of tumor specimens. The patients were enrolled based on local diagnosis of DT, but tumor specimens were used to reconfirm the diagnosis of DT by central review for all patients. It is appropriate that the diagnosis of DT was reconfirmed by central review because it is a rare tumor for which expert diagnosis is important.
- Given that the clinical course of DT is heterogenous, and active surveillance is recommended for patients with indolent and/or asymptomatic DT, it is appropriate for Study NIR-DT-301 to enroll patients with RECIST 1.1-defined progressing DT. FDA revised the indication statement consistent with this eligibility criterion.
- To be eligible for Study NIR-DT-301, patients who were receiving chronic nonsteroidal anti-inflammatory drugs (NSAIDs) as treatment for conditions other than DT must have been receiving them prior to the documentation of DT progression and have been on a stable dose for at least 28 days prior to the first dose of nirogacestat. Patients who were on any treatment (including NSAIDs) for DT must have completed this treatment at least 28 days (or 5 half-lives, whichever is longer) prior to the first dose of nirogacestat. It is unclear whether NSAIDs have anti-tumor efficacy against DT (the data is based on case series with very small sample sizes), but these eligibility criteria in Study NIR-DT-301 are appropriate given NSAIDs are used to treat DT, and the possibility that NSAIDs may have anti-DT effects has not been ruled out.
- Patients who had current or prior treatment with gamma secretase inhibitor or anti-Notch antibody, current or chronic history of hepatobiliary disease (except for Gilbert's syndrome, or gallstones), positive human immunodeficiency virus (HIV) test, positive hepatitis B surface antigen, or positive hepatitis C antibody or RNA, were excluded. Patients were also excluded with clinically significant heart disease or prolonged QTc interval.

Study Efficacy Endpoints

The Applicant's Description:

Primary

- The primary efficacy endpoint was PFS, which was defined as the time from randomization until the date of assessment of progression or death by any cause (whichever occurs first). Progression was determined radiographically by independent, blinded Central Imaging Review using RECIST v1.1 on target tumors identified by the investigator at Screening or clinically as assessed by the investigator and confirmed by blinded independent central review.

Secondary

- ORR, defined as a confirmed BOR of CR or PR by RECIST v1.1 during the DB phase
 - Duration of responses (in months), as supportive, descriptive analyses of ORR, defined as the duration in months from the time measurement criteria are met for CR or PR (whichever comes first) until the date of progression or death (whichever comes first).
- Change in PRO measures from baseline over time:
 - GOunder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS)
 - Brief Pain Inventory (BPI) short form
 - European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QOQ-C30)

The FDA's Assessment:

Amendment 4 (dated July 7, 2020) of the protocol for Study NIR-DT-301 added clinical progression to the definition of PFS. During the review of this NDA, FDA inquired how the Applicant determined which patients experienced clinical progression among the patients who enrolled prior to implementation of this amendment. The Applicant responded that since the initiation of Study NIR-DT-301, the electronic data capture system collected "clinical progression" as a reason for the discontinuation of trial treatment, but there was not a protocol-specified criterion for "clinical progression." A specific criterion was added in Amendment 4, which defined events of clinical progression as follows:

when the investigator determines the participant needs to be withdrawn from the study to start emergent treatment (i.e., radiotherapy, surgery, or systemic therapy including chemotherapy and/or tyrosine kinase inhibitors) for DT/AF due to the development of

DT/AF related intractable pain, vital structure involvement, and/or progression of symptoms resulting in a global deterioration of health status
However, Amendment 4 was submitted to FDA but not activated, and Amendment 5 (dated February 9, 2021) was where the addition of clinical progression to the definition of PFS was implemented. Clinical progression was defined as follows in Amendment 5:

the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF.

FDA inquired who experienced clinical progression (regardless of confirmation of clinical progression by central review) prior to the implementation of the amendment. The Applicant responded that all 9 investigator-determined events of clinical progression (in this blinded trial) were reported prior to the implementation of Protocol Amendment 5 (dated February 9, 2021), and all were adjudicated by a blinded, independent, central clinical review (Source: SpringWorks's response to FDA Information Request in SDN 19, dated 3/23/2023).

Although SpringWorks changed the definition of the PFS endpoint to allow clinical progression events, FDA communicated on multiple occasions (e.g., September 18, 2020, and January 22, 2021, meetings) concerns regarding the change in endpoint (also that inadvertent unblinding due to toxicity could result in bias in the assessment of clinical progression). Ultimately, the FDA review team remains concerned with the use of this endpoint for regulatory purposes. Although FDA acknowledges that patients may clinically progress, the lack of objective assessment (and noting the events are clinician adjudicated and not patient-derived [i.e., via a PRO]) may increase the risk of bias, precluding a definitive determination of a drug's effect in the clinical trial.

These concerns were overcome; however, in this nirogacestat application via the totality of the following information:

- Assessment of PFS results excluding clinical progression events (most events in Study NIR-DT-301 were based on objective radiographic findings)
- Assessment of ORR (tumor shrinkage) between arms
- Assessment of patient reported outcomes

Finally, Study NIR-DT-301 did not evaluate OS as a primary efficacy endpoint. FDA did not object to this approach because DT is rarely fatal and the existing safety data for nirogacestat indicated that it would not be expected to lead to safety-related deaths. Because DT can be

symptomatic however, treatment to induce delay progression, induce tumor shrinkage, and improve symptoms including pain can be beneficial and warranted.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The original SAP (v1.0) was approved on 07 April 2022 and was amended on 12 May 2022 (v2.0).

The study sample size was based on the primary PFS endpoint. A total of 51 events was estimated to provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS in the nirogacestat arm was 20 months and 8 months in the placebo arm (corresponding to a HR of 0.4 relative to placebo). Assuming a 10% dropout rate and a 20% spontaneous regression rate, 118 participants needed to be randomized in a 1:1 ratio to observe the estimated number of events.

While the study planned to randomize approximately 118 participants, all eligible participants in Screening at the time of achieving the target enrollment (n = 118) were allowed to enroll, resulting in a total of 142 participants randomized. A relatively high number of participants were in Screening at the time of achieving the target enrollment rate of 118 participants due to the impact of COVID-19. Specifically, many institutions delayed study enrollment until summer 2020, resulting in a bolus of participants in Screening when the target enrollment rate was achieved.

The intent-to-treat (ITT) population was the primary analysis population for the efficacy analyses. The ITT population consisted of all participants who were enrolled and randomized to study treatment (nirogacestat or placebo). Participants were analyzed according to the treatment they were randomized to and the strata to which they were assigned. Participants who were randomized but did not subsequently go on to receive study treatment were included in the ITT population. The Safety population was the analysis population for the safety analyses and consisted of all participants randomly assigned to study treatment who received at least 1 dose of study treatment. Participants were analyzed according to the treatment they actually received. The Per-Protocol (PP) population consisted of those participants who received study treatment and had no major protocol deviations; this analysis population was used for sensitivity analyses.

The primary and secondary efficacy endpoints were tested in the following order: PFS, ORR, disease symptoms, impact, and quality of life evaluations by PRO. The primary efficacy analysis was performed after 49 events had been observed.

If the null hypothesis was rejected at the specified significance level, the testing could proceed to the next endpoint, but if the null hypothesis was not rejected, all subsequent results were considered descriptive only. All data collected after crossover to nirogacestat in the OLE phase of the study will be analyzed and reported separately.

The FDA's Assessment:

The major changes in SAP V2 were summarized below:

- a) Clarified that the formal statistical testing on PRO-related endpoints is conducted at the 1-sided, 0.025 level of significance.
- b) Supplementary analysis added where GODDESS Total Symptom Score is derived excluding item 2 (dull pain) and item 3 (shooting pain).
- c) Proportion of participants with improvement in BPI-SF API score at Cycle 10 was removed from the hierarchical testing of secondary endpoints and added as an exploratory endpoint.

FDA acknowledges that the primary analysis for PFS was conducted at 49 PFS events, which was earlier than the pre-specified 51 PFS events due to the longer than expected follow up time. According to clinical study report, no new events were reported during Sep 20, 2021, and April 07, 2022, and the study was approaching 3 years since the first patient enrolled. The Applicant performed the primary analysis of PFS at 49 of 51 planned events. As the primary analysis of PFS was strongly statistically significant and clinically meaningful, FDA concurs with the reported PFS results.

Protocol Amendments

The Applicant's Description:

The original global study protocol was finalized on 03 August 2018 and amended 5 times; the final protocol (Protocol Amendment 5) was dated 09 February 2021. None of the amendments impacted the integrity of quality of the study and/or its outcomes.

The FDA's Assessment:

FDA outlines the key protocol amendments below. All the amendments were activated except for Amendment 4. Some of the amendments were made to clarify PRO assessments and analyses. The change to include the clinical progression events could have impacted the outcome of the trial; however, this was addressed in the analyses and interpretation of the data below (and in the discussion of endpoints above). Additionally, although additional information was collected following Amendment 3 regarding ovarian toxicity, this information was not sufficient to fully characterize ovarian toxicity and resolution.

Amendment 1 (dated November 27, 2018)

1. The Applicant revised PRO assessments:

- To capture concepts important to patients with DT, the Applicant proposed to replace the MD Anderson Symptom Inventory (MDASI) with the EORTC QLQ-C30.
- To supplement the DTIS tool, the Applicant added Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a and 3 items from the PROMIS item banks.

2. To describe the localization of disease more precisely, the Applicant changed randomization stratification factor by tumor location from “favorable versus (vs.) nonfavorable” to “intra-abdominal vs. extra-abdominal,” where intra-abdominal includes mesentery and pelvis.

Amendment 2 (dated October 14, 2019)

1. Because DTs can spontaneously regress, the Applicant increased the sample size from 105 to 135 screened patients and from 94 to 118 randomized patients to account for a projected spontaneous regression rate of 20%.
2. The Applicant clarified inclusion criterion #3 pertaining to DT (added bold font, and deleted font with strikethrough):

Participant has:

a. **Treatment naïve Newly diagnosed**, measurably progressing DT/AF that is **deemed** not amenable to surgical resection or radiation therapy **surgery without the risk of significant morbidity;**

OR

b. Recurrent, **measurably** progressing DT/AF following **at least one line of therapy** ~~CR to initial therapy;~~

OR

c. ~~Preexisting~~ **Refractory, measurably progressing** DT/AF ~~and has previously received therapy following at least one line of therapy. and the residual tumor has progressed.”~~

3. The Applicant updated MSK/DTRF DTSS and DTIS to GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DESmoid Symptom/Impact Scale (GODDESS) to reflect the new name of the PRO

Amendment 3 (dated January 27, 2020)

1. Because of reports of primary ovarian dysfunction, the Applicant included a requirement to ask women about their menstrual history and added monitoring of hormone levels in men and women in the Schedule of Activities. The hormones to be monitored were thyroid stimulating hormone (TSH), prolactin, anti-mullerian hormone (AMH), luteinizing hormone

(LH), follicle stimulating hormone (FSH), estradiol, and progesterone for women; and total testosterone, free testosterone, progesterone, FSH, and LH for men.

Amendment 4 (dated July 7, 2020) – not activated

1. The Applicant added clinical progression into the definition of PFS definition as described in “Study Efficacy Endpoints” in Section 8.1.2 of this NDA review.
2. To minimize the potential for bias in the assessment of clinical progression, the Applicant added that patients who discontinue due to clinical progression are not eligible for participation in the optional OLE phase.
3. The Applicant added that patients who discontinue treatment due to clinical progression will be unblinded at the EOT visit for the DB phase to help inform future treatment decisions.
4. The Applicant added that patients who discontinue due to reasons other than disease progression will not be unblinded and will not be eligible for participation in the optional OLE phase of the trial.

Amendment 5 (February 9, 2021)

1. The Applicant revised the definition of clinical progression as described in “Study Efficacy Endpoints” in Section 8.1.2 of this NDA review. See comments above in FDA discussion of endpoints regarding the addition of clinical progression events.
2. The Applicant clarified that only patients who discontinue due to radiographic progression will be eligible for unblinding and participation in the OLE.
3. To minimize the potential for bias in the assessment of clinical progression, the Applicant changed the protocol to state that patients who discontinue treatment due to clinical progression will NOT be unblinded.

8.1.3. Study Results

Compliance with Good Clinical Practices

Data

This study was conducted in accordance with the protocol and the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP guidelines, and all applicable local laws and regulations.

The Applicant's Position:

Study NIR-DT-301 is GCP compliant.

The FDA's Assessment:

Section 10.1.1 of the clinical protocol for Study NIR-DT-301 states the trial was conducted in accordance with the applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

Financial Disclosure

The Applicant's Position:

All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the sponsor.

The FDA's Assessment:

The Applicant submitted a Financial Interests and Arrangements of Clinical Investigators Certification, which states that the Applicant did not enter into any financial arrangements with the clinical investigators. However, FDA inspection revealed that four investigators had financial arrangements, none of which were disclosed by the Applicant. See Section 4.1 for more details.

Patient Disposition

Data

The data cutoff and database freeze dates for this CSR were 07 April 2022 and 17 May 2022, respectively. Only assessments conducted through 07 April 2022 were analyzed for the primary analysis.

A summary of the disposition of all participants enrolled is presented in Table 22. A total of 142 participants were randomized, with 141 participants receiving study treatment (nirogacestat or placebo) in the DB phase. The majority of randomized participants had extra-abdominal (109 participants [77%]) versus intra-abdominal (33 participants [23%]) tumors.

As of the data cutoff, 59 participants were ongoing in the DB phase and 47 participants discontinued study treatment due to progression events meeting the study endpoint. In the table below, progression events meeting the study endpoint reflected the total number of events resulting in the discontinuation of study treatment, not in the analysis of PFS. In the placebo arm, 1 participant discontinued study treatment due to an AE prior to death, which counted as an event in the PFS analysis. Another placebo participant discontinued due to other

reasons prior to receiving central imaging results confirming PD and was also counted as an event in the PFS analysis.

A total of 35 participants prematurely discontinued DB treatment. The most common reasons for premature discontinuation were “Other” (16 participants) and “AE” (15 participants).

At the time of the data cut-off date, 32 of 40 eligible participants enrolled in the OLE phase of the study. The 59 participants that were still ongoing in the DB phase were not included in the count of participants eligible for the OLE phase.

Table 22: Participant Disposition (All Participants Enrolled)

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

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
COVID-19 ^f	0	0	0
Other	5 (7)	11 (15)	16 (11)
Participants who were able to continue into the Open-label Phase ^g	11 (16)	29 (40)	40 (28)
Participants who enrolled in the Open-label Phase ^h	4 (36)	28 (97)	32 (80)
Participants who did not enroll in Open-label Phase ^h	7 (64)	1 (3)	8 (20)

Abbreviations: AE: adverse event; COVID-19: coronavirus disease 2019; CRF: case report form; DB: double-blind; DT: desmoid tumor; PFS: progression-free survival.

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

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

^b The Intent-to-Treat population consisted of all participants who were enrolled and randomized to study treatment.

^c The Safety population consisted of all randomized participants who took at least 1 dose of study treatment.

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

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

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

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

^h Percentages were out of the number of participants who were able to continue into the open-label phase.

The Applicant's Position:

Participants by randomized strata were balanced between treatment arms. A higher proportion of participants in the nirogacestat arm than in the placebo arm were ongoing at the time of the data cut, largely due to a lower proportion of participants with events meeting the study endpoint in the nirogacestat arm compared with the placebo arm, including participants with radiographic PD.

The FDA's Assessment:

FDA agrees with the data presented in Table 22. Most of the ITT population received at least 1 dose of trial treatment (99% vs. 100% in nirogacestat, and placebo arms, respectively). FDA agrees with the Applicant's statement that the randomized strata (intra-abdominal vs. extra-abdominal tumor) were well-balanced between the arms, which is important given that

patients with intra-abdominal tumors have a worse prognosis. Patients in the nirogacestat arm were less likely to have met the PFS endpoint (17% vs. 49% for nirogacestat, and placebo arms, respectively), and more likely to be receiving ongoing treatment at data cutoff date (51% vs. 32% for nirogacestat, and placebo arms, respectively). Only one patient had a qualified clinical progression in the nirogacestat arm, but the central review of this patient's tumor specimen determined that the tumor was not a DT, and this patient was not included in the per-protocol population (PP). Thus, focusing only on the PP population (n=62 in nirogacestat, n=67 in placebo), patients in the nirogacestat arm remain less likely to have met the PFS endpoint, and more likely to be on ongoing treatment at data cutoff date (Table 23).

Table 23: Patient Treatment Status (Per Protocol Population) – FDA analysis

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
Per-protocol population^a	62 (100)	67 (100)	129 (100)
DB treatment status			
Progressions meeting study endpoint ^b	10 (16)	32 (48)	42 (33)
Radiographic progressive disease	10 (16)	26 (39)	36 (28)
Qualified clinical progression	0 (0)	6 (9)	6 (5)
Ongoing	34 (55)	23 (34)	57 (44)

Abbreviations: DB = double-blind, DT = desmoid tumor

Note: Percentages were based out of the number of patients treated per protocol.

^a The Per-Protocol population consisted of all patients who received trial treatment, had no major protocol deviations, were not mis-randomized, had confirmed DT per Central Review, and did not discontinue due to non-compliance with trial treatment.

^b Number of progression events reflected total resulting in the discontinuation of study treatment not in the analysis of PFS.

Source: ADSL (SDN 39; May 5, 2023)

Table 24 presents the reasons for exclusion from the PP population. The reasons for exclusion from PP population were adequately balanced across the two treatment arms.

Table 24: Reasons for Exclusion from Per Protocol Population – FDA analysis

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
Intent-to-treat population	70 (100)	72 (100)	142 (100)
Per-protocol population ^a	62 (89)	67 (93)	129 (91)
Excluded from Per-protocol population	8 (11)	5 (7)	13 (9)
Major protocol deviation	4 (6) ^b	4 (6)	8 (6)
Permanent discontinuation of trial drug due to non-compliance with trial drug	1 (1.4)	1 (1.4)	2 (1.4)
Drug compliance <60%	2 (2.9)	0	2 (1.4)
Did not have DT based on Central Review	1 (1.4)	0	1 (0.7)

Abbreviations: DT = desmoid tumor

Note: Percentages were based out of the number of patients in the ITT population.

^a The Per-Protocol population consisted of all patients who received trial treatment, had no major protocol deviations, were not mis-randomized, had confirmed DT per Central Review, and did not discontinue due to non-compliance with trial treatment.

^b One patient did not receive any trial treatment.

Source: ADSL, and ADDV (both in SDN 39; May 5, 2023)

Most patients in the placebo arm who were eligible to enroll in the OLE phase did enroll (97%, n=28/29), whereas a smaller proportion of the eligible patients in the nirogacestat arm enrolled into the OLE phase (36%, n=4/11), suggesting that patients who had radiographic progression while on nirogacestat preferred to discontinue treatment.

Protocol Violations/Deviations

Data:

A total of 38 participants (54%) in the nirogacestat arm and 47 participants (65%) in the placebo arm had at least 1 CSR-reportable protocol deviation. At least 1 major CSR-reportable protocol deviation occurred in 4 participants (6%) in the nirogacestat arm and 4 participant (6%) in the placebo arm. These major CSR-reportable protocol deviations included mis-stratification based on incorrect tumor location and enrollment without meeting inclusion/exclusion criteria.

The Applicant's Position:

A CSR-reportable protocol deviation is considered a significant deviation that may impact the accuracy, and/or reliability of the study data or participants rights, safety, or well-being. A major CSR-reportable protocol deviation would exclude the participant from the PP population and include participants that did not meet inclusion/exclusion criteria,

mis-randomizations, mis-stratifications, or may impact accuracy and reliability of the study data.

The 8 participants with major CSR-reportable protocol deviations excluded from the PP population were not expected to impact the data integrity for the analysis, which was confirmed by the sensitivity analysis of PFS comparing the ITT population (HR = 0.29 [95% CI: 0.15, 0.55]; $p < 0.001$) versus the PP population (HR = 0.26 [95% CI: 0.13, 0.53]; $p < 0.001$).

The FDA's Assessment:

Table 25 outlines the protocol deviations in Study NIR-DT-301, including the details regarding the major deviations. Based on the protocol deviations dataset (ADDV), most patients had protocol deviations, and 8 patients (6%) had major protocol deviations.

In addition, FDA noted that five patients underwent concomitant excisions of DTs and one patient underwent concomitant radiotherapy of a bleeding DT (see "Treatment Compliance, Concomitant Medications, and Rescue Medication Use" in Section 8.1.2); 3 patients were in the nirogacestat arm, and 3 patients were in the placebo arm. These events were not reported as protocol deviations, and the protocol for Study NIR-DT-301 states that potentially curative radiotherapy, and surgical resection of DT were prohibited concomitant procedures. It is possible that these procedures were not reported as protocol deviations because the excisions were not curative, i.e., the patients likely had other remaining DT lesions that were not excised, and the radiotherapy was not considered therapeutic. However, these procedures still have the potential to effect efficacy outcomes, particularly imaging-based outcomes such as PFS and ORR.

For FDA's sensitivity analysis of PFS comparing the ITT population to the population of patients who did not have major protocol deviations, FDA excluded the five patients who had excisions of DT, and the one patient who underwent radiotherapy from the PP population (i.e., revised PP population). The PFS HR was 0.25 [95% CI: (0.12, 0.52)] with median PFS was not reached for the nirogacestat and 15.4 months for the placebo arm in the revised PP population. FDA agrees with the Applicant that the presence of these protocol deviations did not impact the interpretation of the PFS results.

Table 25: Protocol Deviations – FDA Analysis

	Nirogacestat n (%)	Placebo n (%)	Total n (%)
Intent-to-treat population	70 (100)	72 (100)	142 (100)
Non-major protocol deviation	68 (97)	72 (100)	140 (99)
Major protocol deviation	4 (6)	4 (6)	8 (6)
Randomization mis-stratification based on DT location (IRT reported intra-abdominal location, and EDC reported extra-abdominal location)	1 (1.4)	3 (4.2)	4 (2.8)
Randomized without meeting eligibility criteria	2 (2.9)	1 (1.4)	3 (2.1)
Did not discontinue tamoxifen for treatment of DT at least 28 days prior to signing ICD (it was discontinued 15 days prior to signing ICD)	1 (1.4)	0	1 (0.7)
Did not discontinue NSAIDs at least 28 days prior to signing ICD (aspirin 81 mg daily for coronary artery disease)	1 (1.4)	0	1 (0.7)
Had active infection at the time of screening	0	1 (1.4)	1 (0.7)
Randomized prior to Cycle 1 Day 1 (randomized 4 days prior to Cycle 1 Day 1) and did not receive trial treatment	1 (1.4)	0	1 (0.7)

Abbreviations: DT = desmoid tumor, IRT = interactive response technology, EDC = electronic data capture, ICD = informed consent document, NSAIDs = nonsteroidal anti-inflammatory drugs

Note: Percentages were based out of the number of patients in the ITT population.

Source: ADDV (SDN 39, May 5, 2023)

One patient was reported to be “prematurely” unblinded (patient ID (b) (6)); the patient was on the placebo arm and had a qualified clinical progression. Based on the CRF and narrative, this event was not considered a protocol deviation because the unblinding followed pre-specified unblinding rules, and this was confirmed by the Applicant. The patient was unblinded 22 months after the patient was discontinued from trial treatment. The blind was broken because the patient wanted to start a new therapy and needed to know if they were on the nirogacestat arm or the placebo arm prior to starting new therapy. FDA agrees that this premature unblinding was not a protocol deviation. FDA’s OSI did not observe issues related to accidental unblinding during the inspection of the three clinical sites and the Applicant.

Table of Demographic Characteristics

Data

A summary of the demographic characteristics of the ITT population is presented in Table 26. Overall, Baseline characteristics were similar between treatment groups. A notable difference in demographics and disease characteristics between treatment groups was observed in race, ethnicity, and body mass index (BMI) with more participants in the nirogacestat arm identifying as White and Not Hispanic/Latino, enrolling in rest of world, and having a normal BMI as compared to placebo. The breakdown by age quartile also varied slightly between treatment groups.

Table 26: Demographics and Other Baseline Characteristics (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Sex, n (%)			
Male	25 (36)	25 (35)	50 (35)
Female	45 (64)	47 (65)	92 (65)
Women of childbearing potential ^a , n (%)			
Yes	37 (82)	37 (79)	74 (80)
No	8 (18)	10 (21)	18 (20)
Infertility history, n (%)			
Yes	0	3 (4)	3 (2)
No	67 (96)	66 (92)	133 (94)
Unknown	3 (4)	3 (4)	6 (4)
Infertility history – males ^a , n (%)			
Yes	0	1 (4)	1 (2)
No	25 (100)	23 (92)	48 (96)
Unknown	0	1 (4)	1 (2)
Race, n (%)			
White	64 (91)	54 (75)	118 (83)
Black or African American	4 (6)	5 (7)	9 (6)
Asian	1 (1)	3 (4)	4 (3)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	1 (1)	10 (14)	11 (8)
Ethnicity, n (%)			

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Non-Hispanic or Latino	67 (96)	55 (76)	122 (86)
Hispanic or Latino	1 (1)	9 (13)	10 (7)
Unknown	0	3 (4)	3 (2)
Not reported	2 (3)	5 (7)	7 (5)
Age at informed consent (years)			
n	70	72	142
Mean (SD)	37.5 (14.43)	37.0 (12.89)	37.2 (13.62)
Median (Q1, Q3)	33.5 (26, 50)	34.5 (28, 44)	34.0 (27, 46)
Min, max	18, 73	18, 76	18, 76
Baseline BMI ^{b,c} (kg/m ²)			
n	69	71	140
Mean (SD)	26.275 (6.9440)	27.103 (6.1171)	26.695 (6.5273)
Median (min, max)	23.846 (17.72, 52.34)	25.693 (17.53, 44.83)	25.135 (17.53, 52.34)
Geographic region, n (%)			
North America	44 (63)	53 (74)	97 (68)
Rest of world	26 (37)	19 (26)	45 (32)

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; max: maximum; min: minimum; Q: quartile; SD: standard deviation.

Note: Percentages were based on the number of participants in the ITT population, unless otherwise noted.

Note: Infertility and child-bearing potential were defined by the investigator.

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

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

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

The Applicant's Position:

Overall, baseline characteristics were similar between treatment groups. The study randomized 142 participants, of which 65% were female, which is consistent with the overall DT population that is more commonly reported in females ([Anneberg et al. 2022](#); [Skubitz 2017](#); [de Camargo et al. 2010](#); [Reitamo et al. 1982](#)). Given the eligibility requirement for ≥ 20% disease progression per RECIST v1.1, the study selected a participant population with more severe disease than previously reported in the literature. This is evidenced by the high rate of multi-focal disease (40%) as compared to prior studies (~10%) ([Peng et al. 2012](#)), relatively large median Baseline target tumor(s) size (92 mm), and high rate of prior treatment (74%) including

a median of at least 2 prior lines of therapy with the majority of participants being considered refractory or recurrent following prior treatments.

The FDA's Assessment:

The trial population is adequately representative of the general population of patients with DT in that the ratio of female to male is approximately 2:1, and the average age of the patients was in the mid-30s, which is the age of peak incidence for DT. The trial population's baseline characteristics were generally well-balanced across the arms, except for the numerical differences in race and ethnicity. DT does not have a known predilection for a certain race or ethnicity, so the slight imbalance in the distribution of race and ethnicity in Study NIR-DT-301 does not impact the integrity of the trial. However, because DT is not known to have a predilection for a certain races or ethnicities, it may have been feasible to enroll more racial and ethnic minorities into this trial to better represent the U.S. population, particularly when most of the patients were enrolled in the U.S. (n=90, 63%). For example, in a cohort study of patients with DT across three academic centers in the U.S. (over a 28-year period), 69% were White, 23% were Black, and 9% were reported as "Other race" (Peng et al., 2012).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data

A summary of disease characteristics in the ITT population is presented in Table 27. A higher rate of multifocal disease was observed in this study as compared with prior studies in DT (40% vs ~10% observed in prior studies with DT) ([Peng et al. 2012](#)). The majority of participants had received prior treatment for DT and were classified as refractory or recurrent, 69% and 8%, respectively; the treatment arms were well-balanced.

Genetic results were determined per central review of tumor tissue (somatic) and blood (germline) mutations. The majority (81%) of participants who were evaluable for somatic mutations had somatic mutations in *CTNNB1*. A slightly higher percentage of evaluable participants reported mutations in *APC* (21% versus ~10%) than typically reported in the literature ([Riedel & Agulnik 2022](#); [Kasper et al. 2011](#)). A total of 15 participants reported germline mutations of *APC*, which were consistent with their tumors. Twenty-four participants had a family history of FAP including 12 with confirmed *APC* mutations (Table 27). The remaining 12 participants with FAP did not have germline mutations identified (n = 2) or did not have samples available for germline analysis (n = 10) .

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

Table 27: Disease Characteristics (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Time since diagnosis to randomization (months) ^a			
N	70	72	142
Mean (SD)	59.25 (72.903)	61.70 (76.974)	60.49 (74.739)
Median (min, max)	30.19 (0.7, 307.2)	31.15 (3.4, 343.1)	30.97 (0.7, 343.1)
Focal category, n (%)			
Single	43 (61)	41 (57)	84 (59)
Multifocal	27 (39)	31 (43)	58 (41)
Desmoid tumor treatment status, n (%)			
Treatment naive	18 (26)	14 (19)	32 (23)
Refractory	43 (61)	55 (76)	98 (69)
Recurrent	9 (13)	3 (4)	12 (8)
Number of target tumors, n (%)			
1	50 (71)	45 (63)	95 (67)
2	15 (21)	18 (25)	33 (23)
3	3 (4)	4 (6)	7 (5)
4	1 (1)	4 (6)	5 (4)
5	0	1 (1%)	1 (< 1)
Number of target tumors			
N	69	72	141
Mean (SD)	1.3 (0.64)	1.6 (0.93)	1.5 (0.81)
Median (min, max)	1.0 (1, 4)	1.0 (1, 5)	1.0 (1, 5)
Target tumor location(s), n (%) ^b			
Abdominal wall	12 (17)	19 (26)	31 (22)
Chest wall	9 (13)	9 (13)	18 (13)
Neck and head	8 (11)	6 (8)	14 (10)
Lower extremities	14 (20)	11 (15)	25 (18)
Mesentery and pelvis	16 (23)	16 (22)	32 (23)
Paraspinal	6 (9)	8 (11)	14 (10)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Upper extremities	10 (14)	13 (18)	23 (16)
Other	4 (6)	8 (11)	12 (8)
Baseline target tumor size per RECIST (mm) ^c			
N	69	72	141
Mean (SD)	111.19 (70.563)	121.16 (66.373)	116.28 (68.393)
Median	91.60	115.70	100.35
Q1, Q3	64.7, 134.1	73.5, 161.7	68.9, 155.4
Min, max	22.3, 356.2	19.9, 400.9	19.9, 400.9
Baseline target tumor size group (mm), n (%) ^c			
Baseline target tumor size < 68.90	19 (27)	16 (22)	35 (25)
Baseline target tumor size 68.90 to < 100.35	21 (30)	14 (19)	35 (25)
Baseline target tumor size 100.35 to < 155.35	15 (21)	20 (28)	35 (25)
Baseline target tumor size ≥ 155.35	14 (20)	22 (31)	36 (25)
Family history of FAP, n (%)			
Yes	11 (16)	13 (18)	24 (17)
No	59 (84)	59 (82)	118 (83)

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

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

Note: Participant (b) (6) had a target lesion located in the buttock; however, the number of target lesions was not reported. Due to this missing data, this participant was not included in the summary of number of target lesions.

Note: Number of target and non-target tumors and location(s) of tumors were as assessed by the central reviewers. Number of target tumors was not included for participant (b) (6) who was not treated.

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

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

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

The Applicant's Position:

Disease characteristics were generally balanced between treatment arms and consistent with the disease under study.

The FDA's Assessment:

There were small numerical differences regarding tumor characteristics across the treatment arms (Table 28, and Table 29). Slightly more patients in the placebo arm had protocol-defined refractory disease, larger number and size of target lesions based on RECIST 1.1, and more prior therapy (specifically, NSAIDs, tamoxifen, and surgery). However, slightly more patients in the nirogacestat arm had recurrent disease and larger tumor volumes based on MRI. Patients in the placebo arm had shorter time between diagnosis and first treatment, including first systemic treatment, but patients in the nirogacestat arm had shorter time between last treatment and randomization. Patients in both arms had similar time between diagnosis and randomization. Thus, the disease severity across the two arms appears generally balanced across the two arms.

Table 28: Additional Disease Characteristics (ITT Population) – FDA Analysis

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Baseline Tumor Volume per MRI, n (%)			
n	67	70	137
Mean (SD)	421.2 (764.7)	372 (520)	396 (649)
Median (min, max)	152 (5, 4913)	162 (2, 2601)	160 (2, 4913)
< 53.72 mL	15 (22)	19 (27)	34 (25)
53.72 to < 160.22 mL	19 (28)	15 (21)	34 (25)
160.22 to < 552.97 mL	17 (25)	17 (24)	34 (25)
≥ 552.97 mL	16 (24)	19 (27)	35 (25)
Number of Prior Lines of Therapy			
Median (min, max)	2 (0, 14)	2 (0, 19)	2 (0, 19)
0	18 (26)	14 (19)	32 (23)
1	14 (20)	11 (15)	25 (18)
2	10 (14)	13 (18)	23 (16)
≥3	28 (40)	34 (47)	62 (44)
Any Prior Therapy, n (%)	52 (74)	58 (81)	110 (77)
Prior systemic therapy, n (%)	43 (61)	44 (61)	87 (61)
Prior chemotherapy, n (%)	24 (34)	27 (38)	51 (36)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Prior tyrosine kinase inhibitors, n (%)	23 (33)	24 (33)	47 (33)
Prior sorafenib exposure, n (%)	17 (24)	18 (25)	35 (25)
Prior NSAIDs, n (%)	16 (23)	22 (31)	38 (27)
Prior hormone-based therapy, n (%)	13 (19)	20 (28)	33 (23)
Prior surgery, n (%)	33 (47) ^a	44 (61)	77 (54)
Prior radiation therapy, n (%)	16 (23)	16 (22)	32 (23)
Time Between Diagnosis to Start of First Treatment			
N	51	56	107
Median (min, max), months	1.3 (0.03, 187.5)	0.9 (0.03, 125.4)	1.2 (0.03, 187.5)
Time Between Diagnosis to Start of First Systemic Treatment			
N	32	39	71
Median (min, max), months	12.6 (0.6, 109)	19.6 (0.03, 285.6)	13.2 (0.03, 285.6)
Time Since End of Last Systemic Therapy to Randomization			
n	43	44	87
Median (min, max), months	16.6 (0.8, 120.7)	13.8 (1.0, 96.7)	3.3 (0.8, 120.7)

Abbreviations: SD = standard deviation

^a included two patients who underwent excisional biopsies, and both were in the nirogacestat arm (patient (b) (6) with a left breast mass, and patient (b) (6) with a deep neck mass)

Source: ADSL, ADCM (SDN 39; May 5, 2023)

The genetic characteristics were similar across the treatment arms (Table 29). Most patients (n=110, 77%) in the ITT population had a mutation in CTNNB1 (n=85, 60%) or APC (n=29, 20%). Two additional patients had a somatic mutation in a different gene (data not presented in dataset). FDA agrees with the Applicant in that the proportion of patients with the APC mutation is higher compared to the general population (approximately 10%) although we were not able to confirm the specific numbers described in “data” above (FDA’s analysis is shown in the table below). All detected CTNNB1 mutations were somatic, and 76% (n=22) of all detected APC mutations were somatic. The proportion of patients with germline APC (n=21, 15%) in this trial is slightly higher than the proportion in the general DT population (approximately 5-10%) (de Camargo et al., 2010; Skubitz et al., 2017). The majority, but not all, of the patients with

germline APC mutations had an APC mutation in the DT (Table 29). Similarly, the majority, but not all, of the patients with family history of FAP had germline APC mutations (Table 29).

Four patients (2.8%, n=3 nirogacestat, n=1 placebo) had mutations in both CTNNB1 and APC genes, and mutations were all somatic in all 4 patients, which is expected since somatic mutations of CTNNB1 and germline mutations of APC are probably mutually exclusive (Penel et al., 2017).

Table 29: Genetic Characteristics of Disease (ITT Population) – FDA Analysis

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
CTNNB1 Somatic Mutations, n (%)			
Yes	43 (61)	42 (58)	85 (60)
No	9 (13)	12 (17)	21 (15)
Unknown	18 (26)	18 (25)	36 (25)
CTNNB1 Germline Mutations, n (%)			
No	68 (97)	71 (99)	139 (98)
Unknown	2 (3)	1 (1)	3 (2)
APC Somatic Mutations, n (%)			
Yes	11 (16)	11 (15)	22 (15)
No	41 (59)	43 (60)	84 (59)
Unknown	18 (26)	18 (25)	36 (25)
APC Germline Mutations, n (%)			
Yes	9 (13)	12 (17)	21 (15)
No	59 (84)	59 (82)	118 (83)
Unknown	2 (3)	1 (1)	3 (2)
Have APC Mutation in Tumor	7 (10)	7 (10)	14 (10)
Family History of FAP, n (%)			
Yes	11 (16)	13 (18)	24 (17)
APC germline mutation present	9 (13)	11 (15)	20 (14)
No	59 (84)	59 (82)	118 (83)

Abbreviations: FAP = Familial Adenomatous Polyposis
Source: ADSL (SDN 39; May 5, 2023)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data

Study treatment exposure is presented in Table 30. Median duration of study treatment exposure was 20.57 months in the nirogacestat arm, which was nearly double that observed in the placebo arm (11.40 months) likely due to the greater number of events observed in the placebo arm. The majority of participants receiving nirogacestat (65%) remained on study treatment for more than 13 cycles, suggesting sustained tolerability over an extended period of treatment. The total duration of exposure was 99.18 participant-years for the nirogacestat arm and 79.42 participant-years for the placebo arm.

A total of 139 participants (99%) received any concomitant medication, including 69 participants (100%) in the nirogacestat arm and 70 participants (97%) in the placebo arm. The most frequently reported ($\geq 30\%$ overall) Anatomical Therapeutic Chemical (ATC) classifications were anilides (67 participants [48%]), other viral vaccines (50 participants [35%]), serotonin antagonists (48 participants [34%]), antipropulsives (47 participants [33%]), natural opium alkaloids (47 participants [33%]), and propionic acid derivatives (44 participants [31%]).

A total of 55 participants (39%) had any concomitant procedures, including 33 participants (48%) in the nirogacestat arm and 22 participants (31%) in the placebo arm. Overall, concomitant procedures by system organ class (SOC) were surgical and medical procedures (42 participants [30%]) and investigations (33 participants [23%]).

Table 30: Study Treatment Exposure – DB Phase (Safety Population)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
Duration of study drug exposure (months) ^a			
N	69	72	141
Mean (standard deviation)	17.40 (9.917)	13.31 (8.439)	15.31 (9.385)
Median	20.57	11.40	17.25
Min, max	0.3, 33.6	0.2, 32.5	0.2, 33.6
Participants who received study treatment for at least:			
1 cycle, n (%)	67 (97)	71 (99)	138 (98)
2 cycles, n (%)	61 (88)	71 (99)	132 (94)
3 cycles, n (%)	59 (86)	67 (93)	126 (89)
4 cycles, n (%)	58 (84)	62 (86)	120 (85)
5 cycles, n (%)	56 (81)	58 (81)	114 (81)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
6 cycles to < 13 cycles, n (%)	56 (81)	56 (78)	112 (79)
13 cycles or longer, n (%)	45 (65)	34 (47)	79 (56)
Actual dose intensity (mg/day) ^b			
N	69	72	141
Mean (standard deviation)	262.2 (45.04)	296.5 (11.59)	279.7 (36.75)
Median	288.3	300.0	300.0
Min, max	169, 300	239, 300	169, 300
Relative dose intensity (%) ^c			
n	69	72	141
Mean (standard deviation)	87.397 (15.0134)	98.847 (3.8628)	93.244 (12.2492)
Median	96.104	100.000	100.000
Min, max	56.39, 100.00	79.74, 100.00	56.39, 100.00
Number of participants with a dose modification, n (%) ^d	45 (65)	12 (17)	57 (40)
Adverse event	44 (64)	8 (11)	52 (37)
Other	7 (10)	4 (6)	11 (8)
Number of participants with a dose reduction, n (%)	29 (42)	0	29 (21)
Adverse event	29 (42)	0	29 (21)
Other	2 (3)	0	2 (1)
Number of participants with a dose interruption, n (%)	45 (65)	12 (17)	57 (40)
Adverse event	44 (64)	8 (11)	52 (37)
Other	6 (9)	4 (6)	10 (7)

Abbreviations: DB: double-blind; max: maximum; min: minimum.

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

a Duration of exposure was calculated as: (date of last dose - date of first dose + 1)/ 30.4375.

b Actual dose intensity was calculated as: cumulative dose received/duration of the exposure in days. If a participant's most recent dose modification was an interruption and the participant had not discontinued, days of interruption up until the data cut point were added to the denominator.

c Relative dose intensity was calculated as: $100 \times (\text{cumulative dose received} / \text{planned dose received})$. Planned dose was 300 mg/day $\times$ duration of exposure in days. If a participant's most recent dose modification was an interruption and the participant had not discontinued, days of interruption up until the data cut point were added to the denominator.

d Dose modifications included both reductions and interruptions.

The Applicant's Position:

The median duration of study treatment exposure in the nirogacestat arm was nearly twice that of the placebo arm, likely due to the greater number of events observed in the placebo arm. Consistent with the protocol, which mandated a dose reduction to 100 mg BID for the management of select, persistent Grade ≥ 3 AEs (diarrhea, nausea, vomiting, skin toxicity, hypophosphatemia, hematologic/nonhematologic toxicities) and was optional for Grade 2 OD, 42% of participants receiving nirogacestat had dose reductions. The median duration of study drug exposure after reduction was 19.06 months. The majority of participants receiving nirogacestat (65%) remained on study treatment for more than 13 cycles, suggesting sustained tolerability over an extended period of treatment.

The FDA's Assessment:

FDA agrees with the Applicant's statement that patients in the nirogacestat arm had longer treatment exposure than the patients in the placebo arm, likely due to fewer progression events in the nirogacestat arm. Patients in the nirogacestat arm had lower dose intensity (both actual and relative), likely due to dose reductions and interruptions being more frequent in the nirogacestat arm. Most patients in the nirogacestat arm had dose modifications (65%), with dose interruptions (65%) being more common than dose reductions (42%). TEAEs were the most common reasons for dose modifications in both treatment arms.

FDA conducted additional analysis to investigate the time to first dose modification and total time of dose interruption (Table 31). Patients in the nirogacestat arm interrupted dosing earlier than patients in the placebo arm (mean 4.5 cycles vs. 6.3 cycles, respectively). Patients in the nirogacestat arm had their first dose reduction at approximately the same time as their first dose interruption, i.e., mean of 4.9 cycles; no patients in the placebo arm had a dose reduction. The total duration of dose interruption was similar across the two arms (mean 22.3 vs. 26.7 days for nirogacestat vs. placebo arm, respectively). Note, FDA sent an Information Request to the Applicant to clarify why the sample size for "time to first dose interruption" and "total time interrupted" were different for the nirogacestat arm (see Table 31). The Applicant responded that one patient who had a dose interruption due to an adverse event (ID (b) (6) in the nirogacestat arm) discontinued treatment, so this patient was not counted in the "total time interrupted" because the patient did not restart nirogacestat.

In conclusion, even though the patients in the nirogacestat arm tolerated long exposure to nirogacestat, the earlier and more frequent dose modifications suggest that many patients were not able to tolerate nirogacestat 150 mg PO BID.

Table 31: Trial Treatment Exposure – DB Phase (Safety Population)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
Time to first dose interruption (cycles)			
N	45 (65)	12 (17)	57 (40)
Mean (standard deviation)	4.5 (5.9)	6.3 (7.7)	4.9 (6.3)
Median	2	3	3
Min, Max	0, 26	0, 26	0, 26
Time to first dose reduction (cycles)			
N	29 (42)	0	29 (21)
Mean (standard deviation)	4.9 (6.3)	0	4.9 (6.3)
Median	3	0	3
Min, max	0, 24	0	0, 24
Total time interrupted (days)			
N	44	12	56
Mean (standard deviation)	22.3 (24)	26.7	23.3 (26.6)
Median	13.5	12	13
Min, Max	1, 132	1, 104	1, 132

Source: ADEX (SDN 39; May 5, 2023)

Most patients in Study NIR-DT-301 received concomitant medications (100% and 97% of the safety population in the nirogacestat and placebo arms respectively). FDA analyzed the common indications for concomitant medications (see table below). The most common indication for concomitant medications was pain, and tumor pain occurred more frequently in the placebo arm (46%) than the nirogacestat arm (33%). Diarrhea, nausea, rash or dermatitis, hypophosphatemia, and headache occurred more frequently in the nirogacestat arm, likely due to the adverse reactions associated with nirogacestat. Patients in the nirogacestat arm were also more likely to have received concomitant medications for infections, both COVID-19 and non-COVID-19 related, than patients in the placebo arm. FDA analysis of treatment-emergent adverse events (TEAEs) also demonstrated that patients in the nirogacestat arm had more TEAEs in the System, Organ, Class (SOC) of Infections and Infestations than patients in the placebo arm, 57% (n=39) vs. 33% (n=24), respectively. However, the rate of serious TEAEs in the SOC of Infections and Infestations were similar across the two arms: 6% (n=4) in nirogacestat and 7% (n=5) in placebo arms. The serious infections in the nirogacestat arm were appendicitis, infected cyst, abdominal infection and abscess, and groin abscess (n=1 for each serious infection). The serious infections in the placebo arm were COVID-19 (n=2), sepsis (n=2), and

infection, and sepsis (n=1).

Analysis of the common indications for use of concomitant medications suggest that nirogacestat has anti-tumor efficacy that may lead to decreased pain due to DT but has associated adverse reactions that require medical management. Patients in the nirogacestat arm appeared to require more treatment for infections compared to patients in the placebo arm, but it is reassuring that the rate of serious infections requiring treatment was similar across both arms.

Table 32: Most Common Indications for Concomitant Medications – DB Phase (Safety Population)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
Pain	53 (77)	54 (75)	107 (76)
Tumor (DT) pain	23 (33)	33 (46)	56 (40)
Headache or migraine	17 (25)	13 (18)	30 (21)
Abdominal pain (includes both experienced pain, and pain prophylaxis)	9 ^a (13)	8 (11)	17 (12)
Nausea (includes both experienced nausea ^b , and nausea prophylaxis)	31 ^c (45)	22 ^d (31)	53 (38)
Experienced nausea ^b	29 (42)	21 (29)	50 (35)
Diarrhea	37 (54)	11 ^e (15)	48 (34)
COVID-19 (includes vaccination, prophylaxis, and treatment)	32 (46)	15 (21)	47 (33)
COVID-19 infection or symptoms	16 (23)	7 (10)	23 (16)
Supplements or vitamins	21 (30)	16 (22)	37 (26)
Anxiety (includes both experienced anxiety, and anxiety prophylaxis)	19 ^f (28)	16 ^g (22)	35 (25)
Rash or dermatitis (includes both experienced rash, and rash prophylaxis)	29 (42)	6 ^h (8)	35 (25)
Non-COVID-19 infections, abscess, and sepsis	24 (35)	10 (14)	34 (24)
Constipation (includes both experienced constipation, and constipation prophylaxis)	14 ⁱ (20)	13 ⁱ (18)	27 (19)
Experienced constipation not specified to be due to opioids	11 (16)	9 (13)	20 (14)
Hypophosphatemia	21 (30)	2 (3)	23 (16)
Gastrointestinal acid reflux	10 (14)	8 (11)	18 (13)
Vomiting (includes both experienced vomiting, and vomiting prophylaxis)	6 ⁱ (9)	9 ⁱ (13)	15 (11)
Experienced vomiting	4 (6)	7 (10)	11 (8)

Abbreviations: DT = desmoid tumor

^a One patient received prophylaxis for abdominal pain.

^b Excludes nausea that is specified to be due to non-trial drug or procedure.

^c Eleven patients received prophylaxis for nausea.

^d Four patients received prophylaxis for nausea.

^e One patient had traveler's diarrhea.

^f One patient received prophylaxis for anxiety for CT scan.

^g Two patients received prophylaxis for anxiety from anticancer treatment (n=1) or not specified (n=1).

^h One patient received prophylaxis for rash.

ⁱ Two patients experienced constipation due to opioids or pain medications, and two patients had prophylaxis for constipation.

^j Three patients got prophylaxis for vomiting.

Source: ADCM (SDN 39; May 5, 2023)

FDA also analyzed the use of concomitant medications that have potential anti-DT effects (e.g., based on literature), or whose mechanism of action affects the reproductive hormone levels (see table below). Patients in the nirogacestat arm were less likely to receive medications with potential (reported) anti-DT efficacy, so it is unlikely that use of these concomitant medications detracts from the anti-DT efficacy demonstrated by nirogacestat in Study NIR-DT-301. The concomitant medications whose mechanism of action affects the reproductive hormones were estrogen- and progesterone-analogues, and clomiphene, none of which are known to have anti-DT efficacy. See Section 8.1.2 for the efficacy subgroup analysis for patients who received these concomitant medications.

Table 33: Concomitant Medications with Reported Anti-DT Effects or whose Mechanism of Action Affects the Reproductive Hormones __ DB Phase (Safety Population)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
Medications with potential anti-DT efficacy	13 (19)	20 (28)	33
NSAIDs	9 (13)	13 (18)	22
Sorafenib or pazopanib	3 (4.3)	3 (4.2)	6 (4.3)
Doxorubicin or liposomal doxorubicin	0	3 (4.2)	3 (2.1)
Azathioprine	1 (1.4)	0	1 (0.7)
Medications whose mechanism of action affects the reproductive hormones ^a	10 (14)	6 (8)	16 (11)

Abbreviations: NSAIDs = nonsteroidal anti-inflammatory drugs

^a The medications were estrogen- and progesterone-analogues, and clomiphene.

Source: ADCM (SDN 39; May 5, 2023)

FDA agrees with the Applicant's statement that patients in the nirogacestat arm underwent more concomitant procedures than the patients in the placebo arm. However, similar numbers of patients underwent DT-specific concomitant procedures across both arms, which were excision, nerve block or neurolysis, and radiotherapy (see Table below). The most common DT-specific procedure was excision of a mass, and all excisions were considered therapeutic surgeries by the Applicant. The other two procedures (nerve block or neurolysis, and radiotherapy) were not considered therapeutic procedures by the Applicant. Tumor pain was the most common reason for a DT-specific procedure (n=1 in nirogacestat, and n=2 in the

placebo arm), and the patients were treated with nerve block or neurolysis (n=2, one patient in each arm) or tumor excision (n=1 in placebo arm) to treat the pain.

The use of DT-specific concomitant procedures in Study NIR-DT-301 is unlikely to affect the outcomes of this trial since the number of procedures that were considered therapeutic, i.e., excisions, were balanced across the arms. The ADPR database (database for procedures) did not specify if the procedures were performed on target lesions or non-target lesions, but only 1 patient among the patients who underwent DT-specific excision or DT-specific radiotherapy had a response: patient ID (b) (6) in the nirogacestat arm had a partial response, and this patient underwent an excision of an osteoma of the jaw, which is not a DT. FDA also conducted a sensitivity analysis for PFS that excluded the patients who underwent the excisions for DT (n=5) and radiotherapy (n=1) from the PP population (i.e., revised PP population), and concluded that the revised PP population had a similar PFS to the ITT population (see “Protocol Violations/Deviations” in Section 8.1.2). In addition, the number of patients who underwent excisions or radiotherapy was balanced across the two arms.

Table 34: Concomitant DT-specific Procedures and Their Indications – DB Phase (Safety Population)

	Nirogacestat (N = 69)	Placebo (N = 72)	Total (N = 141)
DT-specific procedures	5	4	9
Excision	3	3	6
<i>Indications</i>	<i>Back pain (n=1) Osteoma of jaw (n=1) Perianal nodule (n=1)</i>	<i>Tumor pain (n=1) DT-progression (n=2)</i>	
Nerve block or neurolysis	2	1	3
<i>Indications</i>	<i>Tumor pain (n=1) Post-op pain from VATS (n=1)</i>	<i>Tumor pain (n=1)</i>	
Radiotherapy	1	0	1
<i>Indications</i>	<i>Tumor bleeding (n=1)</i>		

Abbreviations: DT = desmoid tumor, VATS = video-assisted thoracic surgery
Source: ADPR (SDN 39; May 5, 2023)

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

A summary of PFS from randomization is presented in Table 35. A Kaplan-Meier plot of PFS from randomization is presented in [Figure 2](#).

The number of PFS events were lower in nirogacestat compared to placebo, leading to significantly higher PFS in the nirogacestat arm (12 participants [17%] with an event) versus the placebo arm (37 participants [51%] with an event), demonstrating a 71% reduction in the risk of disease progression or death (HR = 0.29 [95% CI: 0.15, 0.55]; $p < 0.001$).

Assessment of qualified clinical progression events were included in the analysis of PFS. Radiographic progression and qualified clinical progression each occurred at a lower rate in the nirogacestat arm versus the placebo arm (16% vs 42% and 1% vs 8%, respectively). For both treatment arms, the majority of participants with a progression event had radiographic progression (11 of 12 participants in the nirogacestat arm; 30 of 36 participants in the placebo arm). A sensitivity analysis excluding events of qualified clinical progression found results consistent with the primary analysis and supported the inclusion of these events in the analysis of PFS (HR = 0.31 [95% CI: 0.15, 0.62]; $p < 0.001$).

Table 35: Summary of PFS from Randomization – Double-Blind Phase (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)
Number of participants with event Type of event:	12 (17%)	37 (51%)
Progression	12 (17%)	36 (50%)
Radiographic progression	11 (16%)	30 (42%)
Qualified clinical progression	1 (1%)	6 (8%)
Death before progression	0	1 (1%)
Number of participants censored Reason for censoring:	58 (83%)	35 (49%)
No adequate disease status assessment	4 (6%)	1 (1%)
No documented progression or death	53 (76%)	32 (44%)
Early discontinuation by study Investigator and not adjudicated as qualified event	1 (1%)	1 (1%)
New anticancer therapy or procedure started prior to radiographic or clinical progression	0	1 (1%)
Probability of being event free at Month 6 (95% CI ^a)	91.8 (81.4, 96.5)	69.8 (57.5, 79.2)
Probability of being event free at Month 12 (95% CI ^a)	84.7 (72.5, 91.7)	52.8 (40.1, 63.9)
Probability of being event free at Month 24 (95% CI ^a)	76.4 (60.5, 86.6)	44.0 (31.6, 55.7)
Kaplan-Meier estimates of time to event (months) Quartiles (95% CI):		
25%	NE (9.3, NE)	5.6 (3.2, 8.3)

	Nirogacestat (N = 70)	Placebo (N = 72)
50%	NE (NE, NE)	15.1 (8.4, NE)
75%	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI) ^b	0.29 (0.15, 0.55)	
One-sided p-value ^c	< 0.001	

Abbreviations: CI: confidence interval; ITT: intent-to-treat; PFS: progression-free survival.

Note: Progression free survival was calculated as: (earliest date of death/(centrally-read radiographic/qualified clinical) progression or censoring- randomization date +1)/30.4375.

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

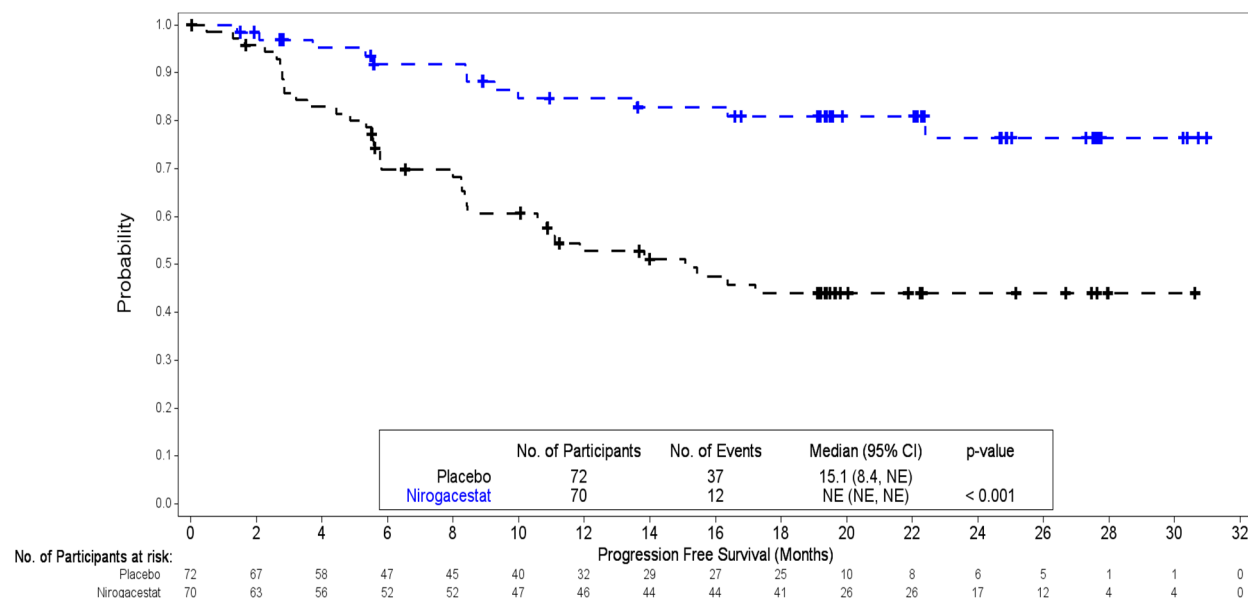
Note: Percentages were based on the number of participants in the Intent-to-treat population.

^a Calculated from the product-limit method.

^b Hazard ratio was estimated from the stratified Cox proportional hazards model using the exact method for ties, stratified by tumor location. Placebo was the reference treatment.

^c p-value was from a one-sided stratified log-rank test with placebo as reference.

Figure 2: Kaplan-Meier Plot of PFS From Randomization – Double-Blind Phase (ITT Population)



Note: Progression free survival was calculated as: (date of death or [radiographic/qualified clinical] progression or censoring date – randomization date + 1)/30.4375.

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

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

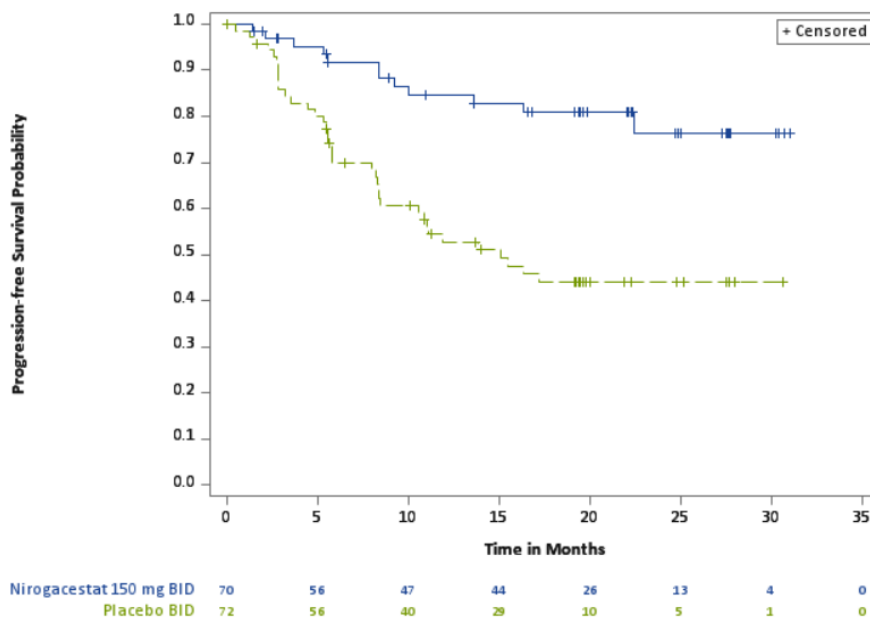
The Applicant's Position:

A statistically and clinically significant improvement in the primary endpoint of PFS was observed for nirogacestat over placebo, with a 71% reduction in the risk of disease progression or death (HR = 0.29 [95% CI: 0.15, 0.55]; $p < 0.001$). The probability of being event free was higher in the nirogacestat arm compared to the placebo arm at Months 6 (91.8% vs 69.8%), 12 (84.7% vs 52.8%), and 24 (76.4% vs 44.0%), supporting a sustained clinical benefit over time.

The FDA's Assessment:

FDA agrees with the Applicant's position that nirogacestat led to a statistically and clinically significant improvement in PFS in patients with DT compared to placebo, where PFS included both clinical and radiographic progression as assessed by blinded independent review. The median PFS was non-evaluable (NE, 95% CI: NE, NE) for patients on nirogacestat, and 15.1 months (95% CI: 8.4, NE) for patients on placebo, with a hazard ratio of 0.29 (95% CI: 0.15, 0.55; p -value < 0.001). Due to the discrepancy identified by the OSI (see Section 4.1), an updated figure of Kaplan-Meier plot of PFS is presented below. Only a censored date for PFS in 1 patient was affected. Therefore, the PFS HR and medians in arms remained the same, and the Kaplan-Meier plot of PFS is generally consistent with the original plot reported by the Applicant.

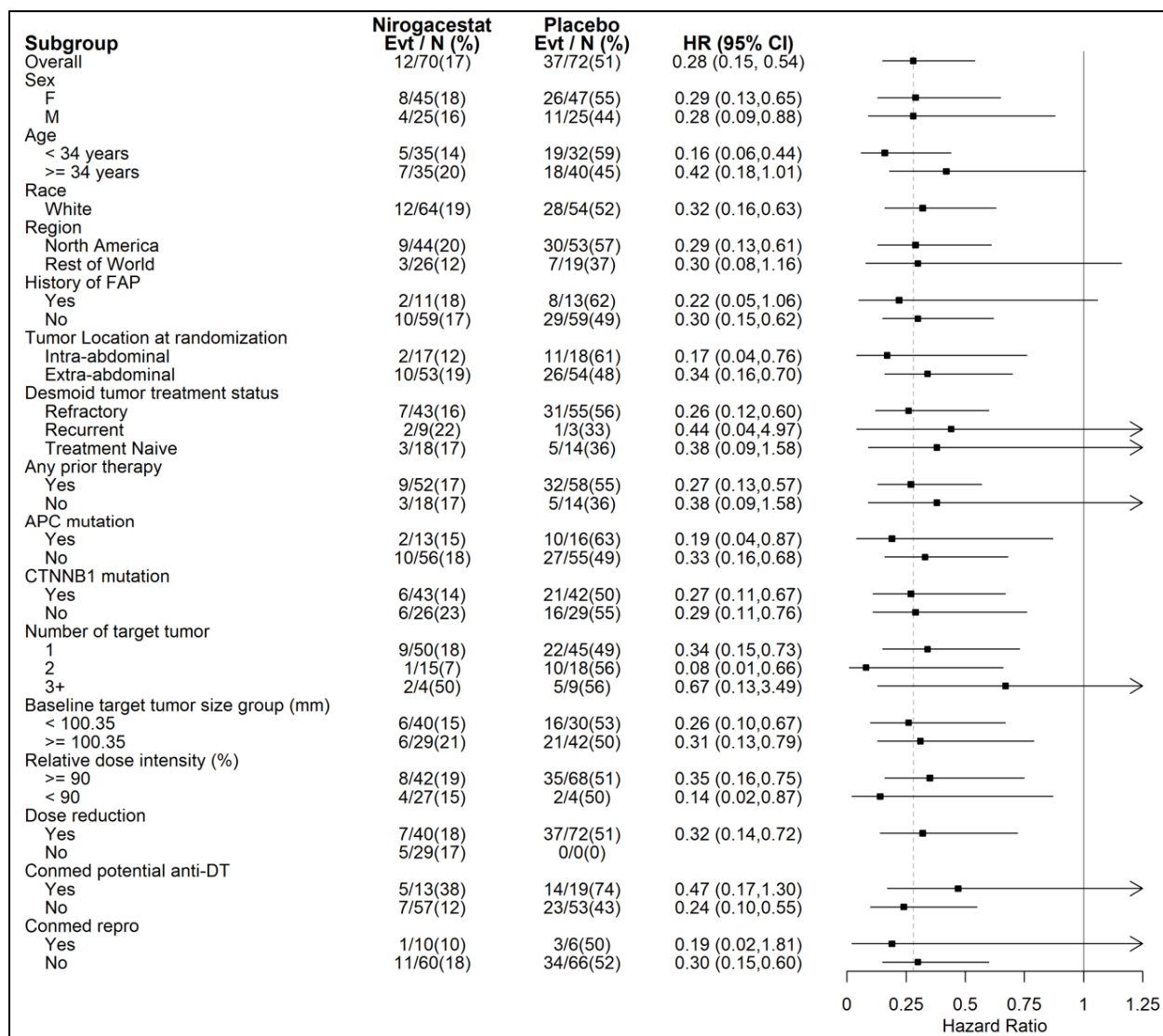
Figure 3: Corrected Kaplan Meier Plot of PFS from Randomization – Double Blind Phase (ITT Population)



Source: ADPR (SDN 39; May 5, 2023)

Treatment benefit in PFS for nirogacestat was generally consistent across all subgroups analyzed (Figure 4).

Figure 4: Subgroup Analysis of PFS



Source: ADPR (SDN 39; May 5, 2023)

Investigators determined that 9 patients had clinical progression, among whom the independent blinded central clinical review committee determined that 7 patients qualified for inclusion in the primary analysis for PFS (n=1 nirogacestat, n=6 placebo), and 2 did not qualify (n=1 for each arm). FDA's summaries of the narratives for clinical progression (qualified and unqualified) are presented in Table 36. Although the final assessments of the independent blinded central clinical review committee were reasonable for these patients, it is difficult to assess for bias (in the determination of clinical progression) because the committee was not necessarily reviewing clinical data for all patients in the trial in a real-time, continuous basis.

Since clinical progression is a more subjective endpoint than radiographic progression, it was reassuring that nirogacestat also demonstrated improved PFS based on radiographic assessment alone compared to placebo, with a median PFS of NE (95% CI: NE, NE), and NE (95% CI: 11.0, NE), with a hazard ratio of 0.31 (95% CI: 0.16, 0.62). This sensitivity analysis in combination with ORR results and PRO analyses (see section below for Efficacy Results – Secondary and other relevant endpoints and section for Efficacy Results – Secondary or exploratory COA [PRO] endpoints) provided confidence that nirogacestat provides benefit to patients, overcoming the weakness of the primary endpoint in Study NIR-DT-301. Note that although the determinations of clinical progression below appeared reasonable, information was not provided (particularly for patients in the experimental arm) regarding whether there was bias in delaying a determination for a clinical progression event.

Table 36. FDA Summary of the Narratives for Patients Determined to have had Clinical Progression

Qualified for inclusion in primary analysis for PFS based on assessment of the independent blinded central clinical review committee	
(b) (6)	: nirogacestat – 51 yo M with previously treated UF DT/AF located in the mesentery and pelvis, who enrolled in NIR-DT-301 14.11 years from diagnosis. Previous treatment was surgery. The Investigator determined that the patient had clinical progression on Trial Day 43, based on hematuria (onset Day 43), abdominal pain, postrenal kidney failure (onset Day 45), hemorrhagic anemia, and left-sided hydronephrosis (onset Day 45). Nirogacestat was discontinued due to “deterioration of health status,” and the last dose of nirogacestat was on Day 43. The patient subsequently developed intestinal obstruction (Trial Day not provided in narrative), and the Investigator noted progression of the pelvis tumor, and vital structure involvement, including bladder, kidney, and intestinal tract. The local RECIST v1.1 read and central imaging review both reported stable disease while the patient was on nirogacestat. The patient started an alternative therapy on the same day as the last dose of nirogacestat.
(b) (6)	: placebo – 23 yo M with previously treated MF DT/AF including 5 target tumors located in the abdominal wall, chest wall, mesentery and pelvis, and paraspinal, and 3 nontarget tumors located in the abdominal wall, who enrolled in NIR-DT-301 4.98 years from diagnosis. Previous treatments were NSAIDs, and tamoxifen; the patient discontinued previous systemic therapy due to disease progression. The Investigator determined that the patient had clinical progression on Trial Day 15, based on an enlarging right anterior chest wall mass that was causing the patient pain and associated ECOG performance status decline to 1-2. The Investigator also attributed the pinching, nerve compression pain in the right shoulder that started Day 57 as clinical progression. Local RECIST v1.1 read of tumor imaging reported progression on Day 97, and the patient remained on trial while awaiting

central review of the imaging. The central imaging review reported that the patient had stable disease while on placebo. The patient was started on hydrocodone for increased pain on Day 103, and there was noticeable skin thinning and erythema over the medial aspect of the mass on Day 113. The Investigator reported decreased quality of life due to pain and increased difficulties with ADL and IADLs. The patient's last dose of placebo was on Day 117. Five days later, the patient started dacarbazine + doxorubicin.

(b) (6) : **placebo** – 29 yo F with previously treated UF DT/AF located in the mesentery and pelvis, who enrolled in NIR-DT-301 0.81 years from diagnosis. Previous treatment were sulindac, and tamoxifen; the patient discontinued previous systemic therapy due to disease progression. The Investigator determined the patient had clinical progression on Trial Day 243, based on tingling and numbness in the right hip to groin area. The Investigator reported that the lesion in the right pelvic sidewall was progressing, with involvement of the regional vasculature. Local RECIST v1.1 read of the MRI obtained on Day 253 reported disease progression. Central imaging review reported that the patient had stable disease while on placebo. The patient's last dose of placebo was on Day 261. The tingling and numbness increased on Day 269, with associated "lumps" visible in the area between the umbilicus and mons pubis. The patient went to the Emergency Department on Day 270, where she was diagnosed with a deep vein thrombosis and was treated with apixaban. The patient started sorafenib 19 days after the last dose of placebo.

(b) (6) : **placebo** – 21 yo F with UF DT/AF located in the chest wall, who enrolled in NIR-DT-301 1.55 years from diagnosis. Previous treatment was sorafenib, which was discontinued due to disease progression. The Investigator determined the patient had clinical progression on Trial Day 168 due to new trouble swallowing pills (onset Day 168); the patient last dose of placebo was on Day 167. The Investigator reported that the left anterior upper chest mass was progressing and causing rightward displacement of the trachea. Both local, and central RECIST v1.1 reads reported that the patient had stable disease while on placebo. Fourteen days after the last dose of placebo, the patient underwent a resection of the chest wall DT.

(b) (6) : **placebo** – 30 yo M with MF DT/AF including 3 target tumors located in the abdominal wall, mesentery, and pelvis, and 1 nontarget tumor in the abdominal wall, who enrolled in NIR-DT-301 1.34 years from diagnosis. Previous treatments were multiple surgeries. The Investigator determined the patient had clinical progression on Trial Day 39 due to worsening right upper quadrant pain (onset Day 39). The Investigator reported that the progressing lesions were a pelvis implant, right abdominal wall, and abdominal implants. Local RECIST v1.1 read on Day 49 reported disease progression. The central imaging review reported that the patient had stable disease while receiving placebo. The patient's last dose of placebo was on Day 57. On Day 64, the patient was hospitalized for

abdominal pain caused by an abdominal abscess, which was drained and treated with antibiotics. The patient started doxorubicin 3 days after the last dose of placebo.

(b) (6) : **placebo** – 37 yo F with UF DT/AF located on the chest wall, who enrolled in NIR-DT-301 1.18 years from diagnosis. Previous treatments were dexamethasone, liposomal doxorubicin, and intratumoral corticosteroid injection; systemic therapies were discontinued due to disease progression, and intratumoral corticosteroid was discontinued due to disease progression. The Investigator determined the patient had clinical progression on Trial Day 69 due to increased pain at tumor site, and pain throughout the right upper extremity. The Investigator also reported fatigue (onset Day 69), and mild anorexia over the prior 2 weeks. The Investigator reported that the progressing lesion was on the chest wall. Both the local and central RECIST v1.1 reads reported stable disease while the patient as on placebo. The patient started alternative treatment 22 days after the last dose of placebo.

(b) (6) : **placebo** – 44 yo M with previously treated MF DT/AF including 2 target tumors located in the chest wall, and 3 nontarget tumors located in the chest wall, who enrolled in NIR-DT-301 6.43 years from diagnosis. Previous treatments were surgery, and radiation. The Investigator determined the patient had clinical progression on Trial Day 148 due to pain in the left lateral chest wall radiating to the left anterior chest wall that was worsening over the prior few weeks, with associated increased swelling, and left upper quadrant fullness, and pain. The Investigator reported that the left lateral and anterior chest wall tumors were increasing in size based on MRI imaging. Both the local and central RECIST v1.1 reads reported stable disease while the patient as on placebo. The patient started alternative treatment 6 days after the last dose of placebo.

Did not qualify for inclusion in primary analysis for PFS based on assessment of the independent blinded central clinical review committee

(b) (6) : **nirogacestat** – 51 yo M with previously treated UF DT/AF located in the mesentery and pelvis, who enrolled in NIR-DT-301 9.70 years from diagnosis. The patient previously received sorafenib, which was discontinued due to disease progression. The Investigator determined that the patient had clinical progression on Trial Day 57, based on tumor pain (onset Day 57), pulmonary metastasis found to be due to spindle cell sarcoma (Day 59), and tumor hemorrhage (Day 66). The Investigator also reported that the tumor was draining, and the patient had a poor appetite. The patient's last dose of nirogacestat was on Day 65. On Day 66, the patient presented with profuse bleeding from his DT, with associated hypotension, and was admitted to the Intensive Care Unit. He received radiation to the bleeding DT, which was 29 days after the last dose of nirogacestat. The following day, he started pazopanib for the sarcoma, and discontinued from the trial. However, the patient continued to decline, and was transitioned to comfort care. He died in hospice 43

days after the last dose of nirogacestat. The local RECIST v1.1 read reported disease progression on Day 59, but the central imaging review assessed that the patient had stable disease while on nirogacestat.

(b) (6) : **placebo** – 33 yo M with previously treated MF DT/AF including 4 target tumors located in the head and neck, and paraspinal, and 4 nontarget tumors located in the chest wall, who enrolled in NIR-DT-301 15.93 years from diagnosis. Previous treatments were chemotherapy, NSAIDs, tamoxifen, investigational agent, imatinib, sorafenib, radiotherapy, and surgery; the patient discontinued previous systemic therapy due to disease progression or unknown reasons. The Investigator determined the patient had clinical progression on Trial Day 52, based on tumor hemorrhage and anemia. The Investigator also attributed more episodes of anemia (onset Days 55, 65, and 67), sepsis (onset Day 66), and skin infection (onset Day 69) to clinical progression. The Investigator reported that the patient's neck mass was progressing with compression of the right internal jugular vein and innominate vein, and other local structures, and on Day 51, a local tumor imaging RECIST v1.1 read reported disease progression. Central imaging review reported the patient had stable disease while on placebo. The patient's last dose was placebo was on Day 65. No new therapies were initiated for the treatment of DT/AF within 30 days following the last dose of placebo.

Abbreviations: PFS= progression free survival, yo=year old, M=male, W=female, UF = unifocal, MF=multifocal, DT/AF=desmoid tumor/aggressive fibromatosis, NSAIDs = nonsteroidal anti-inflammatory drugs, ECOG = Eastern Cooperative Oncology Group, ADLs = activities of daily living, IADLs = instrumental activities of daily living

Data Quality and Integrity

Data:

All participant data relating to the study was entered into the electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data).

The investigator was responsible for verifying that data entries were accurate and correct by electronically signing the CRF. The investigator maintained accurate documentation (source data) that supported the information entered in the CRF. The investigator permitted study-related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) review, and regulatory agency inspections and provided direct access to source data documents.

Monitoring details describing strategy methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (on-site, remote, or central monitoring) were indicated in the monitoring plan to ensure the protocol and GCP was followed.

The sponsor or designee was responsible for the data management of this study including quality checking of the data. The sponsor assumed accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were being protected; and that the study was being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study were retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever was longer. No records were to be destroyed during the retention period without the written approval of the sponsor. No records were to be transferred to another location or party without written notification to the sponsor.

SpringWorks conducts clinical studies according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, SpringWorks undertakes a GCP audit program.

Audits were performed by SpringWorks Quality Assurance (or designees) operating independently of the study monitors. The audits within the clinical program were aimed at study documentation, investigator sites, and CSRs.

The audit program, together with SpringWorks' internal quality control procedures, provide reassurance that study conclusions were based on valid procedures for data management and analysis, and that the clinical study program was carried out in accordance with GCP guidelines.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, or change the conclusions drawn.

The FDA's Assessment:

FDA agrees that Applicant has provided all the datasets and supporting metadata documentation required to validate the results. In addition, FDA conducted a random audit of 10% of the CRFs for Study NIR-DT-301 and verified that the information provided in the CRFs matched with the data presented in the datasets during this audit. See Section 434.1 (Office of Scientific Investigations) for details regarding the results of the FDA inspections.

Efficacy Results – Secondary and other relevant endpoints

Data

A summary of ORR is presented in Table 37. ORR was calculated based on the confirmed best overall response per central review. ORR was significantly higher ($p < 0.001$) in the nirogacestat arm (29 participants [41%]) versus the placebo arm (6 participants [8%]). The ORR in the placebo arm (8%) was lower than the previously reported (20%) in another Phase 3 study of sorafenib in participants with DT ([Gounder et al. 2018](#)), which likely reflected the eligibility requirement for RECIST v1.1 progression in the participants in this study.

The complete response (CR) rate was higher in the nirogacestat arm (5 participants [7%]) versus the placebo arm (no participants) (Table 37). The disease control rate (DCR) was similar between the treatment arms (91% vs 85%), which was due to the higher rate of stable disease in the placebo arm.

Table 37: Summary of ORR – Double Blind Phase (ITT Population)

	Nirogacestat (N = 70)	Placebo (N = 72)
BOR – Confirmed, n (%)		
CR	5 (7)	0
PR	24 (34)	6 (8)
Stable disease	35 (50)	55 (76)
Progressive disease	1 (1)	10 (14)
NE	4 (6)	1 (1)
ORR (ORR: CR+PR) ^a , n (%)	29 (41)	6 (8)
95% CI ^b , %	(30.2, 54.5)	(3.1, 17.3)
Two-sided p-value ^c	< 0.001	
DCR (CR+PR+stable disease) ^d , n (%)	64 (91)	61 (85)
95% CI ^b , %	(83.9, 97.6)	(74.3, 92.1)
Two-sided p-value ^c	0.134	

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

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

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

^b Obtained using exact method based on binomial distribution.

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

^d DCR was defined as having a best response of CR, PR, or stable disease by RECIST v1.1.

The Applicant's Position:

The ORR was significantly higher ($p < 0.001$) in the nirogacestat arm (29 participants [41%]) versus the placebo arm (6 participants [8%]), including 5 (7%) participants with a CR in the nirogacestat arm versus no participants with a CR in the placebo arm. The DCR was similar between the treatment arms (91% vs 85%), which may have been due to the higher rate of stable disease in the placebo arm. Median time to objective response was shorter for participants receiving nirogacestat as compared to placebo at 5.55 and 11.14 months, respectively.

The FDA's Assessment:

FDA agrees with the Applicant's position. Nirogacestat has direct anti-DT effect based on the difference in ORR between the two treatment arms. FDA also agrees that the difference in ORR between in the placebo arms of Study NIR-DT-301 and the trial conducted by *Gounder et al.* is likely due to the latter trial having a less restrictive criteria for radiographic progression for enrollment (i.e., $\geq 10\%$ progression), and permitted enrollment of patients who did not have radiographic progression but had DT that was deemed inoperable or would require extensive surgery, or had symptomatic disease.

FDA also notes that the 95% CI for ORR and DCR in nirogacestat arm are different from FDA's analyses. FDA used Clopper-Pearson Method, an exact method, to calculate the 95% CI for response rate. The 95% CI of ORR in nirogacestat is (29.8, 53.8), and the 95% CI of DCR in nirogacestat is (82.3, 96.8) from FDA's analyses. FDA's calculation of 95% CI for both ORR and DCR in the placebo arm are the same as the numbers reported by the Applicant. Since the DCR was not pre-specified in the hierarchical testing plan, FDA considers the reported p-value for DCR was nominal.

Dose/Dose Response

The Applicant's Position:

All participants were dosed at 150 mg BID; therefore, this is not applicable for this submission.

The FDA's Assessment:

See Section 6 of this review.

Durability of Response

Data:

Median duration of response (DOR) for participants with CR or partial response (PR) was not reached. Similarly, median duration of stable disease (DoSD) for participants with CR, PR, or SD was not reached.

The Applicant's Position:

The Kaplan-Meier median DOR and median DoSD could not be estimated for either treatment arm due to the low number of responses with subsequent progressions or deaths on either arm.

The FDA's Assessment:

FDA agrees with the Applicant's position. The median DOR was not reached for both arms, while the range of the DOR is (2.8, 27.7+) months in nirogacestat and (2.8, 16.4+) months in the placebo.

Persistence of Effect

Data:

Refer to Table 35 and [Figure 2](#).

The Applicant's Position:

Refer to the primary endpoint position.

The FDA's Assessment:

The anti-DT effect of nirogacestat appears durable based on the probability of patients not having a progression event at 2 years from initiation of nirogacestat (76% [95% CI: 61, 87]) compared to placebo (44% [95% CI: 32, 56]) and the difference in median PFS between nirogacestat (15 months [95% CI: 8.4, not evaluable]) and placebo (not evaluable) (Table 35 and Figure 4).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

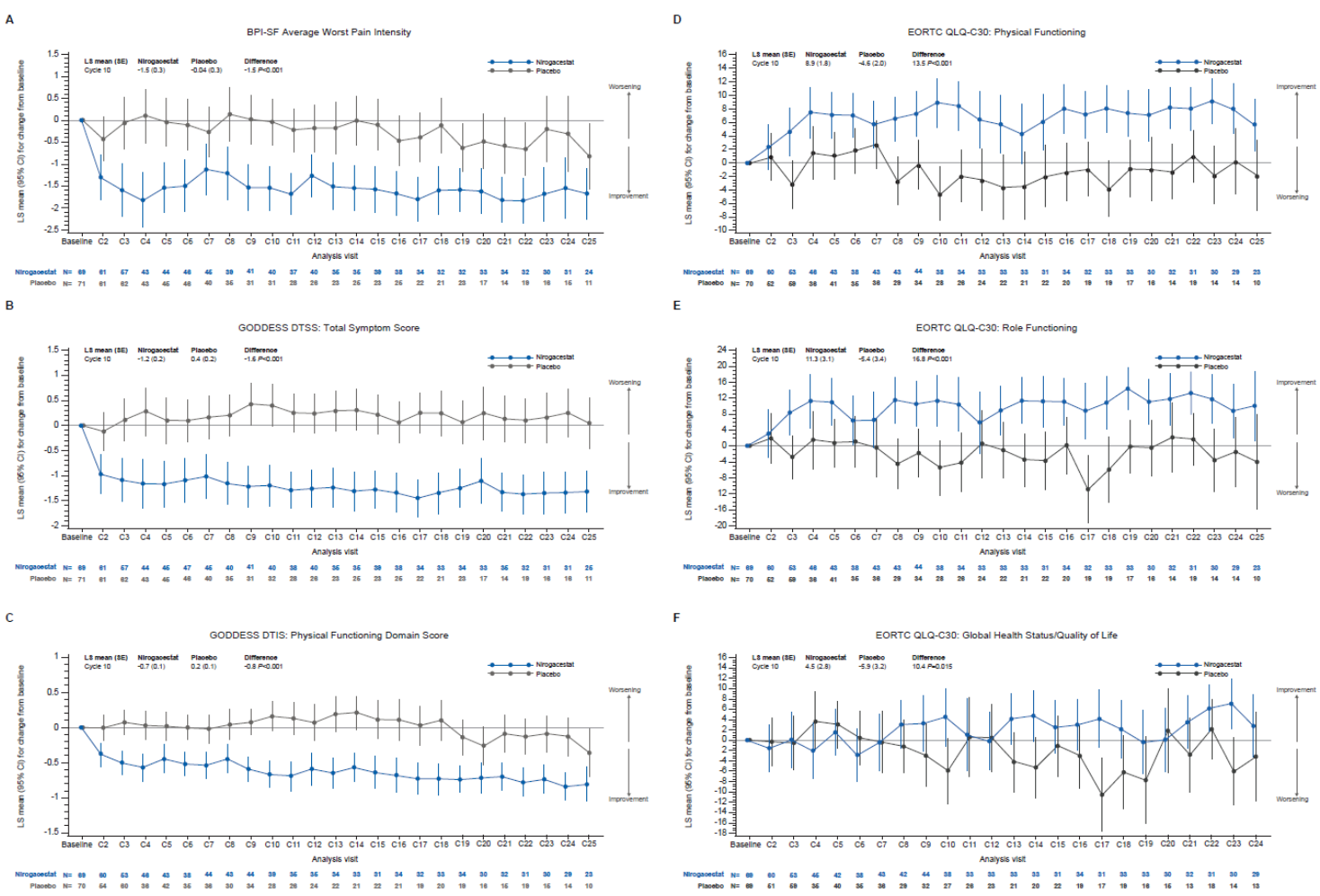
As per the testing hierarchy for PRO assessments, Cycle 10 results are the secondary endpoints while overall results are supportive information (Figure 5).

- For the BPI average pain intensity endpoint, least squares (LS) mean scores were significantly and clinically improved from Baseline in the nirogacestat arm versus the

placebo arm at Cycle 10 (-1.547 vs -0.044; LS mean difference = -1.503; $p < 0.001$) and overall (-1.566 vs -0.253; LS mean difference = -1.314; $p < 0.001$).

- For the GOunder/DTRF DEsmoid Symptom Scale GODDESS Desmoid Tumor Symptom Scale (DTSS) total symptom score (TSS) endpoint, the LS mean change from Baseline scores were significantly and clinically improved in the nirogacestat arm versus the placebo arm at Cycle 10 (-1.200 vs 0.394; LS mean difference = -1.594; $p < 0.001$) and overall (-1.237 vs 0.185; LS mean difference = -1.422; $p < 0.001$).
- For the PRO GODDESS assessment of GODDESS Desmoid Tumor Impact Scale (DTIS) Physical Functioning domain endpoint, the LS mean change from Baseline scores were significantly and clinically improved in the nirogacestat arm versus the placebo arm at Cycle 10 (-0.667 vs 0.161; LS mean difference = -0.829; $p < 0.001$) and overall (-0.635 vs 0.005; LS mean difference = -0.640; $p < 0.001$).
- For the EORTC QLQ-C30 Global Health Status/Quality of Life (GHS/QoL) endpoint, the LS mean change from Baseline scores were significantly and clinically improved at Cycle 10 in the nirogacestat arm versus the placebo arm at Cycle 10 (4.473 vs -5.882; LS mean difference = 10.355; $p = 0.007$) and overall (2.023 vs -2.150; LS mean difference = 4.172; $p = 0.035$).
- LS mean change from Baseline EORTC QLQ-C30 Physical Functioning domain scores were significantly and clinically improved in the nirogacestat arm versus the placebo arm at Cycle 10 (8.894 vs -4.558; LS mean difference = 13.452; $p < 0.001$) and overall (6.836 vs -1.158; LS mean difference = 7.994; $p < 0.001$).
- LS mean change from Baseline EORTC QLQ-C30 Role Functioning domain scores were significantly and clinically improved in the nirogacestat arm versus the placebo arm at Cycle 10 (11.348 vs -5.445; LS mean difference = 16.793; $p < 0.001$) and overall (10.008 vs -1.812; LS mean difference = 11.820; $p < 0.001$).

Figure 5: Mixed Model Repeat Measures: Change from Baseline in PRO Assessments (ITT Population)



The Applicant's Position:

Clinically meaningful and statistically significant improvements were observed with nirogacestat treatment for all PRO assessments evaluated as part of the secondary endpoints at the prespecified timepoint of Cycle 10. Statistically and clinically significant improvements occurred as early as Cycle 2 and were generally sustained throughout the DB phase ([Osoba et al. 1998](#); [Mease et al. 2011](#)). Overall, results from the PRO analyses demonstrated improved health-related quality of life (HRQoL) with nirogacestat as compared to placebo. These findings are notable in DT which has been associated with substantial morbidity including pain and impaired physical functioning ([Constantinidou et al. 2012](#); [Quintini et al. 2012](#); [Penel et al. 2017](#); [Skubitz 2017](#); [Gounder et al. 2020](#); [Schut et al. 2022](#)). Improvements in patient-reported symptoms and impacts have been specifically cited by the Desmoid Tumor Working Group (DTWG) as a treatment goal in their consensus-based guidelines on the management of DT ([DTWG 2020](#)) and highlight the benefit of nirogacestat for patients. The early and consistent benefits observed across patient-reported symptoms and impacts contribute to the robust radiographic findings and demonstrate a clear benefit for patients.

The FDA's Assessment:

The GODDESS (DTSS and DTIS), BPI-SF and EORTC QLQ-C30 instruments were used to collect PROs as secondary endpoints. The average pain intensity (API) score was derived using the average of the daily BPI-SF Item 3 score ("Worst Pain") over the 7-day period prior to each visit with range from 0 to 10, where higher scores indicate greater pain intensity. The DTSS TSS was calculated as the mean of the daily average TSS over a 7-day period if at least 4 out of 7 days were non-missing. The daily average TSS was calculated by averaging the three pain items (items 1-3) first and then averaging with items 4-7. Higher scores indicate greater symptom severity. DTIS Physical Functioning domain was calculated by averaging items 1, 2, 6, 7, and 8 with a 7-day recall period. Higher scores indicate worse physical functioning. The EORTC QLQ-C30 Physical Functioning, Role Functioning, and GHS/QoL domain scores were scored according to the EORTC scoring instructions (i.e., the average of the items that contribute to each scale taken as the raw score). Raw scores are linearly transformed to a 0-100 scale, where higher scores indicate a higher ("better") level of functioning or quality of life. PRO endpoints (mean change from baseline at cycle 10) were formally tested in the following order: BPI-SF API, DTSS, DTIS, EORTC QLQ-C30 GHS/QoL domain, EORTC QLQ-C30 Physical Functioning domain, and EORTC QLQ-C30 Role Functioning domain.

The PRO results reported by the Applicant in the CSR and in the section above were calculated using all data from baseline to cycle 25, which was different from the pre-specified analysis method as described in the SAP. In response to an FDA information request, the Applicant provided corrected analyses on April 21, 2023, redoing the PRO analyses based on data from

baseline to Cycle 10, as pre-specified in the SAP. See Table 38 below for the Applicant's corrected PRO endpoint results. The corrected PRO results were generally consistent with the PRO results reported in the CSR.

Table 38: PRO Endpoint Comparison of Results Reported in CSR vs. Corrected Results

PRO Assessment	Reported in CSR Nirogacestat vs Placebo LSmeans (difference, p-value)	Corrected Results Nirogacestat vs Placebo LSmeans (difference, p-value)
BPI-SF Average Pain Intensity (API)	-1.547 vs -0.044; (-1.503; p < 0.001)	-1.583 vs -0.241; (-1.342; p < 0.001)
DTSS Total Score	1.200 vs 0.394 (-1.594; p < 0.001)	-1.110 vs 0.457 (-1.567; p < 0.001)
DTIS Physical Functioning	-0.667 vs 0.161; (-0.829; p < 0.001)	-0.613 vs 0.094; (-0.706; p < 0.001)
EORTC QLQ-C30	Global health/QoL 4.473 vs -5.882 (10.355; p = 0.007)	Global health/QoL 2.935 vs -8.466 (11.401; p = 0.006)
	Physical functioning 8.894 vs -4.558 (13.452; p < 0.001)	Physical functioning 9.143 vs -5.225 14.368; p < 0.001
	Role functioning 11.348 vs -5.445 (16.793; p < 0.001)	Role functioning 13.293 vs -5.590 (18.884; p < 0.001)

Source: IR response provided on 04/21/2023

FDA considers the EORTC QLQ-C30 GHS/QoL scale (items 29 and 30) as a broad measure that can be impacted by nontreatment/non-disease factors and therefore difficult to interpret. Therefore, FDA considered GHS/QoL to be exploratory and focused its review on the other secondary PRO endpoint results.

In general, FDA concluded that the results from the pre-specified PRO endpoints were challenging to interpret for the following reasons:

1. There were issues with comprehensibility of the DTSS and DTIS:

A definitive conclusion could not be made whether the DTSS and DTIS measures were well-understood and interpreted appropriately due to the limited approach used by the Applicant to evaluate participant comprehension. Specifically, the Applicant did not:

- query participants about understanding and appropriateness of response options for all DTSS and DTIS items, but rather at time of first appearance of the response option type (i.e., queried participants only on DTSS Item 1 and DTIS item 1)
 - consistently query participants about recall period across instructions and items.
2. There was substantial amount of missing data and differential missing data between treatment arms which makes it difficult to reliably interpret the PRO results in terms of efficacy:

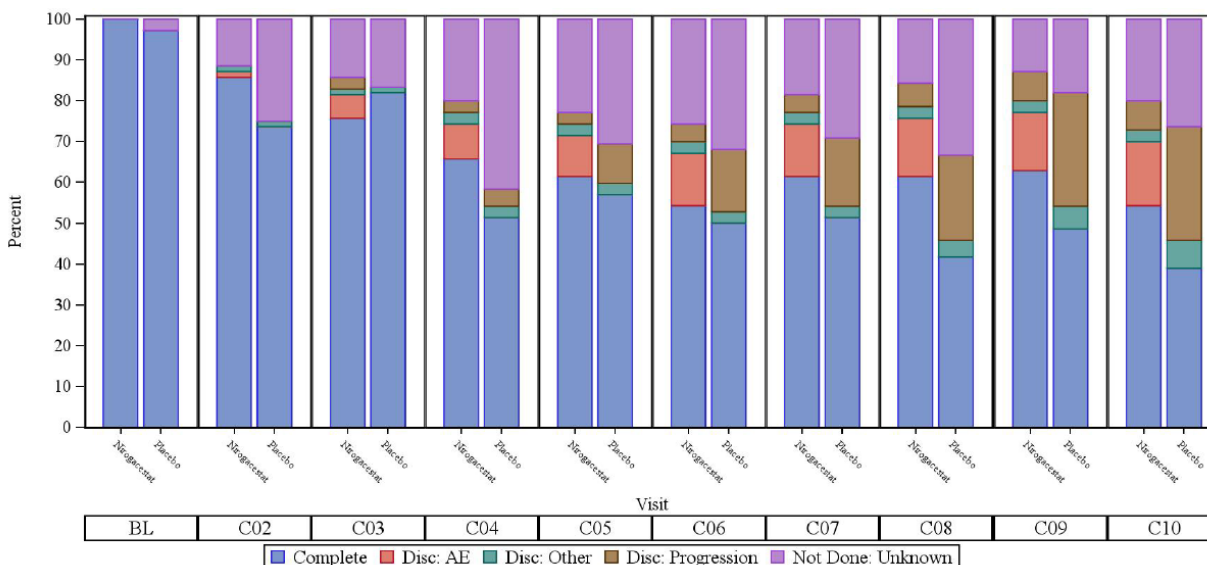
The available data rates (number of PRO completed/ITT population) at baseline and cycle 10 among PRO endpoints are summarized in Table 39 below. Figure 6 also shows the available data rate and reasons for data missingness over time using EORTC QLQ-C30 as an example.

Table 39: Available Data Rate for PRO Endpoints at Baseline and Cycle 10

Available Data Rate	Baseline, N (%)		Cycle 10, N (%)	
	Nirogacestat (N=70)	Placebo (N=72)	Nirogacestat (N=70)	Placebo (N=72)
BPI-SF API	70 (100)	71 (99)	40 (57)	31 (43)
DTSS	70 (100)	71 (99)	40 (57)	32 (44)
DTIS	70 (100)	70 (97)	39 (56)	28 (39)
EORTC QLQ-C30	70 (100)	70 (97)	38 (54)	28 (39)

Source: FDA's analysis.

Figure 6: Available Data Rate and Missing Reasons for EORTC QLQ-C30



Source: IR response provided on 04/21/2023

Using EORTC QLQ-C30 as an example: Available data rates were high at baseline for both nirogacestat and placebo arms; however, less than half of randomized patients were included in the analysis at cycle 10 (Table 39). The available data rate remained above 70% at Cycle 2 and Cycle 3, dropped to 50% from cycle 4 to cycle 7, and decreased to 40% at cycle 8-10 (Figure 6). In addition, the available data rates were differential at cycle 10. The high missing data and differential missing rate may not allow for reliable estimation of clinical benefit from nirogacestat when evaluating PROs using mean change from baseline at cycle 10.

- There was an insufficient level of symptom and physical function impairment at baseline:

Based on item-level distributional data from Study NIR-DT-301,

- >20% of participants endorsed the least severe response category (i.e., participants reported “None” as it related to their symptom experience) for the majority of the items in the DTSS TSS (n= 7/11, 63.6%).
- >20% of participants endorsed the least severe response category at baseline (i.e., participants reported “None” as it related to their physical function experience) for the majority of the items in the DTIS Physical Functioning domain (n= 7/9, 77.8%).

Because of limited impairment, there was no to very little room for improvement to occur in the trial for the DTSS and DTIS scores.

Evaluation of BPI-SF API

Although available data rates for BPI-SF at cycle 10 were low, FDA noted higher available data rates for BPI-SF at cycle 2 and cycle 3 (> 80%). Also, because of the issues outlined above with the DTSS and DTIS, FDA performed additional descriptive analyses on the BPI results. FDA performed additional analyses on change from baseline at cycle 2 and change from baseline at cycle 3 on BPI-SF API to further evaluate the pain improvement for patients in the study. For patients who reported pain at baseline with API ≥ 2 score, the pain improvement at cycle 2 was 2.7-points and 1-point in the nirogacestat and placebo arms, respectively. Similarly, for the same group of patients, pain improved by 3.5-points in the nirogacestat arm and 1.2-points in the placebo arm at cycle 3.

Additional Analyses Conducted on the Individual Trial

Data:

Analysis of exploratory efficacy endpoints showed the following:

- Mean tumor volumes were larger in the nirogacestat arm (421.166 mL vs 371.999 mL) at Baseline as compared to the placebo arm. There were significantly greater decreases in tumor volume in the nirogacestat arm than in the placebo arm at Cycles 7, 13, 19, 25, and 31 ($p < 0.003$), and numerically smaller tumor volume at EOT ($p = 0.065$).
- Mean MRI T2 hyperintensity was numerically more reduced from Baseline in the nirogacestat arm than the placebo arm at Cycles 7, 13, 25, and 31, and at EOT. A total of 23 participants receiving nirogacestat reported a change in T2 hyperintensity from > 90% to < 90%, which has been shown to be prognostic in participants with DT ([Cassidy et al. 2020](#)).
- Efficacy analyses were performed within the nirogacestat arm for participants who had a dose reduction to 100 mg BID versus those who did not have a dose reduction. There was no notable difference in PFS and ORR between participants who dose reduced versus those who did not. PRO analyses of BPI, DTSS, DTIS, and EORTC showed no apparent loss of efficacy with a dose reduction to 100 mg BID.
 - The genetics exploratory endpoint of frequency and distribution of each mutation (*APC* and *CTNNB1* genes) showed that among the 105 participants with evaluable tumor samples, 85 participants (81%) had a *CTNNB1* mutation and 22 participants (21%) had an *APC* mutation. Mutation frequencies were similar between treatment arms and generally consistent with the expected disease etiology although a slightly higher percentage of participants had *APC* mutations

than previously reported in the literature ([Kasper et al. 2011](#); [Riedel & Agulnik 2022](#)). There were no apparent correlations between identified genetic mutations and PFS, suggesting that nirogacestat is an effective treatment for DT regardless of genetic mutation.

- Exploratory analyses of PRO endpoints supported the clinically meaningful benefit of nirogacestat.

The Applicant's Position:

Given the limitations of RECIST in DT, other imaging modalities were evaluated as exploratory endpoints including volumetric MRI and T2 hyperintensity. These supportive analyses demonstrated a greater reduction in tumor volume and T2 hyperintensity among participants receiving nirogacestat as compared to placebo and may represent a more precise measure of tumor changes in DT as compared to RECIST v1.1 ([Kummar et al. 2017](#)). Volumetric MRI may also allow an earlier estimate of disease progression than RECIST v1.1 ([Lefkowitz 2015](#); [DTWG 2020](#); [Subhawong et al. 2021](#)). Data from the volumetric MRI and T2 hypersensitivity analyses provide additional radiographic evidence supporting the benefit of nirogacestat in the treatment of DT as compared to placebo.

Exploratory analyses did not show differences in PFS, ORR, or PRO endpoints between participants who dose reduced to 100 mg BID versus those who did not have a dose reduction.

The FDA's Assessment:

No difference in efficacy was detected between the subgroup of patients who reduced the dose of nirogacestat to 100 mg BID and the subgroup who did not have a dose reduction; however, the analysis of PFS considering dose reduction should be interpreted with caution because there is not a comparable group in the control arm (and, more importantly, the analyses would have been a post randomization analysis). Note that the p-values reported for exploratory endpoints in this section were considered nominal.

FDA interpretation of the statement regarding PRO analyses (in Data above) is that these analyses provided support for the primary assessment of PFS and ORR. The PRO analyses, however, have limitations as described in FDA's review above.

8.1.4. Study A8641014

8.1.5. Trial Design

The Applicant's Description:

Study A8641014 was an open-label, non-randomized, Phase 1 dose-finding study ([Messersmith et al. 2015](#)) in participants with advanced solid tumors conducted to determine the MTD and

recommended Phase 2 dose (RP2D) for the future clinical development of nirogacestat. In the dose-finding portion of the study, the MTD of nirogacestat administered BID continuously for 21 days was established at 220 mg BID in participants with advanced solid tumors. Additional participants were subsequently enrolled in the expansion cohort at 150 mg or 220 mg BID. The RP2D in participants with advanced solid tumors, including DT, was determined to be 150 mg BID by comparing the tolerability, PK, and PDx profile of nirogacestat at these 2 doses.

The FDA's Assessment:

Study A8641014 was a first-in-patient, multicenter, open-label, non-randomized, dose-finding Phase 1a/1b trial that employed a 3+3 dose-escalation design. The primary objective in the original protocol was to determine the MTD of nirogacestat BID as a single agent or in combination with dexamethasone in patients with advanced solid tumors. In the Phase 1b portion of the trial, the primary objective was to determine the safety and tolerability of nirogacestat at the MTD in patients with advanced solid tumors and acute T-cell lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL). Amendment 6 (dated October 26, 2011) of the protocol removed the plan to investigate nirogacestat with dexamethasone from both the dose-escalation and dose-expansion portions of the trial because after analysis of the data of nirogacestat as a single-agent, the Applicant decided that the addition dexamethasone was not necessary for patients with advanced solid tumors.

Eight patients with T-ALL/LBL and 64 patients with advanced solid tumors received nirogacestat on this trial. Based on the results of the Phase 1a portion of the trial, the Applicant determined that the MTD of nirogacestat was 220 mg BID for patients with advanced tumors and investigated nirogacestat 150 mg BID and 220 mg BID in the Phase 1b portion of the trial. The Applicant determined that there were more treatment-related Grade 3 TEAEs with the 220 mg BID dose compared to the 150 mg BID and chose nirogacestat 150 mg BID as the RP2D for patients with advanced solid tumors. The MTD was not determined for patients with T-ALL/LBL because dose escalation was terminated early due to low enrollment rate and early data suggesting that the proof-of-mechanism was unlikely to be achieved in T-ALL/LBL.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria included:

- Men and women $\geq$ 16 years old.
- Eastern Cooperative Oncology Group (ECOG) performance status of:
 - 0 or 1 for participants with advanced solid tumor.
 - 0, 1, or 2 for participants with refractory or relapsed T-ALL.

- Participants with advanced solid tumor malignancy (with measurable disease as per RECIST v1.0 criteria for participants enrolled in the expansion cohort) that was resistant to standard therapy or for which no standard therapy was available, or
- Participant was > 3 weeks (advanced solid tumor malignancy) or > 2 weeks (T-ALL/LBL) from last anticancer treatment (except hydroxyurea, and intrathecal prophylaxis in T-ALL population) at study entry and all acute adverse events (AEs) of any prior therapy had resolved or, if persisting, were not considered to be clinically important.

The FDA's Assessment:

Patients with T-ALL/LBL must have had refractory disease, disease that was resistant to current treatment options, or had no standard therapy available. Patients who previously had their cancer treated with a gamma secretase inhibitor were not eligible. Patients taking tamoxifen were excluded. Patients with the following diseases were also excluded: clinical evidence of CNS disease, active hepatitis B infection, hepatitis C infection, or known HIV or acquired immunodeficiency syndrome (AIDS)-related illness.

Study Efficacy Endpoints

The Applicant's Description:

Primary:

No efficacy endpoint was defined as primary endpoint in this study.

Secondary:

- Objective response (OR) was defined as confirmed CR or confirmed PR according to RECIST (version 1.0).
- Time to tumor progression (TTP) was defined as the time from Cycle 1 Day 1 to date of first documentation of objective progression.
- DOR was only defined for participants with an OR. It was defined as the time from start date (date of first documentation of PR or CR) to date of first documentation of objective progression or death
- PFS was defined as the time from Cycle 1 Day 1 to date of first documentation of progression or death due to any cause.
- Time to response (TTR), defined as the time from first date of receiving study treatment until the first OR date for participants whose best overall response is a CR or PR.

The FDA's Assessment:

FDA would like to clarify that evaluation of TTP, TTR, and PFS were included as a secondary endpoints in the protocol for Study A8641014. However, time-to-event endpoints are not

interpretable in nonrandomized trials, and the primary objective of this trial was to determine the MTD, not the efficacy of nirogacestat.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The final statistical analysis plan (SAP), Amendment 3, was dated 26 March 2012.

The number of participants to be enrolled in the study depended on the observed safety profile, which was to determine the number of participants per dose level and the number of dosing cohorts in the study. Each dose level in the dose escalating components was to enroll at least 3, and up to 6 DLT eligible participants. Once the MTD for solid tumors had been determined, approximately 22 additional participants with advanced solid tumor, including participants with DT, soft tissue sarcoma, lung cancer, breast cancer and other solid tumors, were enrolled to help determine RP2D.

All enrolled participants who were eligible, received study treatment, and had baseline assessments and at least 1 on study tumor assessment prior to any new anticancer therapies were considered evaluable for response. Participants who were treated and discontinued from treatment prior to on study tumor assessment because of clinical disease progression were considered evaluable for efficacy and counted as failures.

Due to the exploratory nature of the study, no confirmatory inferential analyses were planned. Summary tables were produced by dose level. If there were sufficient numbers of participants accrued in certain malignancies, the efficacy endpoints were also to be tabulated for those malignancies separately. Descriptive statistics such as means, medians, standard deviations and ranges for continuous data and frequencies and percentages for categorical data were presented. Tumor response was tabulated and displayed graphically, where appropriate.

A point estimate of the ORR and a 2-sided 95% confidence interval (CI) were calculated using an exact method. Survival endpoints, i.e., TTP, TTR, duration of response, and PFS, were summarized using the Kaplan-Meier method, and the Brookmeyer Crowley method was used to calculate the 95% CI for the median.

The FDA's Assessment:

FDA agrees that this study should be considered exploratory and supportive. The primary efficacy assessment supporting the approval of nirogacestat for patients with progressing DTs was based on Study NIR-DT-301.

Protocol Amendments

The Applicant's Description:

The original protocol dated 15 December 2008 was amended 8 times. None of the amendments impacted the integrity of quality of the study and/or its outcomes.

This study was originally designed to have 4 additional components: an expansion cohort in participants with T-ALL/LBL; an optional dose-finding component in participants with solid tumor for combinational treatment of nirogacestat plus dexamethasone; an optional dose-finding component in participants with T-ALL/LBL for combinational treatment of nirogacestat plus dexamethasone; and an optional expansion component in participants with advanced solid tumor for combinational treatment of nirogacestat plus dexamethasone. These components were later removed due to operational and scientific reasons. As agreed upon at the Pre-NDA meeting, participants with T-ALL/LBL were excluded from the integrated safety analyses as these hematologic malignancies were anticipated to be sufficiently different from DT to preclude any comparisons regarding safety data.

The FDA's Assessment:

FDA outlines below the key protocol amendments that pertained to the advanced solid tumor cohorts. Thus, it excludes descriptions of Amendment 7 (dated February 2, 2012) and Amendment 8 (dated May 14, 2012) whose revisions pertained to the T-ALL/LBL cohorts, including halting of enrollment into the T-ALL/LBL cohorts in Amendment 8 due to low enrollment rate, and early data suggesting that proof-of-concept mechanism unlikely to be achieved for T-ALL/LBL. The following amendments are also not described below because the revisions were not substantive and did not lead to major changes to the trial conduct or trial objectives: Amendment 2 (dated March 11, 2010), Amendment 4 (dated August 27, 2010), and Amendment 9 (dated April 19, 2013). All the amendments were activated except for Amendment 3; Amendment 4 was activated, and it was similar to Amendment 3. The original protocol was dated December 15, 2008.

Amendment 1 (dated November 5, 2009)

1. The Applicant changed the dosing and schedule of dexamethasone.
2. The Applicant allowed enrollment of patients who were 16 years old (previously enrolled only patients who were older than 16 years old).

Amendment 3 (dated August 16, 2010)

1. The Applicant amended the protocol to focus on characterizing the safety and tolerability of nirogacestat as a single-agent.
2. The Applicant added a food effect analysis for patients with solid tumors treated at the MTD in the expansion cohort.

Amendment 5 (dated May 2, 2011)

1. The Applicant increased the number of patients to be enrolled in the expansion cohort from 12 to approximately 22, and enrollment into this cohort was restricted to patients with measurable disease based on RECIST.
2. The Applicant added collection of hair follicles and matched peripheral blood samples from patients with solid tumor for biomarker evaluation.

Amendment 6 (dated October 26, 2011)

1. In the dose expansion cohort, the Applicant allowed enrollment of patients with solid tumors to dose levels lower than the MTD.
2. The Applicant updated the list of tumors that may be enrolled into the dose expansion cohorts.
3. The Applicant removed the plan to investigate nirogacestat with dexamethasone from both the dose-escalation and dose-expansion portions of the trial because after analysis of the data of nirogacestat as a single agent, the Applicant decided that the addition dexamethasone was not necessary for patients with advanced solid tumors.

8.1.6. Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in compliance with Good Clinical Practice (GCP) guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the countries of conduct, including the archiving of essential documents.

The Applicant's Position:

Study A8641014 was GCP compliant.

The FDA's Assessment:

Section 12.2 of the protocol stated that the trial will be conducted "in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws."

Financial Disclosure

The Applicant's Position:

All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the sponsor.

The FDA's Assessment:

The data from Study A8641014 is supportive of the pivotal data that supports this NDA, i.e., Study NIR-DT-301. As such, FDA did not require formal submission of the financial disclosure form for this supportive clinical trial.

Patient Disposition

Data:

The disposition for participants with solid tumors is summarized in Table 40.

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Nirogacestat (PF-03084014)

Table 40: Participant Evaluation Groups; PF-03084014 in Participants with Solid Tumor

Number of Participants	20 mg BID	40 mg BID	80 mg BID	100 mg BID	130 mg BID	150 mg BID	220 mg BID	330 mg BID
Assigned to study treatment	64							
Treated	3	3	4	8	4	23	16	3
Ongoing at data cutoff	0	0	2	0	0	3	0	1
Discontinued from treatment	3	3	2	8	4	20	16	2
Patient died	0	0	0	1	0	0	0	0
Patient refused continued treatment for reason other than AE	0	0	0	1	1	3	1	0
Other ^a	0	0	0	1	0	1	2	0
Objective progression or relapse	2	3	1	2	3	13	8	0
Global deterioration of health status	1	0	1	2	0	2	2	0
AE ^b (related to study drug)	0	0	0	1	0	1	1	1
AE ^b (not related to study drug)	0	0	0	0	0	0	2	1
Analyzed for safety								
Safety analysis set	3	3	4	8	4	23	16	3
AE	3	3	4	7 ^c	4	23	16	3
Laboratory data	3	3	4	8	4	23	16	3
DLT	3	3	3	6	3	6	6	2
Analyzed for efficacy								
Response evaluable set	3	3	3	5	3	18	10	1

Table 40: Participant Evaluation Groups; PF-03084014 in Participants with Solid Tumor

Number of Participants	20 mg BID	40 mg BID	80 mg BID	100 mg BID	130 mg BID	150 mg BID	220 mg BID	330 mg BID
Pharmacokinetic analysis set	3	3	4	8	4	23	16	3
Pharmacodynamic analysis set	0	0	0	0	0	12	7	1
Full analysis set	3	3	4	8	4	23	16	3

Abbreviations: AE: adverse event, BID: twice daily, DLT: dose-limiting toxicity.

^a Other reasons included progressive disease and pulmonary embolism ((b) (6)), patient withdrew consent ((b) (6)), non-compliance ((b) (6)) and ((b) (6)).

^b AE was the primary reason for discontinuation.

^c Due to a database error, AE page for 1 patient ((b) (6)) was missing at the time of data cutoff (09 January 2013). This patient was later found to have a Grade 1 AE of upper respiratory infection that was considered unrelated to study drug. This error did not affect the study's conclusions.

The Applicant's Position:

All 64 participants assigned to treatment received treatment and all 64 are accounted for as either ongoing or permanently discontinued. Data from all 64 participants are contained in the safety analysis set.

The FDA's Assessment:

FDA did not independently verify the results presented in this Assessment Aid by the Applicant for early phase trials, such as Study A8641014, because the evaluation of efficacy of nirogacestat for the treatment of patients with progressing DTs is based on the pivotal trial NIR-DT-301.

Based on the information presented by the Applicant on Table 71, FDA agrees with the Applicant's position. Most patients received the nirogacestat 150 mg BID dose (n=23), followed by 220 mg BID (n=16). The highest dose investigated was nirogacestat 330 mg BID (n=3). The most common reason for discontinuing nirogacestat at all dose levels was objective progression or relapse.

Among the 9 patients with DT, the reasons for discontinuation from treatment were withdrawal by patient (n=3), adverse event (n=2), unqualified clinical progression (n=1), and other (n=3).

Protocol Violations/Deviations

Data:

A summary of important protocol deviations is provided in Table 41.

Table 41: Important Protocol Deviations

Protocol Deviation	Number of Participants
Investigational product	
Patient took the incorrect (higher) dose of study drug in one instance	1
Other	
A patient's partner became pregnant while the patient was on study.	1
Informed Consent	
Patient did not sign ICD & did not give verbal consent	1

Abbreviations: ICD: informed consent document.

The Applicant's Position:

A formal acknowledgement by the study team was made that deviations were reviewed and GCP compliance was maintained. None of the observed protocol deviations appeared to impact the conclusions of the CSR.

The FDA's Assessment:

In addition to the protocol deviations the Applicant listed in Table 41, FDA considers the following protocol deviations important because an increased frequency of these deviations may impact the trial's ability to achieve its objective of determining the MTD, and the subsequent determination of the RP2D: patients were not adherent to documentation of nirogacestat administration (n=11/72, 15%), patients missed one or more doses of nirogacestat (n=7/72, 10%), tumor assessments were not conducted on one or more occasion (n=3/72, 4.2%), a trial clinical visit was not conducted (n=3/72, 4.2%), and end of treatment visit was not conducted (n=1/72, 1.4%).

Data from Study A8641014 were adequate for FDA to review the analysis that led to the Applicant's determination that the MTD for nirogacestat was 220 mg BID. FDA agrees that the MTD for nirogacestat appears to be 220 mg BID. Thus, the protocol deviations did not appear to impact the ability of Study A8641014 to achieve its objective.

Table of Demographic Characteristics

Data:

Demographic characteristics for the Safety Analysis Set are summarized in Table 42.

Table 42: Demographic Characteristics – Safety Analysis Set

Number (%) of Participants	Participants with Solid Tumors			Participants with T-ALL/LBL		
	Male N = 31	Female N = 33	Total N = 64	Male N = 6	Female N = 2	Total N = 8
Age, years						
18-44	7 (22.6)	8 (24.2)	15 (23.4)	6 (100.0)	2 (100.0)	8 (100.0)
45-64	15 (48.4)	13 (39.4)	28 (43.8)	0	0	0
≥ 65	9 (29.0)	12 (36.4)	21 (32.8)	0	0	0
Mean (StD)	55.4 (14.8)	55.8 (14.7)	55.6 (14.7)	30.2 (10.4)	32.5 (3.5)	30.8 (9.0)
Range	23-80	23-76	23-80	18-43	30-35	18-43
Race, n						
White	28 (90.3)	29 (87.9)	57 (89.1)	5 (83.3)	1 (50.0)	6 (75.0)
Black	1 (3.2)	3 (9.1)	4 (6.3)	1 (16.7)	0	1 (12.5)
Asian	1 (3.2)	0	1 (1.6)	0	0	0
Other	1 (3.2)	1 (3.0)	2 (3.1)	0	1 (50.0)	1 (12.5)
Weight, kg						
Mean (StD)	80.5 (12.9)	77.4 (22.2)	78.9 (18.2)	68.4 (10.0)	64.2 (4.5)	67.4 (8.9)
Range	55.0- 104.2	42.5-167.1	42.5-167.1	54.0-79.6	61.0-67.4	54.0-79.6
Height, cm						
Mean (StD)	175.3 (6.0)	163.8 (6.6)	169.4 (8.5)	179.5 (5.4)	165.0 (7.1)	175.9 (8.6)
Range	161.0- 185.0	147.0- 175.0	147.0-185.0	171.0- 185.0	160.0-170.0	160.0-185.0

Abbreviations: n/N: number of participants, StD: standard deviation, T-ALL: T-cell acute lymphoblastic leukemia, T-LBL: T-cell lymphoblastic lymphoma.

The Applicant's Position:

The population in this study had a range of age, weight, and height that was appropriate for evaluation of nirogacestat in a Phase 1 dose-escalation study.

The FDA's Assessment:

FDA did not independently verify the results presented in this Assessment Aid by the Applicant for early phase trials, such as Study A8641014, because the evaluation of efficacy of nirogacestat for the treatment of patients with progressing DTs is based on the pivotal trial NIR-DT-301.

Based on the results presented by the Applicant on Table 42, among the patients with solid tumors, the distribution of male and female patients was well-balanced, the mean weight reflected the U.S. population, and the spread of ages was appropriate for a first-in-patient trial. This trial, like Study NIR-DT-301, enrolled mostly White patients, and the proportion of non-White patients did not reflect the diversity of the U.S. population.

Among the 9 patients with DT, 5 patients were men, and 4 were women. The mean age was 32 years (standard deviation 6.9 years, range: 23-41 years). Eight patients were White, and 1 was Black. Eight patients were not Hispanic or Latino, and 1 patient was Hispanic or Latino. This was a small sample size, but the age distribution was reflective of the general population with DT. Due to the small sample size, the sex distribution was not reflective of the general population with DT. As stated above, the distribution of race and ethnicity in this trial was not reflective of the diversity of the U.S. population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

A summary of primary diagnoses and durations for the participants with solid tumors is provided in Table 43. The most common primary diagnoses were DT (aggressive fibromatosis) (9 participants), colon cancer (7 participants) and breast cancer (7 participants).

Table 43: Primary Diagnoses (≥2 Participants) and Durations for Participants with Solid Tumors – Safety Analysis Set

Primary Diagnosis MedDRA Preferred Term	Participants with Solid Tumor (N = 64)
Breast Cancer	
Number of participants	5
Duration since histopathological diagnosis, years	
Mean (range)	10.5 (2.7-19.7)
Breast Cancer Metastatic	
Number of participants	2
Duration since histopathological diagnosis, years	
Mean (range)	7.4 (1.2-13.7)
Colon Cancer	
Number of participants	7
Duration since histopathological diagnosis, years	
Mean (range)	4.1 (1.6-6.8)
Colorectal Cancer	
Number of participants	4
Duration since histopathological diagnosis, years	
Mean (range)	4.0 (1.4-7.9)
Desmoid Tumor	
Number of participants	9
Duration since histopathological diagnosis, years	
Mean (range)	7.7 (0.1-28.6)
Hepatic Neoplasm Malignant	
Number of participants	2
Duration since histopathological diagnosis, years	
Mean (range)	4.5 (3.0-5.9)
Leiomyosarcoma of endometrium ^a	
Number of participants	2

Duration since histopathological diagnosis, years	
Mean (range)	4.4 (0.9-7.9)
Lung Neoplasm Malignant	
Number of participants	3
Duration since histopathological diagnosis, years	
Mean (range)	1.9 (1.3-2.5)
Pancreatic Carcinoma	
Number of participants	2
Duration since histopathological diagnosis, years	
Mean (range)	3.7 (3.0-4.3)
Thyroid Cancer	
Number of participants	6
Duration since histopathological diagnosis, years	
Mean (range)	11.6 (0.9-21.5)

Abbreviation: MedDRA: Medical Dictionary for Regulatory Activities.

^a Endometrium was not reported in the source table.

The Applicant's Position:

The study design included an expansion cohort that specified the inclusion of DT and soft tissue sarcomas, among other solid tumor types. The demographics reflect this study design feature.

The FDA's Assessment:

The Applicant's Table 74 does not combine the diagnostic terms that may be a description of similar cancers. For example, in Study A8641014, 12 patients had a diagnosis of colorectal cancer (colon cancer [n=7], colorectal cancer [n=4], and rectal cancer [n=1]), 5 patients had a diagnosis of lung cancer (lung neoplasm malignant [n=3], non-small cell lung cancer [n=1], and small cell lung cancer [n=1]), 3 patients had liver cancer (hepatic cancer metastatic [n=1], and hepatic neoplasm malignant [n=2]), 3 patients had leiomyosarcoma (leiomyosarcoma at an unspecified site [n=2] or uterine leiomyosarcoma [n=1]), and 2 patients had kidney cancer (renal cancer [n=1] or renal cell carcinoma [n=1]). One patient each had a diagnosis of the remaining unlisted cancers.

Among the patients with DT, 1 patient had a diagnosis of FAP. The APC and CTNNB1 status of the tumors were unknown for all the patients. All 9 patients with DT had previous therapy: radiotherapy (n=9), systemic therapy (n=7), and surgery (n=6). None of the patients had previous treatment with a tyrosine kinase inhibitor, and 3 patients had prior treatment with chemotherapy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

All participants received concomitant drug treatments during the study. The most commonly reported concomitant drug treatments included antiemetics and antinauseants (for example, prochlorperazine and ondansetron), anti-diarrheal (for example, diphenoxylate hydrochloride and atropine [Lomotil]) and analgesics (for example, oxycodone and ibuprofen).

A total of 9 solid tumor participants (1, 4, 3, and 1 in the 130 mg, 150 mg, 220 mg and 330 mg BID cohorts, respectively) had planned dose reductions and 3 of them had reductions in the first cycle. All of these dose reductions were caused by treatment-related AEs, which were Grades 1 to 3, not reported as SAEs, and resolved following temporary discontinuations or dose reductions.

The Applicant's Position:

Commonly reported concomitant drug treatments were appropriate supportive care for known adverse reactions to nirogacestat. Treatment compliance was high, with dose reductions caused by treatment-related AEs as mandated by the protocol.

The FDA's Assessment:

Patients with DT were treated in the following dose levels of nirogacestat (all BID dosing): 80 mg (n=2), 150 mg (n=2), 220 mg (n=3), and 330 mg (n=2). One patient each had a dose reduction at the higher dose levels: 150 mg, 220 mg, and 330 mg. Patients with DT had a high relative dose intensities and long treatment exposures with nirogacestat (Table 44).

Table 44. Treatment Exposure Among the Nine Patients with DT in Study A8641014

	Median (interquartile range)	Mean (standard deviation)
Relative dose intensity (%)	95 (63, 98)	82 (22)
Duration on nirogacestat (months)	42 (7, 68)	38 (32)

Abbreviations: DT = desmoid tumor

Source: ISE Analysis Dataset ADEX In Module 5.3.5.3 (SDN 5; December 27, 2022)

Among the 64 patients with solid tumors, the most common indications for concomitant drug treatments were pain (n=45, 70%), nausea or nausea prophylaxis (n=36, 56%), diarrhea or diarrhea prophylaxis (n=34, 53%), hypertension or hypertension prophylaxis (n=27, 42%), nutritional supplementation (n=27, 42%), constipation or constipation prophylaxis (n=25, 39%), acid reflux (n=23, 36%), hypophosphatemia or hypophosphatemia prophylaxis (n=19, 30%), insomnia (n=17, 27%), hypothyroidism (n=16, 25%), depression (n=16, 25%), and hypokalemia (n=14, 22%).

The most common indications for the use of concomitant medications in Study A8641014 were similar to those of Study NIR-DT-301, and consistent with the effects of the tumor (i.e., pain) or

with the adverse reactions associated with nirogacestat, such as nausea, diarrhea, and electrolyte loss. The remaining indications are for conditions that are common among the general population in the U.S., namely hypertension, constipation, acid reflux, insomnia, hypothyroidism, and depression. The Applicant did not submit the dataset for concomitant procedures for Study A8641014. However, because efficacy was not the primary objective of this trial, this dataset is not required for the review of the data from this trial.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

No efficacy endpoint was defined as primary endpoint in this study.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Data Quality and Integrity

Data:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, and change the conclusions drawn.

The Applicant's Position:

All study sites were initiated during a sponsor investigator meeting or a site visit by the sponsor or designated representative. Each site was provided with an instructional manual to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data. Central laboratory services were used in this study for consistency.

The sponsor monitored the study through routine center visits. At these visits, study procedures were reviewed, CRF data compared to original clinical records, data queries resolved, and protocol deviations discussed with the investigator. Telephone and e-mail contact was maintained with the investigators between center visits. In addition, the overall study conduct was subject to internal quality review by the sponsor.

Quality assurance audits were performed at 2 sites by the sponsor's own independent quality assurance group under the group's discretion. These audits were conducted according to the sponsor's procedures and GCP guidelines.

The CSR was subject to quality control review in accordance with the sponsor's standard operating procedures (SOPs).

An independent third-party data monitoring committee was not established for this study. But an internal safety review team comprising physicians, safety specialists, and statisticians was set up to review individual and summary data collected in the safety and clinical databases periodically.

The FDA's Assessment:

FDA agrees that Applicant has provided all the datasets and supporting metadata documentation required to validate the results.

Efficacy Results – Secondary and other relevant endpoints

Data:

There were 46 participants with solid tumors evaluable for response. Overall, the ORR (95% CI) was 13.0% (4.9%, 26.3%) for participants with solid tumors and 71.4% (95% CI [29.0%, 96.3%]) in participants with DT (Table 45). Six participants had an OR: 1 CR was in a participant with thyroid cancer and 5 out of 7 participants with DT had PRs. There were no other responders. As of the time of data cutoff, all 6 responders were censored in the calculation of DoR. All 5 DT responders had not progressed and were censored at the time of data cutoff, with 4 still on study and 1 discontinued due to non-compliance. The participant with thyroid cancer with a CR later had recurrence of disease but was censored at the last disease assessment of CR due to missed tumor assessments.

Median DoR for the 6 participants with ORs was not reached due to censoring, with a range of 1.7+ to 24.2+ months, at the time of data cutoff on 09 January 2013. Overall, the median (95% CI) of TTR for the 5 responders with DT was 8.5 (2.9, 30.4) months (Table 45).

For median (95% CI) of both TTP and PFS, the Kaplan-Meier estimates were 1.6 (1.4, 6.0) months for the 150 mg BID cohort and 1.5 (1.1, 4.2) months for the 220 mg BID cohort. The probability (95% CI) of TTP at 6 months and of PFS at 12 months for the 150 mg BID cohort was 33.6% (13.8%, 54.8%) and 26.8% (9.2%, 48.5%), respectively. The probability (95% CI) of TTP at 6 months for the 220 mg BID cohort was 20.0% (3.1%, 47.5%) but the probability of PFS at 12 months was not available for this dose level.

Table 45: Best Overall Response for Participants with Solid Tumors – Desmoid Tumors – Response Evaluable Analysis Set

Number (%) of Participants	80 mg BID N = 2	150 mg BID N = 2	220 mg BID N = 2	330 mg BID N = 1	Total N = 7
Complete response	0	0	0	0	0
Partial response	2 (100)	1 (50.0)	1 (50.0)	1 (100)	5 (71.4)
Stable/no response	0	1 (50.0)	1 (50.0)	0	2 (28.6)
Objective progression	0	0	0	0	0
Objective response rate					
95% Exact CI ^a	2 (100) [15.8, 100.0]	1 (50.0) [1.3, 98.7]	1 (50.0) [1.3, 98.7]	1 (100) [2.5, 100.0]	5 (71.4) [29.0, 96.3]

Abbreviations: BID: twice daily, CI: confidence interval, N: number of participants.

^a Using exact method based on binomial distribution.

Table 46: Time to Response for Responders with Desmoid Tumors

	80 mg BID	150 mg BID	220 mg BID	330 mg BID	Total
Number of participants with BOR ^a = CR/PR	2	1	1	1	5
Time to response (months)					
Median	19.4	2.9	10.1	5.9	8.5
95% CI ^b	8.5, 30.4	-	-	-	2.9, 30.4

Abbreviations: BID: twice daily, BOR: best overall response, CR: complete response, PR: partial response, RECIST: Response Evaluation Criteria in Solid Tumors.

^a BOR was determined according to RECIST (version 1.0).

^b Based on the Brookmeyer and Crowley method.

The Applicant's Position:

The clinical efficacy results showed encouraging activity of nirogacestat at the 150 mg and 220 mg dose level specifically in those participants with DT.

The FDA's Assessment:

FDA did not independently verify the efficacy results because FDA considered Study NIR-DT-301 to be the primary basis for determining efficacy of nirogacestat. Responses were reported at all dose levels that were tested in patients with DT; therefore, FDA cannot determine based on this assessment in a limited number of patients which dose of nirogacestat is most promising for patients with DT. Refer to the clinical review of pharmacology for a more thorough discussion of the dose.

Dose/Dose Response

Data:

Table 45 shows the best overall response for participants with DT by dose group.

The Applicant's Position:

Responses in DT were seen across all dose levels spanning 80 mg BID to 330 mg BID, and therefore a conclusion on dose response cannot be drawn.

The FDA's Assessment:

FDA agrees with the Applicant's position that there were responses at dose levels spanning 80 mg BID to 330 mg BID. However, given the small number of patients per dose cohort in patients with DT, FDA cannot determine based on an assessment of this trial whether there is a dose-response relationship for patients with DT. Refer to clinical pharmacology review above for additional details regarding FDA assessment of the dosing regimen.

Durability of Response

Data:

Median DOR for participants with ORs was not reached.

The Applicant's Position:

Response was durable among participants with ORs.

The FDA's Assessment:

FDA agrees with the Applicant's position, but this conclusion is limited by the small sample size of patients with DT in Study A8641014.

Persistence of Effect

Data:

The median (95% CI) PFS for participants with solid tumors was 1.6 (1.4, 4.2) months and the probability (95% CI) of PFS at 12 months was 29.8% (17.1%, 43.7%). The median (95% CI) of TTP for participants with solid tumors was 1.6 (1.4, 6.0) months for the 150 mg BID cohort and 1.5 (1.1, 4.2) months for the 220 mg BID cohort.

The Applicant's Position:

No obvious trend was observed in the analysis of TTP and PFS.

The FDA's Assessment:

Time-to-event endpoints are not interpretable in nonrandomized trials. See FDA's Assessment regarding Durability of Response.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not applicable; PROs were not collected during this trial.

The FDA's Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA did not conduct additional analyses.

8.1.7. Study 14-C-0007

8.1.8. Trial Design

The Applicant's Description:

Study 14-C-0007 is an NCI-sponsored, open-label Phase 2 study conducted to determine the ORR (CR + PR) of nirogacestat in participants with DT; no randomization or blinding was performed. Nirogacestat was administered orally at a dose of 150 mg BID continuously in 21-day cycles. This is an ongoing study; results are based on a data cutoff of 04 November 2020.

The FDA's Assessment:

FDA agrees with the Applicant's Description.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria included:

- Participants ≥ 18 years of age with histologically confirmed DT confirmed by the Laboratory of Pathology, NCI, that progressed after receiving ≥ 1 line of standard

treatment and that was not amenable to surgical resection or definitive radiation therapy.

- Had measurable disease by CT scan defined as those that could be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam.
- Had ECOG performance status ≤ 2 .
- Had a life expectancy > 3 months with normal organ and marrow function.

The FDA's Assessment:

FDA agrees with the Applicant's Description but clarifies that patients must not have been amenable to *curative* surgical resection to be eligible to enroll and must have had *adequate* organ and marrow function (e.g., patients with anemia or mild renal dysfunction were eligible to enroll if hemoglobin ≥ 9 g/dL, or creatinine clearance ≥ 60 mL/min/1.73 m² if creatinine levels > 1.5 mg/dL, respectively). Patients who were previously treated with gamma secretase inhibitors or anti-Notch antibodies were not eligible to enroll. Patients with HIV who were being treated with combination antiretroviral therapy were ineligible.

Study Efficacy Endpoints

The Applicant's Description:

Primary:

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

Secondary:

- ORR and DCR by mutation type of *APC* and *CTNNB1* genes.

The FDA's Assessment:

FDA clarifies that Study 14-C-0007 did not have secondary endpoints, but did have exploratory objectives, which included correlation of response to nirogacestat with genotype.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The original SAP, dated 08 December 2021, was amended once; the final version is dated 01 April 2022. As of the data cut, there were no changes between the protocol-defined statistical analyses and those presented in the SAP.

This study was conducted as a single stage Phase 2 study to rule out an unacceptably low 10% clinical response rate (PR + CR; $p_0 = 0.10$) in favor of a modestly high response rate of 35% ($p_1 = 0.35$). A type I error rate (alpha, probability of accepting a poor treatment) of 0.10 with a response rate of 0.10 and a statistical power of 0.90 (beta = 0.10, probability of rejecting a good treatment) when the true response rate was 0.35 was assumed, which justified a sample size of 17 participants. With 16 evaluable participants and all other assumptions the same, the statistical power is still above 0.90.

The analysis of disease response was derived based on actual tumor measurements reported in the eCRF. This analysis may have differed from the clinical review of RECIST, which was performed by the NCI during the conduct of the study and used to make treatment decisions on-study.

ORR was presented along with frequency for best overall response (BOR) and for confirmed BOR. The BOR was derived using tumor measurements per RECIST v1.1. BOR is defined as the best response recorded from the start of the treatment until disease progression or recurrence, in the order of CR, PR, stable disease (SD), not evaluable, and PD. The BOR was considered confirmed if both the measurement and confirmation criteria were achieved. The overall ORR was calculated using the confirmed BOR, which was based on the derived analysis of tumor response.

ORR for mutation type *APC* and *CTNNB1* genes were determined in the same manner as the primary analysis.

Important analyses performed by [Kummar et al \(2017\)](#) such as change in target tumor size, DOR, and DoSD were conducted for the data cut dates used in this interim CSR, for the purpose of updating and confirming the results. At the time of the interim CSR data cut, tumor volume data were not centrally databased through NCI, so this analysis was not performed for this interim report.

The FDA's Assessment:

FDA did not independently verify the results presented in this Assessment Aid by the Applicant for early phase trials, such as Study 14-C-0007, because the evaluation of efficacy of nirogacestat for the treatment of patients with progressing DTs is based on the pivotal trial NIR-DT-301.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 12 times; the final protocol (Protocol Amendment 12) was dated 10 April 2020. Consistent with NCI standard practice, the protocol was amended

approximately annually. None of the amendments impacted the integrity of quality of the study and/or its outcomes.

The FDA's Assessment:

There are 15 versions of Study 14-C-0007, Amendments A through O. The original protocol was dated October 15, 2013. Most of the amendments were limited to administrative changes to the protocol. The following amendments were noteworthy:

- Amendment H (dated April 27, 2018) – NCI clarified that a treatment cycle is considered complete if a patient received $\geq 90\%$ of the planned dose of nirogacestat because “missing a small percentage of doses is unlikely to have a large effect on patients.”
- Amendment I (dated September 4, 2018) – NCI clarified that the correlative objectives for this trial are exploratory and changed them from secondary objectives to exploratory objectives.
- Amendment L (dated April 10, 2020) – added information regarding the risk of “primary ovarian insufficiency in women of childbearing potential based on an IND/CIOMS safety report from the randomized phase 3 trial of Nirogacestat”

8.1.9. Study Results

Compliance with Good Clinical Practices

Data

This study was conducted in accordance with the ethical principles of GCP and according to the ICH Harmonized Tripartite Guideline.

The Applicant's Position:

Study 14-C-0007 was GCP compliant.

The FDA's Assessment:

The CSR for Study 14-C-0007 stated that the clinical trial was “designed in accordance with Good Clinical Practice as required by the major regulatory authorities and in accordance with the ethical principles of the Declaration of Helsinki.”

Financial Disclosure

The Applicant's Position:

The 14-C-0007 study was a single center study sponsored by the NCI. Consistent with NCI requirements, no investigators were identified as having financial interests/arrangements with the sponsor.

The FDA's Assessment:

The data from Study 14-C-0007 is supportive of the pivotal data that supports this NDA, i.e., Study NIR-DT-301. As such, FDA did not require formal submission of the financial disclosure form for this supportive clinical trial.

Patient Disposition

Data

A summary of participant disposition is presented in Table 47.

Table 47: Participant Disposition (Safety Population)

Disposition Category	Total (N = 17) n (%) ^a
Treated	17 (100%)
Evaluable for Response	16 (94%)
Treatment Status	
On-going	5 (29%)
Discontinued	12 (71%)
Reason for Treatment Discontinuation ^b	
Refused further Treatment	10 (83%)
AE/Side Effects	1 (8%)
Death on Study	1 (8%)
Study Completion Status	
On-going	5 (29%)
Discontinued	12 (71%)
Reason for Study Discontinuation ^c	
Follow-up period Completed	7 (58%)
Refused further Treatment	3 (25%)
Refused further follow-up	1 (8%)

Death on Study	1 (8%)

Abbreviations: AE: adverse event.

^a Percentages were based on Safety Population unless otherwise specified. % = n/N.

^b Percentages were based on number of participants who discontinued from the treatment.

^c Percentages were based on number of participants who discontinued from the study.

The Applicant's Position:

As of the data cutoff, most participants discontinued treatment; the most common reason for treatment discontinuation was refusal of further treatment. Of note, no participants reported disease progression as a reason for treatment discontinuation.

The FDA's Assessment:

FDA agrees with the Applicant's position. Most patients refused further treatment with nirogacestat and disease progression was not a reason for treatment discontinuation. Based on the submitted dataset, it is unclear why the patients refused further treatment with nirogacestat. However, these patients were treated for a long duration, though as expected, not as long as the patients who are on ongoing treatment (see table below). The patient who discontinued treatment due to an adverse event was treated with nirogacestat for 0.2 years, and the patient who died was treated with nirogacestat for 5.1 years.

Table 48: Average Duration on Treatment with Nirogacestat

	Median (interquartile range), years	Mean (standard deviation), years
Patients who refused further treatment with nirogacestat, n=10	1.3 (0.7, 4.4)	2.4 (2.1)
Patients who had ongoing treatment with nirogacestat, n=5	6.6 (6.6, 6.8)	6.7 (0.1)

Source: ADSL (SDN 4; November 10, 2022)

Protocol Violations/Deviations

Data

Per the protocol, a deviation was defined as any change, divergence, or departure from the IRB approved study procedures in a research protocol.

There were two cases of incorrect dosing of nirogacestat by the participants. One participant was approved for a 1-week delay to the start of cycle due to the participant's work schedule. The participant reported using "leftover pills" to dose with nirogacestat on three days during the scheduled delay period. Another participant notified the research nurse that for the last 4 days of Cycle 5, the participant was out of town and did not take enough nirogacestat for the

duration of the trip. The participant took 100 mg nirogacestat BID instead of the prescribed 150 mg BID.

The Applicant's Position:

The deviations were reviewed and GCP compliance was maintained. None of the observed protocol deviations impacted the primary objective of the study and did not affect the overall safety and efficacy outcomes of the study.

The FDA's Assessment:

FDA agrees with the Applicant's position that the protocol deviations do not affect the trial's ability to achieve its objective of determining the ORR in patients with DT. Based on the list of protocol deviations provided by the Applicant for Study 14-C-0007, only one patient had a delay in tumor imaging (one month delay not due to adverse events).

FDA agrees with the Applicant's description of the two dosing errors. In addition, there were 6 dosing delays, where 4 delays were due to adverse events, and 2 delays were not due to adverse events. The 4 adverse events that led to dose delays were motor vehicle accident, squamous cell carcinoma, swelling of clitoris, and bronchitis (n=1 per event). For the 2 dosing delays not related to adverse events, one patient did not receive nirogacestat as planned, and the other patient wanted to discuss with the Principal Investigator whether to continue treatment with nirogacestat. One patient was not adherent or inconsistent self-reporting of nirogacestat administration and returning leftover nirogacestat supply. These are minor protocol deviations and are unlikely to affect the trial's ability to determine the efficacy, safety, and tolerability of nirogacestat in patients with DT.

Table of Demographic Characteristics

Data:

Of the 17 participants, 3 (18%) were male and 14 (82%) were female. The median age at entry was 34 years (range: 19 to 69 years). The majority (15 [88%]) of participants reported race as white. A total of 9 participants [53%]) had a CTNNB1 T41A tumor mutation, 3 participants (18%) had a CTNNB1 S45F tumor mutation, 2 participants (12%) had an APC germline tumor mutation, and 1 participant had an APC somatic tumor mutation. There were no cases of more than one mutation type reported per participant. Two participants (12%) reported no mutation types. Twelve (71%) participants had a single tumor, and 5 participants (29%) had multi-focal disease. Focality was determined programmatically based on the target tumor and imaging modality used for the evaluation for RECIST. The median time from diagnosis to start of nirogacestat was 89.2 months (range: 14.5 months to 223.3 months).

The Applicant's Position:

Demographic characteristics were consistent with the general population with DT.

The FDA's Assessment:

The distribution of female to male was modestly higher than the distribution in the general population of patients with DT. The distribution of ages in this trial is reflective of the age distribution of patients with DT. This trial, like Study NIR-DT-301 and Study A8641014, enrolled mostly White patients (the remaining two patients were Black), and the proportion of non-White did not reflect the diversity of the U.S. population. The proportion of patients with CTNBB1 mutation (71%) is consistent with what is found in the general population with DT. Most patients had extra-abdominal disease (82%).

All the patients had previous therapy: systemic therapy (100%), surgery (76%), and radiotherapy (35%). Most patients received chemotherapy (82%), and the remainder of the patients received "drug and/or immunotherapy." Stable disease was the most common best response to previous therapy (76%), and one patient (6%) had a partial response to previous therapy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

All 17 participants received at least one dose of nirogacestat. As of this data cut, the median duration of nirogacestat was 49.7 months (range: 2-82). The majority (10 [59%]) of participants were on nirogacestat for at least 3 years or longer, 2 participants (12%) were on nirogacestat for at least 1 year but less than 2 years and 5 participants (29%) were on nirogacestat for less than one year. The data are mutually exclusive and represent the longest time on study. The median number of cycles completed was 13 (range: 0 – 102). A cycle was considered completed if 90% of the planned dose was administered. The planned dose intensity was 300 mg/day. The median dose was 243 mg, less than the prescribed dose, which was not unexpected in a study of this duration given the number of dose modifications.

Fifteen participants had a total of 48 AEs leading to dose modifications. Four participants had 4 AEs that led to dose reductions (PTs included diarrhea, fatigue, memory impairment, and weight decreased). All 4 participants had a confirmed BOR of SD and 3 of the 4 had sustained response with a lower dose of nirogacestat. Participant (b) (6) experienced a > 20% increase in tumor size from nadir and is shown as a PD in the derived response that occurred after the dose was reduced.

Fifteen participants had 37 AEs that led to drug interruptions, 1 participant had 1 AE that led to drug withdrawal (hypersensitivity), and 5 participants had 6 AEs that led to drug interruption

followed by dose reduction. The 5 participants with dose interruptions that led to dose reductions were also counted in the drug interruptions total but were not counted in the total for dose reductions. A total of 9 participants out of 17 (53%) had eventual dose reductions.

All participants received concomitant treatments during the study. The most commonly (> 50%) reported ATC Class 3 of concomitant medications included: antipropulsives, antiemetics and antinauseants, antiinflammatory and antirheumatic products (non-steroids), other mineral supplements and opioids.

The Applicant's Position:

Nirogacestat was well tolerated with a median (range) duration of treatment of 49.7 months (2, 82). The most commonly reported concomitant medications were antipropulsives, antiemetics and antinauseants, antiinflammatory and antirheumatic products (non-steroids), other mineral supplements and opioids to manage diarrhea, nausea, and pain.

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment adherence. The relative dose intensity was high (median 96%, range 0.8-263%; mean 86%, standard deviation 21%).

The AEs that led to dose interruption followed by dose reduction in the 5 patients were breast tenderness, QT prolongation, hypocalcemia, myalgia, and rash maculopapular (one patient each experienced these AEs except for rash, which was experienced by 2 patients). Only three AEs that led to a dose modification were experienced by more than 1 patient: rash maculopapular (n=3), hypophosphatemia (n=2), and nausea (n=2).

The most common indications for use of concomitant medications were pain (n=16, 94%), diarrhea (n=14, 82%), nausea and prophylaxis of nausea (n=13, 76%), hypophosphatemia (n=12, 71%), infection (n=10, 59%), rash (n=10, 59%), and supplement (n=9, 53%).

The most common indications for the use of concomitant medications in Study 14-C-0007 were similar to those of Study NIR-DT-301 and Study A8641014, and consistent with the effects of the tumor (i.e., pain) or with the adverse reactions associated with nirogacestat, such as diarrhea, nausea, hypophosphatemia, rash, and infection.

All the patients underwent concomitant procedures. Procedures that were performed on more than one patient that were not imaging or electrocardiograms were biopsy (n=6), incision and drainage (n=4), culture (n=2), and curative surgery (n=2; for non-DT reasons). Three patients underwent procedures due to DT (n=1 each for incision and drainage, surgery, and hysterectomy). Because Study 14-C-0007 was not a randomized trial and had a small sample size, the data from the concomitant procedure dataset did not contribute to our assessment to the safety and efficacy of nirogacestat.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Among the 17 participants included in the study, there were 16 participants evaluable for response. One participant was not included in the efficacy analysis because the participant did not have any tumor measurements taken after starting nirogacestat. The ORR (95% CI) was 31% (11%-58.7%). Five participants achieved a confirmed BOR of PR and 10 participants achieved a confirmed BOR of SD by RECIST v1.1. One participant had tumor imaging performed post-dose and met the target lesion measurement criteria to be an SD; however, because tumor imaging was assessed only 3 weeks after starting study drug, this participant was considered not evaluable for BOR because a minimum of 4 weeks was required between scans to confirm a response.

The Applicant's Position:

Nirogacestat was effective at sustained disease stabilization, as shown by the ORR of 31%, SD of 63%, and PD of 0%.

The FDA's Assessment:

FDA did not independently verify the results presented in this Assessment Aid by the Applicant for early phase trials, such as Study 14-C-0004, because the evaluation of efficacy of nirogacestat for the treatment of patients with progressing DTs is based on the pivotal trial NIR-DT-301.

Data Quality and Integrity

Data:

All data were collected in a timely manner and reviewed by the investigator or a lead associate investigator. Any safety concerns, new information that affected either the ethical and or scientific conduct of the study, or protocol deviations and violations were immediately reported to the IRB using iRIS and to the sponsor.

The investigator reviewed AE and response data on each participant to ensure safety and data accuracy. The investigator conducted or supervised the investigation and provided appropriate delegation of responsibilities to other members of the research staff.

This study was monitored by personnel on contract to the NCI, NIH. Monitors were qualified by training and experience to monitor the progress of this clinical study. Personnel monitoring this study were not affiliated in any way with the study conduct.

At least 25% of enrolled participants were randomly selected and monitored at least biannually or as needed, based on accrual rate. The participants selected had 100% source document

verification done. Additional monitoring activities included: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of AEs to the NCI IRB and FDA, and informed consent requirements. Written reports were generated in response to the monitoring activities and submitted to the investigator and Clinical Director or Deputy Clinical Director, Center for Cancer Research, NCI.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, or change the conclusions drawn.

The FDA's Assessment:

FDA agrees that Applicant has provided all the datasets and supporting metadata documentation required to validate the results.

Efficacy Results – Secondary and other relevant endpoints

Data:

ORR by Mutation Type

Of the 9 participants (53%) who had a CTNNB1 T41A tumor mutation, 3 had a BOR of PR and 5 had a BOR of SD; one additional participant was not evaluable for disease response. The ORR (95% CI) for the CTNNB1 T41A somatic mutation was 33% (7.5%-70.1%). The DCR (95% CI) was 89% (51.8%-99.7%).

Three participants had the CTNNB1 S45F tumor mutation, and all 3 had a BOR of SD. The ORR (95% CI) for the CTNNB1 S45F somatic mutation was 0% (0.0%-70.8%). The DCR (95% CI) was 100% (29.2%-100.0%).

Two participants had the APC A972G germline tumor mutation, and one participant had a BOR of PR. One participant was not evaluable as the participant did not have any tumor measurements taken. With only one evaluable participant, ORR and DCR were 100% (2.5%-100.0%).

The one participant that had the APC somatic tumor mutation had a BOR of SD. With only one evaluable participant, the ORR was 0% and the DCR was 100% (2.5%-100.0%).

Two participants did not have any mutation type and one participant had a BOR of PR and one had a BOR of SD. The ORR was 50% (1.3%-98.7%) and the DCR was 100% (15.8%-100.0%).

DOR

Among the 5 participants with a confirmed BOR of CR or PR, the median duration of response was not reached due to censoring (range: 41.1 – Not evaluable). One participant died before

progression and was censored at the time of death. Four participants were censored due to no documented disease progression (2 participants) and off study due to reasons other than disease progression (2 participants).

Duration of Disease Control

The DCR based on confirmed BOR (95% CI) was 94% (69.8%-99.8%).

Among the 15 participants with a confirmed BOR of CR, PR, or SD, the median duration of response was not reached due to censoring. One participant died before disease progression and one participant, with a BOR of SD, experienced a > 20% increase in tumor size from nadir. Four participants were censored due to no documented progression or death and 9 participants went off study due to reasons other than disease progression.

The Applicant's Position:

Clinical benefit was observed regardless of mutational status of CTNNB1 or APC genes ([Kummar et al. 2017](#)). The DOR, DoSD, and DCR suggest that treatment with nirogacestat at 150 mg BID results in long-term disease stabilization and support the continued evaluation of nirogacestat for the treatment of DT.

The FDA's Assessment:

FDA did not independently verify the results presented in this Assessment Aid by the Applicant for early phase trials, such as Study 14-C-0007, because the evaluation of efficacy of nirogacestat for the treatment of patients with progressing DTs is based on the pivotal trial NIR-DT-301. In addition, the sample size per type of mutation is too small in Study 14-C-0007 for FDA to draw any conclusions on effect of mutation on the efficacy of nirogacestat in patients with DT.

Dose/Dose Response

The Applicant's Position:

All participants were dosed at 150 mg BID; therefore, this is not applicable for this submission.

The FDA's Assessment:

Nine patients underwent dose reduction, among whom 8 were evaluable for efficacy. Among the 8 evaluable-patients, one patient had a partial response, and the remaining patients had stable disease (n=6) or were not evaluable (n=1). All 9 patients who did not undergo dose reduction were evaluable for efficacy, among whom 4 patients had a partial response, and 4 patients had stable disease. The ORRs among patients who had dose reductions versus who did not were 12.5% (95% CI: 0.003, 0.527), and 50% (95% CI: 0.16, 0.84), respectively. The difference in ORR between these two subgroups suggests that there might be a dose-response

relationship for nirogacestat in patients with DT. However, the small sample size, and post-hoc nature of this subgroup analysis precludes the ability of the FDA to determine if there is a dose-response relationship based on Study 14-C-0007, since there could be confounders in this analysis.

Durability of Response

Data:

Median DOR for participants with ORs was not reached.

The Applicant's Position:

Response was durable among participants with ORs.

The FDA's Assessment:

FDA agrees with the Applicant's position; however, FDA did not independently verify the results presented by the Applicant for Study 14-C-0007 because the evaluation of efficacy of nirogacestat is based on the pivotal trial NIR-DT-301.

Persistence of Effect

Data:

Refer to efficacy results – secondary and other relevant endpoints above.

The Applicant's Position:

The study has demonstrated persistence of effect over time.

The FDA's Assessment:

FDA did not independently verify the results presented by the Applicant for Study 14-C-0007 because the evaluation of efficacy of nirogacestat is based on the pivotal trial NIR-DT-301.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

All participants were evaluable for PROs by using the MD Anderson Symptom Inventory. Results from this analysis were not centrally databased for inclusion in the CSR; however, they were published in [Kummar et al. \(2017\)](#). As described in this publication, partial responders had a 1.65-point improvement in mean symptom severity ($p = 0.008$). The five participants with stable disease as their best response had a 0.8-point improvement in mean symptom severity ($p = 0.08$). Of the 7 participants whose treatment was discontinued or who withdrew from the study, mean change in symptom severity was negligible.

The Applicant's Position:

Significant improvements in PROs were observed among participants receiving nirogacestat.

The FDA's Assessment:

FDA limited its analysis of PROs to the results submitted from trial NIR-DT-301, as the design and sample size of Study 14-C-0007 precludes FDA's ability to meaningfully interpret these PRO results. See Section 8.1.1.2.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.1.10. Integrated Review of Effectiveness

The FDA's Assessment:

See Section 8.1.11.

8.1.11. Assessment of Efficacy Across Trials

Primary Endpoints

Data

Integrated efficacy analyses are based on the Full Analysis Set (FAS). The FAS population consisted of all participants in the DB phase of Study NIR-DT-301 who were randomized to study treatment (nirogacestat or placebo) per the primary analysis data cut (07 April 2022), all participants enrolled in Study 14-C-0007 per a 20 November 2020 data cut, and the 2 participants from Study A8641014 with DT who received nirogacestat at the 150 mg BID dose level per a 09 January 2013 cutoff. The FAS population included 89 participants assigned to nirogacestat (1 participant did not receive nirogacestat) and 72 participants assigned to placebo.

In the Full Analysis Set (FAS) population, there was a statistically significant improvement in PFS in the nirogacestat arm versus the placebo arm, with a 78% reduction in the risk of disease progression or death (HR = 0.22; 95% CI: 0.11, 0.42; $p < 0.001$); this was consistent with the ITT population in Study NIR DT-301 ([Section 8.1.1](#)). Of the 13 (15%) participants in the nirogacestat

arm and 36 (50%) participants in the placebo arm who progressed, most were due to radiographic progression (11 [12%] participants and 30 [42%] participants, respectively). One participant in each arm died before PD.

The probability of being event-free at Months 12 and 24 was higher in the nirogacestat arm (88.0% and 82.2% respectively) than the placebo arm (52.8% and 44.0%, respectively) supporting a sustained clinical benefit over time.

The Applicant's Position:

Treatment with nirogacestat across studies resulted in a clinically meaningful and statistically significant improvement in PFS compared with placebo.

The FDA's Assessment:

Among the three trials used to support this NDA, only Study 14-C-0007 and Study NIR-DT-301 evaluated efficacy as a primary endpoint. The primary objective of the remaining trial, Study A8641014, was to determine the MTD and RP2D of nirogacestat for further development. Because Study NIR-DT-301 was the only randomized trial investigating nirogacestat, only the data from this trial can be used to evaluate PFS since time-to-event endpoints such as PFS cannot be evaluated in single-arm trials. FDA does not agree with pooling data across these three trials as they all had different research objectives and patients in the trials may have different characteristics. In addition, pooling data from non-randomized trials with data from randomized trials is not an appropriate approach as it breaks randomization such that patients' characteristics will be imbalanced between arms. This pooling approach will make results difficult to interpret as the treatment effect estimates will be unreliable. Thus, FDA does not agree with the Applicant's pooled analysis for PFS.

Study 14-C-0007 was a single-arm trial in 16-evaluable patients with DT, with a reported ORR of 31% (95% CI: 11, 59) and the median DoR was not reached (range: 41 months - NE).

Study NIR-DT-301 was a randomized trial in patients with DTs progressing based on RECIST 1.1, and it demonstrated a statistically and clinically significant improvement in the primary endpoint of PFS in patients treated with nirogacestat compared to placebo. The median PFS was not reached (95% CI: NE, NE) for patients on nirogacestat, and 15.1 months (95% CI: 8.4, NE) for patients on placebo, with a hazard ratio of 0.29 (95% CI: 0.15, 0.55; p-value <0.001). This PFS included both clinical and radiographic progression as assessed by blinded independent review, and FDA agrees with the adjudication for clinical progression.

Secondary and Other Endpoints

Data:

ORR

In the FAS population, the ORR was statistically significantly higher ($p < 0.001$) in the nirogacestat arm (35 [40%] participants) versus the placebo arm (6 [8%] participants), including 5 (6%) participants with CR in the nirogacestat arm versus no (0%) participants in the placebo arm. Results in the FAS population were similar to the ITT population of Study NIR-DT-301.

DOR

Similar to the Study NIR-DT-301 ITT population, the Kaplan-Meier estimates of median DOR were not reached for either treatment arm ([Messersmith et al. 2015](#); [Kummar et al. 2017](#)).

DCR

In the FAS population, the DCR was similar between the nirogacestat and placebo arms (93% and 85%; $p = 0.088$), respectively, which may have been due to the higher rate of SD in the placebo arm. The DCR was similar between the Study NIR-DT-301 ITT population and the FAS population.

DoSD

Similar to the NIR-DT-301 ITT population, the Kaplan-Meier estimates of DoSD were not reached for either treatment arm due to the low number of progressions or deaths in the FAS population.

The Applicant's Position:

Treatment with nirogacestat across studies resulted in a clinically meaningful and statistically significant improvement in ORR compared with placebo. While data are limited, responses appear durable. Other efficacy analyses including change in tumor volume as assessed by volumetric MRI and change in T2 hypersensitivity and change in PRO measures demonstrate improvements with nirogacestat, further supporting the primary efficacy analysis.

The FDA's Assessment:

FDA does not agree with Applicant's pooled analysis for endpoints including ORR, DOR, DCR, and DoSD. See FDA's comments above for Assessment of Efficacy Across Trials for the primary endpoint of PFS for more details regarding issues with pooling data across the three trials.

Subpopulations

Data

PFS

A statistically significant improvement in the primary endpoint of PFS in the nirogacestat arm compared with the placebo arm (FAS population) was observed across most demographic; disease characteristic; prior treatment; and genetic mutation, dose intensity, and AE subgroups. While the upper boundary of the CIs for a few subgroups were > 1 , in all instances this was due to a small sample size.

ORR

The statistically significant improvement in ORR for nirogacestat over placebo with the FAS population was maintained across most demographic, disease characteristics, prior treatments, and genetic mutation, dose intensity, and AE subgroups.

DCR

In the FAS population, the DCR was similar between the nirogacestat and placebo arms across most subgroups. Statistically significant improvements in DCR in the nirogacestat arm versus the placebo arm were observed in participants with baseline tumor size ≥ 89.575 to < 140.35 mm ($p = 0.033$), no history of FAP ($p = 0.019$), and participants who did not receive prior radiation therapy ($p = 0.049$).

DoSD

Similar to the overall population, no conclusions regarding DoSD evaluated by subgroup can be drawn due to the low number responses and subsequent events observed.

Exposure

Exposure was evaluated by subgroup; no notable differences between treatment arms were observed.

The Applicant's Position:

Results of subgroup analyses were consistent across studies, with statistically significant improvements in PFS and ORR observed across most subgroups as compared to placebo.

The FDA's Assessment:

FDA does not agree with Applicant's presentation of subgroup analyses based on the pooled data. See FDA's comments above for Assessment of Efficacy Across Trials for the primary endpoint of PFS for more details regarding issues with pooling data across the three trials.

Additional Efficacy Considerations

The FDA's Assessment:

OS was not evaluated in the three trials submitted to support this NDA. FDA did not object to this plan because DT is rarely fatal and the existing safety data for nirogacestat indicated that it is not expected to lead to safety-related deaths.

8.1.12. Integrated Assessment of Effectiveness

Data:

Overall, analyses performed on the FAS population for the integrated summary of efficacy yielded similar results to analyses of the ITT population performed for the pivotal NIR-DT-301 Study.

- In the FAS population, participant disposition, demographics, and baseline characteristics in the nirogacestat arm were similar to those in the placebo group. The nirogacestat arm had a lower proportion of participants with events meeting the study endpoint than the placebo arm (14% vs 49%, respectively) and a higher proportion of participants in the nirogacestat arm than in the placebo arm were ongoing at the time of the data cut (48% vs 32%, respectively).
- In the FAS population, there was a statistically significant improvement in PFS in the nirogacestat arm versus the placebo arm, with a 78% reduction in the risk of disease progression or death (HR = 0.22; 95% CI: 0.12, 0.43; $p < 0.001$); this was consistent with the ITT population from Study NIR-DT-301. The ORR was significantly higher ($p < 0.001$) in the nirogacestat arm (34 [40%] participants) versus the placebo arm (6 [8%] participants), including 5 (6%) participants with CR in the nirogacestat arm versus no (0%) participants in the placebo arm.

The Applicant's Position:

In summary, treatment with nirogacestat resulted in statistically significant improvements in PFS, ORR, and patient-reported symptoms and impacts, demonstrating a clear and consistent benefit in participants receiving nirogacestat as compared to placebo. The durability of the PFS advantage over a time scale of up to 7 years, combined with substantial reduction in disease progression, increase in response rate, and significant improvements in pain, DT symptom burden, physical functioning, role functioning, and HRQoL, support a clinically meaningful benefit conferred by nirogacestat. Ultimately, these data support the efficacy of nirogacestat in the treatment of DT.

The FDA's Assessment:

FDA does not agree with the analyses performed using pooled data as described by the Applicant in the integrated summary of efficacy. See FDA's comments above for Assessment of Efficacy Across Trials for the primary endpoint of PFS for more details regarding issues with pooling data across the three trials. However, FDA agrees that in the pivotal Study NIR-DT-301, nirogacestat led to an improvement in PFS, and ORR that was durable and consistent across subgroups, and pain improvement in those who experienced ≥ 2 BPI at baseline in patients with DT.

8.2. Review of Safety

Data:

Refer to [Section 8.2.4](#) for summaries of deaths, AEs, SAEs, AEs leading to discontinuations, and other safety data.

The Applicant's Position:

Nirogacestat had a manageable and acceptable safety profile in participants with DT.

The FDA's Assessment:

In general, FDA agrees with the above statement; however, refer to Section 1 above and the safety review below regarding additional considerations. For example, the FDA review team recommended revising the indication statement to specify patients have progressing DT who need systemic treatment as select patients may be appropriate for a watch-and-wait approach or surgery. Given that nirogacestat can cause severe toxicities including diarrhea and given the potential for ovarian toxicity and hepatotoxicity, patients will need close monitoring as described in labeling and patients should be adequately consented (standard practice in oncology) for the safe and effective use of nirogacestat.

8.2.1. Safety Review Approach

The Applicant's Position:

The data pooling strategy for this SCS was agreed upon by the FDA at the Pre-NDA meeting. The studies are grouped into the following study pools depending on the study design, participants, dosing regimen, and targeted underlying conditions:

- All DT Pool (All DT Pool) to inform labeling (Studies NIR-DT-301, 14-C-0007, and A8641014 [participants with DT only])
- All Cancer Participants Treated with Monotherapy (All CM Pool) (All DT Pool, all participants in A8641014, and Study A8641020)

- HVs Treated with Single Dose (HV Pool) (Studies A8641001, A8641008, NIR-DT-101, NIR-DT-102 and NIR-DT-103)

The studies in the All DT Pool and All CM Pool were pooled to characterize the overall safety of nirogacestat monotherapy in participants with DT and solid tumors including DT, respectively. Five single dose HV studies (HV Pool), were summarized by active drug and by placebo or other comparator. In addition, given that the OLE phase of Study NIR-DT-301 is still ongoing and the data are considered interim, descriptive statistics from this phase of the study were provided; however, this phase of the study was not pooled with other study data and is presented separately in select outputs (OLE Group).

Data from 8 participants with T-ALL/LBL in the A8641014 study and 3 completed studies (A8641002, A8641016, and A8641019) with nirogacestat were excluded from the data pooling for this summary of safety. As agreed upon at the Pre-NDA meeting, participants with T-ALL/LBL were excluded from the integrated safety analyses as these hematologic malignancies were anticipated to be sufficiently different from DT to preclude any comparisons regarding safety data. In addition, given that Study A8641002 was the only study evaluating multi-dose administration of nirogacestat in a HV participant population, these data were summarized separately from the single dose HV studies.

Note that there is overlap of the populations of the nirogacestat pools analyzed. The focus of this Assessment Aid will be on the All DT Pool, with comparisons to the NIR-DT-301 data since this is the only study that includes a placebo comparator arm.

The All DT Pool included 141 participants from the DB phase of Study NIR-DT-301 (69 participants exposed to nirogacestat and 72 participants exposed to placebo), 17 participants from Study 14-C-0007, and 9 participants from Study A8641014.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the safety population included in the primary safety analyses. FDA clarifies that the FDA primary safety analysis was performed on patients who were enrolled to NIR-DT-301 and received at least one dose of study treatment (N= 141) including 69 patients who received nirogacestat and 72 patients who received placebo in the double-blind portion of the trial. Verbatim descriptions of AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 for AEs. The severity of AEs and laboratory abnormalities were graded according to CTCAE v5.0. The safety monitoring period was from the time informed consent was signed until 30 days after the last treatment dose. The data cutoff for the primary safety analysis was April 7, 2022. A safety update was provided on March 27, 2023, which consisted of data from the final database lock (June 30, 2022) for NIR-DT-301 double-blind portion and data for the ongoing NIR-DT-301 open-label extension (OLE) portion (October 24, 2022, interim data cut) and ongoing Study 14-C-0007

(December 1, 2022, interim safety data cut). The data was reviewed for congruence with the primary safety analysis.

Although the primary safety analysis focused on the results of Study NIR-DT-301, and these results are described in product labeling with agreed upon group terms, the review of safety in certain sections below (for example, deaths and SAEs) also included an assessment of the broader safety pools.

The FDA safety review focused on the incidence of TEAEs regardless of causality assessment. The safety analysis including fatal and non-fatal SAEs, AEs leading to permanent treatment discontinuation, treatment interruption and treatment delay.

FDA analysis utilized clinically relevant grouped terms independent of the analyses provided by the Applicant. Therefore, there may be some discrepancies between the results for the safety table presented in this section.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Key aspects of exposure and compliance for participants receiving nirogacestat 150 mg BID are shown in the table below. The mean duration of exposure for the nirogacestat 150 mg BID group was similar in Study NIR-DT-301 and the All CM Pool, and longer in the All DT Pool. While the median duration of exposure for the 150 mg dose group was similar for Study NIR-DT-301 and the All DT Pool, it was shorter in the All CM Pool. The relative dose intensity for nirogacestat 150 mg BID was similar across Study NIR-DT-301, the All DT, and All CM Pools for both the mean and median values.

Table 49: Summary of Exposure and Compliance for Participants who Received Nirogacestat 150 mg BID (Safety Population)

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All CM 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	69	88	128	28	4
Mean duration of exposure (months)	13.31	17.40	23.269	16.707	13.126	26.045
Median duration of exposure (months)	11.40	20.57	21.109	10.136	13.552	29.355

Mean relative dose intensity (%)	98.847	87.397	85.480	85.436	91.395	76.500
Median relative dose intensity (%)	100.000	96.104	91.535	91.301	100.000	73.388

Abbreviations: BID: twice daily; CM: cancer monotherapy; DT: desmoid tumor; N: participants; mg: milligram; OLE: open-label extension.

The Applicant's Position:

The overall exposure to nirogacestat is adequate to support characterization of the safety profile.

The FDA's Assessment:

A total of 69 patients received at least one dose of nirogacestat in NIR-DT-301. The median exposure of approximately 21 months in Study NIR-DT-301 in patients randomized to nirogacestat provided for a reasonable assessment of the common toxicities related to the chronic use of this drug, particularly considering the rarity of the intended population. The duration of exposure may not be adequate to fully characterize long term ovarian toxicity (refer to review below and consult from Division of Urology, Obstetrics, and Gynecology [DUOG]).

Relevant Characteristics of the Safety Population:

Data:

The demographics and other characteristics of the groups receiving nirogacestat 150 mg BID in the All DT, All CM Pool, and OLE Pools are shown in [Table 50](#). In general, the participants in Study NIR-DT-301 and the All DT Pool were representative of the DT population, with a female predominance of 2-3 fold ([Reitamo et al. 1982](#); [de Camargo et al. 2010](#); [Skubitz 2017](#); [Anneberg et al. 2022](#)).

Overall, the demographic characteristics in the All DT Pool were similar between treatment groups, considering the small number of participants in the nirogacestat treatment groups other than 150 mg BID. The dose groups other than 150 mg BID included no participants ≥ 46 years of age, or from parts of the world other than North America.

Table 50: Demographics for Participants Randomized to Nirogacestat 150 mg BID (ITT Population)

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All Cancer CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	70	88	128	28	4
Sex						
Male	25 (35%)	25 (36%)	29 (33%)	37 (29%)	7 (25%)	2 (50%)

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All Cancer CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	70	88	128	28	4
Female	47 (65%)	45 (64%)	59 (67%)	91 (71%)	21 (75%)	2 (50%)
Age (at time of informed consent)						
Mean (SD)	37.0 (12.89)	37.5 (14.43)	37.5 (14.31)	44.0 (17.09)	35.8 (12.81)	27.0 (9.06)
Median	34.5	33.5	33.0	42.0	33.5	24.5
Min, max	18, 76	18, 73	18, 73	18,84	18, 76	20, 39
< 27 Years	14 (19%)	20 (29%)	23 (26%)	24 (19%)	7 (25%)	2 (50%)
27 to < 34 Years	18 (25%)	15 (21%)	22 (25%)	23 (18%)	7 (25%)	1 (25%)
34 to < 46 Years	25 (35%)	13 (19%)	17 (19%)	24 (19%)	8 (29%)	1 (25%)
≥ 46 Years	15 (21%)	22 (31%)	26 (30%)	57 (45%)	6 (21%)	0
≥ 65 Years	3 (4%)	3 (4%)	4 (5%)	19 (15%)	1 (4%)	0
≥ 70 Years	2 (3%)	2(3%)	2 (2%)	9 (7%)	1 (4%)	0
≥ 75 Years	2 (3%)	0	0	4 (3%)	1 (4%)	0
Race, n (%)						
Asian	3 (4%)	1 (1%)	1 (1%)	2 (2%)	2 (7%)	0
Black or African American	5 (7%)	4 (6%)	6 (7%)	6 (5%)	1 (4%)	0
White or Caucasian	54 (75%)	64 (91%)	80 (91%)	118 (92%)	21 (75%)	4 (100%)
Other	10 (14%)	1 (1%)	1 (1%)	2 (2%)	4 (14%)	0
Ethnicity						
Hispanic or Latino	9 (13%)	1 (1%)	1 (1%)	2 (2%)	7 (25%)	0
Non- Hispanic or Latino	55 (76%)	67 (96%)	68 (77%)	88 (69%)	20 (71%)	4 (100%)
Unknown	3 (4%)	0	0	0	0	0
Not reported	5 (7%)	2 (3%)	19 (22%)	38 (30%)	1 (4%)	0

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All Cancer CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	70	88	128	28	4
Geographic region						
North America	53 (74%)	44 (63%)	63 (72%)	90 (70%)	22 (79%)	3 (75%)
Rest of world	19 (26%)	26 (37%)	25 (28%)	38 (30%)	6 (21%)	1 (25%)
Baseline BMI (kg/m ²) ^{a b}						
Median	25.693	23.846	23.916	24.464	25.234	22.472
Min, max	17.53, 44.83	17.72, 52.34	17.72 52.34	17.22, 52.34	17.53, 46.23	20.80, 23.29
Baseline ECOG						
0	52 (72%)	51 (73%)	51 (58%)	68 (53%)	20 (71%)	2 (50%)
1	20 (28%)	18 (26%)	19 (22%)	41 (32%)	8 (29%)	2 (50%)
2	0	1 (1%)	1 (1%)	2 (2%)	0	0

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

^b Baseline Body Mass Index (BMI) was calculated as: Baseline weight in kg/(Baseline Height in m)².

The Applicant's Position:

In general, the participants in Study NIR-DT-301 and the All DT Pool were representative of the DT population, with a female predominance of 2 to 3-fold. Participants in the nirogacestat 150 mg BID group of All CM Pool were older than the participants in NIR-DT-301 and the All DT Pool, which was expected given the different indications under study and the fact that DT typically occurs in a younger population as compared to the other solid tumors evaluated.

The FDA's Assessment:

FDA agrees with the Applicant's assessment regarding the primary safety analysis. FDA clarifies that the FDA primary safety analysis was performed on patients who were enrolled to NIR-DT-301 and received at least one dose of study treatment (N= 141) including 69 receiving nirogacestat and 72 receiving placebo in the double-blind portion of the trial.

With respect to applicability of the Study NIR-DT-301 population to the US population, the median age (33.5 years in nirogacestat-treated patients), increased prevalence in women, appears consistent with DT in the US. There were insufficient numbers of patients to assess treatment effects among non-White patients and among older patients with DT.

Adequacy of the Safety Database:

Data

Key aspects of exposure and compliance for participants receiving nirogacestat 150 mg BID are shown in [Table 49](#).

The Applicant's Position:

The evaluation of safety is based on data from Study NIR-DT-301 and the nirogacestat 150 mg BID dose level in the All DT Pool. These populations allow for an informed assessment of the safety profile of nirogacestat 150 mg BID and the overall risk-benefit in patients with DT.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of exposure and compliance for patients receiving nirogacestat 150 mg BID. FDA clarifies that the FDA primary safety analysis was performed on patients who were enrolled to NIR-DT-301 which provides an informed assessment of the safety profile of nirogacestat 150 mg BID in patients with DT. The size and exposure of the overall safety data set is reasonable in this rare patient population to provide an estimate of common adverse reactions over time.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and AE databases were consistent.

The FDA's Assessment:

During review of the Application, the OSI audit noted that the Applicant provided corrected and updated datasets that affected up to 16 tables and six figures for laboratory summary and shift tables, and one table for concomitant medications. These updated tables and figures were received on May 5, 2023. In addition, incomplete information to assess the PRO data which led to Information Requests for compliance and completion rates, and updated datasets were received from the Applicant on April 21, 2023, May 5, 2023, May 30, 2023, and on June 7, 2023. Refer to Section 4 of this review (Office of Scientific Investigation) for further details.

Categorization of Adverse Event

The Applicant's Position:

Safety analyses included drug exposure and compliance, AEs, clinical laboratory and electrocardiogram (ECG) parameters, ECOG Performance Status, and vital signs.

All AEs were coded using the MedDRA coding system (MedDRA Version 24) and displayed in tables and data listings using SOC and PT. Analyses of AEs were performed for those events that were considered treatment-emergent adverse events (TEAEs), where treatment-emergent is defined per protocol as any AE with initial onset or increasing in severity after the first dose of study treatment through 30 days after the last dose of study treatment. To facilitate a better understanding of specific topics of interest that may have comprised multiple PTs, select TEAEs were evaluated by pre-defined categories.

The FDA's Assessment:

In general, FDA agrees with the Applicant's categorization of adverse events. The Applicant provided appropriate definitions and reporting requirements for AEs and serious AEs (SAEs). AE evaluation was performed at the time of informed consent up to 30 days after the last dose of study treatment. In the ADAE dataset, there were 2912 individual listed AEs of which 128 were not treatment emergent (88 from the primary treatment phase and 40 from the open-label extension phase). Of the 88 AEs in the primary treatment phase, all but 29 occurred prior to the start date. Of these 29, 9 events [7 nirogacestat and 2 placebo] did not have a start date and the rest occurred 37 or more days after the start date. None of the 9 events without a start date were serious and no AE term among these 9 occurred more than once. Overall the TEAE definition used by the sponsor appeared acceptable.

During the course of Study NIR-DT-301, Patients reporting AEs/AESIs/SAEs associated with ovarian dysfunction (amenorrhea, ovarian failure, or premature menopause) had hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment) since Amendment 3 dated January 27, 2020. FDA analyses were conducted irrespective of attribution and group terms were used that may be different than what is in the final USPI for nirogacestat.

Routine Clinical Tests

The Applicant's Position:

Laboratory, ECGs, and vital signs assessments were performed according to the Schedule of Activities in each protocol. Available data were summarized using the Safety population from all the study pools as well as the OLE Phase of Study NIR-DT-301. Laboratory results were not available for Study 14-C-0007.

Clinical laboratory values were expressed in conventional units. Normal ranges were determined based on the ranges supplied by the laboratory and were not normalized. Missing normal ranges were replaced by ranges from the central laboratory from the same study or standard laboratory ranges.

If ECG results were collected in triplicates, the average of the triplicate ECG records was calculated and used as analysis values for each visit. Additionally, for the All CM Pool and All DT Pool, the most extreme value, and its change from baseline per Cycle (1, 2, 3, 4 - 6, 7-12 and 13 and onward) was summarized. The most extreme ECGs were defined as the highest post-baseline value for QT, QTcF, QRS and PR intervals and the largest absolute change for heart rate.

The FDA's Assessment:

FDA agrees with the Applicant's statement. FDA further notes blood chemistries, hematology assessments were obtained at baseline, Cycle 1 Days 1, 8, 15, and 22, Cycle 2 day 28, Cycle 4 Day 1 and every third cycle thereafter on Day 1. Pregnancy tests were conducted in WOCBP at baseline, prior to first dose of study treatment, on Cycle 1 Day 22, Cycle 2 Day 28, then monthly. With institution of amendment #3 (January 27, 2020) menstrual history and female and male hormone levels were collected. Female hormones (TSH, Prolactin, AMH, LH, FSH, estradiol, and progesterone) were collected at baseline, Cycle 1 Day 22, Cycle 2 Day 28, Cycle 4 Day 1 and every 3 cycles thereafter. Male hormones (total testosterone, free testosterone, progesterone FSH, and LH) were collected prior to first treatment of study drug, Cycle 4 Day 1 and every 3 cycles thereafter.

8.2.4. Safety Results

Deaths

Data:

A total of 3 deaths were reported in the All DT Pool and all were assessed by the investigator as unrelated to nirogacestat. The incidence of TEAEs that led to death was the same in both the nirogacestat and placebo treatment groups. In Study NIR-DT-301, one participant in the placebo arm died due to sepsis. One participant in the nirogacestat 150 mg BID arm of Study NIR-DT-301 died due to multi-organ failure more than 30 days after discontinuing study treatment in the setting of aggressive tumor progression and a new diagnosis of spindle cell sarcoma. One participant from Study 14-C-0007 died from a cerebrovascular accident.

All other TEAEs with fatal outcome were reported from participants being treated for advanced cancer in the All CM Pool. In this pool, there were 7 deaths (4%) across all dosing groups, including 3 deaths (2%) in the nirogacestat 150 mg arm. Five of the deaths in this pool were

attributed to disease progression; the other 2 reported deaths were due to other causes in Studies 14-C-0007 and A8541020. The increase in number of deaths in the All CM Pool compared to the All DT Pool was driven by the older and sicker population of participants in these early studies of participants with advanced cancer.

The Applicant's Position:

Nirogacestat was not considered as a cause of death for any reported event. TEAEs leading to death were consistent with the underlying disease or disease progression.

The FDA's Assessment:

At the time of the NDA submission, one patient who received nirogacestat died in Study NIR-DT-301; one death was also reported in the placebo arm. The patient who died in the nirogacestat arm in Study NIR-DT-301 had an identified APC mutation and was diagnosed with spindle cell sarcoma which had previously been reported as a pulmonary nodule. The patient discontinued nirogacestat on Day 65 and subsequently died on Day 108 of multiorgan failure. FDA agrees with the investigator (and Applicant) that this patient's death is unlikely related to nirogacestat.

One additional patient with desmoid tumor died in NCI trial 14-C-0007. This patient was 60-years-old person who died of a cerebrovascular accident with a CT-confirmed pontine hemorrhage. The patient had atrial fibrillation in the hospital and the investigator deemed the event as unlikely related. This attribution appears reasonable noting that the patient was on his sixth year of treatment and the patient also had severe hypertension as a potential contributing factor for the CVA.

Other deaths reported in nirogacestat development occurred in patients with advanced malignancies. All but two were attributed in the application to underlying disease or disease progression. One of the two patients died of thrombosis prior to randomization and one patient with advanced TNBC and ischemic heart disease experienced dyspnea and died. The investigator deemed the event as unrelated; however, additional details were lacking for this patient; therefore there is uncertainty regarding this patient's cause of death.

No new deaths were reported at the time of the 120-day safety update.

Serious Adverse Events

Data:

In the All DT Pool, SAEs were reported in 23 participants (26%) in the nirogacestat 150 mg BID arm. In the nirogacestat 150 mg BID arm, premature menopause (3 participants) and hematuria (2 participants) were the only PTs reported in more than 1 participant; in the placebo arm; sepsis (3 participants) and COVID-19 (2 participants) were reported in more than 1 participant.

All 3 reports of premature menopause were reported in Study NIR-DT-301 as an unexpected event early in the study (prior to identification of OD as an adverse event of special interest [AESI]) and were considered serious due to medical importance; more information is provided in [Section 8.2.5](#). Overall, the findings in the All DT Pool align with those described in Study NIR-DT-301.

The Applicant's Position:

The events and rates of SAEs were generally consistent across studies and are representative of the overall safety profile. The only SAE reported by > 2 participants receiving nirogacestat was premature menopause. The relatively low incidence of SAEs supports a favorable benefit:risk profile with nirogacestat in the treatment of patients with DT.

The FDA's Assessment:

In Study NIR-DT-301 (in the double-blind phase), SAEs were reported in 20% of patients in the nirogacestat arm versus 11% among patients in the placebo arm. Overall SAEs of infections were similar between arms (6% for nirogacestat versus 7% for placebo) and were therefore, not included in product labeling. The only organ system with a difference between arms was for ovarian toxicity (4% versus 0% among placebo) (*note that the group term of ovarian toxicity differs from the more general term of reproductive system disorders described in the original application*). Among the 4% of patients with ovarian toxicity SAEs, there were three patients with an SAE of premature menopause and one patient with reported ovarian failure.

In Study NCI-14-C-0007, following an update to the safety database, there were two SAEs considered by the investigators as possibly related to nirogacestat: squamous cell carcinoma and vulvovaginal inflammation. These were Grade 2 in severity. No SAE occurred in more than one patient. The labeling for the nirogacestat includes a Warning for non-melanoma skin cancers (in NIR-DT-301, cutaneous squamous cell carcinoma and basal cell carcinoma occurred in 2.9% and 1.4% of patients, respectively).

When considering the combined DT pool of patients, the only terms that occurred in more than one patient were premature menopause (n=3) and hematuria (n=2).

The safety update described additional SAEs in the placebo to nirogacestat group in NIR-DT-301. One patient experienced an SAE of proctalgia and one of pyelonephritis. Both events were considered by the investigator/sponsor as unrelated to nirogacestat. One additional patient in the safety update was diagnosed with Grade 3 intestinal fistula and intestinal abscess. This patient with FAP had a prior history of pelvic abscesses and fistulas and these events were considered unrelated to nirogacestat.

In summary, although there is a slight increase in SAEs among patients who received nirogacestat versus placebo in Study NIR-DT-301 (double-blind phase), the major explanation

for this difference was ovarian toxicity (also, exposure was longer in the nirogacestat arm). In general, it is difficult to ascribe most of the specific SAEs to nirogacestat due to low frequency of individual events (however, non melanoma skin cancers, an event observed in the NCI study, is described in product labeling).

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Events leading to treatment discontinuation that occurred in > 1 participant in the All DT Pool were consistent with what was observed in Study NIR-DT-301. In the All DT Pool, 17 participants (19%) treated with nirogacestat 150 mg BID discontinued study treatment compared to 2 participants (3%) treated with placebo (dysphagia and drug-induced liver injury). The most frequently reported PTs (occurring in > 1 participant in the nirogacestat 150 mg arm) were: diarrhea (4 participants), ALT increased (3 participants), premature menopause (3 participants), and AST increased (2 participants).

The Applicant's Position:

The profile of TEAEs leading to treatment discontinuation was consistent with the known safety profile of nirogacestat and GSIs.

The FDA's Assessment:

In the DeFi study, per the AE dataset, 16 of 69 patients (23%) who received nirogacestat in the DB phase discontinued due to an AE vs 2 (3%) in patients who discontinued placebo. Per the CSR, two of these 16 patients in the nirogacestat arm discontinued due to disease progression with a concomitant AE occurring at the time of treatment discontinuation (such that 14 patients or 20% discontinued due to a nirogacestat AE, as described in product labeling). The AE for one of the two patients was tumor hemorrhage. The AE for the other patient was hematuria occurring in a patient with a tumor located in the pelvis with vital structure involvement, including bladder, kidney, and intestinal tract. This patient's narrative is discussed in the review above (clinical progression event)

The most common PTs occurring in more than one patient in the nirogacestat arm were those listed by the Applicant: diarrhea (4 participants), ALT increased (3 participants), premature menopause (3 participants), and AST increased (2 participants). One of the 4 patients who discontinued nirogacestat with diarrhea also had hot flushes at the time of discontinuation. One additional patient discontinued nirogacestat due to ovarian failure.

Significant Adverse Events

Data:

For the purposes of this Assessment Aid, Grade ≥ 3 TEAEs are considered significant.

TEAEs of Grade ≥ 3 in the All DT Pool occurred in 60% of participants treated with nirogacestat 150 mg and comprised of 5% of total TEAE events (130/2543 events). Fifty participants (57%) reported Grade 3 events, 2 participants reported Grade 4 events (spindle cell sarcoma and appendicitis), and 1 participant reported a death (cerebrovascular accident). The most frequently reported Grade 3 TEAEs across all groups were diarrhea (15 participants; 16%) and hypophosphatemia (15 participants; 16%). For the nirogacestat 150 mg BID group in the All DT Pool, the most frequently reported Grade 3 TEAEs were diarrhea (14 participants [16%]) and hypophosphatemia (11 participants [13%]). Grade 3 hypophosphatemia was notably higher in the All DT Pool 150 mg BID group compared to Study NIR-DT-301 (11 participants [13%] vs 2 participants [3%]) (See Table below).

The incidences of TEAEs of Grade 3 occurring in the groups receiving nirogacestat 150 mg BID in the All DT, All CM Pool, and OLE Pools were generally aligned with the nirogacestat 150 mg BID arm in Study NIR-DT-301.

Table 51: Incidence of Grade ≥ 3 TEAEs Occurring in ≥ 2 Participants who Received 150 mg BID Nirogacestat

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	69	88	128	28	4
Any Grade ≥ 3 TEAE in all participants	12 (17%)	38 (55%)	53 (60%)	78 (61%)	15 (54%)	0
Diarrhoea	1 (1%)	11 (16%)	14 (16%)	18 (14%)	3 (11%)	0
Folliculitis	0	4 (6%)	4 (5%)	4 (3%)	1 (4%)	0
Rash maculo-papular	0	4 (6%)	4 (5%)	4 (3%)	1 (4%)	0
Stomatitis	0	3 (4%)	3 (3%)	3 (2%)	3 (11%)	0
Hypophosphataemia	0	2 (3%)	11 (13%)	21 (16%)	0	0
Hypertension	0	2 (3%)	5 (6%)	5 (4%)	1 (4%)	0
Anaemia	1 (1%)	2 (3%)	3 (3%)	5 (4%)	1 (4%)	0
Weight increased	1 (1%)	2 (3%)	4 (5%)	4 (3%)	1 (4%)	0
Fatigue	0	2 (3%)	3 (3%)	5 (4%)	0	0

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	69	88	128	28	4
Alanine aminotransferase increased	1 (1%)	2 (3%)	2 (2%)	3 (2%)	1 (4%)	0
Aspartate aminotransferase increased	1 (1%)	2 (3%)	2 (2%)	3 (2%)	0	0
Hypokalaemia	0	1 (1%)	2 (2%)	7 (5%)	0	0
Nausea	0	1 (1%)	1 (1%)	2 (2%)	2 (7%)	0
Abdominal pain	0	1 (1%)	2 (2%)	2 (2%)	0	0
Small intestinal obstruction	0	1 (1%)	1 (1%)	2 (2%)	1 (4%)	0
Tumour pain	2 (3%)	1 (1%)	1 (1%)	1 (1%)	0	0
Hypoalbuminaemia	0	1 (1%)	1 (1%)	2 (2%)	0	0
Pneumonia	1 (1%)	0	1 (1%)	2 (2%)	0	0
Vomiting	0	0	1 (1%)	3 (2%)	0	0
Oedema peripheral	0	0	1 (1%)	2 (2%)	0	0
Pain	0	0	1 (1%)	2 (2%)	0	0
Rash	0	0	0	2 (2%)	1 (4%)	0
Sepsis	3 (4%)	0	0		0	0
COVID-19	2 (3%)	0	0	0	0	0
Dehydration	0	0	0	2 (2%)	0	0
Muscular weakness	0	0	0	2 (2%)	0	0

The Applicant's Position:

Ninety-five percent of all reported TEAEs were Grade 1 or 2. Overall, the incidence of Grade 3 TEAEs was relatively low and only 2 Grade 4 events reported among participants with DT at any dose level; neither of these events were considered related to nirogacestat. The most frequently reported Grade 3 TEAE was diarrhea; Grade 3 hypophosphatemia was also frequently reported in the All DT Pool. These observations were effectively managed with

appropriate interventions and are consistent with the safety profile of GSIs supporting a favorable benefit:risk profile.

The FDA's Assessment: FDA would generally not agree that the incidence of Grade 3 TEAEs was low noting that 55% of patients treated with nirogacestat in DeFi were described as having a Grade 3 or greater TEAEs vs 17% for placebo. Nevertheless, most of the severe toxicities are those that can be managed or mitigated by supportive care or dose modifications. For example, the most common clinical Grade 3 AE was diarrhea. Skin toxicities such as folliculitis and rash also occurred in 6% of patients each.

DeFi used CTCAE version 5 to assess severity of AEs which potentially resulted in a lower incidence of Grade 3 hypophosphatemia because CTCAE v5 requires clinical sequelae for Grade 3. Nevertheless, 20% of patients in DeFi experienced phosphate levels less than 2 mg/dL (similar to criteria in CTCAE version 4).

With respect to Grade 4 events occurring in DeFi, there were three listed patients in the ADAE dataset. One patient was described above in this review (diagnosis of spindle cell sarcoma) and one patient was diagnosed with appendicitis. One additional patient was listed as having Grade 4 obesity with a start date one day after switching from placebo to OLE (as such would not consider this as related to treatment with nirogacestat).

Refer to sections below (TEAEs and Application-Specific Safety Issues) for further exploration of TEAEs of all grades (including Grade 3 or above).

Treatment Emergent Adverse Events and Adverse Reactions

Data:

The incidences of frequently ($\geq 20\%$ of participants) occurring TEAEs in the groups receiving nirogacestat 150 mg BID in the All DT, All CM Pool, and OLE Group were generally aligned with the population in Study NIR-DT-301 ([Table 52](#)). Overall, the most frequently ($> 30\%$) reported TEAEs in the NIR-DT-301 study and All DT Pool were diarrhea, nausea, fatigue, hypophosphatemia, and rash maculopapular, which are expected with GS inhibition ([Krop et al. 2012](#); [Tolcher et al. 2012](#); [Richter et al. 2014](#); [Messersmith et al. 2015](#); [Pant et al. 2016](#)).

Table 52: Incidence of Frequently ($\geq 20\%$ of Participants in Any Pool) Occurring TEAEs in Participants who Received 150 mg BID Nirogacestat (In Descending Order of Frequency in the NIR-DT-301 150 mg BID Group)

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	69	88	128	28	4
Any TEAE	69 (96%)	69 (100%)	88 (100%)	127 (99)	28 (100%)	4 (100%)
Diarrhoea	25 (35%)	58 (84%)	75 (85%)	100 (78%)	23 (82%)	0
Nausea	28 (39%)	37 (54%)	50 (57%)	72 (56%)	13 (46%)	0
Fatigue	26 (36%)	35 (51%)	44 (50%)	65 (51%)	11 (39%)	0
Hypophosphataemia	5 (7%)	29 (42%)	43 (49%)	56 (44%)	9 (32%)	0
Rash maculopapular	4 (6%)	22 (32%)	32 (36%)	32 (25%)	6 (21%)	0
Headache	11 (15%)	20 (29%)	35 (40%)	36 (28%)	8 (29%)	0
Stomatitis	3 (4%)	20 (29%)	26 (30%)	29 (23%)	9 (32%)	0
Dermatitis acneiform	0	15 (22%)	22 (25%)	24 (19%)	2 (7%)	0
Vomiting	14 (19%)	14 (20%)	21 (24%)	37 (29%)	6 (21%)	0
Hot flush	4 (6%)	13 (19%)	22 (25%)	22 (17%)	4 (14%)	0
Ovarian failure	0	13 (19%)	13 (15%)	13 (10%)	8 (29%)	0
ALT increased	6 (8%)	12 (17%)	21 (24%)	23 (18%)	8 (29%)	1 (25%)
COVID-19	12 (17%)	12 (17%)	12 (14%)	12 (9%)	6 (21%)	0
Cough	3 (4%)	11 (16%)	18 (20%)	27 (21%)	7 (25%)	0
Abdominal pain	9 (13%)	11 (16%)	19 (22%)	22 (17%)	5 (18%)	0
AST increased	8 (11%)	11 (16%)	23 (26%)	27 (21%)	8 (29%)	1 (25%)
Weight increased	5 (7%)	11 (16%)	13 (15%)	13 (10%)	3 (11%)	1 (25%)
Folliculitis	0	9 (13%)	13 (15%)	14 (11%)	4 (14%)	1 (25%)
Pruritus	6 (8%)	9 (13%)	11 (13%)	14 (11%)	6 (21%)	0
Influenza like illness	2 (3%)	7 (10%)	13 (15%)	13 (10%)	2 (7%)	1 (25%)
Weight decreased	7 (10%)	6 (9%)	10 (11%)	12 (9%)	8 (29%)	0
Anxiety	5 (7%)	6 (9%)	9 (10%)	10 (8%)	1 (4%)	1 (25%)
Urinary tract infection	2 (3%)	3 (4%)	6 (7%)	9 (7%)	2 (7%)	1 (25%)

	NIR-DT-301 Placebo	NIR-DT-301 150 mg BID	All DT Pool 150 mg BID	All CM Pool 150 mg BID	OLE Placebo to 150 mg BID	OLE Continuing Nirogacestat
Total N	72	69	88	128	28	4
Chest pain	0	1 (1%)	1 (1%)	2 (2%)	0	1 (25%)
Oestradiol increased	0	1 (1%)	1 (1%)	1 (1%)	0	1 (25%)
Gynaecomastia	0	0	0	0	0	1 (25%)

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; TEAE: treatment-emergent adverse event.

The TEAEs that occurred in $\geq 15\%$ of participants and in $\geq 5\%$ of participants receiving nirogacestat as compared to placebo in Study NIR-DT-301 are shown in [Table 53](#).

Table 53: Adverse Reactions Reported in at least 15% Participants and at a $\geq 5\%$ Rate in the Nirogacestat Arm than the Placebo Arm in Study NIR-DT-301

	Nirogacestat 150 mg BID (N = 69)		Placebo (N = 72)	
Adverse Reaction	All Grades n (%)	Grade 3* n (%)	All Grades n (%)	Grade 3* n (%)
Gastrointestinal				
Diarrhea	58 (84%)	11 (16%)	25 (35%)	1 (1%)
Nausea	37 (54%)	1 (1%)	28 (39%)	0
Stomatitis	20 (29%)	3 (4%)	3 (4%)	0
Reproductive system				
Ovarian dysfunction ^a	27 (75%)	0	0	0
Skin and subcutaneous tissue				
Rash ^b	44 (64%)	4 (6%)	10 (14)	0
Alopecia	13 (19%)	0	1 (1%)	0
General				
Fatigue	35 (51%)	2 (3%)	26 (36%)	0
Nervous system				
Headache	20 (29%)	0	11 (15%)	0
Respiratory				
Cough	11 (16%)	0	3 (4%)	0
Dyspnea	11 (16%)	0	4 (6%)	0

	Nirogacestat 150 mg BID (N = 69)		Placebo (N = 72)	
Adverse Reaction	All Grades n (%)	Grade 3* n (%)	All Grades n (%)	Grade 3* n (%)
Infections				
Upper respiratory tract infection ^c	11 (16%)	0	1 (1%)	0
Metabolism				
Hypophosphatemia	29 (42%)	2 (3%)	5 (7%)	0
Investigations				
ALT increased	12 (17%)	2 (3%)	6 (8%)	1 (1%)
AST increased	11 (16%)	2 (3%)	8 (11%)	1 (1%)

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; URTI: upper respiratory tract infection; WOCBP: women of childbearing potential.

* No Grade 4 or 5 adverse reactions were reported in Study NIR-DT-301.

^a Rash included rash maculo-papular (22 [32%]), dermatitis acneiform (15 [22%]), rash (13 [19%]), rash erythematous (2 [3%]), rash pruritic (1 [1%]), rash papular (1 [1%]).

^b Ovarian dysfunction included ovarian failure (13 [19%]), premature menopause (11 [16%]), amenorrhea (3 [4%]), and menopause (1 [1%]); the number of WOCBP in each arm is used as the denominator (nirogacestat N = 36, placebo N = 37).

^c URTI included URTI, viral URTI, acute sinusitis, and sinusitis.

The Applicant's Position:

The most frequently reported AEs (> 20% in Study NIR-DT-301) were diarrhea, nausea, fatigue, hypophosphatemia, rash maculopapular, stomatitis headache, dermatitis acneiform, and vomiting (with vomiting being reported with a similar incidence in the placebo arm). OD occurred in 75% of WOCBP. Additional frequently reported AEs in the All DT Pool include AST increased, hot flush, ALT increased, abdominal pain, and cough. These were generally consistent with the effects of GS inhibition. The majority of participants (97%) reported their first TEAE in Cycle 1, and 95% of all reported TEAEs were Grade < 3.

The FDA's Assessment:

In general, FDA was able to reproduce the incidence rate of individual adverse events in Study NIR-DT-301 described in Table 52 above using standard FDA-run analyses/scripts (of SDTM datasets) with the exception of nausea (FDA script 55% for nirogacestat, headache 30% nirogacestat, and ALT increased 17% for nirogacestat). With alternative (but similar) methodology, grouping TEAEs in the dataset by patient ID, organ class, preferred term (by max toxicity grade), and arm, FDA was able to replicate the applicant's results for these three AE terms.

Although there were potentially relevant adverse terms below the 20% AE threshold described in the heading of Table 52, (b) (4) or inclusion as a grouped term, for example, as shown in Table 53 for rash, fatigue, and ovarian dysfunction.

The following additional (preferred) terms not described in Table 52 occurred at less than 20% but greater than 10% in nirogacestat-treated patients (per FDA run standard analyses/scripts), but the difference between arms was less than 5%: COVID-19, decreased appetite, abdominal pain, hypertension, pruritis, back pain, arthralgia, SARS-COV-2 test positive, constipation, and anemia.

(b) (4)
differences in the FDA agreed upon definitions for composite terms that comprised different preferred terms. (b) (4)

Table 54: FDA Analysis of Composite Terms (b) (4) (that Differ from the Above Table)

Adverse Reaction	Nirogacestat (n=69)		Placebo (n=72)	
	All Grade (%)	Grade 3 (%)	All Grades (%)	Grade 3 (%)
Stomatitis	39	4	4	0
Abdominal pain	22	1.4	14	1.4
Rash	68	6	14	0
Fatigue	54	2.9	38	0
Headache	30	0	15	0
Cough	20	0	6	0
Upper respiratory tract infection	17	0	2.8	(b) (4)

Table 55 below lists the AE group terms (other than ovarian dysfunction) (b) (4) and the individual preferred terms that were used to define the incidence of each composite term. FDA was able to confirm the per patient incidence of the grouped adverse event terms described in Table 54 above (b) (4). The incidence rates of the individual AE terms below are based on the FDA run standard analyses/scripts of STDM data (*note that the incidence rates may not add up to the numbers in the table above as more than one preferred term may have been reported per patient, and the table above describes the per patient incidence rate*). Note that the overall incidence of ovarian toxicity is described below in this review and was based on the denominator consisting of women of child bearing potential.

Table 55: Grouped AE Terms (b) (4)

Composite Term	Preferred Terms	Nirogacestat (n=69) All Grade %	Placebo (n=71) All Grade %
Stomatitis	Stomatitis	29	4.2
	Glossitis	1.4	0
	Mouth ulceration	5.8	0
	Aphthous ulcer	4.3	0
Abdominal pain	Abdominal pain upper	7.2	1.4
	Abdominal pain	15.9	12.5
	Abdominal discomfort	1.4	0
	Abdominal pain lower	0	1.4
	Gastrointestinal pain	0	1.4
	Abdominal tenderness	1.4	0
Rash	Rash maculo-papular,	31.9	5.6
	Dermatitis acneiform	21.7	0
	Rash papular	1.4	1.4
	Rash	18.8	6.9
	Eczema	1.4	0
	Rash erythematous	2.9	0
	PPED syndrome	2.9	0
	Dermatitis	1.4	0
	Rash pruritic	1.4	0
Fatigue	Fatigue	50.7	36.1
	Asthenia	1.4	1.4
	Malaise	2.9	0
Headache	Headache	30.4	15.3
	Migraine	2.9	0
Cough	upper-airway cough syndrome	4.3	1.4
	Cough	15.9	4.2
	Productive cough	5.8	0
Upper respiratory infection	Upper respiratory tract infection, ,	7.2	1.4
	Nasal congestion	10.1	2.8
	Viral upper respiratory tract infection	1.4	0

Table 56 below describes additional TEAEs $\geq 10\%$ to $<20\%$ in NIR-301-DT (based on FDA standard analyses of SDTM data). The list does not include laboratory terms (better described in laboratory section), terms listed in Table 53 above, Table 55 above, or terms with a less than 5% difference in the two arms (which are described in a paragraph above). The following adverse events described in the table below are included as adverse reactions in product labeling: epistaxis, folliculitis, and influenza like illness. Hot flushes and increased weight

(generally was limited to women diagnosed with ovarian toxicity) were considered sequelae in patients who were otherwise diagnosed with ovarian toxicity. Dry skin and pruritis were sequelae in patients with rash. Although less than 10%, hidradenitis (8.7% versus 0% in the FDA standard analysis) was limited to nirogacestat-treated patients and was listed as an adverse reaction in product labeling.

Table 56: Additional TEAEs (≥10% to Less than 20% in Nirogacestat arm)

PT	NIROGACESTAT	PLACEBO
Hot Flush	18.8%	5.6%
Dry Skin	15.9%	6.9%
Weight Increased	15.9%	6.9%
Epistaxis	14.5%	1.4%
Folliculitis	13.0%	
Pruritus	13.0%	8.3%
Dizziness	11.6%	5.6%
Dry Mouth	11.6%	4.2%
Influenza Like Illness	10.1%	2.8%

Laboratory Findings

Data from physical examinations, ECOG scores, vital signs, and laboratory safety evaluations were not centrally databased for Study 14-C-0007 and were therefore not included in the integrated analyses of these data.

Data:

Hematology

In the All DT Pool and All CM Pools, an increase from baseline in basophils and eosinophils was observed by the first cycle and persisted into the third cycle. Concurrently, the percentage of basophils and eosinophils out of total leukocytes also increased from baseline.

In Study NIR-DT-301, post-treatment eosinophil values consistently trended higher among participants receiving nirogacestat as compared to placebo; this finding did not appear to correlate with an increased rate of AEs of eosinophilia or AEs associated with the development of allergic reactions. A persistent increase in the basophil/leukocyte and eosinophil/leukocyte ratios, along with a transient small decrease in absolute lymphocyte count, is suggestive of a mild inflammatory state associated with on-target activity of nirogacestat.

Laboratory data from clinical studies do not suggest that nirogacestat 150 mg BID is associated with changes in lymphocyte or neutrophil count values that are different from those observed in the placebo arm of Study NIR-DT-301. Participants from studies other than NIR-DT-301 in the All DT Pool did not contribute meaningful data to inform this aspect of the safety profile of

nirogacestat. Observations from the data in the All CM Pool and OLE Group were aligned with those from Study NIR-DT-301.

Clinical Chemistry

There was a trend toward increased ALT and AST values and decreased phosphate and potassium in the All DT Pool and All CM Pool compared to placebo. Alkaline phosphatase, glucose, total bilirubin, albumin, total protein, creatinine, and chloride remained relatively stable in both treatment arms.

The Applicant's Position:

A persistent increase in the basophil/leukocyte and eosinophil/leukocyte ratio along with a transient small decrease in absolute lymphocyte count is suggestive of a mild inflammatory state associated with on-target activity of nirogacestat. The data described above concerning the effect of nirogacestat on lymphocytes and neutrophils do not suggest that GS inhibition due to nirogacestat is having adverse effect on their numbers, and the data are not consistent with an immunosuppressed state.

The FDA's Assessment:

In general, the most important (clinically) laboratory abnormalities appeared to be increases liver enzymes and depletion of electrolytes. Because laboratory data generally describe the finding more accurately than AE data, FDA recommended inclusion of a separate laboratory finding table in product labeling. Overall, the incidence of hyperbilirubinemia was slightly higher in the placebo arm (11% versus 6%) with one Grade 3 or greater event in both arms. No case of Hy's law was observed in nirogacestat-treated patients in Study NIR-DT-301.

FDA recommend inclusion of phosphate levels < 2 mg/dL in Section 5 of labeling in patients treated with nirogacestat (20%) because below 2 mg/dL represents hypophosphatemia that should be acted upon to prevent development of symptomatic disease.

Table 57: Clinically Relevant Laboratory Abnormalities in DeFi

Laboratory Abnormality	Nirogacestat		Placebo	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Decreased phosphate ^{a,b}	65	N/A	11	N/A
Increased aspartate aminotransferase ^a	33	2.9	18	1.4
Increased alanine aminotransferase ^a	30	6	21	1.4
Decreased potassium ^a	22	1.4	4.2	0

^a The denominator used to calculate the rate was 69 for nirogacestat and 72 for placebo based on the number of patients with a baseline value and at least one post-treatment value.

^b CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).

The rate of decreased neutrophils was similar in the two arms in NIR-DT-301 with no shifts (Grade) in 93% of patients in both arms. There was a slightly higher rate of no shift in (low) lymphocyte values in the nirogacestat arm versus placebo (83% versus 76%).

Urinalysis

Data

There was an increased incidence of Grade 1 proteinuria and Grade 1 glucosuria in the nirogacestat arm of Study NIR-DT-301 compared to the placebo arm.

The Applicant's Position:

The observation of an increased incidence of Grade 1 proteinuria and glucosuria in participants receiving nirogacestat compared to placebo, along with a plausible effect of GS inhibition on the functioning of renal tubule epithelium, supports recognizing proteinuria and glycosuria as identified risks for nirogacestat.

The FDA's Assessment:

Overall and as described in CSR, more patients in the nirogacestat arm with no Grade proteinuria at Baseline showed Grade 1 at the end of cycle 2 (27% versus 12%); however, there was no difference at the beginning of cycle 4 and no reported events that were Grade 2 or greater. There was a small difference in rate of Grade 1 proteinuria at Cycle 10 (20% versus 12%) as well as a difference in glycosuria between arms (b) (4)

Vital Signs

Data:

No clinically significant trends were identified in vital sign parameters when compared to placebo or across dose subgroups.

The Applicant's Position:

Nirogacestat did not appear to have clinically meaningful adverse effects on participant vital signs during any study.

The FDA's Assessment:

FDA agrees that there did not appear to be sustained clinically significant changes in blood pressure or heart rate upon review of box-whisker plots in the application.

Electrocardiograms (ECGs)

Data:

No clinically significant trends were identified in ECG parameters. In the All DT Pool, 9 participants (10%) reported QTcF increases of 30-60 msec. This was increased compared to placebo (1 participant [1%]) and was consistent across subgroups of age, gender, BMI, race, dose intensity, and prior therapy. No increases in QTcF > 60 msec were identified in the All DT Pool nirogacestat 150 mg arm.

The Applicant's Position:

Nirogacestat did not appear to have clinically meaningful adverse effects on ECG values during any study.

The FDA's Assessment:

See below for QT assessment. Per the QT-IRT review, there were no patients who experienced PR values > 220 msec with 25% increase over baseline or QRS value > 120 msec with 25% increase over baseline in Study NIR-DT-103 or in Study A8641014.

QT

A concentration-QT (C-QT) analysis was conducted using time-matched PK and triplicate 12-lead ECG data from five Phase 1 studies in healthy participant studies (A8641001, A8641002, NIR-DT-101, NIR-DT-102, and NIR-DT-103) and 2 studies in participants with DT (NIR-DT-301) and advanced solid tumors or T-ALL/LBL (A8641014). The final C-QT model was used to predict the nirogacestat concentration-related change in QTcF in participants with DT and in participants with other advanced solid tumors or T-ALL/LBL. For participants with DT, the mean

predicted Δ QTcF and 90% CI were below 10 msec for each evaluated concentration of interest, including $2 \times C_{\max}$ at steady-state in the presence of strong CYP3A4 inhibition. For participants with other advanced malignancies, as evaluated in Study A8641014, the mean predicted Δ QTcF and 90% CI were below 10 msec for each evaluated concentration of interest, including $2 \times C_{\max}$ at steady-state in the presence of moderate CYP3A4 inhibition.

The Applicant's Position:

The results of a C-QT analysis do not support the existence of a clinically significant prolongation of QTcF intervals associated with therapeutic dosing of nirogacestat alone or with moderate CYP3A4 inhibition.

The FDA's Assessment:

Although the maximum change in QT from baseline was slightly higher in the nirogacestat arm IN Study NIR-DT-301 (12% vs 1% with a 30 msec increase or greater, per the applicant's CSR), a detailed review by via FDA QT-IRT determined that nirogacestat does not cause large mean increases in mean QTc interval (i.e., 20 msec or more) at the approved dose. There were no subjects in Study NIR-DT-103 who experienced a QTcF of greater than 450 msec.

Immunogenicity

The Applicant's Position:

Nirogacestat is a small molecule and not expected to elicit an immune response.

The FDA's Assessment:

FDA agrees.

8.2.5. Analysis of Submission-Specific Safety Issues

In Study NIR-DT-301, designation of an event as an AESI was an investigator decision based on guidance provided in the protocol. According to the protocol, most AESI PTs (except drug reactions) had to be Grade ≥ 2 to qualify for designation as an AESI. AESIs were not specified in other studies included in this summary.

To better characterize AESIs and to account for legacy studies in which no AESIs were prospectively identified per the protocol, AESIs for the integrated safety analyses were identified by reported PT and included the following topics: OD; skin events of rash, hidradenitis suppurativa, and folliculitis; electrolyte insufficiency events of hypophosphatemia and hypokalemia; elevated liver enzymes; and hypersensitivity drug reactions. Of note, events of Grade ≥ 3 hypomagnesemia were listed as AESIs in the NIR-DT-301 protocol; however, no Grade ≥ 3 events of hypomagnesemia were reported in the NIR-DT-301 study or in the All DT, All CM, or OLE Pools at any dose level.

Data:

Ovarian Dysfunction

OD emerged as an AESI for nirogacestat based on observations made early in the conduct of Study NIR-DT-301. Evaluation of the data concerning this event, and review of the literature concerning the role of GS in ovarian function, support recognizing OD as an important identified risk for nirogacestat.

Note that OD was not available as a PT at the time of the amendment or in MedDRA v24.1, which is the MedDRA version used for this summary; therefore, for the purposes of identifying participants with this condition, OD was defined narrowly by the PTs of ovarian failure, premature menopause, amenorrhea, and menopause.

The majority of WOCBP receiving nirogacestat 150 mg BID in Study NIR-DT-301 reported OD (27 of 36 WOCBP [75%]) as compared to 0 of 37 WOCBP receiving placebo. OD events resolved in all participants (n = 11; 100%) following discontinuation of nirogacestat with available follow-up data and also in the majority of participants (n = 9; 64%) remaining on study treatment with nirogacestat. OD events were accompanied by suppression of AMH and estradiol production, and increases in FSH, LH, and progesterone; however, nirogacestat treatment did not appear to result in a prolonged suppression of estradiol. Leading possibilities for the mechanism behind the observed ovarian events involve disruption of the growth and development of the ovarian follicle from the primary stage to the corpus luteum rather than damage or destruction of ovarian tissue or primordial follicles. The increased incidence observed in participants receiving nirogacestat 150 mg BID compared to placebo, nature of the event, and its potential impact on the WOCBP experiencing it support OD being designated an important risk.

Skin Events

Skin events were an AESI in Study NIR-DT-301 based on observations with other GSIs ([Takebe et al. 2014](#)) and in early clinical studies of nirogacestat ([Messersmith et al. 2015](#)). Evaluation of the data concerning these events, and review of the literature concerning the role of GS in skin homeostasis, support recognizing skin rashes (rash maculopapular, dermatitis acneiform, rash, rash erythematous, rash pruritic, and rash papular), hidradenitis, folliculitis, and alopecia as identified risks for nirogacestat. In addition, based on the reports of Grade 3 events of maculopapular rash, hidradenitis, and folliculitis, these events have been designated as important risks.

Skin events were reported at a higher incidence in the nirogacestat 150 mg BID groups compared to the placebo group. Only 2 skin event reports were serious: 1 report of rash maculopapular from a participant in the nirogacestat 150 mg arm in Study NIR-DT-301 and

1 report of rash in a participant transitioning from placebo to nirogacestat 150 mg BID in the OLE Pool.

Due to the increased incidence of skin events observed in participants receiving nirogacestat 150 mg BID compared to placebo and the severity of the events in affected participants, hidradenitis suppurativa, folliculitis, and rash maculopapular are considered important identified risks.

Electrolyte Insufficiency Events

Hypophosphatemia and hypokalemia emerged as AESIs based on observations with other GSIs ([Takebe et al. 2014](#)) and in early clinical studies of nirogacestat ([Messersmith et al. 2015](#)). The increased incidence of hypophosphatemia and hypokalemia in the nirogacestat arm of Study NIR-DT-301 compared to the placebo arm, along with a plausible role for GS inhibition, the occurrence of Grade 3 events, and the frequent need for management with phosphate or potassium supplementation supports their recognition as important identified risks for nirogacestat.

The increased incidence of hypophosphatemia in the nirogacestat arm of Study NIR-DT-301 compared to the placebo arm, along with a plausible role for GS inhibition, supports its recognition as an identified risk of nirogacestat. The occurrence of Grade 3 events, and the frequent need for management with phosphate supplementation, support designating hypophosphatemia as an important event.

The possible mechanisms described for hypophosphatemia may also affect potassium homeostasis. The increased incidence of hypokalemia in the nirogacestat arm of Study NIR-DT-301 compared to the placebo arm and severity of the reported events, along with a plausible role for GS inhibition, supports recognizing hypokalemia as an important identified risk of nirogacestat.

Elevated Liver Transaminases

Effects on hepatic function were an AESI for nirogacestat based on observations of mild hepatic vacuolation in nonclinical studies in rats, and transient transaminase elevations in early clinical studies with nirogacestat.

The clinically relevant increased incidence of elevated transaminases in the nirogacestat 150 mg BID arm compared to the placebo arm in Study NIR-DT-301, and the time to first onset of the events during the first 3 cycles for most participants reporting an event, supports the identification of elevated transaminases as an identified risk associated with the use of nirogacestat. The occurrence of Grade 3 increases in transaminase values, along with a need to inform prescribers that some of these events may be managed with drug interruption followed

by dose reduction, rather than permanent drug discontinuation, supports designation of this risk as important.

Hypersensitivity Drug Reactions

A total of 5 participants receiving nirogacestat reported clinically relevant drug hypersensitivity / anaphylaxis events; however, only 2 events were suggestive of a hypersensitivity reaction to nirogacestat. The other 3 events were either associated with another concomitant medication (trimethoprim/sulfamethoxazole or morphine) or did not necessitate the immediate discontinuation of nirogacestat.

Overall, the infrequent occurrence of relevant events and the details of the individual events are not supportive of recognizing drug reactions (hypersensitivity and anaphylactic reaction) as risks for nirogacestat.

Applicant's Position

The data support recognizing OD, skin events, electrolyte insufficiency events, and elevated transaminases as important identified risks of nirogacestat. The recommended dose modifications for these events are provided in [Table 58](#); diarrhea is not an AESI but it is an important identified risk described in [Section 8.2.6](#). For other severe adverse reactions, or in the event of life-threatening adverse reactions, nirogacestat should be withheld until resolved to Grade 1 or baseline. Only restart at a dose of 100 mg BID after carefully considering the potential benefit and likelihood of recurrence of the adverse reaction. Nirogacestat should be permanently discontinued for recurrence of severe or life-threatening nirogacestat-related toxicity upon rechallenge at the reduced dose.

Table 58: Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Intervention
Diarrhea	
Grade 3 diarrhea persisting for ≥ 3 days despite maximal medical therapy	Withhold drug until resolved to Grade ≤ 1 or baseline, then restart at a dose of 100 mg twice daily.
(b) (4)	
Electrolyte Abnormalities	

Adverse Reaction	Intervention
Grade 3 hypophosphatemia persisting for $\geq$ ^(b) ₍₄₎ days despite maximal replacement therapy	Withhold drug until resolved to Grade $\leq$ 1 or baseline, then restart at a dose of 100 mg twice daily
Grade 3 hypokalemia despite maximal replacement therapy	Withhold drug until resolved to Grade $\leq$ 1 or baseline, then restart at a dose of 100 mg twice daily
Elevated Liver Transaminases	
ALT or AST $\geq$ 3 to 5 times ULN	Withhold drug until ALT, AST or both are resolved to $<$ 3 times ULN or baseline, then restart at a dose of 100 mg twice daily
ALT or AST $>$ 5 times ULN	Permanently discontinue

(b) (4)

The FDA's Assessment:

Ovarian toxicity: Labeling contains an FDA-recommended Warning with respect to ovarian toxicity informing prescribers that female reproductive function and fertility may be impaired following treatment with nirogacestat. Labeling recommends monitoring patients for changes in menstrual cycle regularity or the development of symptoms of estrogen deficiency, including hot flashes, night sweats, and vaginal dryness. Overall 75% of women with reproductive potential (n=36) were reported to have an adverse event related to ovarian toxicity versus no patient in the control arm. Reported terms included ovarian failure, premature menopause, amenorrhea, and menopause. All events were Grade 2 in severity per the CTCAE definition. Per the ISS, 20 out of 27 patients reported resolution, including 11 that resolved off nirogacestat; however, per FDA analysis, the criteria to assess resolution were not adequate and therefore, additional study is needed.

Ultimately, because of potential overlap between terms such as ovarian failure, menopause, premature menopause, etc., a combined term was used in labeling. Additional sequelae of ovarian toxicity occurred during DeFi, such as hot flushes and weight gain (weight gain was similar to placebo in men but greater than placebo in women). These are not specifically described in labeling because they appeared to be downstream symptoms of ovarian toxicity (and there may have been variability with respect to reporting these symptoms versus a more global term such as premature menopause). With respect to hot flush events, 12 of 13 occurred in the setting of ovarian toxicity.

Due to limitations in the selected patient population, timing of reproductive hormone measurements, missing laboratory values, definitions of adverse events, and criteria to designate recovery, FDA was not able to clearly describe the incidence and severity of ovarian toxicity. Given these limitations, DUOG consultants (and DO3 agrees) recommended a Post Marketing Requirement to conduct a new study to characterize ovarian toxicity more adequately.

Consistent with reports of ovarian toxicity, changes in hormone levels were reported following treatment with nirogacestat including FSH, LH, AMH, and estrogen, and progesterone.

Skin toxicity/events: Based on the results observed in DeFi, cutaneous squamous cell carcinoma and basal cell carcinoma were diagnosed in 2.9% and 1.4% of patients, respectively. With respect to squamous cell carcinoma of the skin, one patient was diagnosed with a lesion on the left cheek and underwent Mohs surgery. The other patient's lesion occurred on the anterior thigh. FDA recommended inclusion of non-melanoma skin cancers in product labeling.

As described above, GS may have a role in skin homeostasis. Rash, as a grouped (composite) term was identified in 68% of patients who received nirogacestat versus 14% in placebo with 6% of patients in the nirogacestat arm with Grade 3 rash. Dermatological events (terms) included rash maculo-papular, rash papular, rash, eczema, rash erythematous, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, dermatitis, and rash pruritic. The most common of these terms were rash maculopapular (32%), dermatitis acneiform (22%), and rash (19%). Alopecia and hidradenitis suppurativa were also reported. Dry skin and pruritis were reported; however, these were generally co-reported with other dermatological adverse events (consistent with a manifestation of the other rash-events). Specifically 10 of the 11 nirogacestat-treated patients with dry skin reported another skin event, compared to 1 of the 5 patients in the placebo arm.

Per the ISS, the median onset to first skin rash was 22 days with most patients having onset in the first cycle. Rash led to dose reduction in seven patients, dose interruption in 10 patients, and nirogacestat discontinuation in one patient. During DeFi, agents used to manage rash included topical steroids, antibiotics, and acne treatments.

Of note, FDA sent an information request to SpringWorks regarding bacterial infections given the potential signal noted during the assessment of all PTs and HLTs. The majority of bacterial infections in patients treated with nirogacestat in DeFi were folliculitis (9 of 14 events) which is described in labeling. Most other bacterial infections were also related to skin (e.g., paronychia, cellulitis, and staph abscess).

Electrolyte insufficiency: Electrolyte depletion, particularly for potassium and phosphorus can occur following treatment with nirogacestat. Labeling describes these risks in Section 5. In DeFi, these included decreased phosphate (65%) and decreased potassium (22%). Phosphate <2

mg/dL occurred in 20% of patients who received OGSIVEO. Grade 3 decreased potassium occurred in 1.4% of patients. Final Labeling for nirogacestat recommends withholding nirogacestat (with future dose reduction) for Grade 3 or 4 hypophosphatemia persisting for 3 or more days despite maximal medical therapy and for Grade 3 or 4 hypokalemia despite maximal medical therapy.

There were no adverse event reports of magnesium; however, this electrolyte was not routinely collected during the conduct of the study.

With regard to hypophosphatemia, these events were frequently recurrent and six patients underwent dose modification (interruption, dose reduction, or discontinuation) for hypophosphatemia. Hypophosphatemia frequently occurred early with most patients being diagnosed with low phosphate during the first cycle.

With respect to potassium, per the CSR, the median onset to first hypokalemia event was 15 days in the nirogacestat arm. No patient was reported to have an SAE due to hypokalemia and there were no dose modifications due to hypokalemia.

Elevated liver transaminases: The FDA review team recommended inclusion of hepatotoxicity in the Warnings section of product labeling as ALT or AST elevations occurred in 30% and 33% of patients who received nirogacestat in DeFi, respectively. ALT or AST greater than 5 times the upper limit of normal occurred in 6% and 2.9% of patients, respectively. No report of Hy's law was observed during DeFi. Median onset to first increase AST or ALT was reported to be 22 days in the nirogacestat arm and the median duration of increased AST or ALT was 29 days.

In DeFi, nirogacestat led to dose reduction in one patient and drug discontinuation in three patients. In addition to the Warning, labeling also includes recommendations regarding increased AST or ALT including withholding nirogacestat for Grade 2 transaminitis (with a dose reduction).

Hypersensitivity drug reactions: In the application, SpringWorks identified 5 potential cases of clinically relevant drug hypersensitivity or anaphylaxis. At least two of the cases, upon review of narrative summaries in the SCS, appeared to be more likely related either trimethoprim / sulfamethoxazole or morphine. In the other three patients, the events appeared likely related to nirogacestat; however, based on the narratives, it was difficult to ascertain whether the events were hypersensitivity events or manifestations of other known nirogacestat-related adverse events, particularly rash and stomatitis.

8.2.6. Other Noteworthy Adverse Events

The Applicant's Position:

Some of these events had also been identified as being of interest based on the available nirogacestat nonclinical data and information concerning other GSIs.

Clinically relevant increases in incidences in the nirogacestat 150 mg BID groups compared to the placebo arm in Study NIR-DT-301 were observed in the PTs of diarrhea, nausea, stomatitis, fatigue, epistaxis, upper respiratory tract infection, cough, dyspnea, and headache, along with the laboratory findings of Grade 1 proteinuria and glucosuria. Most of these events are not identified as important risks due to the absence or very low incidence of SAEs or Grade ≥ 3 events for these risks; however, diarrhea is an important risk.

In Study NIR-301-DT, diarrhea occurred in 84% of participants who received nirogacestat compared to 35% in participants given placebo; Grade 3 diarrhea occurred in 16% of participants. Participants should be monitored and managed according to [Table 58](#).

The FDA's Assessment:

Diarrhea commonly occurred following treatment with nirogacestat with 84% of patients reporting diarrhea in DeFi versus 35% in the placebo arm (Grade 3: 16% versus 1.4%). Per the ISS, non-clinical data have suggested that GS inhibition "may interfere with the integrity of the lower gastrointestinal tract epithelium and control of intestinal motility." In total, 129 diarrhea events were reported among the 58 nirogacestat-treated patients with diarrhea. Per the ISS, the median time to first reporting diarrhea was 9 days. Supportive medicines for diarrhea (e.g., loperamide) were used in 62% of patients with diarrhea in the nirogacestat arm.

Stomatitis in labeling consists of a composite term of different but related PTs. There was one event of an SAE due to stomatitis occurring on Day 9 where the patient developed Grade 3 stomatitis requiring treatment for infection and tramadol. The patient was later able to re-start treatment with a dose reduction.

Dyspnea occurred in 16% of patients in the nirogacestat arm versus 6% among patients who received placebo. Although the CSR assessed potential risk factors, e.g., based on location of disease, FAP status, or prior chemotherapy there were too few patients to provide any conclusions. Dyspnea could be long-lasting however, with the median duration of dyspnea reported as 197 days in the nirogacestat-treated arm.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

PROs are discussed in [Section 8.1.3](#) and [Section 8.1.9](#).

The FDA's Assessment:

See FDA's assessments in [Section 8.1.3](#) and [Section 8.1.9](#).

8.2.8. Safety Analyses by Demographic Subgroups

Data:

Intrinsic factors

The safety of nirogacestat was analyzed by the following subgroups: age, sex, race, ethnicity, BMI, other illness, and organ dysfunction. There were no overall differences in safety among participants based on age and the small numbers of non-White and Hispanic or Latino participants limits the ability to draw conclusions based on race or ethnicity.

As previously discussed, events associated with OD were reported at a higher incidence in female participants in the nirogacestat arm of Study NIR-DT-301 compared to the placebo arm ([Section 8.2.5](#)). Other TEAEs that occurred more frequently in females and in the nirogacestat arm include nausea, stomatitis, alopecia, influenza-like illness, hypokalemia, sinusitis, and dizziness. Hypophosphatemia was the only TEAE that occurred more frequently in males and had a higher incidence in the nirogacestat arm. These trends were also observed in the All DT and All CM Pools.

Apparent trends observed in the TEAEs by BMI subgroup analyses included: pruritis and dyspnea appeared to increase in incidence as BMI rose, at a level that was greater than that in the placebo group. Stomatitis and alanine aminotransferase increase occurred with greater incidence in the lower BMI subgroups, at a level that was greater than in the placebo group. However, no definitive conclusions could be made regarding the rates of TEAEs in select subgroups given the small number of participants within each subgroup.

Extrinsic factors

The safety of nirogacestat was analyzed by geographic location; no overall differences in safety among participants in these subgroups were observed.

The Applicant's Position:

There were no overall differences in safety among participants in most subgroups.

The FDA's Assessment:

There were too few non-White or older patients to assess whether differences in safety exist in Study NIR-DT-301. Only 6 nirogacestat-treated patients were non-White and one nirogacestat-treated patient was Hispanic or Latino. Likewise, only 3 patients were 65 years of age or older (consistent with overall demographics of DT) in Study NIR-DT-301.

In the safety population, about two thirds of patients in both arms were women (44 of 69 for nirogacestat and 47 of 72 for placebo) with 25 men in both arms. Although the applicant conduct analyses of AEs by sex, such analyses should be considered exploratory and non-conclusive given the small number of patients. In general the AEs listed above in Data were those that occurred at a higher incidence rate in men or women. Per the CSR there were a limited additional terms (e.g., back pain in men or non-cardiac chest pain in women); however, the overall number of patients/events was low.

Most importantly, ovarian toxicity (see above) was limited to women enrolled in the trial. Alopecia occurred at a relative higher rate among women as compared to men (27% versus 4%).

8.2.9. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No studies have been conducted with nirogacestat specifically to address safety concerns.

The FDA's Assessment:

FDA agrees; however, further assessment of ovarian toxicity will be requested in the post-marketing setting as a PMR (to further characterize the extent and reversibility of this finding).

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies have been conducted with nirogacestat.

The FDA's Assessment:

FDA agrees. Note that the non-clinical study was negative for carcinogenicity risk (refer to Section 5 above).

Human Reproduction and Pregnancy

Data:

Studies with nirogacestat have not been conducted in women who are pregnant or lactating.

Reproductive toxicology studies in rats have been completed with nirogacestat and confirm the reproductive hazard of nirogacestat as a result of gamma-secretase inhibition in the developing fetus. In the fertility and early embryo toxicity studies (Studies 01214013 and 01214026), nirogacestat administration of doses of 20, 40, and 80 mg/kg/day prior to and during early pregnancy induced lower mating, fertility, and pregnancy indices compared to untreated rats and those dosed at 5 mg/kg/day. In pregnant rats treated with nirogacestat doses of 0, 5, 20, 50, or 150 mg/kg/day on gestation days 6 through 17, during the period of organogenesis, nirogacestat induced fetal loss and resorptions (Study 01214011). These fetal effects occurred at systemic exposures that are below those observed in participants at the proposed 150 mg dose level.

The Applicant's Position:

(b) (4)
the patient should be apprised of the potential hazard to the fetus.

Since drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breastfeed during treatment with nirogacestat and for at least 1 week after the last dose of nirogacestat.

The FDA's Assessment:

Nirogacestat may cause ovarian toxicity in women of child bearing potential (see review above). A post marketing requirement to further assess reproductive function / ovarian toxicity is being requested to characterize the effects of nirogacestat more fully. Additionally, labeling will contained a warning regarding the risk of ovarian toxicity.

The non-clinical section of this review above describes findings from animal studies. In summary, oral administration of nirogacestat to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity and death at maternal exposures below the human exposure at the recommended dose of 150 mg twice daily.

Based on these findings, labeling will state that nirogacestat can cause fetal harm when administered to pregnant women. Labeling will advise women and men of reproductive potential to use effective contraception during treatment with OGSIVEO and for 1 week after the last dose. Labeling will also recommend against breast feeding during treatment with nirogacestat and for one week after the last dose.

Pediatrics and Assessment of Effects on Growth

Data:

No pediatric studies are included in this NDA submission; however, the open-label COG Study ARST1921 of nirogacestat in pediatric participants with DT is currently ongoing. A signal assessment was conducted following 2 AE reports (1 of epiphysiolysis and 1 of hip fracture) occurring in pediatric participants in Study ARST1921 and SpringWorks subsequently identified 2 additional relevant reports in 2 pediatric participants receiving nirogacestat via the compassionate use program for the treatment of DT (1 event of epiphyseal disorder and 1 event of osteonecrosis). At the time of the signal assessment analysis through the 13 December 2021 data cutoff, 26 pediatric participants have been exposed to nirogacestat in the compassionate use program (N = 8) and in the COG Study ARST1921 (N = 18). The total of 4 events occurring in 4 participants out of 26 participants is higher than would be expected in the healthy pediatric population ([Peck et al. 2017](#); [Palocaren 2018](#); [Perry et al. 2018](#); [Duffy et al. 2020](#)).

The Applicant's Position:

The safety and effectiveness of nirogacestat have not been established in pediatric patients. Epiphyseal disorder, manifesting as a widening of the epiphyseal growth plate, has been reported in pediatric participants with open growth plates treated with nirogacestat. Increased physeal cartilage thickening and retention of the hypertrophic zone of the growth plate have been observed in rodents in animal studies with nirogacestat. (b) (4)

The available data support recognizing epiphyseal disorder as a potential risk for nirogacestat in pediatric participants with open growth plates, and the possible impact of this event on bone growth supports designating this potential risk as an important risk for pediatric participants.

The FDA's Assessment:

The pediatric section of product labeling will contain a statement that the safety and effectiveness of nirogacestat have not been established in pediatric patients. Epiphyseal disorder, manifesting as a widening of the epiphyseal growth plate, has been reported in pediatric patients with open growth plates treated with nirogacestat.

The Children's Oncology Group (COG) is conducting study ARTST1921 to characterize the effects of nirogacestat in children with DT (> 1 year of age). SpringWorks will submit the results of this study as a PMR with a projected study completion date milestone of September 2025. The results of this study may further inform labeling with respect to risk and benefit in younger patients with DT.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

The NIR-DT-301 protocol defined overdose as any dose greater than 450 mg daily within a 24-hour period. The largest treatment dose of nirogacestat administered to oncology participants is 330 mg BID in Study A8641014 during the dose-finding stage of development, which 3 participants with solid tumors received. No Grade 4 or 5 TEAEs were reported by participants with solid tumors who received this dose. Dose-limiting toxicities were evaluable in 2 participants which included Grade 3 rash in 1 participant and Grade 1 palpitations and Grade 1 oropharyngeal pain in the other participant. TEAEs for all 3 participants with solid tumors who received this dose included the following PTs in more than one participant: diarrhea (2, Grade 1 and 2), rash (2, Grade 1 and 3), vomiting (2, both Grade 2).

Single doses of nirogacestat larger than these amounts should be managed by close observation and supportive measures as needed. Due to very high protein binding, dialysis is not anticipated to be effective for removing nirogacestat from the blood in participants with normal serum protein levels.

The potential for drug abuse, withdrawal, and rebound were assessed by reviewing reported TEAEs in the nervous system and psychiatric disorders SOCs for the presence of events that would suggest that nirogacestat has psychoactive properties, and for events that are included in the drug abuse and dependence SMQ. No TEAEs suggested nirogacestat could cause a psychoactive effect that could lead to drug abuse, physical dependence, or symptoms of withdrawal.

The Applicant's Position:

No potential for drug abuse, withdrawal, or rebound has been identified for nirogacestat.

The FDA's Assessment:

FDA agrees.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees as this is an NME.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities appear to have been adequately represented in the studies with nirogacestat. Potential safety concerns beyond the risks described in the proposed labeling are not expected. Enhanced pharmacovigilance will be conducted to monitor for OD events and routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

In general FDA agrees; however, uncertainty exists with respect to long-term ovarian toxicity.

8.2.12. Integrated Assessment of Safety

Data

The most frequently (> 30%) reported TEAEs in Study NIR-DT-301 and the All DT Pool were diarrhea, nausea, fatigue, hypophosphatemia, and rash maculopapular, which are expected with GS inhibition ([Krop et al. 2012](#); [Tolcher et al. 2012](#); [Richter et al. 2014](#); [Messersmith et al. 2015](#); [Pant et al. 2016](#)) and were generally aligned with the most commonly reported events in the All CM Pool and OLE Group.

Consistent with the NIR-DT-301 study, most participants in the All DT Pool reported their first TEAE during Cycle 1 (98% in the nirogacestat 150 mg BID group).

The incidences of TEAEs of Grade 3 occurring in the groups receiving nirogacestat 150 mg BID in the All DT, All CM Pool, and OLE Group were generally aligned with the population in Study NIR-DT-301, with diarrhea and hypophosphatemia being the most frequently reported Grade 3 TEAEs across all groups.

Nirogacestat was not considered as a cause of death for any reported event. The SAE data did not reveal any additional events with causality attributable to nirogacestat that were not already identified during the TEAE review. No new safety signals were observed in reviewing treatment-related SAEs.

Events leading to treatment discontinuation and occurring in > 1 participant in the All DT Pool and All CM Pool were consistent with what was observed in Study NIR-DT-301. The most frequently (occurring in > 1 participant in the nirogacestat 150 mg arm) reported PTs resulting in treatment discontinuation were diarrhea (4 participants), ALT increased (3 participants), premature menopause (3 participants), and AST increased (2 participants).

The following events are recognized as important identified risks for nirogacestat because of their increased incidence relative to placebo and also the potential impact to patients: OD, hidradenitis suppurative, folliculitis, rash maculopapular, hypophosphatemia, hypokalemia,

elevated transaminases, and diarrhea. With the exception of OD, these events have been observed in prior studies with GSIs and are expected events associated with gamma secretase inhibition ([Krop et al. 2012](#); [Tolcher et al. 2012](#); [Richter et al. 2014](#); [Messersmith et al. 2015](#); [Pant et al. 2016](#)). OD emerged as a new safety signal during the NIR-DT-301 study given the younger participation population included in studies of DT as compared to prior studies of other GSIs that were predominantly conducted in an older participant population for the treatment of Alzheimer's disease ([Coric et al. 2012](#); [Doody et al. 2013](#); [Henley et al. 2014](#)).

The following PTs were reported at an increased incidence relative to placebo and are recognized as identified risks, but not designated as important risks as these events were generally Grade 1 or 2 and did not result in discontinuation of study treatment: stomatitis, skin rashes (excluding rash maculopapular), alopecia, nausea, fatigue, epistaxis, URTI, cough, dyspnea, headache, proteinuria, and glucosuria.

The clinical data from the studies discussed in this NDA support epiphyseal disorder being recognized as a potential risk for nirogacestat in pediatric patients with open growth plates.

Nonclinical data support embryofetal toxicity being recognized as an important potential risk for nirogacestat (b) (4). Impaired fertility in both male and female rats were also observed; however, effects on male and female fertility in humans are unknown.

The following relevant observations were made, but they do not represent adverse clinical findings: increased eosinophil values, increased basophil/leukocyte ratio, and increased eosinophil/leukocyte ratio.

No clinically significant changes in chemistry (other than hypophosphatemia, hypokalemia, and elevated transaminases), vital signs, ECG, or ECOG score data were observed.

The most clinically impactful identified risks associated with the use of nirogacestat 150 mg BID in the treatment of DT are OD, hidradenitis suppurative, folliculitis, rash maculopapular, hypophosphatemia, hypokalemia, elevated transaminases, and diarrhea. Except for OD and elevated liver transaminases, concomitant medications were frequently used to manage these events. Severe instances of these events were also managed with dose interruptions, followed by dose reductions in some instances. OD was observed to resolve both with continued dosing of nirogacestat and in all participants with drug discontinuation and did not appear to be associated with prolonged estrogen suppression. None of these events, nor any of the other risks associated with the use of nirogacestat, in isolation or in aggregate, would preclude the use of nirogacestat 150 mg BID for the treatment of patients with DT.

The Applicant's Position:

Overall, the safety population included in Study NIR-DT-301 and the All DT Pool is representative of the intended real-world population of patients with DT ([Constantinidou 2012](#); [Penel 2017](#); [DTWG 2020](#); [Anneburg 2022](#); [Federman 2022](#)). Therefore, the observed safety profile described in this SCS can be reasonably expected to reflect the safety profile when nirogacestat is used to treat adult patients with DT. No aspects of the observed safety profile would preclude the use of nirogacestat for treating adult patients with DT and the benefit:risk profile is favorable.

The FDA's Assessment:

Treatment with nirogacestat resulted in frequent gastrointestinal toxicity, ovarian toxicity (in premenopausal women), dermatological toxicity, electrolyte wasting, and LFT abnormalities. In general, these adverse events were manageable with supportive care or dose modifications. Adverse events resulted in permanent discontinuation in 20% of patients, so a subset of patients may not be able to tolerate nirogacestat. Although there is uncertainty with respect to reversibility of ovarian toxicity (and a PMR will be requested), most adverse events appeared to be reversible following discontinuation. Furthermore, most adverse events were Grade 1 or 2 in severity; however, 16% of patients experienced Grade 3 diarrhea.

Although nirogacestat can cause moderate toxicity in some patients, DT is a rare disease without available systemic therapies. Approval of nirogacestat will allow for an additional treatment option in addition to local therapies, and prescribers (generally oncologists with expertise in sarcomas) can consider the optimal treatment for each patient (preferably in a multi-disciplinary setting). If not tolerated, most patients can discontinue without sequelae. Although nirogacestat can cause toxicity, patients also may benefit from treatment (e.g., due to pain reduction).

8.3. SUMMARY AND CONCLUSIONS

8.3.1. Statistical Issues

The FDA's Assessment:

The FDA evaluation of efficacy of nirogacestat was primarily based on the pivotal Study NIR-DT-301. Study NIR-DT-301 showed statistically significant improvements in PFS and ORR for nirogacestat compared to placebo. It should be noted that the primary PFS endpoint included both clinical and radiographic progression as assessed by blinded independent review. A sensitivity analysis of PFS based only on radiographic progression was consistent with the primary analysis of PFS. Although the PRO endpoints showed statistical significance, the estimates may not be reliable due to the large amount of missing data at cycle 10 and

differential missingness between arms. However, additional analyses conducted at earlier timepoints using patient-reported pain were supportive of the primary PFS results. Overall, FDA concluded that a clinically meaningful benefit for nirogacestat was demonstrated.

8.3.2. Conclusions and Recommendations

The FDA's Assessment:

Based on the totality of evidence, the multidisciplinary review teams recommend granting regular approval of nirogacestat 150 mg BID for the treatment of adult patients with progressing desmoid tumors who require systemic treatment. FDA recommends approval of nirogacestat for patients for whom systemic therapy is recommended because consensus guidelines recommend initial active surveillance for patients who do not need immediate treatment (e.g., vital organ involvement, and intolerable symptoms) (DTWG 2020, NCCN 2.2023). For patients with DT who do need to initiate treatment, management is heterogenous, but systemic therapy is sometimes preferred over local therapy, such as surgery or radiotherapy (DTWG 2020).

The Applicant submitted data from 3 trials, among which Study NIR-DT-301 was the pivotal, randomized, placebo-controlled trial, and the remaining two trials (Study A8641014, and Study 14-C-0007) provided supporting data.

Study NIR-DT-301 demonstrated that nirogacestat 150 mg BID provided clinically meaningful and statistically significant improvement in PFS, where the median was not reached (NR, 95% CI: NE, NE), compared to placebo 15.1 months (95% CI: 8.4, NE) in patients with progressive DT based on RECIST 1.1. The ORR was also statistically different between the two arms with 41% (95% CI: 30, 54) and 8% (95% CI: 3, 17) in the nirogacestat, and placebo arms, respectively. The responses were durable with a median duration that was NR in both arms, NR (95% CI: NE, NE) with nirogacestat, and NR (95% CI: 8.3, NE) with placebo. Patient-reported pain improvement in the nirogacestat arm in patients experiencing baseline pain ≥ 2 supports the PFS and ORR results. Because DT is rarely fatal and the safety data for nirogacestat indicated that it would not lead to safety-related deaths, OS was not formally tested.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

The Division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions regarding the role of nirogacestat for patients with progressing DTs that would benefit from an external committee of experts.

10 PEDIATRICS

The Applicant's Position:

Reference is made to the Agreed iPSP letter (25 April 2022). The iPSP outlines a request for a partial product specific waiver for the subset of the pediatric population from birth to less than 24 months of age. In addition, the iPSP includes a deferral request for the results of Study ARST1921 to be submitted post-approval.

Study ARST1921 is an ongoing Phase 2 study to evaluate the safety, PK, and efficacy of nirogacestat in children and adolescents with progressive, surgically unresectable DT. The ARST1921 study was activated in September 2020 and is expected to take approximately 3 years to accrue. Participants will be followed for 2 years to evaluate the 2-year PFS rate allowing for the primary analysis including PFS in approximately 2026.

The FDA's Assessment:

FDA granted the partial waiver request of PREA requirements for pediatric patients with DT from birth to less than 24 months of age. FDA will grant a deferral of the PREA requirements for patients aged 2 to 17 years where SpringWorks will submit the results of ARST1921 in the post-approval setting as a PMR (see Section 13 below).

An initial Pediatric Study Plan (iPSP) was agreed upon between FDA and SpringWorks on April 25, 2022, for a partial waiver of PREA requirements for patients 0-<2 years of age and a deferral

in older pediatric patients awaiting the results of Children's Oncology Group (COG) Study ARST1921, which will be submitted post-approval. ARST1921 is an ongoing Phase 2 study evaluating the safety, pharmacokinetics, and efficacy of nirogacestat in pediatric patients >1 to <18 years-old with progressive, surgically unresectable DT. Study ARST1921 was activated in September 2020 and was expected to take approximately 3 years to accrue; per clinicaltrials.gov, updated on 11/22/2023, this study is active but no longer accruing patients. Patients are being followed for 2 years to evaluate outcomes including safety.

Although Study ARST1921 allowed for the enrollment of patients above one year of age (rather than 2 years as described in the Waiver of the PREA requirement for patients ages 0-<2), FDA agreed with the waiver for children under age 2 years given the following:

- Recent research and guidelines espousing a conservative strategy for desmoid-type fibromatosis in children (Orbach D et al. 2017, DTWG Guidelines 2020);
- COG study requirements for non-resectable tumors, progressing tumors, and previous systemic treatment;
- Observed risk of widening of growth plates, and theoretical risk on organ maturation (however, this risk would be solely based on non-clinical embryonic studies of the NOTCH pathway and not on data observed in patients), and
- Age distribution of 59 patients (over 63 months) in prior COG trial ARST0321 (Skapek SX, et al, 2013) with 78% of 59 patients being 10 years of age or older (additionally ARST0321 did not require previous systemic treatment).

Given the above factors, enrollment of a sufficient number of patients younger than 24 months of age would be highly impracticable for this rare disease.

11 LABELING RECOMMENDATIONS

Data

This is an original application. The proposed label is included in the NDA.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved labeling
1. Indications and Usage	OGSIVEO is indicated for the treatment of adult patients with desmoid tumors	OGSIVEO is indicated for adult patients with progressing desmoid tumors who require systemic treatment.
2. Dosage and Administration 2.3 Dosage Modifications for Drug Interactions	Dosage modifications for use with CYP3A4 inhibitors, inducers or substrates Concomitant use with gastric reducing agents	Section 2.3 deleted and drug interactions moved to Section 7
3. Dosage Forms and Strengths	Each tablet contains 50 mg nirogacestat as 66.525 mg nirogacestat hydrobromide.	Each tablet contains 50 mg nirogacestat. (per salt policy)
4. Contraindications	(b) (4)	None (insufficient data available to justify contraindication)
5. Warnings and Precautions	The following warnings were included:	FDA did not agree that safety data were adequate to support (b) (4); however, FDA added "New Primary Cutaneous Malignancies" (revised to "Non-Melanoma Skin Cancers" in final USPI) and re-ordered warnings based on clinical significance. Ovarian warning revised to more accurately describe seriousness of the adverse reaction; proposed language on (b) (4) to reflect currently available data and understanding of this risk 5.1 Diarrhea

	5.1 Diarrhea 5.2 (b) (4) 5.3 Ovarian Dysfunction 5.4 Electrolyte Abnormalities 5.5 Elevated Liver Transaminases 5.6 Embryo-Fetal Toxicity	5.2 Ovarian Toxicity 5.3 Hepatotoxicity 5.4 Non-Melanoma Skin Cancers 5.5 Electrolyte Abnormalities 5.6 Embryo-Fetal Toxicity
6. Adverse Reactions	Applicant included adverse reactions from NIR-DT-301 study but not the lab abnormalities	Lab abnormalities added; minor edits per oncology labeling practice.
7. Drug Interactions	Included effects and management of effects of CYP3A4 inhibitors and CYP3A4 inducers and gastric acid reducing agents on OGSIVEO; included effects and management of effects of OGSIVEO on CYP3A4 and CYP2C19 substrates	Management advice for use with gastric acid reducing agents revised to include avoidance of use with both PPI and H2 receptor antagonists
8. Use in Specific Populations	Recommendations for pregnancy, breastfeeding, contraception pediatric use, and geriatric use were included.	FDA generally agreed but revised to align with recommendations in the <i>Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry</i> and current labeling practice.
12. Clinical Pharmacology	12.1 Mechanism of action Nirogacestat is (b) (4) gamma secretase that blocks proteolytic activation of Notch and other receptors. When dysregulated, Notch can (b) (4) pathways that contribute to tumor growth.	12.1 Mechanism of action Nirogacestat is a gamma secretase inhibitor that blocks proteolytic activation of the Notch receptor. When dysregulated, Notch can activate pathways that contribute to tumor growth. Minor edits to 12.2 Pharmacodynamics and 12.3 Pharmacokinetics

13. Nonclinical Toxicology	Nonclinical data on carcinogenesis, mutagenesis, and impairment of fertility included.	Minor edits for clarity
14. Clinical Studies	Description and results from NIR-DT-301 study included. Patient reported outcomes from BPI and GODDESS DTSS were also included.	Edited to align with current oncology labeling practice. (b) (4) General statement “PFS results were supported by change in patient-reported worst pain favoring the Ogsiveo arm” was retained.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA’s Assessment:

There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies.

13 POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA’s Assessment:

As a Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) PMR as described above in this review, SpringWorks will submit the results of the following study that will assess safety and anti-DT effects in the pediatric population:

4550-1 - Complete clinical Study ARST1921, “A Safety, Pharmacokinetic and Efficacy Study of a gamma Secretase Inhibitor, Nirogacestat (PF-03084014), in Children and Adolescents with Progressive, Surgically Unresectable Desmoid Tumors” in pediatric patients to further characterize the safety, pharmacokinetics, and anti-tumor activity of nirogacestat in pediatric patients 2 to 17 years with desmoid tumors. The study will include long-term monitoring to characterize epiphyseal disorders and ovarian toxicity in pediatric patients.

Study Completion: 09/2025

Final Report Submission: 09/2026

As discussed above and in the consult from DUOG, FDA is requiring SpringWorks, under Section 505(o)(3) of the FDCA to conduct a clinical trial to further assess the known serious risk of ovarian toxicity. As stated in the consult from DUOG, there were limitations of the DeFi design in the selected patient population, timing of reproductive hormone measurements, missing laboratory values, definitions of adverse events, and criteria to designate recovery. Given these limitations, a clinical trial was needed to ensure proper selection of patients, documentation of adverse events, assessment of labs (including timing), and recovery. SpringWorks will conduct the following trial:

4550-2 - Conduct a prospective, open-label, single-arm clinical trial in adult premenopausal females with desmoid tumor to further characterize the incidence and severity of ovarian toxicity after a minimum of 12 months of nirogacestat treatment. Ensure that ovarian safety assessments after 12 months of continuous treatment are available from a minimum of 40 subjects. Post-treatment follow-up assessments including reproductive hormone measurements should be obtained at regularly scheduled intervals and after treatment cessation to assess time to ovarian function recovery.

Draft Protocol Submission:	07/2024
Final Protocol Submission:	10/2024
Trial Completion:	12/2028
Final Report Submission:	06/2029

Additionally, as a PMC, SpringWorks has agreed to assess the effects of proton pump inhibitors on the bioavailability of nirogacestat. SpringWorks may conduct a PBPK modeling study; however, if needed, depending on the results of the study, SpringWorks will conduct a clinical PK trial to assess the effects of proton pump inhibition on the PK of nirogacestat. The following in the language regarding the PMC:

4550-3 - Conduct physiologic-based pharmacokinetic (PBPK) modeling study and subsequently a clinical pharmacokinetic trial if needed, to evaluate the effect of proton pump inhibitors (PPIs) on the bioavailability of nirogacestat. Design and conduct the trials and modeling analyses in accordance with the FDA guidance for industry, "Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications" and "Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry."

Interim Report Submission (Final PBPK Analysis):	06/2024
Draft Protocol Submission:	01/2025

Final Protocol Submission:	04/2025
Trial Completion:	02/2026
Final Report Submission:	08/2026

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:	Is a PMC/PMR needed?
☐ The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☐ Yes ☒ No
☐ Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☒ Yes ☐ No (pediatrics and assessment of ovarian toxicity)
☐ Other considerations (e.g.: PK/PD), if applicable:	☐ Yes ☒ No

14 DIVISION DIRECTOR (DHOT) (NME ONLY)

X

15 DIVISION DIRECTOR (OCP)

X

16 DIVISION DIRECTOR (OB)

X

17 DIVISION DIRECTOR (CLINICAL)

I agree with the review teams' recommendations to approve this application. I also agree with the description of Substantial Evidence of Effectiveness in Section 1 of this review noting that the totality of data (described in Section 1) were able to overcome limitations due to the inclusion of clinical events in the PFS definition.

X

18 OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 APPENDICES

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

See [Sections 8.1.1](#) through [Section 8.1.7](#) for financial disclosure information.

The FDA's Assessment:

The Applicant submitted a Financial Interests and Arrangements of Clinical Investigators Certification for Study NIR-DT-301, which stated that the Applicant did not enter into any financial arrangements with the clinical investigators. However, FDA inspection revealed that four investigators had financial arrangements, none of which were disclosed by the Applicant. The FDA clinical reviewer requested the Applicant to provide details regarding these financial arrangements. After reviewing the Applicant's response, FDA concluded that the financial disclosure forms submitted by the Applicant were accurate, and that no investigators had financial interests or arrangements that were disclosable as defined in 21CFR54.2. See Section 4.1 for more details.

Covered Clinical Study (Name and/or Number): Study NIR-DT-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>49</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): _____		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The FDA's Assessment:

See Section 5

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Review

19.4.2. OSIS Executive Summary

There are thirteen clinical studies submitted to support this NDA, in which eleven clinical studies include pharmacokinetic (PK) data/information. OSIS reviewed the following method validation and bioanalytical reports which support eleven of the clinical studies. This review focuses on the data quality and reliability of (a) four method validations for the quantification of nirogacestat in human serum and human urine, (b) one method validation for the

quantification of [¹⁴C]-nirogacestat in human serum, and (c) fifteen bioanalytical reports associated with eleven clinical studies.

OSIS finds (1) the results of 32 samples from bioanalytical study A2007079.01 are unreliable due to analysis outside of the established long-term stability window and (2) limited details were provided in the method validation 193/006V to support the quantification of ¹⁴C-nirogacestat in human serum. These concerns related to bioanalytical report A2007079.01 (for clinical study NIR-DT-301) and method validation 193/006V (for clinical study NIR-DT-102) have been communicated to the Office of Clinical Pharmacology (OCP) review team.

Method Validation Report No.	Bioanalytical Report No.	Analyte	Matrix	Clinical Studies
DM2006-03084014-025	DM2007-03084014-028 (b) (4) DM2007-03084014-029 (b) (4)	Nirogacestat	Serum	A8641001 A8641008
AR0308A	Report 25933 (b) (4) Report 28585 (b) (4) Report 30854 (b) (4) Report 31325 (b) (4) Report 34408 (b) (4) Report 34559-1 (b) (4)			A8641002 A8641014 A8641016 A8641019 NIR-DT-101 NIR-DT-102
	Report (b) (4) 2009104.01 (b) (4) Report (b) (4) 2101086 (b) (4) Report (b) (4) 2007079.01 (b) (4)			NIR-DT-103 NIR-DT-104 NIR-DT-301
	Report 25933 (b) (4) Project No. 34408 (b) (4) Project No. 34459-2 (b) (4)			
			Urine	A8641002 NIR-DT-101 NIR-DT-102
193/006V	193/007	[¹⁴ C]- Nirogacestat	Serum	NIR-DT-102

19.4.3. OSIS Review

The Applicant submitted method validation and bioanalytical reports for measuring nirogacestat (originally PF-03084014) and other analytes of interest (Table 59; data from the [Summary of Biopharmaceutical Studies and Associated Analytical Methods](#) in Table 3 of Module 2.7.1). Thirteen method validations were provided: six were for measuring nirogacestat in different biological matrix (three in serum, two in cerebrospinal fluid (CSF), and one in urine), one was for measuring [¹⁴C]-nirogacestat in serum, and six were for measuring the drugs midazolam, docetaxel, gemcitabine, dabigatran, nab-paclitaxel, and itraconazole in plasma.

Table 59 Bioanalytical Reports and Method Validation Reports Supporting the Submitted Clinical Studies

Clinical Studies	Analyte	Matrix	Analytical Lab	Bioanalytical Report No.	Method Validation Report No.
A8641001	Nirogacestat	Serum	(b) (4)	DM2007-03084014-028	DM2006-03084014-025
A8641002	Nirogacestat	Serum		A8641002 Appendix 8.1	AR0308A
	Nirogacestat	Urine		A8641002 Appendix 8.4	AR0308B
	Nirogacestat	CSF		A8641002 Appendix 8.3	AR0308C
	Midazolam	Plasma		A8641002 Appendix 8.2	(b) (4) Plasma Method LCMS 97
A8641008	Nirogacestat	Serum		DM2007-03084014-029	DM2006-03084014-025
	Nirogacestat	CSF		CSR PF-03084014	DM2007-03084014-026
A8641014	Nirogacestat	Serum		(b) (4) Project No. 28585	AR0308A
A8641016	Nirogacestat	Serum		(b) (4) Project No. 30854	AR0308A
	Docetaxel	Plasma		(b) (4) Project 8290-575	8232-056
A8641019	Nirogacestat	Serum		(b) (4) Project No. 31325	AR0308A
	Gemcitabine	Plasma		(b) (4) Project 8320-543	(b) (4) Study No. 2100-687
	Nab-Paclitaxel	Plasma		(b) (4) Project 8320-683	(b) (4) Study No. 8301-257
NIR-DT-101	Nirogacestat	Serum		(b) (4) Project No. 34408	AR0308A
	Nirogacestat	Urine		(b) (4) Study No. SAC-2019-016	AR0308B
NIR-DT-102	Nirogacestat	Serum		(b) (4) Project 34459-1	AR0308A
	Nirogacestat	Urine		(b) (4) Project 34459-2	AR0308B
	[¹⁴ C]-Nirogacestat	Serum		(b) (4) Study 193/007	(b) (4) Study No. 193/006V
NIR-DT-103	Nirogacestat	Serum		(b) (4) Report (b) (4) 2009104.01	V2007078.02
	Total Dabigatran, Itraconazole and Hydroxyitraconazole	Plasma		(b) (4) DCN 5011566	1004603 (Dabigatran) 1004513 (Itraconazole,

					Hydroxyitraconazole)
NIR-DT-104	Nirogacestat	Serum	(b) (4)	Report (b) (4) 2101086	V2007078.02
NIR-DT-301	Nirogacestat	Serum		Report (b) (4) 2007079.01	V2007078.02

Based on the PK data information presented in each of the clinical studies, OSIS's review focused on the method validations and bioanalytical reports used to support the following clinical studies (Table 60 and Table 66).

Table 60 Method Validations and Bioanalytical Reports Quantifying Nirogacestat in Human Matrices

Method Validation Report No.	Bioanalytical Report No.	Analyte	Matrix	Clinical Studies
DM2006-03084014-025	DM2007-03084014-028 (b) (4) DM2007-03084014-029 (b) (4)	Nirogacestat	Serum	A8641001 A8641008
AR0308A	Report 25933 (b) (4) Report 28585 (b) (4) Report 30854 (b) (4) Report 31325 (b) (4) Report 34408 (b) (4) Report 34559-1 (b) (4)			A8641002 A8641014 A8641016 A8641019 NIR-DT-101 NIR-DT-102
V2007078.02	Report (b) (4) 2009104.01 (b) (4) Report (b) (4) 2101086 (b) (4) Report (b) (4) 2007079.01 (b) (4)			NIR-DT-103 NIR-DT-104 NIR-DT-301
AR0308B	Report 25933 (b) (4) Project No. 34408 (b) (4) Project No. 34459-2 (b) (4)		Urine	A8641002 NIR-DT-101 NIR-DT-102
193/006V	193/007	[¹⁴ C]- Nirogacestat	Serum	NIR-DT-102

– **Nirogacestat Quantification in Human Serum**

(1) Method Validation Report DM2006-03084014-025

OSIS's review of method validation report DM2006-03084014-025 for measuring nirogacestat in human serum is presented in Table 61 below. This method validation was used to support bioanalytical reports DM2007-03084014-028 and DM2007-03084014-029. These bioanalytical studies are used to support clinical studies A8641001 and A8641008 for evaluating safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD).

Table 61 Summary of Method Validation Report DM2006-03084014-025 and Bioanalytical Reports DM2007-03084014-028 and DM2007-03084014-029

Method Validation Report DM2006-03084014-025 (b) (4)		Additional Details	OSIS Acceptability
Analyte	Nirogacestat (PF-03084014)	Lot # 109191-83-8F, Stock 200 µg/mL	N/A
Internal standard	PF-04510856	Lot # 101673-181-1	N/A
Biological Matrix	Human Serum	N/A	N/A
Methodology	LC/MS/MS	Run/assay dates: 11/15/2006 to 11/27/2006	N/A
Calibration curve range	0.5 to 500 ng/mL	0.500, 1.00, 5.00, 10.0, 50.0, 100, 400, 500 ng/mL, n=8 from LLOQ to ULOQ	Yes
Capability of dilution (concentration tested; dilution factor)	1000 ng/mL, 20-fold dilution	Table 5 of report # DM2006-03084014-025	Yes
Addenda, amendments, cross-validations, or partial validations	Long-term stability extension for PF-03084014 in human serum and correction on the preparation of syringe wash 1; Amendment to Validation Report DM2006-03084014-025	Report # DM2007-03084014-027 Run/assay date: 12/14/2006 Updates/corrections: (1) updated long-term stability and (2) corrected description of preparation of Syringe Wash 1.	Yes
Selectivity (number of lots tested/passed) and matrix effect	6/6, no significant interference observed	Table 7 of report # DM2006-03084014-025	Yes
Inter-run accuracy (%bias) for each QC concentration	LLOQ: 11.2% LQC: 6.7% MQC: 5.6% HQC: 8.0%	Table 4 of report # DM2006-03084014-025	Yes
Inter-run precision (%CV) for each QC concentration	LLOQ: 6.9% LQC: 4.2% MQC: 4.2% HQC: 3.5%	LLOQ5 (0.500 ng/mL) LQC4 (1.50 ng/mL) MQC3 (25.0 ng/mL) HQC2 (375 ng/mL)	
Short-term or bench-top temperature stability	20 hours/24 hours at room temperature on bench top	Table 1 and 9 of report # DM2006-03084014-025; Table 4 of M.2.7.1	Yes
Long-term stability	12 days/29 days at -20°C	Table 1 of report # DM2007-03084014-027; Table 4 of M.2.7.1	Yes
Freeze-thaw stability	4 freeze-thaw cycles at -20°C	Table 10 of report # DM2006-03084014-025; Table 4 of M.2.7.1	Yes
Stock solution stability	200 µg/mL of PF-03084014 solution in 1:1 Acetonitrile:Water, 76 days at 4°C, 7 hours at ambient temperature	Table 1 of report # DM2006-03084014-025	Yes

Processed sample stability	5 days at room temperature	Table 11 of report # DM2006-03084014-025	Yes
Recovery: extraction efficiency	Not determined	N/A	N/A
Hemolysis and lipemia	Hemolysis: Not determined Lipemia: Not determined	N/A	N/A
Carry-over	Not reported. Divert valco valve was removed due to suspected contribution to carry over.	Section 4 of report # DM2006-03084014-025, page 4	Yes
Method Performance in Study A8641001 Bioanalytical Report DM2007-03084014-028, p661 of A8641001 Study Report ((b) (4))		Additional Details	OSIS Acceptability
Assay passing rate	11 of 12 runs (91.7%), total 972 samples analyzed	Table 1 of report # DM2007-03084014-028	Yes
Standard curve performance	Concentration range: 0.5 to 500 ng/mL Number of calibration standards: 8 Cumulative bias range for standard curve: -2.8 to 2.0% Cumulative precision for standard curve (CV%): 1.6-4.3% Cumulative bias range for QC: 4.29-6.28% Cumulative precision for QC (CV%): 2.0-5.23%	Table 1 and 2 of report # DM2007-03084014-028 Table 4 of M.2.7.1	Yes
QC performance	% Bias	% CV	Yes
	LQC: 4.1% MQC: 2.0% HQC: 5.2%	LQC: 6.3% MQC: 4.5% HQC: 4.3%	
Method reproducibility (ISR)	Not determined	N/A	N/A
Study sample analysis/stability	Samples received: N/A Samples assayed: 11/30/2006 to 03/14/2007 29 days at -20°C	Table 1 of report # DM2007-03084014-028 Table 4 of M.2.7.1	Yes
Method Performance in Study A8641008 Bioanalytical Report DM2007-03084014-029, p468 of A8641008 Study Report ((b) (4))		Additional Details	OSIS Acceptability
Assay passing rate	4 of 4 runs (100%), total 130 samples analyzed	Table 1 of report # DM2007-03084014-029	Yes
Standard curve performance	Cumulative bias range: -5.6 to 3.5% Cumulative precision (%CV): 1.0 to 6.1% CV	Table 2 of report # DM2007-03084014-029	Yes
QC performance	% Bias	% CV	Yes
	LQC: 15.0% MQC: 6.3%	LQC: 36.3% MQC: 6.7%	

	HQC: 2.6%	HQC: 3.4%	
Method reproducibility (ISR)	Not determined	N/A	N/A
Study sample analysis/stability	Samples received: N/A Samples assayed: 05/29/2007 to 06/18/2007 50 days at -20°C	Table 1 of report # DM2007-03084014-029	Yes
OSIS Reviewer's Assessment			
Method validation (DM2006-03084014-025) appears appropriate for quantifying nirogacestat in human serum for bioanalytical studies DM2007-03084014-028 and DM2007-03084014-029, which appear to be acceptable to support clinical studies A8641001 and A8641008.			

(2) Method Validation Report AR0308A

OSIS's review of method validation report AR0308A for measuring nirogacestat in human serum is presented in Table 62 below. This method validation was used to support bioanalytical reports 25933, 28585, 30854, 31325, 34408, and 34559-1. These bioanalytical studies are used to support the Phase 1 clinical study A8641002, Phase 1 clinical study A8641014, Phase 1B clinical study A8641016, Phase 1/2 clinical study A8641019, Phase 1 clinical study NIR-DT-101, and Phase 1 clinical study NIR-DT-102.

Table 62 Summary of Method Validation Report AR0308A and Bioanalytical Reports 25933, 28585, 30854, 31325, 34408, 34559-1

Method Validation Report AR0308A (b) (4)		Additional Details	OSIS Acceptability
Analyte	Nirogacestat (PF-03084014)	Lot # 109191-83-8F	N/A
Internal standard	PF-04510856	Lot # 101673-181-1	N/A
Biological Matrix	Human serum	N/A	N/A
Methodology	LC-API/MS/MS	Run/assay dates: 03/09/2007 to 05/04/2007	N/A
Calibration curve range	0.500 to 500 ng/mL	0.500, 1.00, 5.00, 10.0, 50.0, 100, 400, 500 ng/mL	Yes
Capability of dilution (concentration tested; dilution factor)	1000 ng/mL in human serum, 50-fold dilution	Table 8 of report # AR0308A	Yes
Addenda, amendments, cross-validations, or partial validations	Validation of an LC-API/MS/MS Assay Method for the determination of PF-03084014 in human serum - Addendum 1	Report # AR0308A.A1 Run/assay dates: 05/04/2007 to 03/21/2008 Updates/corrections: (1) added frozen matrix storage stability and (2) added selectivity for concomitant medication midazolam.	Yes
	The Validation of an LC-API/MS/MS Assay Method for the determination of PF-03084014 in human serum -	Report # AR0308A.A2 Run/assay date: 04/17/2013	Yes

	Addendum 2	Updates/corrections: (1) added frozen matrix storage stability, (2) added freeze-thaw stability, (3) added stock solution stability, and (4) added substock and working solution stability.	
	Cross Validation of an LC-API/MS/MS Method for the determination of PF-03084014 in human serum at (b) (4) Sites in (b) (4) and (b) (4)	Report # A8649011 Run/assay dates: 06/19/2015 to 09/23/2015 Updates/corrections: After Intertek acquired (b) (4) cross-validation for (b) (4) and (b) (4) sites.	Yes
Selectivity (number of lots tested/passed) and matrix effect	10 of 10 runs, no significant interference observed	Table 5 of report # AR0308A	Yes
Inter-run accuracy (%bias) for each QC concentration	0.500 ng/mL: 0.3% 1.50 ng/mL: 2.1% 25.0 ng/mL: 0.9% 375 ng/mL: -0.2%	Table 4 of report # AR0308A	Yes
Inter-run precision (%CV) for each QC concentration	0.500 ng/mL: 11.2% 1.50 ng/mL: 7.2% 25.0 ng/mL: 5.5% 375 ng/mL: 6.8%		
Short-term or bench-top temperature stability	24 hours at room/ambient temperature	Table 11 of report # AR0308A	Yes
Long-term stability	322 days at -70°C	Table 5 of report # AR0308A.A1	Yes
	520 days at -20°C	Table 5 of report # AR0308A.A2	
Freeze-thaw stability	4 freeze-thaw cycles at -20°C	Table 6 of report # AR0308A.A2	Yes
Stock solution stability	280 days at 4°C	Table 7 of report # AR0308A.A2	Yes
	21 days at room temperature	Table 8 of report # AR0308A.A2	
Processed sample stability	108 hours at room temperature	Table 14 of report # AR0308A	Yes
Recovery: extraction efficiency	Mean recovery from QCL, QCM, QCH 86.6%	Table 6 of report # AR0308A	Yes
Hemolysis and lipemia	Hemolysis: Not determined Lipemia: Not determined	N/A	N/A
Carry-over	<20%, except when noted	Section 10.3 of report # AR0308A, 3, 10.2, and 12 of report # AR0308A.A1, Methodology comments in A8649007	Yes
Method Performance in Study A8641002 Bioanalytical Report 25933, p715 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	11 of 11 runs (100%), 880	Summary and Tables 1 and 4	Yes

	samples analyzed (total 1190 sample received). No reinjections. 1 sample was reanalyzed due to ALQ.		of report # 25933	
Standard curve performance	Cumulative bias range: -2.3 to 1.4% Cumulative precision: ≤ 6.7% CV%		Table 6 of report # 25933	Yes
QC performance	% Bias	% CV	Table 7 of report # 25933	Yes
	1.5 ng/mL: 1.2%	1.5 ng/mL: 4.8%		
	25.0 ng/mL: 1.4%	25.0 ng/mL: 5.9%		
	375 ng/mL: -2.0%	375 ng/mL: 7.0%		
Method reproducibility (ISR)	Not determined		N/A	N/A
Study sample analysis/stability	Samples received: 05/16/2007 to 12/11/2007 Samples assayed: 05/17/2007 to 12/13/2007		Sample Receipt Section of report # 25933	Yes
Method Performance in Study A8641014 Bioanalytical Report 28585 (b) (4))			Additional Details	OSIS Acceptability
Assay passing rate	36 of 38 runs (94.7%), 1635 samples were analyzed (1642 samples received. One plasma, one extra sample, three duplicates, and two samples were returned to sponsor, but not analyzed per sponsor). 83 samples were reanalyzed, 52 (62.7%) of them were reanalyzed due to ALQ, 29 (34.9%) of them were reanalyzed due to 'Unacceptable Analytically', 2 (2.4%) of them were reanalyzed due to sponsor's request.		Report Summary and Tables 1 and 4 of report # 28585	Yes
Standard curve performance	Cumulative bias range: -3.3 to 2.0% Cumulative precision: ≤ 4.9% CV%		Table 6 of report # 25858	Yes
QC performance	% Bias	% CV	Table 7 of report # 25858	Yes
	1.5 ng/mL: -01.0%	1.5 ng/mL: 6.4%		
	25.0 ng/mL: -1.4%	25.0 ng/mL: 5.4%		
	375 ng/mL: -2.9%	375 ng/mL: 4.3%		
Method reproducibility (ISR)	166 of 1635 (10.2%) samples		Table 9 of report # 25858	Yes

	were assessed; 91.6% within $\pm 20\%$ (167 run; 1 ISR sample omitted due to value sample ALQ)		
Study sample analysis/stability	Samples received: 09/15/2009 to 02/15/2013 Samples assayed: 09/16/2009 to 02/20/2013	Sample Receipt section and Table 1 of report # 25858	Yes
Method Performance in Study A8641016 Bioanalytical Report 30854 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	16 of 17 runs (94.1%), 596 samples were analyzed. No reinjections were stated. 34 samples were reanalyzed, 26 (76.5%) of them were due to ALOQ, 10 (29.4%) of them were due to unacceptable result, 3 (8.8%) of them were due to sponsor's request.	Report Summary and Table 4 of report # 30854	Yes
Standard curve performance	Cumulative bias range: -2.4 to 2.6% Cumulative precision: $\leq 6.75\%$ CV%	Table 6 of report # 30854	Yes
QC performance	% Bias	% CV	Yes
	1.5 ng/mL: 2.6% 25.0 ng/mL: 2.4% 375 ng/mL: -1.3%	1.5 ng/mL: 5.1% 25.0 ng/mL: 5.2% 375 ng/mL: 3.6%	
Method reproducibility (ISR)	60/596 (10.1%) samples assessed, 95.0% within $\pm 20\%$	Table 9 of report # 30854	Yes
Study sample analysis/stability	Samples received: 05/15/2014 to 08/21/2015 Samples assayed: 05/22/2014 to 10/19/2015 Eight samples were assayed outside of 520-day long-term stability timeframe (SSID 10021003), with maximum testing time at 565 days.	Report Summary, Sample Receipt section, Assay Methodology section, and Table 1 of report # 30854	Yes
Method Performance in Study A8641019 Bioanalytical Report 31325 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	1 of 1 run (100%), 19 samples were analyzed (20 received; 1 was not analyzed due to low volume)	Report Summary and Table 1 of report # 31325	Yes

Standard curve performance	Cumulative bias range: -6.2 to 4.8% Cumulative precision: N/A		Table 5 of report # 31325	Yes
QC performance	% Bias	% CV	Table 6 of report # 31325	Yes
	1.5 ng/mL: 13.0% 25.0 ng/mL: 9.6% 375 ng/mL: -2.1%	N/A		
Method reproducibility (ISR)	N/A		N/A	N/A
Study sample analysis/stability	Samples received: 02/03/2015 Samples assayed: 09/30/2015		Table 7 of report # 31325	Yes
Method Performance in Study NIR-DT-101 Bioanalytical Report 34408 (b) (4)			Additional Details	OSIS Acceptability
Assay passing rate	5 of 5 runs (100%), 254 samples were analyzed (566 received, including 283 duplicates; 29 samples were not analyzed per sponsor's request). No reinjections. 7 samples were reanalyzed, all due to ALQ.		Summary and Tables 1 and 7 of report # 34408	Yes
Standard curve performance	Cumulative bias range: -3.0 to 2.9% Cumulative precision: ≤ 6.4% CV%		Table 3 of report # 34408	Yes
QC performance	% Bias	% CV	Table 5 of report # 34408	Yes
	1.5 ng/mL: -6.2% 25.0 ng/mL: -2.2% 375 ng/mL: -4.5%	1.5 ng/mL: 5.1% 25.0 ng/mL: 2.5% 375 ng/mL: 4.3%		
Method reproducibility (ISR)	30 of 283 (10.6%) samples assessed, 96.7% within ±20%		Table 8 of report # 34408	Yes
Study sample analysis/stability	Samples received: 09/17/2019 – 11/06/2019 Samples assayed: 09/27/2019 to 10/09/2019		Table 1 of report # 34408	Yes
Method Performance in Study NIR-DT-102 Bioanalytical Report 34559-1 (b) (4)			Additional Details	OSIS Acceptability
Assay passing rate	7 of 7 runs (100%), 336 samples were analyzed. No reinjections. 15 samples were reanalyzed, all due to ALQ.		Summary and Table 1 and 7 of report # 34559-1	Yes
Standard curve performance	Cumulative bias range: -4.7 to 2.5% Cumulative precision: ≤ 4.4%		Table 3 of report # 34559-1	Yes

	CV%			
QC performance	% Bias	% CV	Table 5 of report # 34559-1	Yes
	1.5 ng/mL: - 0.8%	1.5 ng/mL: 4.6%		
	25 ng/mL: - 0.5%	25 ng/mL: 3.3%		
	375 ng/mL: - 5.3%	375 ng/mL: 3.3%		
Method reproducibility (ISR)	36 of 336 (10.7%) samples were assessed, 100% within $\pm 20\%$		Table 8 of report # 34559-1	Yes
Study sample analysis/stability	Samples received: 01/07/2020 and 01/14/2020 Samples assayed: 02/13/2020 to 02/24/2020		Section 9.1 and Table 1 of report # 34559-1	Yes
OSIS Reviewer's Assessment				
Since the method cross-validation between the two (b) (4) locations was conducted and appears to be appropriate (report A864901), the method's inter-site reliability is considered established and acceptable. In addition, the method showed acceptable performance in the presence of 20 ng/mL midazolam (report AR0308A.A1) during assay. Therefore, method validation AR0308A appears to be appropriate for quantifying nirogacestat in human serum for bioanalytical studies 25933, 28585, 30854, 31325, 34408, 34559-1, which are appropriate to be used to support clinical studies A8641002, A8641014, A8641016, A8641019, NIR-DT-101, and NIR-DT-102.				

(3) Method Report V2007078.02

OSIS's review of method validation report V2007078.02 for measuring nirogacestat in human serum is presented in Table 63 below. This method validation was used to support bioanalytical reports 2007079.01, 2009104.01, and 2101086. These bioanalytical studies are used to support the Phase 3 clinical study NIR-DT-301, Phase 1 clinical study NIR-DT-103, and Phase 1 clinical study NIR-DT-104.

Table 63 Summary of Method Validation Report V2007078.02 and Bioanalytical Reports 2007079, 2009104, and 2101086

Method Validation Report V2007078.02 (b) (4)		Additional Details	OSIS Acceptability
Analyte	Nirogacestat (PF-03084014)	Lot # CPo122567-02-11-02-26-01-RS, purity 75.10%	N/A
Internal standard	Nirogacestat-d5 (PF-04510856)	Lot # CDo123541-01-WFY-5435-22, purity 99.47%	N/A
Biological Matrix	Human serum	Lot # HMN443973, HMN443974, HMN443975, HMN443976, HMN94949, HMN94951, HMN470212	N/A
Methodology	LC-MS/MS	Run/assay dates: 09/16/2020 to	N/A

		10/01/2020	
Calibration curve range	0.500 to 500 ng/mL	0.500, 1.00, 5.00, 10.0, 50.0, 100, 400, 500 ng/mL	Yes
Capability of dilution (concentration tested; dilution factor)	1000 ng/mL in human serum, 10-fold dilution; Precision (%CV): 4.5%; Accuracy 97.9%	Summary Table and Table 5 of report # V2007078.02	Yes
Addenda, amendments, cross-validations, or partial validations	Validation of an LC-MS/MS method for the quantification of Nirogacestat in human serum (Addendum No. 1)	Report # V2007078.02 Addendum 1 Run/assay dates: 03/25/2021 to 05/28/2021 Updates/corrections: (1) extended freeze-thaw stability and (2) added dabigatran specificity.	Yes
	Validation of an LC-MS/MS method for the quantification of Nirogacestat in human serum (Addendum No. 2)	Report # V2007078.02 Addendum 2 Run/assay date: 11/27/2021 Updates/corrections: (1) added itraconazole specificity.	
	Validation of an LC-MS/MS method for the quantification of Nirogacestat in human serum (Addendum No. 3)	Report # V2007078.02 Addendum 3 Run/assay dates: 07/25/22 to 08/10/2022 Updates/corrections: (1) extended long-term stability (failed).	
Selectivity (number of lots tested/passed) and matrix effect	6 of 6 lots of matrix tested; no significant interference observed. Precision (%CV): 1.8%-3.1%.	Tables 6, 7, and 13 of report # V2007078.02	Yes
Inter-run accuracy (%bias) for QC samples	LLOQ-QC: -1.2% LQC: -5.3% MQC: 2.0% HQC: 0.0%	Table 4 of report # V2007078.02 LLOQ-QC (0.500) LQC (1.50 ng/mL) MQC (150 ng/mL) HQC (375 ng/mL)	Yes
Inter-run precision (%CV) for QC samples	LLOQ-QC: 5.4% LQC: 5.9% MQC: 4.1% HQC: 4.6%		
Short-term or bench-top temperature stability	24 hours at room temperature Precision (%CV): 4.7%-6.7% Accuracy: 94.0%-96.3%	Table 20 of report # V2007078.02	Yes
Long-term stability	14 days at -20°C	Table 22 of report # V2007078.02	Yes

	Precision (%CV): 1.6%-3.8% Accuracy: 92.7%-97.3%	(long-term stability in report # V2007078.02 Addendum 3) Refers to 520 days at -20°C in A8649007	
Freeze-thaw stability	7 freeze-thaw cycles at -20°C	Table 3 of report # V2007078.02 Addendum 1	Yes
Stock solution stability	Not determined	Refers to 280 days at 4°C and 21 hours at room temperature in method validation report A8649007	Yes
Processed sample stability	15 days at 2-8°C	Table 19 of report # V2007078.02	Yes
Recovery: extraction efficiency	Mean recovery from LQC, MQC, HQC 95.7%	Table 14 of report # V2007078.02	Yes
Hemolysis and lipemia	Hemolysis: No significant effect of hemolysis Lipemia: No significant effect of lipemia	Tables 13, 15, and 16 of report # V2007078.02	Yes
Carry-over	No significant carry-over observed	Section 3.10 of report # V2007078	Yes
Method Performance in Study NIR-DT-301 Bioanalytical Report A2007079.01 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	29 of 32 runs (90.6% all passed but 3 of 32 runs rejected). 1266 samples were analyzed (2174 received, including 908 back-ups). Reinjections were not stated. 162 samples were reanalyzed, 154 (95.1%) of them were due to ALQ, 5 of (3.1%) them were due to accidental re-assay, 2 (1.2%) of them were due to carry-over, and 1 (0.6%) of them was due to no IS in initial analysis.	Sample Analysis section and Tables 1 and 7 of report (b) (4) 2007079.01	Yes
Standard curve performance	Cumulative bias range: -3.4 to 2.0% Cumulative precision: ≤ 6.0% CV%	Table 3 of report (b) (4) 2007079.01	Yes
QC performance	% Bias	Table 4 of report (b) (4) 2007079.01 LQC (1.50 ng/mL) MQC (150 ng/mL) HQC (375 ng/mL) DQC (1000 ng/mL)	Yes
	% CV LQC: 0.7% MQC: 1.3% HQC: -1.9% DQC: 2.6% LQC: 6.4% MQC: 5.5% HQC: 5.3% DQC: 5.5%		
Method reproducibility (ISR)	128 of 1266 (10.1%) samples were assessed, 92.2% within ±20%	Table 7 of report # A2007079.01	Yes

Study sample analysis/stability	Samples received: 09/15/2020 to 08/04/2021 Samples assayed: 12/15/2020 to 12/03/2021	Sample Analysis and Study Information sections of report # (b) (4) 2007079.01	See OSIS Review's Assessment
Method Performance in Study NIR-DT-103 Bioanalytical Report A2009104.01 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	40 of 48 (83.3%) runs, 1566 samples were analyzed (3132 samples were received, including 1566 back-ups). Reinjections were not stated. 258 samples were reanalyzed, 254 (98.4%) of them were due to ALQ and 4 (1.6%) of them were due to variation in internal standard.	Summary and Table 1 and 6 of report # 34559-1	Yes
Standard curve performance	Cumulative bias range: -1.4 to 1.4% Cumulative precision: ≤ 5.7% CV%	Table 3 of report (b) (4) 2009104.01	Yes
QC performance	% Bias	Table 4 of report (b) (4) 2009104.01	Yes
	% CV LQC: 6.0% MQC: 6.0% HQC: -0.8% DQC: -9.7%	LQC (1.50 ng/mL) MQC (150 ng/mL) HQC (375 ng/mL) DQC (1000 ng/mL)	
Method reproducibility (ISR)	128 of 1566 (8.2%) samples were assessed, 97.7% within ±20%	Table 7 of report (b) (4) 2009104.01	Yes
Study sample analysis/stability	Samples received: 12/29/2020 to 06/08/2021 Samples assayed: 01/12/2021 to 06/10/2021	Sample Analysis and Study Information sections of report # 2009104.01	Yes
Method Performance in Study NIR-DT-104 (Ongoing, interim PK report), Addendum 1 Bioanalytical Report A2101086.02 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	11 of 11 (100%) runs, 480 samples were analyzed (780 received). Reinjections were not stated. 9 samples were reanalyzed; reason was not stated.	Sample Analysis section and Table 1 and 6 of report (b) (4) 2101086.02	Yes
Standard curve performance	Cumulative bias range: -2.2 to 3.0% Cumulative precision: ≤ 5.7% CV%	Table 3 of report (b) (4) 2101086.02	Yes
QC performance	% Bias	Table 4 of report (b) (4) 2101086.02	Yes
	% CV LQC: 27.3%* MQC: 9.3% HQC: 9.9%	LQC* (1.50 ng/mL) MQC (150 ng/mL)	

	DQC: 5.0%	DQC: 5.4%	HQC (375 ng/mL) DQC (1000 ng/mL) *One LC outlier; reviewed with and without outlier included in statistics.	
Method reproducibility (ISR)	32 of 480 (6.7%) samples were assessed, 84.4% within $\pm 20\%$		Table 7 of report (b) (4) 2101086.02	Yes
Study sample analysis/stability	Samples received: 03/29/2022 to 08/03/2022 Samples assayed: 04/11/2022 to 08/22/2022		Sample Analysis section and Table 1 of report (b) (4) 2101086.02	Yes

OSIS Reviewer's Assessment

The method showed the acceptable performance for nirogacestat in the presence of 32,400 ng/mL rifampicin, 2,360 ng/mL digoxin, 300 ng/mL dabigatran etexilate (V2007078.02 Addendum 1), or 4000 ng/mL itraconazole (V2007078.02 Addendum 2). Hemolysis and lipemia had no notable effect on assay performance. Seven cycles of freeze-thaw stability were established and acceptable. For assessments not evaluated in method validation V2007078.02 (i.e., stock solution stability, long-term stability), references were made to the nirogacestat method validation report A8649007 conducted by (b) (4), which is considered acceptable.

It was noted that in clinical study NIR-DT-301, there were 604 human serum samples initially analyzed by (b) (4) then reanalyzed by (b) (4). The explanation for reanalysis and the dataset of the 604 samples initially analyzed by (b) (4) were requested in the Information Request (conveyed on 04/05/2023). The Applicant provided response and dataset on 04/12/2023. This Reviewer calculated the mean difference of the drug concentration values between the initially analyzed from (b) (4) and the reanalyzed from (b) (4), resulting in $3.5\% \pm 10.9\%$ SD by using the equation for incurred sample reanalysis (ISR): $(\text{repeat} - \text{original}) / \text{average} * 100$. The Information Request response appears reasonable per the OSIS perspective, but OSIS finds the results of the 32 samples analyzed outside of the 520-day long-term stability unreliable (please see Information Request and Response section below for details).

Overall, partial method validation V2007078.02 and related amendments appear to be appropriate for quantifying nirogacestat in human serum for bioanalytical studies (b) (4) 2007079.01, (b) (4) 009104.01, and (b) (4) 101086.02 supporting clinical studies NIR-DT-301, NIR-DT-103, and NIR-DT-104.

Information Request and Response

(b) (4)

OSIS Recommendation

Due to the inability of (b) (4) to extend the long-term stability from the 520 days established by (b) (4) the results of the 32 samples assayed by (b) (4) outside of the 520-day stability window are unreliable. This concern has been communicated to OCP.

– Nirogacestat Quantification in Human Urine

OSIS's review of method validation report AR0308B for measuring nirogacestat in human urine is presented in Table 64 below. This method validation was used to support bioanalytical reports 25933, 34408, and 34559-2. These bioanalytical studies are used to support the Phase 1 clinical study A8641002, Phase 1 clinical study NIR-DT-101 (part 1 only), and Phase 1 clinical study NIR-DT-102.

Table 64 Summary of Method Validation Report AR0308B and Bioanalytical Reports 25933, 34408, and 34559-2

Method Validation Report AR0308B (b) (4)		Additional Details	OSIS Acceptability
Analyte	Nirogacestat (PF-03084014)	Lot 109191-83-8F	N/A
Internal standard	PF-04510856	Lot 101673-181-1	N/A
Biological Matrix	Human urine with 21mM CHAPS	N/A	N/A
Methodology	LC-API/MS/MS	Run/assay dates: 04/27/2007 to 07/17/2008	N/A
Calibration curve range	1.00 to 500 ng/mL	1.00, 2.00, 5.00, 10.0, 50.0, 100, 400, 500 ng/mL	Yes
Capability of dilution (concentration tested; dilution factor)	1000 ng/mL in human urine, 50-fold dilution	Table 9 of report # AR0308B	Yes
Addenda, amendments, cross-validations, or partial validations	Partial Method Validation Report for the determination of PF-03084014 in human urine using LC-API/MS/MS	Report # AR0308BPV Run/assay dates: 01/13/2020 to 02/03/2020 Updates/corrections: (1) partial method validation for upgraded LCMS instrument and (2) evaluated impact of reversing nonspecific binding for the analyte in samples not containing detergent CHAPS.	Yes
Selectivity (number of lots tested/passed) and matrix effect	10 of 10 lots of matrix tested; no significant interference observed	Validation Summary of report # AR0308B and Table 6 of report # AR0308BPV	Yes
Inter-run accuracy (%bias) for	1.00 ng/mL: -1.2%	Table 8 of report # AR0308B	Yes

each QC concentration	3.00 ng/mL: -2.1% 75.0 ng/mL: -2.8% 375 ng/mL: -4.3%	Intra-run precision (%CV) ≤ 13.5%, accuracy -8.53 to 3.30%	
Inter-run precision (%CV) for each QC concentration	1.00 ng/mL: 5.0% 3.00 ng/mL: 9.6% 75.0 ng/mL: 6.8% 375 ng/mL: 6.9%	Inter-run precision (%CV) ≤ 9.64%, accuracy -4.33 to -1.15%	
Short-term or bench-top temperature stability	5 hours at room temperature 25°C) 21 hours at refrigerator (4°C)	Table 11 of report # AR0308B	Yes
Long-term stability	277 days at -70°C 370 days at -20°C	Table 14 of report # AR0308B Table 13 of report # AR0308B	Yes
Freeze-thaw stability	3 freeze-thaw cycles at -20°C and -70°C	Table 15 of report # AR0308B	Yes
Stock solution stability	Not determined	Note: Validation Summary states stock solution stability would be added to an addendum, but no addendum was included with the assessments.	N/A
Processed sample stability	69 hours at 25°C in [(85:10:5 acetonitrile:water:methanol) with 2 mM ammonium acetate, ~0.1% formic acid]	Table 16 of report # AR0308B	Yes
Recovery: extraction efficiency	Mean recovery from 3.00, 75.0, 375 ng/mL 65.8%	Table 5 of report # AR0308B	Yes
Hemolysis and lipemia	Not applicable	N/A	N/A
Carry-over	No significant carry-over	Validation Summary of report # AR0308B	Yes
Method Performance in Study A8641002 Bioanalytical Report 25933, p1314 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	2 of 2 runs (100%). 54 samples analyzed (70 received) No reanalysis noted.	Report Summary	Yes
Standard curve performance	Cumulative bias range: -1.5 to 1.4% Cumulative precision: ≤ 4.7% CV%	Table 5 of report # 25933	Yes
QC performance	% Bias	% CV	Yes
	3.0 ng/mL: 2.3% 75.0 ng/mL: 2.5% 375 ng/mL: -0.3%	3.0 ng/mL: 6.0% 75.0 ng/mL: 4.0% 375 ng/mL: 3.1%	
Method reproducibility (ISR)	Not determined	N/A	N/A
Study sample analysis/stability	Samples received: 06/20/2007 to 08/29/2007	Sample Receipt section and Table 1 of report # 25933	Yes

	Samples assayed: 11/17/2007 to 11/16/2007			
Method Performance in Study NIR-DT-101 Bioanalytical Report 34408 (b) (4)		Additional Details	OSIS Acceptability	
Assay passing rate	5 of 5 runs (100%). 154 samples were analyzed (307 samples received, including 153 backups). 1 reinjection due to poor chromatography. 1 sample was reanalyzed due to failure to meet IS acceptance criteria.		Summary and Tables 1 and 6 of report # 34408	Yes
Standard curve performance	Cumulative bias range: -2.5 to 2.5% Cumulative precision: ≤ 6.6% CV%		Table 3 of report # 34408	Yes
QC performance	% Bias	% CV	Table 5 of report # 34408	Yes
	3.0 ng/mL: -3.8%	3.0 ng/mL: 4.9%		
	75.0 ng/mL: -4.5%	75.0 ng/mL: 4.2%		
	375 ng/mL: -9.3%	375 ng/mL: 2.5%		
Method reproducibility (ISR)	23 of 154 (14.9%) samples were assessed, 95.7% within ±20%		Table 7 of report # 34408	Yes
Study sample analysis/stability	Samples received: 12/17/2019 and 12/18/2019 Samples assayed: 02/07/2020 to 02/17/2020		Sample Receipt and Storage and Summary sections of report # 34408	Yes
Method Performance in Study NIR-DT-102 Bioanalytical Report 34559-1 (b) (4)		Additional Details	OSIS Acceptability	
Assay passing rate	4 of 6 (66.7%) runs. 192 samples were analyzed (384 samples received, including 192 backups) No reinjections or reanalysis were reported. Both failed runs were ISR runs, rejected due to QCs. Unclear if samples were reinjected.		Summary and Table 1 of report # 34559-2	Yes
Standard curve performance	Cumulative bias range: -1.4 to 1.0% Cumulative precision: ≤ 10.8% CV%		Table 3 of report # 34559-2	Yes
QC performance	% Bias	% CV	Table 5 of report # 34559-2	Yes
	3.0 ng/mL: -1.3%	3.0 ng/mL: 7.7%		
	75.0 ng/mL: 1.1%	75.0 ng/mL: 8.2%		

	375 ng/mL: - 4.3%	375 ng/mL: 11.8%		
Method reproducibility (ISR)	24 of 192 (12.5%) samples were assessed, 83.3% within ±20%		Table 6 of report # 34559-2	Yes
Study sample analysis/stability	Samples received: 01/10/2020 and 01/14/2020 Samples assayed: 2/18/2020 to 03/03/2020		Sample Receipt and Storage and Summary sections of report # 34559-2	Yes
OSIS Reviewer’s Assessment				
Method validation AR0308B appears to be appropriate for quantifying the nirogacestat in human urine to support bioanalytical studies 34408 and 34559-1 and the related clinical studies NIR-DT-101 and NIR-DT-102.				

– **[¹⁴C]-Nirogacestat Quantification in Human Serum**

OSIS's review of method validation report 193/006V for measuring [¹⁴C]-nirogacestat in human serum is presented in Table 65 below. This method validation was used to support analytical report 193/007, which is used to support the Phase 1 clinical study NIR-DT-102.

Table 65 Summary of Method Validation Report 193/006V and Analytical Report 193/007

Method Validation Report 193/006V (b) (4)		Additional Details	OSIS Acceptability
Analyte	¹⁴ C- PF-03084014	N/A	N/A
Internal standard	PF-03084014	N/A	N/A
Biological Matrix	Human serum	N/A	N/A
Methodology	HPLC-AMS	Experiment dates: 02/05/2020 to 03/01/2020	N/A
Calibration curve range	0.166 to 2.00 dpm/mL	0.166, 0.181, 0.500, 0.844, 1.13, 1.50, 2.00 dpm/mL	Yes
Capability of dilution (concentration tested; dilution factor)	Not determined	Deviations section of report # 193/006V	N/A, See Additional Details
Addenda, amendments, cross-validations, or partial validations	N/A	N/A	N/A
Selectivity (number of lots tested/passed) and matrix effect	Not determined	N/A	N/A
Inter-run accuracy (%bias) for each QC concentration	LLQC: 3.6% LQC: 5.4% MQC: 8.1% HQC: 3.3%	Table 6 of report # 193/006V Inter-run accuracy 89.4-116%, %CV 4.24-14.9%	Yes
Inter-run precision (%CV) for each QC concentration	LLQC: 12.4% LQC: 5.3% MQC: 6.9% HQC: 3.9%	LLQC: 0.167 dpm/mL; 3.28 pg/mL LQC: 0.500 dpm/mL; 9.81 pg/mL MQC: 0.750 dpm/mL; 14.7 pg/mL	

		HQC: 1.50 dpm/mL; 29.5 pg/mL	
Short-term or bench-top temperature stability	Not determined	N/A	N/A
Long-term stability	Not determined	N/A	N/A
Freeze-thaw stability	Not determined	N/A	N/A
Stock solution stability	Not determined	N/A	N/A
Processed sample stability	Not determined	N/A	N/A
Recovery: extraction efficiency	Not determined	N/A	N/A
Hemolysis and lipemia	Not determined	N/A	N/A
Carry-over	No significant carry-over observed	Table 7 of report # 193/006V	N/A
Method Performance in Study NIR-DT-102 Analytical Report 193/007 (b) (4)		Additional Details	OSIS Acceptability
Assay passing rate	5 of 8 runs, 162 serum samples analyzed (348 samples received, including 174 back-ups.)	Section 11.5 and Table 21 of report # 193/070	Yes
Standard curve performance	Cumulative bias range: -2.5 to 6.0% Cumulative precision: ≤ 7.3% CV%	Table 22 of report # 193/070	Yes
QC performance	% Bias	Table 23 of report # 193/070 LQC (0.50 dpm/mL) MQC (0.75 dpm/mL) HQC (1.50 dpm/mL)	Yes
	% CV LQC: 0.7% MQC: 3.8% HQC: 3.6%		
Method reproducibility (ISR)	18 of 168 (10.7%) samples were assessed, 88.9% within ±20%	Table 25 of report # 193/070	See Additional Details
Study sample analysis/stability	Samples received: (not provided) Samples assayed: 12/11/2019 to 06/24/2020	Responsible Personnel section of report # 193/070	See Additional Details
OSIS Reviewer's Assessment			
Due to the limited data included in method validation report 193/006V and study 193/007, the quantification of ¹⁴ C-nirogacestat in human serum is considered not fully validated from the OSIS perspective. For the percentage of ¹⁴ C radioactivity in excretion reported in other matrices (i.e., urine, feces and expired air), there was no method validation for OSIS to review (please see Information Request and Response section below for details). These issues have been communicated to OCP.			

Information Request and Response

(b) (4)

OSIS Recommendation

Due to the limited data information included in method validation report 193/006V, the quantification of ^{14}C -nirogacestat in human serum is considered not fully validated from the OSIS perspective, particularly with diluted samples (e.g., those listed in section 11.5 of report 193/007). For the percentage of ^{14}C radioactivity in excretion reported in other matrices (i.e., urine, feces, and expired air), there was no method validation for OSIS to review. OSIS has communicated these issues to OCP review team and will defer OCP's final determination of the usage of the data to support labeling (OCP's assessment is described in the review above).

19.4.4. Population PK Analysis

19.4.5. Executive Summary

A series of clinical studies (including DDI and ADME studies) have been completed to characterize the clinical pharmacology of nirogacestat. Nirogacestat was rapidly absorbed and T_{max} was reached between 0.5-2 hours across all evaluated doses. Nirogacestat concentration-time profiles showed multi-phasic disposition. Following repeat doses of nirogacestat, steady-state appears to have been achieved by approximately Day 7. The absolute bioavailability (F) of nirogacestat following oral administration of a 150 mg dose was 19.2%.

Nirogacestat is a sensitive substrate of CYP3A4 and subject to DDI based on CYP3A4 metabolism. Following administration of 100 mg nirogacestat with itraconazole, a strong CYP3A4 inhibitor and clinical inhibitor of P-gp, nirogacestat C_{max} and AUC_{inf} were increased by 2.5- and 8.2-fold, respectively, compared to when given alone. Renal excretion of nirogacestat is negligible (0.020 to 0.042% recovered unchanged in urine).

A PopPK model was developed to support the dose rationale for nirogacestat and is included in this NDA. This activity included the following objectives:

- Develop a PopPK model to characterize the PK of nirogacestat in healthy subjects and participants;
- Evaluate the effect of covariates on the variability of the PK of nirogacestat;
- Evaluate the magnitude and clinical relevance, when possible, of the statistically significant findings from the analysis;
- Predict exposures following doses of nirogacestat under scenarios of clinical importance, if applicable

Methods: Nonlinear mixed effects modeling was used to develop the PopPK model using data from healthy volunteers and oncology participants following single or multiple dose oral administration of nirogacestat. Model building started with a simple one compartment, first-order absorption model and increased step-wise in complexity until further improvement in fit was not supported by the data. The impact of structural covariates (e.g. dose and DDI), study-specific parameters and individual subject characteristics (e.g. body weight and participant population) were assessed using manual forward addition/backward elimination. The final model was qualified by numerical and graphical goodness of fit (GOF) checks, including visual predictive checks (VPCs).

Results: PK data from 335 healthy adult volunteers and oncology participants, collected in six healthy volunteer (A8641001, A8641002, A8641008, NIR-DT-101, NIR-DT-102, and NIR-DT-103) and two oncology participant studies (A8641014 and NIR-DT-301), were available for the PopPK analysis. The disposition and elimination of nirogacestat in serum was best described by a three-compartment model with lag-time, first-order absorption kinetics after oral administration.

Clearance (CL) was 9.09 L/h in healthy volunteers and participants with DT. In participants with solid tumors or T-ALL/LBL, CL was lower and estimated to be 4.4 L/h. Estimates for central volume of distribution (V_c), peripheral volume of distribution - shallow compartment (V_{p1}) and peripheral volume of distribution – deep compartment (V_{p2}) were 7.74 L, 11.5 L, and 115 L, respectively.

Following oral administration, nirogacestat was rapidly absorbed through a lag-time, first-order absorption process. Absorption in Study NIR-DT-301 was slower (absorption rate constant (k_a) = 0.38 h⁻¹) compared to the Phase 1 studies (k_a = 0.876 h⁻¹).

In addition to the participant-specific elimination, body weight, CYP3A4 inhibition, and dose were each found to have a statistically significant influence on the nirogacestat PK. V_{p2} was found to increase proportionally with weight. Nirogacestat was subject to CYP3A4-based DDI with approximately 4.7-fold lower CL (CL = 1.94 L/h) and F increased 2-fold (absolute F = 38%) following co-administration with the strong CYP3A4 inhibitor itraconazole. Other co-medications did not appear to affect nirogacestat PK, but inference may be inconclusive given the overall low number of subjects.

A trend between F and dose was seen at lower doses. F was found to be dose-dependent and asymptotically increased to a value of 19.2% as dose levels increased. The dose-dependent effect was not meaningful at doses equal or greater than 10 mg.

Conclusions:

- Nirogacestat PK was adequately characterized by a three-compartment, lag-time, first-order absorption model.
- Study-phase specific differences in k_a and residual variability were observed, with slower nirogacestat absorption, shorter Tlag, and a distinct error model for Study NIR-DT-301 – residual variability was also dependent on the bioanalytical lab used for serum quantification.
- Administration of nirogacestat with a powder-in-bottle formulation in early Phase 1 studies resulted in a shorter Tlag and lower F as compared to tablet formulations.
- CL was lower in participants with solid tumors or T-ALL/LBL (4.4 L/h) compared to healthy volunteers and participants with DT (9.09 L/h).

- V_{p2} was found to increase proportionally with weight.
- Strong CYP3A4 inhibitors affected nirogacestat PK, with approximately 4.7-fold lower CL and 2-fold higher F following itraconazole co-administration.
- F was dose-dependent and asymptotically increased with increasing doses. For doses equal or greater than 20 mg, F converged to a value of 19.2%.

The FDA's Assessment:

FDA agrees.

19.4.6. PPK Assessment Summary

The Applicant's Position:

The disposition and elimination of nirogacestat in serum is best described by a three-compartment model with lag-time and first-order absorption kinetics after oral administration. Key clinically relevant covariate relationships described include an effect for CYP3A4 inhibition on CL and F, weight on the peripheral volume compartments, and participant population on CL. Notably, the PK of nirogacestat in participants with DT was more similar to that observed in healthy volunteers than to nirogacestat PK described in participants with advanced solid tumors (other than DT) and T-ALL/LBL (collectively referred to as advanced malignancies for the PopPK analyses). This difference was explained by a 52% reduction in the fixed effects estimate for CL in participants with advanced malignancies relative to healthy volunteers and participants with DT.

General Information		
Objectives of PPK Analysis		• Characterize nirogacestat's PK profile • Identify the source of PK variability to support individualized dosing • Predict individual exposure for E-R assessment
Studies Included		A8641001, A8641002, A8641008, NIR-DT-101, NIR-DT-102, NIR-DT-103, A8641014, NIR-DT-301
Dose(s) Included		1, 2.5, 5, 10, 25, 40, 50, 65, 100, 120, and 150 mg QD (single dose) 7, 40, and 95 mg QD (multiple dose) 20, 40, 80, 100, 130, 150, 220, and 330 mg BID (multiple dose)
Population Included		Healthy volunteers, participants with T-ALL/LBL, participants with solid tumors other than DT, participants with DT (ITT)
Population Characteris	General	Age median (range): 37.0 yrs (18 – 80.0), 25 (7.5%) participants ≥ 65 yr, 4 (1.2%) participants ≥ 75 yr

tics (PopPK Report Table 2)		Weight median (range): 79.3 kg (42.5-167) Male: 236 (70.4%) Asian: 7 (2.1%) Black/African American: 88 (26.3%) Native American: 1 (0.3%) Other: 19 (5.7%) White/Caucasian: 220 (65.7%)
	Organ Impairment	Hepatic impairment - none Renal impairment – eGFR mean (range) 88.1 mL/min/1.73m ² (40.7-234), 14 (4.2%) participants w/eGFR ≤ 60 mL/min/1.73m ² . 3 (0.9%) participants w/eGFR ≤ 45 mL/min/1.73m ²
	Pediatrics (if any)	None
No. of Patients, PK Samples, and BLQ		335 adult participants; 5473 PK samples 374 (96.6%) of pre-dose samples were BLQ 323 (5.5%) of post-dose samples were BLQ
Sampling Schedule	Rich Sampling	A8641001: 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96h A8641002 (Time after Day 1): 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 73, 144, 145, 264, and 288h A8641002 (Day 14): 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96h A8641008: 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, and 72h NIR-DT-101: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 1536, and 2880h NIR-DT-102: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 648h NIR-DT-103: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96h
	In ITT population	A8641014: Cycle 1/Day 1 - 0, 0.5, 1, 2, 4 and 10h Cycle 1/Day 8 – pre-dose Cycle 1/Day 15 – pre-dose, 1h Cycle 1/Day 21 – pre-dose, 0.5, 1, 2, 4, 10, 24, 48, 96, 120 Cycle 2 to Cycle 8/Day1 – 1h, Day 15 – pre-dose NIR-DT-301: Cycle 1/Day 1 – pre-dose, 0.25, 0.5, 1, 1.5, 2 and 3h Cycle 1/Day 8, 15 and 22 – pre-dose Cycle2/Day 28, Cycle 4/Day 1 and every 3 cycles – pre-dose
Covariates Evaluated	Static	Body weight, participant population, dose, BMI, sex, age, body surface area, race, ethnicity, tumor type, participant status, formulation, fed status

	Time-varying	Bilirubin, AST, ALT, albumin, eGFR, creatinine clearance, CYP3A co-medication, other comedications including antacid, H2-receptor antagonist, PPI, P-gp inhibitors and inducers, diarrhea	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		NONMEM (Version 7.4)	Yes
Model Structure		Three-compartment, lag-time, first-order absorption model	Yes
Model Parameter Estimates		Table 66	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		In the final model, all parameters were estimated with sufficient precision with RSE < 50%. η-shrinkage was determined to be 11%, 57%, 15%, 18%, 28%, 42%, and 19% for the evaluated parameters of F, ka, CL, Vc, Vp2, Tlag, and itraconazole-mediated inhibition of CYP3A4, respectively. IIV (%CV) for these parameters were 62% (F), 13% (ka), 32.9% (CL), 93.7% (Vc), 30.1% (Vp2), 24.1% (Tlag), and 27.2% (itraconazole inhibition). Residual variability was described by a proportional error model with estimates of 17.8% CV ((b) (4) bioanalytical lab), 47.1% CV (patient studies), 24.1% CV ((b) (4) and 13.3% CV ((b) (4) lab). Generally, residual variability was larger in the patient studies (A8641014 and NIR-DT-301) compared to the healthy volunteer studies. Large inter- and intra-study variability was observed in serum exposures; however, the model was able to reasonably capture the central tendency and observed variability. The model tended to under predict serum concentrations around Tmax in Study NIR-DT-301. The under-prediction, however, may be the consequence of the complex, variable absorption of nirogacestat, which may not be entirely captured by the simple lag-time, first order absorption model, particularly with highly variable data from the Phase 3 trial.	Yes. Despite that underprediction of Cmax was observed, individual profiles of patients with DT in Study NIR-DT-301 fit the sparse PK observed on Cycle 1 Day 1 and steady state reasonably well.

BLQ for Parameter Accuracy	The LLOQ for all methods was 0.5 ng/mL. BLQ values were assumed to be 0.5*LLOQ (0.25 ng/mL). Since post-dose BLQ frequency was relatively low and rather inflated by the low doses of Study A8641001 and the late sampling times in NIR-DT-101 and NIR-DT-102, it was deemed that missing values did not unduly influence model building. As such, likelihood-based approaches to handling BLQ were not considered.	Yes
GOF, VPC	Diagnostic GOF plots from final model are in figures below. VPCs are in figures below.	Yes
Significant Covariates and Clinical Relevance	Study population and Itraconazole-mediated CYP3A4 inhibition has a large effect on CL (data below). Weight has a proportional effect on Vp2. Formulation and itraconazole-mediated CYP3A4 inhibition had a dose-dependent effect on absolute bioavailability, converging to 19.2% for tablet doses ≥ 10 mg (Table 69 below).	Yes. Only CYP3A strong inhibitors (i.e., itraconazole) is expected to have clinically meaningful impact on exposure (9.3 folds higher) and is recommended against concomitant use.
Analysis Based on Simulation (optional)	Predicted exposures provided in Table 70 below.	Yes. PK profile of patients with DT was not characterized by NCA analysis due to sparse sampling. Full PK profiles were predicted based on individual parameters estimated by the final popPK model, which is then analyzed by NCA to derive NCA parameters (e.g., Cmax, T1/2, accumulation ratio, etc) for labeling.
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	General nirogacestat PK parameters are summarized in USPI Table 6. Nirogacestat is rapidly absorbed with bioavailability limited by significant first-pass metabolism. Exposure is similar between fed and fasted states, and nirogacestat was dosed without regard to food in Study NIR-DT-301. Nirogacestat is highly protein bound and widely distributed throughout the body. Nirogacestat is	Generally acceptable. PK parameters in Table 6 of USPI were updated based on popPK analysis to provide values for patients with desmoid tumor in place of values for patients with T-ALL/LBL and solid tumors who had 52% lower CL.

	extensively metabolized by CYP3A4, with metabolized drug product recovered in feces, urine, and expired air. Less than 0.1% of unchanged nirogacestat is recovered in urine. <u>Specific Populations</u> <i>Effects of Age, Gender and Race</i> A PopPK analysis of nirogacestat was performed, which found no clinically meaningful effect of age, gender, or race on the PK of nirogacestat. <i>Effects of Hepatic Impairment</i> The PK of nirogacestat were evaluated in participants with moderate to severe hepatic impairment based on Child-Pugh classification and moderate hepatic impairment based on NCI-ODWG classification. Participants classified as moderate by Child-Pugh classification with total bilirubin levels $1.5 \times \text{ULN}$ or lower (i.e., those that did not meet the criteria for moderate impairment by NCI-ODWG) did not exhibit significant differences in nirogacestat PK. Some participants that met the criteria for moderate impairment by NCI-ODWG (total bilirubin $> 1.5 \times \text{ULN}$) exhibited lower C_{max}, higher volume of distribution, longer half-lives, and greater overall exposure compared to healthy controls. Therefore, nirogacestat is contraindicated in patients diagnosed with moderate or severe hepatic impairment per NCI-ODWG criteria (total bilirubin $> 1.5 \times \text{ULN}$). <i>Effects of Renal Impairment</i> The effects of renal impairment on nirogacestat PK have not been evaluated in a clinical trial; however, in a PopPK model no meaningful relationship was observed between renal function tests and nirogacestat PK. Clinical studies determined that nirogacestat is extensively metabolized, and no major metabolites were found in urine. Only small amounts of unchanged nirogacestat were detected in the urine.	The effect of hepatic impairment has only been assessed in dedicated study given no patients with hepatic impairment was included in PPK assessment. Based on PPK assessment, CYP3A strong inhibitors (i.e., itraconazole) is expected to have clinically meaningful impact on exposure (9.3 folds higher) and is recommended against concomitant use.

	<u>Drug Interaction Studies</u> <i>Effect of other drugs on nirogacestat</i> Nirogacestat is a sensitive CYP3A4 substrate. In vitro studies with human liver microsomes indicated that nirogacestat is primarily metabolized by the drug-metabolizing enzyme CYP3A4 (85%). The effect of CYP3A4 inhibitors on nirogacestat was evaluated with itraconazole, a strong CYP3A4 inhibitor, in healthy participants. Using clinical and in vitro data, a mechanistic PBPK model was developed to simulate interaction scenarios with various CYP3A4 inhibitors and inducers. Co-administration of nirogacestat with strong and moderate inhibitors of CYP3A4 may increase serum nirogacestat concentrations exceeding those observed at the maximum tolerated dose. Co-administration of nirogacestat with strong and moderate inducers of CYP3A4 may decrease serum nirogacestat concentration to poorly effective levels. Co-administration of nirogacestat with strong CYP3A4 inducers may result in negligible nirogacestat exposure. Co-administration of nirogacestat with moderate CYP3A inducers may result in significant decrease of nirogacestat exposure, but not to a negligible level. In vitro permeability studies and knockout mouse studies indicate that nirogacestat may be a substrate of the P-gp transporter. Since itraconazole may also inhibit P-gp, the results of the clinical evaluation with itraconazole may also be in part due to P-gp inhibition. CYP3A4 inhibition, however, is the dominant interaction. The solubility of nirogacestat is substantially reduced at pH greater than 6.0. No clinical studies have been conducted to evaluate the effects of drugs that increase gastric pH, such as proton pump inhibitors or H2-receptor antagonists, on nirogacestat; however, co-administration of these drugs with	

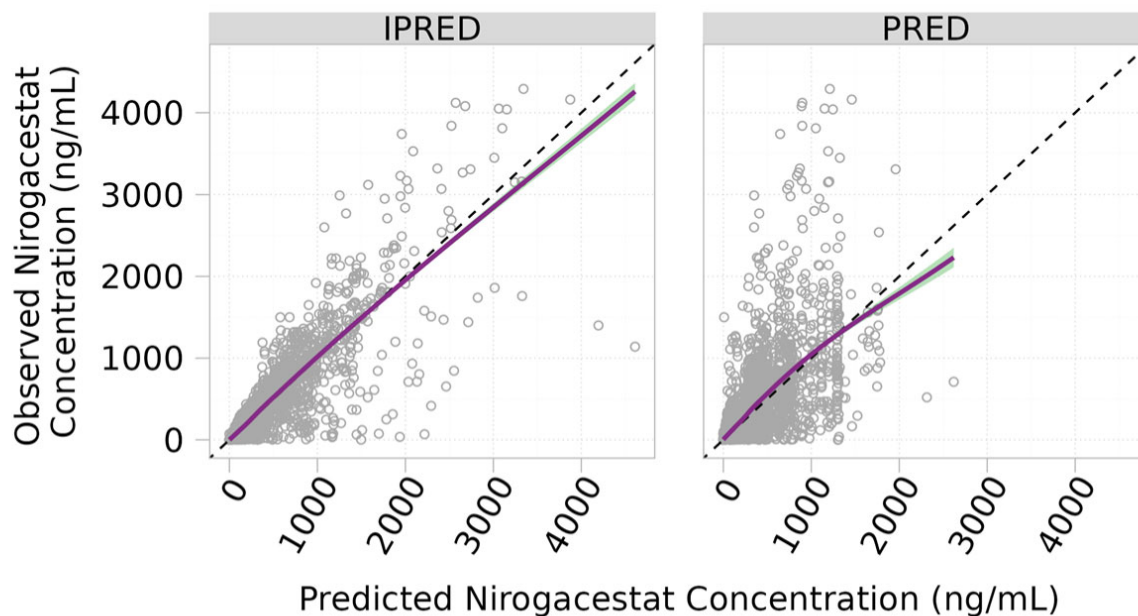
	nirogacestat may reduce the bioavailability of nirogacestat. <i>Effect of nirogacestat on other drugs</i> The effects of nirogacestat on midazolam, a sensitive CYP3A4 substrate, were evaluated in clinical studies of healthy participants. Using clinical and in vitro data, a mechanistic PBPK model was developed to simulate interaction scenarios with substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Nirogacestat is a weak inhibitor of CYP3A4 and administration of nirogacestat may increase the exposure of CYP3A substrates. No meaningful effects were predicted for nirogacestat on substrates of CYP2B6, CYP2C8, and CYP2C9. PBPK simulations predicted minimal-to-weak induction of CYP2C19, however a sensitivity analysis under worst-case conditions predicted potential for moderate induction. Effects of nirogacestat on CYP2C19 substrates have not been evaluated in a clinical study; however, weak-to-moderate induction may be possible.	

Table 66 Parameter Estimates of the Final PopPK Model

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

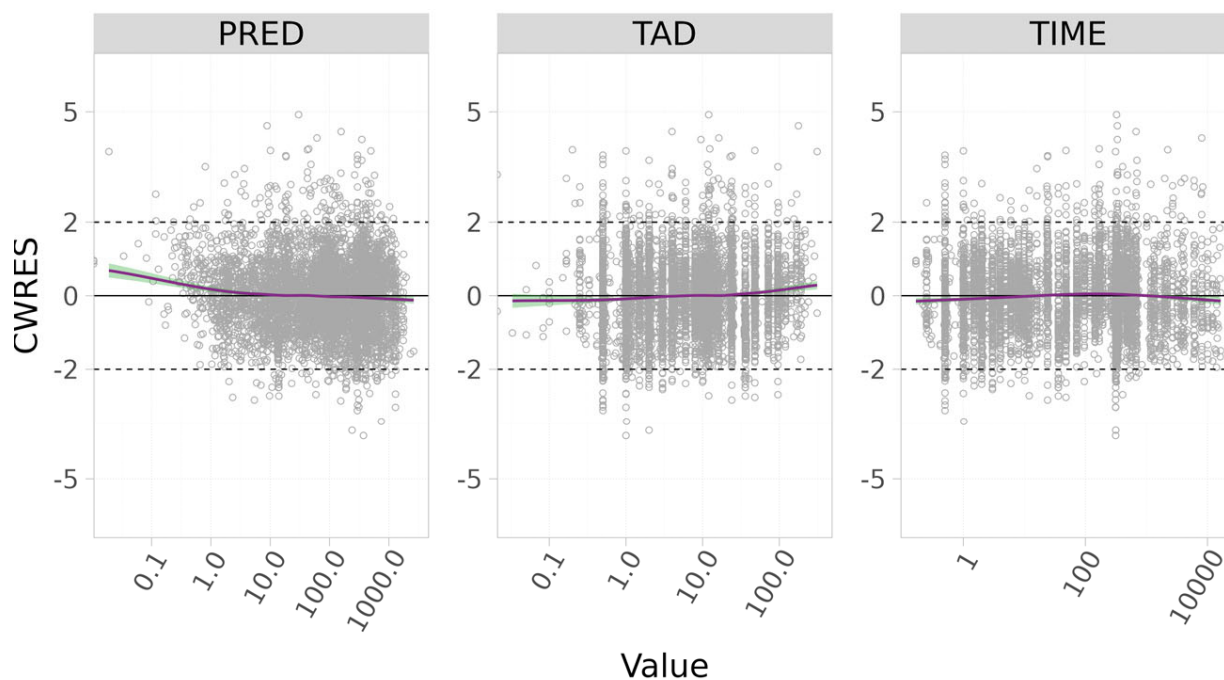
CI95: 95% Confidence interval; **NA:** not applicable for fixed parameters; ω_X^2 : variance of inter-individual variability of parameter X; **Vp1:** Peripheral volume of distribution - shallow compartment; **Vp2:** Peripheral volume of distribution - deep compartment

Figure 7 **Observed versus Individual and Population Predicted Concentrations – Final PopPK Model**



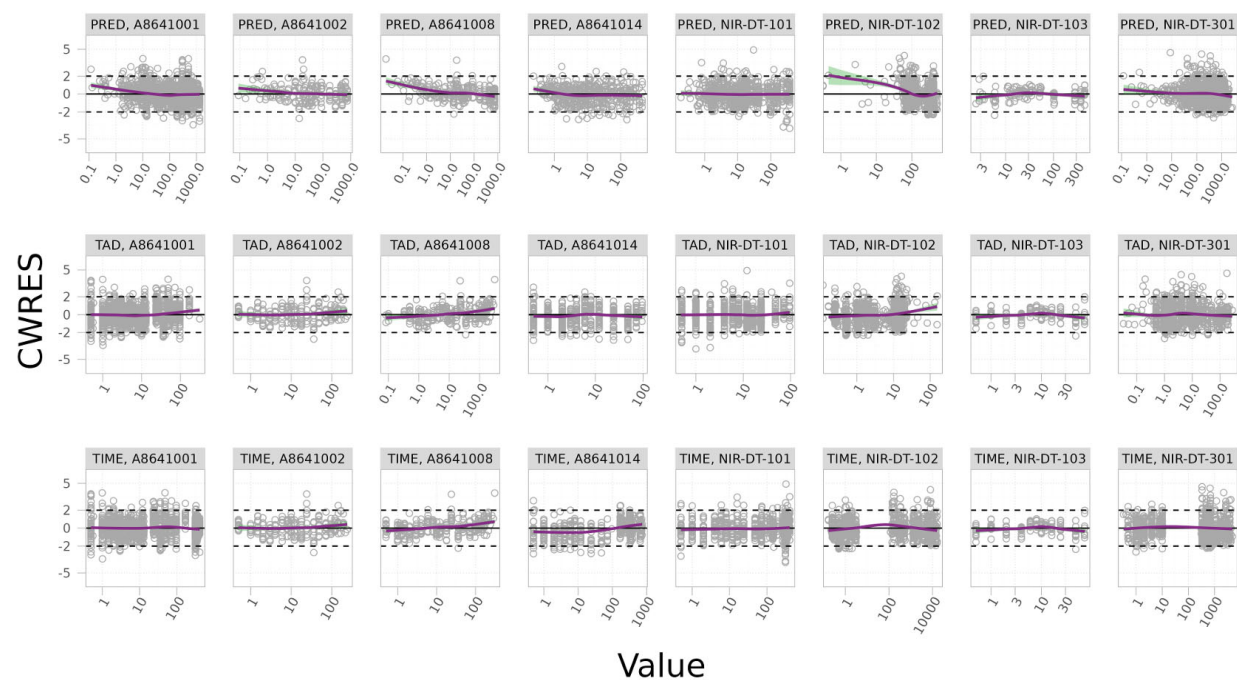
Purple line and green shaded area: Loess smooth with corresponding 95% confidence interval; **Dashed line:** Line of unity; **PRED:** Population prediction; **IPRED:** Individual predictions

Figure 8 **Conditional Weighted Residuals versus Time After Dose and Predictions by Matrix- Final PopPK Model**



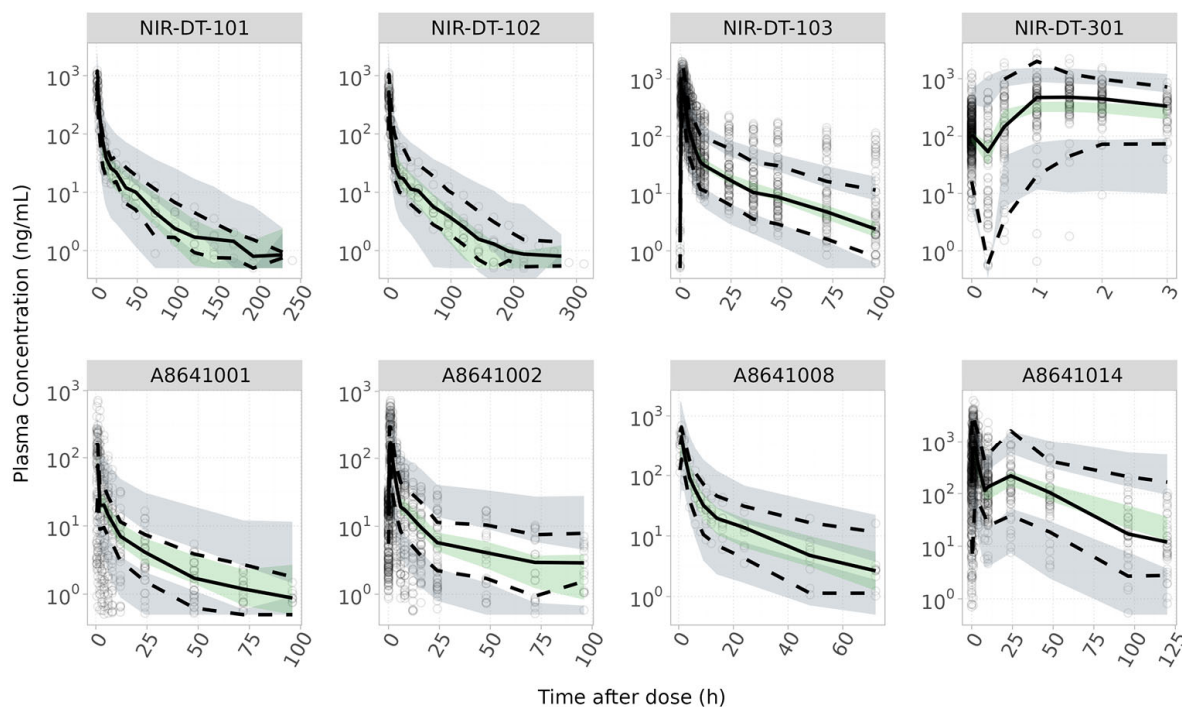
Purple line and green shaded area: Loess smooth with corresponding 95% confidence interval; **PRED:** Population prediction in ng/mL; **TAD:** Time after Dose in hours; **TIME:** Time after First Dose in hours; **Solid line:** Mean zero; **Dashed lines:** Denote 95% distribution interval

Figure 9 Conditional Weighted Residuals versus Time After Dose and Predictions by Study – Final PopPK Model



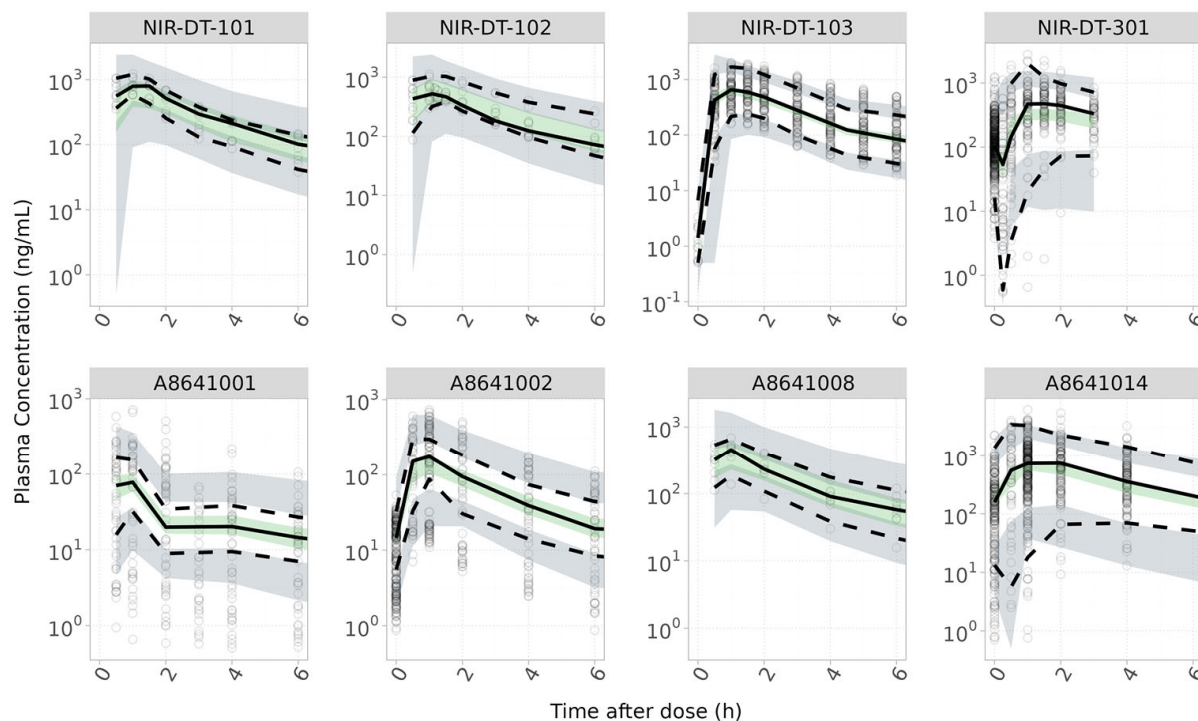
Purple line and green shaded area: Loess smooth with corresponding 95% confidence interval; **PRED:** Population prediction in ng/mL; **TAD:** Time after Dose in hours; **TIME:** Time after First Dose in hours; **Solid line:** Mean zero; **Dashed lines:** Denote 95% distribution interval

Figure 10 Prediction-corrected Visual Predictive Check by Study – Final PopPK Model



Circles: Observations, **Solid Blue Line:** Median of the observed nirogacestat concentrations, **Dashed Lines:** 2.5th and 97.5th percentiles of the observed nirogacestat concentrations, **Shaded Area:** The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5th and 97.5th percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. ([Bergstrand et al., 2011](#)); data was truncated at 0.5 ng/mL (LLOQ)

Figure 11 Prediction-corrected Visual Predictive Check by Study, Truncated at 6 Hours – Final PopPK Model



Circles: Observations, Solid Blue Line: Median of the observed nirogacestat concentrations, Dashed Lines: 2.5th and 97.5th percentiles of the observed nirogacestat concentrations, Shaded Area: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5th and 97.5th percentiles of the simulated concentrations (grey areas). Data truncated at 72 hours post-dose for legibility purposes. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. (Bergstrand et al., 2011); data was truncated at 0.5 ng/mL (LLOQ)

Table 67: Impact of Study Population and Itraconazole-mediated CYP3A4 Inhibition on Serum Clearance – Final PopPK Model

Study Population	No itraconazole		Itraconazole DDI	
	Typical CL L/h	Mean CL (95%) L/h	Typical CL L/h	Mean CL (95%) L/h
HVs/DT	9.09	9.59 (4.74-17.5)	1.93	2.18 (0.716-5.1)
Solid Tumor/T-ALL/LBL	4.39	4.66 (2.32-8.44)	0.934	1.07 (0.35-2.55)

Typical: value of typical individual based on fixed effects estimates; Predicted mean and 95 percent prediction interval are simulation based estimates; HVs: healthy volunteers; T-ALL/LBL: T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma

Table 68 Impact on Weight on Peripheral Volumes of Distribution – Final PopPK Model

Weight <i>kg</i>	Typical Vp2 <i>L</i>	Mean Vp2 (95%) <i>L</i>
55.4	81.2	85.2 (44.8-148)
79	116	121 (65-210)
105	154	161 (85.7-275)

Body weight values are observed 5th, 50th and 95th percentiles; Vp2: peripheral volume of distribution - deep compartment; Typical: value of typical individual based on fixed effects estimates; Predicted mean and 95 percent prediction interval are simulation based estimates

Table 69 Impact of Dose, Formulation, and Itraconazole-mediated CYP3A4 Inhibition on Absolute Bioavailability – Final PopPK Model

Formulation	Dose	No Itraconazole		Itraconazole DDI	
		Typical F1 <i>ratio</i>	Mean F1 (95%) <i>ratio</i>	Typical F1 <i>ratio</i>	Mean F1 (95%) <i>ratio</i>
PiB	<10 mg	0.0795	0.0922 (0.0251-0.234)	0.157	0.18 (0.0501-0.449)
PiB	≥10 mg	0.146	0.161 (0.0477-0.363)	0.29	0.325 (0.0948-0.74)
Tablet/CBS	<10 mg	0.107	0.121 (0.0341-0.284)	0.212	0.24 (0.0677-0.566)
Tablet/CBS	≥10 mg	0.192	0.211 (0.0651-0.453)	0.38	0.417 (0.129-0.896)

PiB: Powder in bottle; CBS: Citrate buffer solution; F1: Bioavailability; Typical: value of typical individual based on fixed effects estimates; Predicted mean and 95 percent prediction interval are simulation based estimates

Table 70 Predicted Exposures and Probability of Target Attainment at Steady-state in Patients with DT

Dose <i>mg</i>	AUCtau (95%) <i>ng/mL</i>	% (95%) ≥ 4030 <i>ng · h/mL</i>	% (95%) ≥ 6900 <i>ng · h/mL</i>
80	1700 (475 - 5100)	5.8 (7.2 - 4.4)	0.7 (1.2 - 0.18)
100	2130 (593 - 6370)	14 (16 - 11)	2.1 (3 - 1.2)
150	3200 (890 - 9560)	36 (39 - 33)	7.4 (9 - 5.8)
220	4690 (1310 - 14000)	59 (62 - 56)	26 (29 - 23)

AUCtau: median of simulated area under the concentration vs. time curve within a dosing interval with corresponding 95% prediction interval; %: percentage of subjects in virtual population above efficacy thresholds with corresponding 95% prediction interval

The FDA's Assessment:

FDA verified the Applicant's analysis and agreed with the Applicant's position. The population PK model described the observed data reasonably well and was considered adequate to predict individual PK estimates for subsequent PK/PD and E-R analysis.

19.4.7. PPK Review Issues

None.

19.4.8. Reviewer's Independent Analysis

None.

19.4.9. Exposure-Response Analysis

19.4.10. ER (efficacy) Executive Summary

PK/PDx models were developed to evaluate the PK/PDx and exposure-response relationship (ERR) between nirogacestat and efficacy endpoints in participants with DT, which included the following objectives:

- Characterize the PopPKPDx relationship of nirogacestat exposure and changes in tumor size;
- Characterize the PopPKPDx relationship of nirogacestat exposure and PFS;
- Characterize the ERR between nirogacestat exposure and BOR and DOR;

Methods: The previously developed nirogacestat PopPK model was used to derive individual exposure parameters. Nonlinear mixed effects modeling was employed to develop PKPDx models to characterize safety and efficacy of nirogacestat in participants with DT, participants with solid tumors other than DT, and participants with T-ALL/LBL. The binary outcome for PFS was analyzed using a time to event model, whereas tumor size was analyzed as a continuous variable. Model development was carried out sequentially, first describing disease progression and placebo response, followed by assessment of the nirogacestat ERR. Covariate-parameter relationships of interest were explored graphically and formally tested if substantial trends were evident. Final PKPDx models were qualified by VPCs, in addition to numerical checks of parameter precision and model robustness.

Bayesian posthoc PK parameter estimates were used to estimate nirogacestat exposures (nominal steady state or exposure at day of onset) for the subsequent exposure-response analysis. For each safety endpoint, nominal steady state exposure was used for participants with no event. To assess the impact of changes in exposure for DOR and BOR, exposure-

response relationships were graphically evaluated in all participants and in nirogacestat treated participants only. Significant relationships were further examined by comparing treatment effect models (i.e., to assess response for nirogacestat treated participants compared to placebo participants) to exposure-response models (i.e., to assess changes in response as nirogacestat concentration changes). DOR was evaluated using exploratory Kaplan-Meier plots and BOR, was evaluated by logistic regression.

Results: A total of 212 participants were available for PFS evaluation. Of those, 150 (70.8%) were participants with DT. The hazard for DT, as a measure of PFS, was 19-fold lower than for other tumors. PFS probability was associated with nirogacestat treatment, independent of nirogacestat exposures, at the evaluated dose range. The PFS HR estimate for treatment relative to no treatment was 0.26. Age and sex were not associated with PFS.

Changes in tumor size over time were characterized by RECIST (DT and other tumors) and tumor volume (DT only) models comprising a first-order tumor growth rate, which was flexible to describe both disease progression and regression in the tumor volume model, and a first-order tumor shrinkage rate. Nirogacestat-mediated tumor regression was described by an on-off treatment effect. An ERR between nirogacestat AUC and tumor sizes could not be established at the evaluated nirogacestat exposure ranges. Tumor size was predicted to change by -22% (RECIST sum of longest diameter) and -55% (tumor volume) following treatment with nirogacestat at doses ≥ 100 mg BID for 24 months. Tumor type, APC tumor suppressor genotype and β -catenin genotype (CTNNB1) were not associated with change in tumor size.

Thirty-six nirogacestat-treated participants (17.3%) and 5 placebo participants (2.4%) were found to have a CR or PR. A statistically significant negative trend was found for nominal C_{max} , C_{min} , AUC at steady state only when placebo participants were excluded from evaluation, indicating that responses occur at lower exposures compared to non-responders across in the nirogacestat treated groups. However, the negative trend was driven by the lack of efficacy and higher exposures observed in patients with non-DT tumor types. The BOR relationship with nominal steady state nirogacestat exposure was not found to be significant in participants with DT alone. Higher exposure did appear to correlate with a longer response, though exposure was not a statistically significant predictor of duration of response.

Conclusion: This analysis represents a comprehensive examination of PKPDx data collected from a Phase 1 trial of nirogacestat in participants with advanced solid tumors and participants with relapsed or refractory T-ALL/LBL, and a Phase 3 trial of nirogacestat in participants with DT. Principal findings of the efficacy analyses are described below.

Efficacy:

- For PFS, the HR estimate for solid tumors and T-ALL/LBL relative to DT tumors was 19. The PFS probability for all tumors was not associated with nirogacestat exposures at the

evaluated dose range but was described by a nirogacestat treatment effect. The HR estimate for treatment relative to no treatment was 0.26.

- There was a nirogacestat-mediated treatment effect on tumor size, which was independent of nirogacestat exposure at the evaluated dose range in participants with DT and non-DT solid tumors.
- Predicted change in tumor size following treatment with nirogacestat at doses ≥ 100 mg BID after 24 months was -22% (RECIST sum of longest diameter) and -55% (tumor volume), respectively.
- Thirty-six nirogacestat-treated participants (17.3%) and 5 participants receiving placebo (2.4%) were found to have a CR or PR. A negative trend for nominal steady state exposure was observed for nirogacestat-treated participants, indicating that responses may occur at lower exposures compared to non-responders. This assessment, however, is confounded by the larger exposures and lack of efficacy in participants with non-DT tumors. The BOR relationship with nominal steady state nirogacestat exposure was not found to be significant in participants with DT alone.
- Higher exposure appeared to correlate with a longer response, though no exposure-response relationship was observed for the duration of response.

The FDA's Assessment:

FDA agrees; however, the analyses above are for modeling purposes only and should not be considered as an FDA agreement of any anti-tumor effects of nirogacestat in other tumor type (beyond DT as described above in the clinical section of this review). Additionally, FDA considers all descriptions of statistical significance in the section to be nominal only.

19.4.11. ER (efficacy) Assessment Summary

The Applicant's Position:

Exposure-response and PKPDx analyses were conducted using a nirogacestat PopPK model and response data obtained from Studies A8641014 and NIR-DT-301. PKPDx analyses characterized nirogacestat-mediated treatment effects for PFS and tumor size that were independent of pharmacological exposure at the evaluated dose ranges. For analyses of nirogacestat exposure and tumor size, an exposure-response plateau was achieved within the exposure ranges predicted for the ≥ 100 mg BID to 150 mg BID dose range. A significant relationship between nirogacestat exposure and OR was not identified at the evaluated dose ranges. There was an apparent trend towards longer responses in the higher exposure group; however, it was not found to be a statistically significant predictor of DOR.

General Information		
Goal of ER analysis		PKPDx models were developed to evaluate the PKPDx and ERR for nirogacestat in participants with DT, which included the following objectives: • Characterize the PopPKPDx relationship of nirogacestat exposure and changes in DT size; • Characterize the PopPKPDx relationship of nirogacestat exposure and PFS; • Characterize the ERR between nirogacestat exposure and BOR and DOR.
Study Included		A8641014 and NIR-DT-301. A8641014 included a range of doses in oncology participants, NIR-DT-301 only included participants with DT
Endpoint		PFS; tumor Volume (MRI, NIR-DT-301 only); tumor size (RECIST)
No. of Patients (total, and with individual PK)		214 total participants (169 participants included individual PK)
Population Characteristics (PopPKPDx Report Table 2)	General	Age median (range): 39.0 yrs (18.0 – 80.0), 27 (12.6)% participants ≥ 65 yr, 5 (2.3)% participants ≥ 75 yr Weight median (range): 73.0 kg (42.5-167) Male: 87 (40.7%) Asian: 5 (2.3%) Black/African American: 14 (6.5%) Other: 14 (6.5%) White/Caucasian: 181 (84.6%)
	Pediatrics (if any)	None
Dose(s) Included		A8641014: multiple oral doses of 20, 40, 80, 100, 130, 150, 220, 330 mg BID in 21-day cycles (7 days off treatment for PK assessments after Cycle 1 only) NIR-DT-301: multiple oral doses of 150 mg BID in 28-day cycles
Exposure Metrics Explored (range)		Efficacy: AUC (0.00 – 55200 ng·h/mL), C _{min} (0.00 – 1780 ng/mL), and C _{max} (0.00 – 4410 ng/mL)
Covariates Evaluated		The following pre-specified covariate-parameter relationships were examined for inclusion: • Population (tumor type), age, and sex for PFS; • Baseline tumor size, population (tumor type; for RECIST only), APC genotype and CTNNB1 genotype for tumor size.
Final Model Parameters		Acceptability [FDA's comments]
Model Structure		The relationships between nirogacestat exposure and efficacy and endpoints were evaluated as PKPDx or ERR models. The PKPDx model development for PFS and tumor size used individual parameter estimates Yes. PK/PD model for tumor size (RECIST or tumor volume)

	from the final PopPK model added to the PKPDx datasets. For the ERR analyses of DOR and BOR, the final PopPK model was used to calculate individual estimates of exposure at nominal steady state. The treatment effect and exposure-response models were parameterized as follows (shown here including covariate effects): Efficacy analysis: Treatment effect: $h(t) = h_0(t) * \exp(\text{Effect} * I_{\text{nirogacestat}} + b1 * (\text{Cov}-\text{median}) + b2_i * I_{\text{Covi}})$ Exposure-response: $h(t) = h_0(t) * \exp(\alpha * (\text{Exposure}-\text{Median Exposure}) + b1 * (\text{Cov}-\text{median}) + b2_i * I_{\text{Covi}})$ where $h_0(t)$ is the hazard in the participant with nominal covariate effects. For the treatment effect model, $h_0(t)$ is the hazard for placebo-treated participants. For the exposure-response model, $h_0(t)$ is the hazard for participants with median exposure. Relative risk ($h(t)=h_0(t)$) is provided by the righthand-side of the equations for specified treatment or exposure and covariate values. Exposure is the estimated nominal steady state AUC for each nirogacestat-treated participant and 0 for placebo-treated participants, and α is the parameter estimate of the slope of the exposure-response relationship. $I_{\text{nirogacestat}}$ is a binary variable with value 0 for placebo participants and value 1 for nirogacestat treated participants. Effect is the parameter estimate of the treatment effect of nirogacestat over placebo. For continuous covariates, a slope ($b1$) was estimated for the median-centered covariate (Cov). For categorical covariates, a separate effect ($b2_i$) was estimated for each categorical value of the covariate (I_{Covi}).	was characterized by a first-order tumor growth (evaluated with placebo data) and first order elimination by nirogacestat treatment.
Model Parameter Estimates	PFS, tumor volume, and RECIST tumor size	Yes
Model Evaluation	Final PKPDx models were determined based on maximized likelihood (lowest stable OFV), physiological plausibility of parameter values, successful numerical convergence, parameter precision and acceptable VPC.	Yes. The PK/PD model for tumor dynamics described data reasonably well.
Covariates and Clinical Relevance	Neither age nor sex had an impact on PFS or tumor size. Tumor type was a significant covariate on the hazard function for PFS. Baseline tumor size was modeled as a parameter in both tumor size models; however, genotypes had no impact in either model, and tumor type had no impact in the RECIST model.	Yes

Simulation for Specific Population	Disease progression (based on the natural history model from placebo participants) and nirogacestat-mediated tumor shrinkage were simulated (Table 74 below).	Yes
Visualization of E-R relationships	PFS is plotted over time by tumor type and treatment (Figure 12 below) and by nirogacestat exposure quartiles (Figure 13 below). Changes from baseline in tumor size are plotted over time by dose and study (Figure 14 below), and by AUCtau (Figure 15 below). Logistic regression of objective response relationship with nirogacestat exposure is plotted for DT only (Figure 16 below). DOR is presented as a KM plot based on nominal AUCtau at steady-state groups (above and below median; Figure 17 below).	Yes. Tumor size change from baseline correlates well with PFS in patients with DT (refer to 19.4.3.6 Reviewer's Independent Analysis for details).
Overall Clinical Relevance for ER	- For PFS, the HR estimate for participants with solid tumors and T-ALL/LBL relative to DT tumors was 19. - The PFS probability for all tumors was not associated with nirogacestat exposures at the evaluated dose range but was described by a nirogacestat treatment effect. The HR estimate for treatment relative to no treatment was 0.26. - There was a nirogacestat-mediated treatment effect on tumor size, which was independent of nirogacestat exposure at the evaluated dose range in participants with DT and non-DT solid tumors. - Predicted change in tumor size following treatment with nirogacestat at doses ≥ 100 mg BID after 24 months was -22% (RECIST sum of longest diameter) and -55% (tumor volume), respectively. 36 nirogacestat treated participants (17.3%) and 5 placebo participants (2.4%) were found to have a CR or PR. A negative trend for nominal steady state exposure was observed for nirogacestat-treated participants, indicating that responses may occur at lower exposures compared to non-responders. This assessment, however, is confounded by the larger exposures and lack of efficacy in participants with non-DT tumors. The BOR relationship with nominal steady state nirogacestat exposure was not found to be significant in participants with DT alone. - Higher exposure appeared to correlate with a longer response, though no exposure-response	Yes. E-R and PK/PD models both support a flat exposure-response relationship in patients with DT treated with nirogacestat. Further analysis with the Applicant's PK/PD model of tumor dynamics that substantiates maintenance of efficacy in patients who need dose reduction is detailed in 19.4.3.6 Reviewer's Independent Analysis.

	relationship was observed for the duration of response.	
Labeling Language	Description	
12.2 Pharmacodynamics	No statements related to Exposure-Efficacy models are made in the proposed label.	Proposed to add language describing exposure-response relationships for Grade 3 hypophosphatemia

Table 71 Parameter Estimates of the PFS Model

Parameter	Descriptor	Estimate	CI95
θ_1	Gompertz rate (/day)	0.00213	(0.00142 - 0.00285)
θ_2	Gompertz shape (–)	-0.00187	(-0.00272 - -0.00103)
θ_3	Tumor type effect (other) (–)	2.94	(2.28 - 3.61)
θ_4	Treatment effect (–)	-1.34	(-1.96 - -0.711)

CI95: 95% confidence interval

Table 72 Parameter Estimates of the Tumor Volume Model

Parameter	Descriptor	Estimate	CI95	Bootstrap Estimate	Bootstrap CI95
θ_1	Tumor Volume Baseline (mm^3)	143	(106 - 179)	144	(111 - 185)
θ_2	Growth Rate ($week^{-1}$)	0.00123	(0.000220 - 0.00685)	0.00128	(0.000340 - 0.00353)
θ_3	Treatment Shrinkage Rate ($week^{-1}$)	0.00853	(0.00600 - 0.0121)	0.00872	(0.00623 - 0.0119)
$\omega_{1.1}$	$\omega_{TumorVolumeBaseline}^2$	2.36	(1.78 - 2.94)	2.32	(1.82 - 2.88)
$\omega_{2.2}$	$\omega_{GrowthRate}^2$	1.56e-06	(9.50e-07 - 2.16e-06)	1.52e-06	(8.26e-07 - 2.61e-06)
$\sigma_{1.1}$	$\sigma_{ProportionalError}^2$	0.15	(0.123 - 0.177)	0.149	(0.109 - 0.201)

CI95: 95% confidence interval; ω_X^2 : variance of the IIV of parameter θ_X .

Table 73 Parameter Estimate of the RECIST Tumor Size Model

Parameter	Descriptor	Estimate	CI95	Bootstrap Estimate	Bootstrap CI95
θ_1	Tumor Size Baseline (mm)	98.9	(90.9 - 107)	98.7	(89.2 - 110)
θ_2	Growth Rate ($week^{-1}$)	0.000414	NA	0.000414	NA
θ_3	Treatment Shrinkage Rate ($week^{-1}$)	0.00227	(0.000435 - 0.0119)	0.00404	(0.00227 - 0.00573)
$\omega_{1.1}$	$\omega_{TumorSizeBaseline}^2$	0.439	(0.337 - 0.541)	0.434	(0.349 - 0.520)
$\omega_{2.2}$	$\omega_{GrowthRate}^2$	1.22e-07	(4.08e-08 - 2.03e-07)	4.00e-07	(4.24e-11 - 1.55e-06)
$\omega_{3.3}$	$\omega_{TreatmentShrinkageRate}^2$	1.06	(-0.196 - 2.32)	1.22	(0.689 - 2.03)
$\sigma_{1.1}$	$\sigma_{ProportionalError}^2$	0.0456	(0.0446 - 0.0466)	0.0440	(0.0199 - 0.0817)

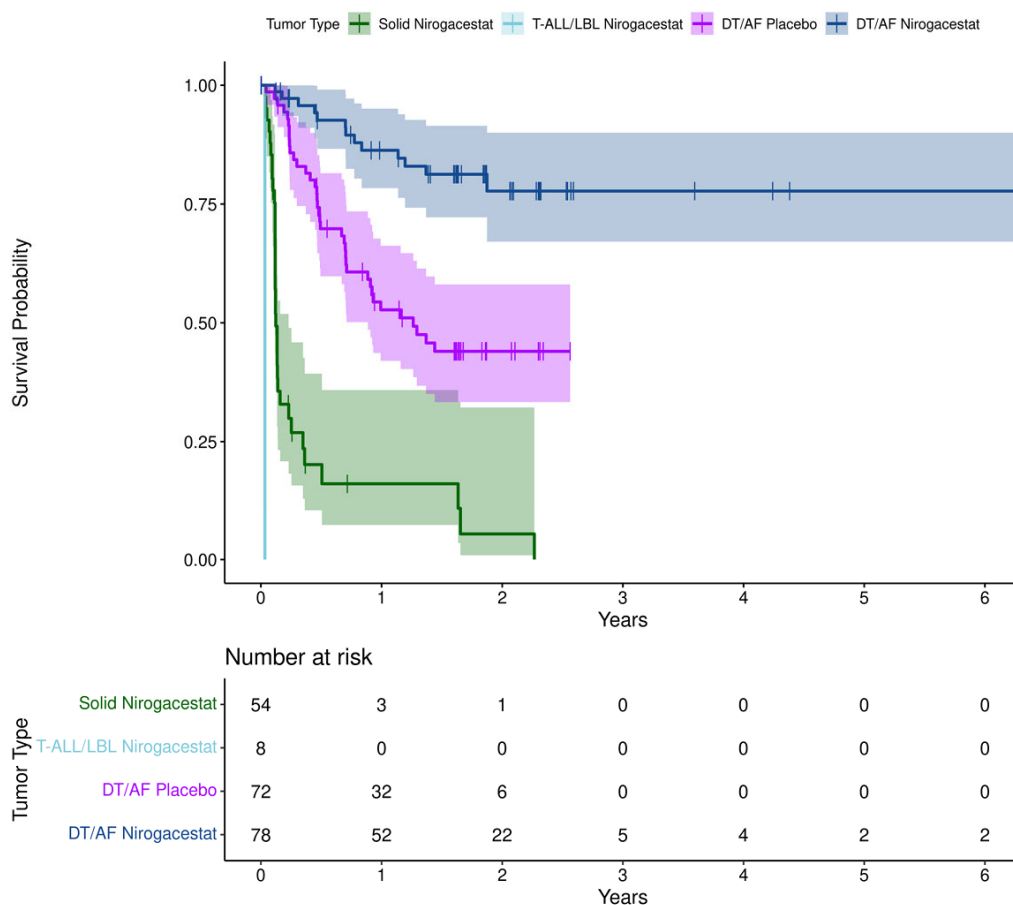
CI95: 95% confidence interval; ω_X^2 : variance of the IIV of parameter θ_X ; NA: not applicable (fixed parameter).

Table 74 Simulated Tumor Sizes – Nirogacestat BID Treatment

Endpoint	Time (Weeks)	Tumor Size		%CFB Tumor Size	
		Disease Progression (95% PI)	Nirogacestat Treatment (95% PI)	Disease Progression (95% PI)	Nirogacestat Treatment (95% PI)
RECIST SLD (mm)*	0	99.9 (28.7 - 322)	100 (28.7 - 322)	0 (0 - 0)	0 (0 - 0)
	26	101 (29.6 - 330)	92.9 (24.8 - 313)	0.9 (-8.15 - 10.6)	-5.98 (-33.7 - 6.16)
	52	101 (29 - 335)	85.2 (20 - 297)	1.81 (-15.6 - 22.3)	-11.6 (-56 - 12.7)
	78	103 (28.6 - 355)	80.3 (15.4 - 292)	2.72 (-22.5 - 35.2)	-16.9 (-70.9 - 19.6)
	104	104 (28.5 - 382)	74.2 (12.6 - 286)	3.66 (-28.8 - 49.5)	-21.9 (-80.7 - 27)
Tumor Volume (mm ³)*	0	146 (8.14 - 2210)	147 (8.14 - 2210)	0	0
	26	148 (8.52 - 2410)	119 (6.82 - 1930)	2.6 (-26.7 - 42.4)	-17.9 (-41.3 - 13.9)
	52	156 (7.99 - 2780)	99.6 (5.12 - 1780)	5.25 (-46.3 - 103)	-32.6 (-65.6 - 29.8)
	78	164 (7.45 - 3240)	84.3 (3.82 - 1660)	7.98 (-60.6 - 188)	-44.6 (-79.8 - 47.9)
	104	163 (6.92 - 3680)	67 (2.84 - 1510)	10.8 (-71.1 - 311)	-54.5 (-88.2 - 68.5)

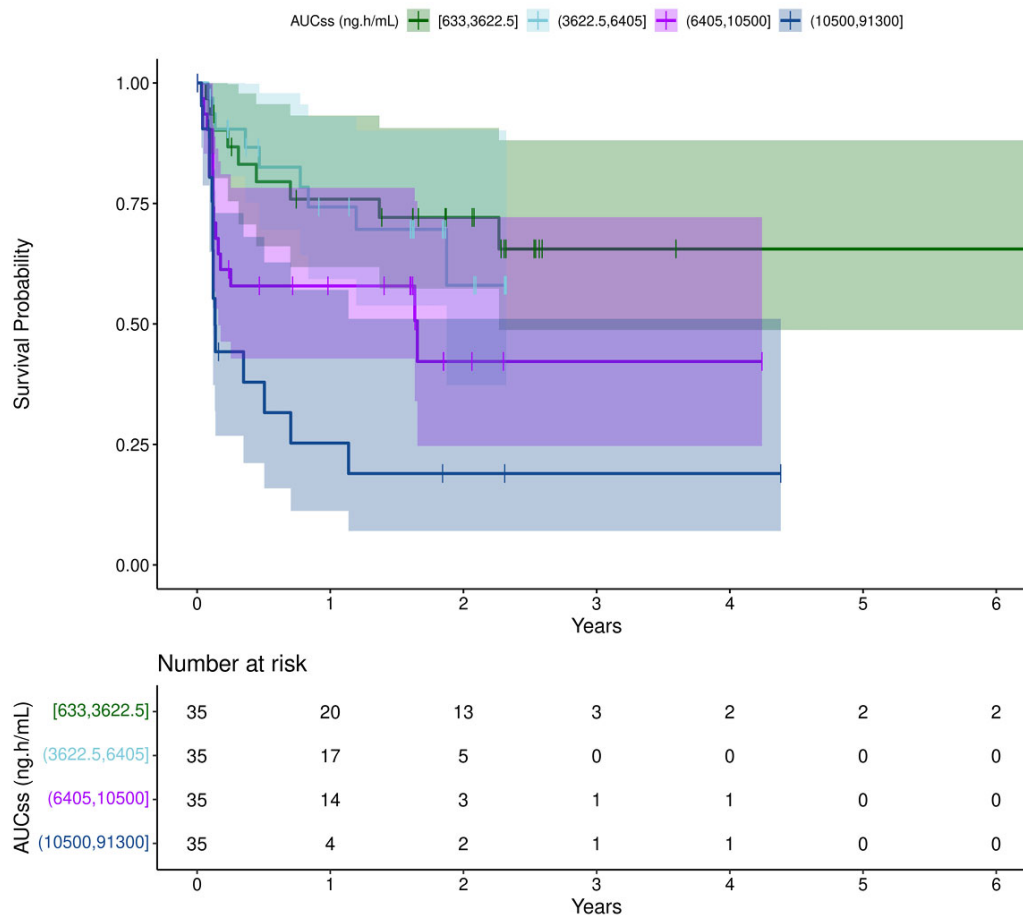
*units only applicable for tumor sizes, CFB results are displayed in %; **PI**: prediction interval; **CFB**: change from baseline; **RECIST**: Response Evaluation Criteria in Solid Tumors; **SLD**: sum of longest diameters.

Figure 12 PFS vs Time, Stratified by Tumor Type and Treatment



Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; **Solid:** advanced solid tumors without DT; **T-ALL/LBL:** T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma; **DT/AF:** desmoid tumor/aggressive fibromatosis.

Figure 13 PFS vs Time, Stratified by Nirogacestat Exposure Quartiles (All Tumor Types)



Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; exposure quartiles denote area under the concentration vs. time curve within a dosing interval (AUC_{tau}) in ng*h/mL; placebo-treated patients were excluded.

Figure 14 Tumor Size Change from Baseline vs. Time, Stratified by Dose and Study

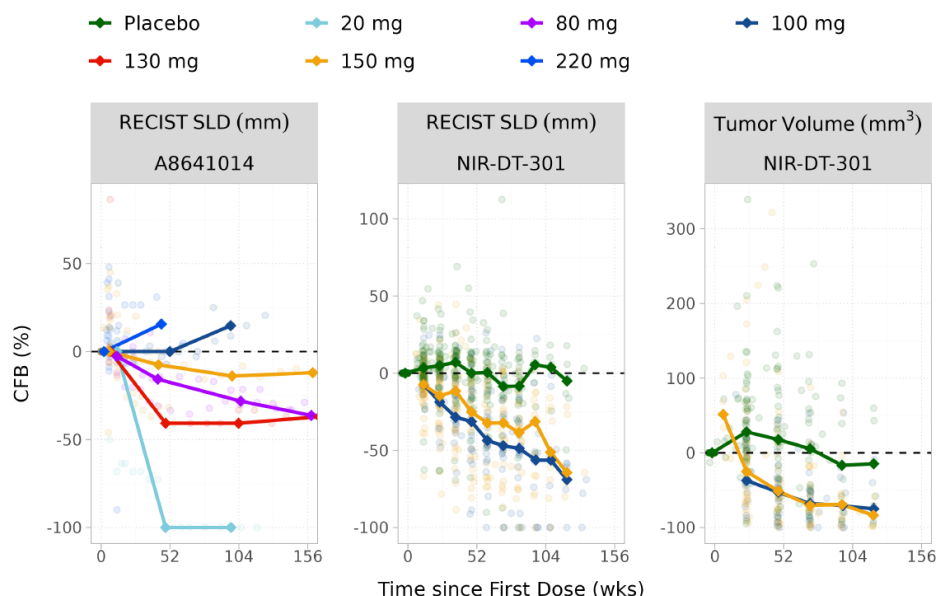


Figure 15 Tumor Size Change from Baseline vs Nirogacestat Serum AUC, Stratified by Study

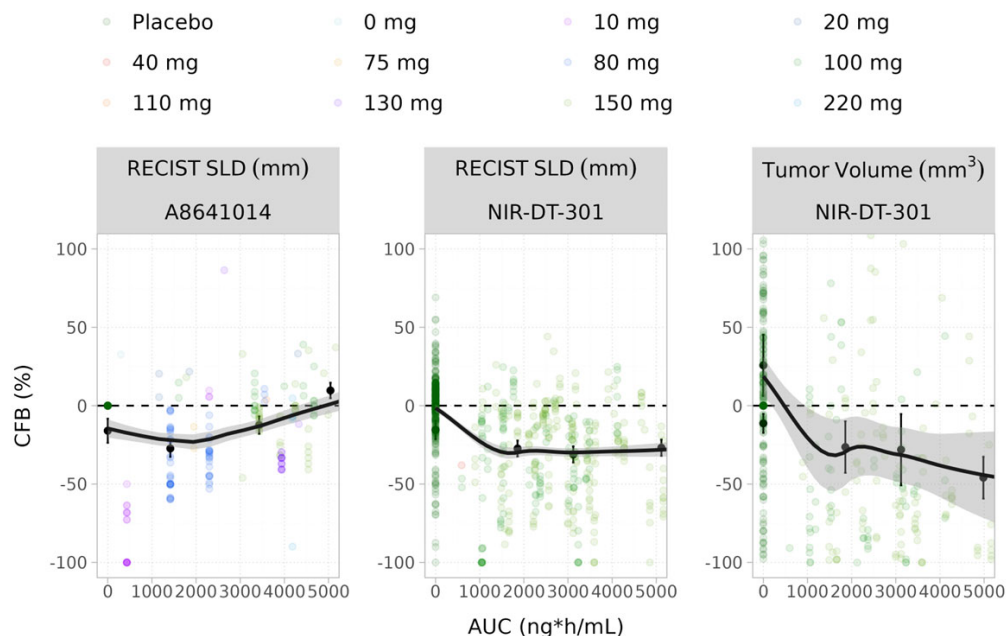
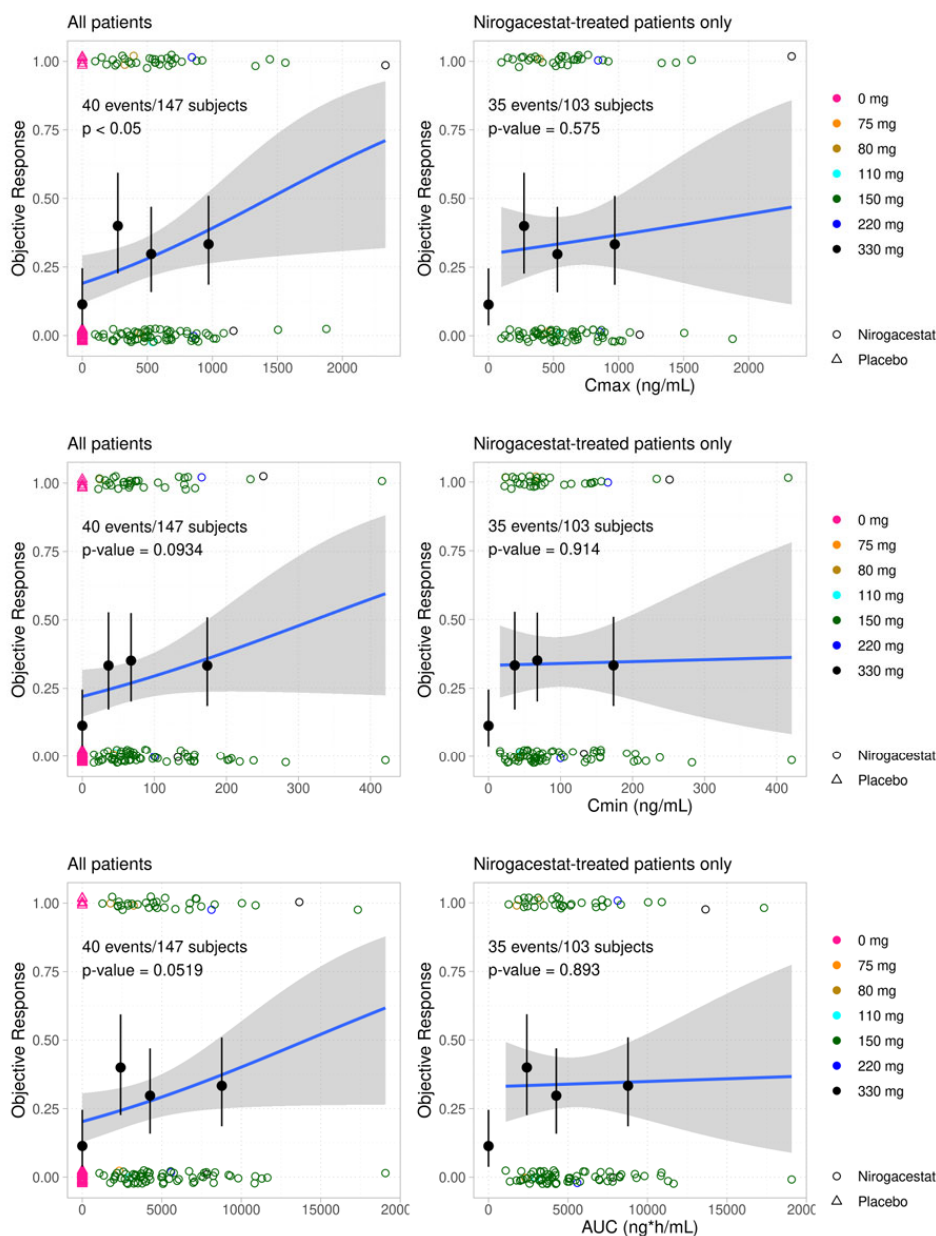
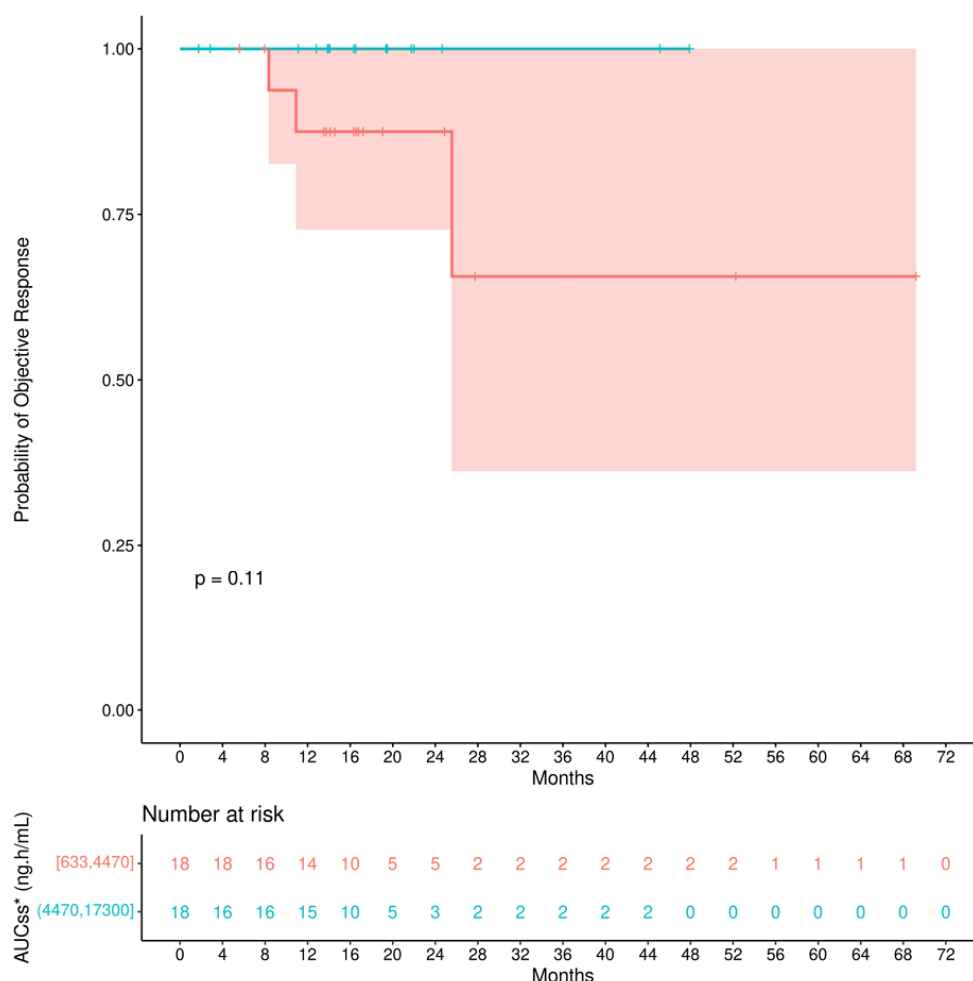


Figure 16 Logistic Regression Relationships for Objective Response for Patients with DT and Nirogacestat-Treated Patients with DT Only



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

Figure 17 Exposure-Response Relationship for Duration of Objective Response



AUC_{avg,ss} = nominal steady-state area under the concentration-time curve. The upper panel shows the Kaplan-Meier curves stratified by exposure (colored from lowest exposure to highest: red, blue respectively). The plus signs (+) indicate censored patients. The number of patients per exposure group at risk is indicated in the lower panel.

19.4.12. ER (safety) Executive Summary

PK/PDx models were developed to evaluate the PK/PDx and exposure-response relationship (ERR) between nirogacestat and efficacy endpoints in participants with DT, which included the following objectives:

- Characterize the PopPKPDx relationship of nirogacestat exposure and changes in FSH over time;
- Characterize the PopPKPDx relationship of nirogacestat exposure and OD;

- Characterize the ERR between nirogacestat exposure and the incidence of the Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, Grade ≥ 3 treatment-related AEs, any treatment-related AE, any treatment-related SAE, any treatment-related AE leading to dose modification, Grade ≥ 3 TEAEs, any TEAE, any TESA, and any TEAE leading to dose modification ;
- Characterize the ERR between nirogacestat exposure and the duration of Grade ≥ 3 hypophosphatemia, Grade ≥ 3 diarrhea, Grade ≥ 3 rash, and OD.

Methods: The previously developed nirogacestat PopPK model was used to derive individual exposure parameters. Nonlinear mixed effects modeling was employed to develop PKPDx models to characterize safety and efficacy of nirogacestat in participants with DT, participants with solid tumors other than DT, and participants with T-ALL/LBL. The binary outcome OD was analyzed using a time to event model, whereas FSH and phosphate maximum reduction from baseline were analyzed as continuous variables. Model development was carried out sequentially, first describing disease progression and placebo response, followed by assessment of the nirogacestat ERR. Covariate-parameter relationships of interest were explored graphically and formally tested if substantial trends were evident. Final PKPDx models were qualified by VPCs, in addition to numerical checks of parameter precision and model robustness.

Bayesian posthoc PK parameter estimates were used to estimate nirogacestat exposures (nominal steady state or exposure at day of onset) for the subsequent exposure-response analysis. For each safety endpoint, nominal steady state exposure was used for participants with no event. To assess the impact of changes in exposure for binary safety endpoints, exposure-response relationships were graphically evaluated in all participants and in nirogacestat treated participants only. Significant relationships were further examined by comparing treatment effect models (i.e., to assess response for nirogacestat treated participants compared to placebo participants) to exposure-response models (i.e., to assess changes in response as nirogacestat concentration changes). Safety endpoints were evaluated by logistic regression.

Results: A total of 73 WOCBP were available for FSH evaluation, all of which were participants with DT from Study NIR-DT-301. FSH was found to linearly increase with nirogacestat serum concentrations. The delay between serum concentrations and FSH change was characterized by an indirect response model. A time-dependent drug effect was used to characterize the reduction of FSH observed in some participants. Variability in FSH, drug effect, and time-dependent drug effect decay were relatively high and could not be further explained by covariates.

A total of 82 WOCBP were available for OD evaluations, including 76 participants with DT, 3 with solid tumors other than DT, 2 with T-ALL/LBL, and 1 participant with a missing

description for tumor type. Time to OD occurrence was related to nirogacestat treatment, independent of nirogacestat exposures, at the evaluated dose range. The HR for nominal treatment relative to placebo was estimated to be 3.3. No relationships between OD and population or age were observed.

A total of 214 participants were available for evaluation of AE endpoints. Eleven endpoints were available for safety analysis: Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, Grade ≥ 3 treatment-related AEs, any treatment-related AE, any treatment-related SAE, any treatment-related AE leading to dose modification, Grade ≥ 3 TEAEs, any TEAE, any TESA, and any TEAE leading to dose modification. Nirogacestat exposure was found to be a significant predictor of any Grade ≥ 3 TEAE, though further exposure response models showed that this was a treatment effect rather than an exposure effect. Of these binary endpoints, only Grade ≥ 3 hypophosphatemia was found to have a relationship with nirogacestat exposure. Compared to treatment, C_{max} was found to be the best predictor of Grade ≥ 3 hypophosphatemia occurrence. At a 100 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 5.89%. For a 150 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 6.78%.

Dose modifications, such as dose interruptions (or holds) and dose reductions, during Study NIR-DT-301 DB phase or OLE phase were also compared against nominal nirogacestat exposure at steady state. Both C_{min} and AUC were found to be significant predictors of dose modifications for NIR-DT-301, with higher exposure predictive of a subject decreasing their dose, though C_{max} was not.

Phosphate maximum reduction from baseline was modeled by linear and nonlinear regression. Treatment effect, linear, exponential, E_{max} , and sigmoid E_{max} models were tested with and without an intercept. Models with an intercept were found to be more significant than those without due to the non-zero phosphate change from baseline seen in the placebo group. For the nirogacestat treated group, at treatment effect model was found to best describe the relationship of phosphate change from baseline and nirogacestat.

The duration of four endpoints (Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, and OD) were explored through Kaplan-Meier plots. No significant ERR relationships were detected within the range of nirogacestat exposure.

Conclusion: This analysis represents a comprehensive examination of PKPDx data collected from a Phase 1 study of nirogacestat in participants with advanced solid tumors and participants with relapsed or refractory T-ALL/LBL, and a Phase 3 trial of nirogacestat in participants with DT. Principal findings of the safety analyses are described below:

- FSH linearly increased with nirogacestat serum concentrations in WOCBP. The temporal difference between nirogacestat serum concentrations and FSH changes was described

by an indirect response model. A reduction of nirogacestat effect on FSH over time was detected. Although the typical half-life attenuation was 49 weeks, the effect was associated with high variability.

- A nirogacestat treatment effect on OD occurrence was observed, which was exposure independent at the evaluated dose range of 80 mg BID to 330 mg BID. The HR for nominal treatment relative to placebo was estimated to be 3.3.
- A statistically significant and plausible ERR ($p < 0.05$) was observed for Grade ≥ 3 hypophosphatemia. Compared to treatment, $C_{\max}$ was found to be the best predictor of Grade ≥ 3 hypophosphatemia occurrence. At a 100 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 5.9%. For a 150 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 6.78%. No ERRs were observed for the other binary safety events.
- A Treatment effect model with an intercept was found to best describe the relationship of phosphate maximum reduction from baseline and nirogacestat.
- Sixty participants were found to have dose modifications during Study NIR-DT-301 or OLE. Nominal nirogacestat exposure at steady state ($C_{\min}$ and AUC) was found to be a significant predictor ($p < 0.05$) of dose modifications.
- No ERRs were detected within the range of nirogacestat exposure for the duration of Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, or OD.

The FDA's Assessment:

FDA agrees. Positive E-R relationships for Grade 3 hypophosphatemia was well characterized over the dose range from 20 mg BID to 330 mg BID. We added the following statement in section 12.2 in the USPI label.

Exposure-Response Relationships

There is an exposure response relationship between OGSIVEO exposure and Grade 3 hypophosphatemia with a higher risk of Grade 3 hypophosphatemia at higher exposure. Additionally, increased rate of Grade 3 hypophosphatemia occurred more frequently with higher nirogacestat doses (0.13 to 2.2 times the recommended dose).

19.4.13. ER (safety) Assessment Summary

The Applicant's Position:

Exposure-response and PKPD analyses were conducted using a nirogacestat PopPK model and safety data obtained from Studies A8641014 and NIR-DT-301. A linear relationship between FSH and nirogacestat serum concentration in WOCBP was observed. However, high variability in

the drug effect, presumably due to menstrual cycle oscillation and sparse sampling, made precise estimation of drug effects difficult. A nirogacestat treatment effect was described for OD occurrence, which was also independent of exposure at the evaluated dose ranges. Significant relationships between nirogacestat exposure and Grade ≥ 3 hypophosphatemia were described, with a 0.91% absolute increase in risk estimated at the 150 mg dose compared to the 100 mg dose. Finally, a statistically significant relationship between nirogacestat exposure (trough concentration and AUC_{tau}) and dose modification was identified; however, the relationship with C_{max} was not statistically significant. This suggests that the need for dose modifications may be associated with inter-individual differences in CL. Thus, individuals with higher nirogacestat CL are less likely to require dose reductions or interruptions than individuals with lower nirogacestat CL.

General Information	
Goal of ER analysis	PKPDx models were developed to evaluate the PKPDx and ERR for nirogacestat in participants with DT, which included the following objectives: • Characterize the PopPKPDx relationship of nirogacestat exposure and changes in FSH over time; • Characterize the PopPKPDx relationship of nirogacestat exposure and OD; • Characterize the ERR between nirogacestat exposure and the incidence of the Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, Grade ≥ 3 treatment-related AEs, any treatment-related AE, any treatment-related SAE, any treatment-related AE leading to dose modification, Grade ≥ 3 TEAEs, any TEAE, any TESAE, and any TEAE leading to dose modification; • Characterize the ERR between nirogacestat exposure and phosphate maximum reduction from baseline; • Characterize the ERR between nirogacestat exposure and the duration of Grade ≥ 3 hypophosphatemia, Grade ≥ 3 diarrhea, Grade ≥ 3 rash, and OD.
Study Included	A8641014 and NIR-DT-301 – A8641014 included a range of doses in oncology participants, NIR-DT-301 only included participants with DT.
Population Included	FSH – 73 WOCBP in Study NIR-DT-301 OD – 82 WOCBP from A8641014 and NIR-DT-301 All 214 participants were included in the remaining safety analysis.
Endpoint	FSH OD Maximum phosphate CFB The primary exposure-safety analysis tested treatment-emergent laboratory variables:

		• Grade ≥ 3 diarrhea • Grade ≥ 3 hypophosphatemia • Grade ≥ 3 rash (taken from the narrow list including alopecia, rash erythematous, rash, folliculitis, rash macular, rash erythematous, and rash maculo-papular) • Grade ≥ 3 treatment-related AEs • Any treatment-related AE • Any treatment-related SAE • Any treatment-related AE leading to dose modification • Grade ≥ 3 TEAEs • Any TEAE • Any TESAE • Any TEAE leading to dose modification		
No. of Patients (total, and with individual PK)		214 total participants (169 participants included individual PK)		
Population Characteristics (PopPKPDx ReportTable 2)	General	Age median (range): 39.0 yrs (18.0 – 80.0), 27 (12.6)% participants ≥ 65 yr, 5 (2.3)% participants ≥ 5 yr Weight median (range): 73.0 kg (42.5-167) Male: 87 (40.7%) Asian: 5 (2.3%) Black/African American: 14 (6.5%) Other: 14 (6.5%) White/Caucasian: 181 (84.6%)		
	Organ impairment	Hepatic impairment - none Renal impairment – eGFR mean (range) 88.1 mL/min/1.73m ² (40.7-234), 14 (4.2%) subj w/eGFR ≤ 60 mL/min/1.73m ² . 3 (0.9%) subj w/eGFR ≤ 45 mL/min/1.73m ²		
	Pediatrics (if any)	None		
	Geriatrics (if any)	Described in General Population Characteristics		
Dose(s) Included		A8641014: multiple oral doses of 20, 40, 80, 100, 130, 150, 220, 330 mg BID in 21-day cycles (7 days off treatment for PK assessments after Cycle 1 only) NIR-DT-301: multiple oral doses of 150 mg BID 28-day cycles		
Exposure Metrics Explored (range)		Safety: AUC (0.00 – 55200 ng·h/mL), C _{min} (0.00 – 1780 ng/mL), and C _{max} (0.00 – 4410 ng/mL)		
Covariates Evaluated		Age, weight, race, tumor type, β-catenin gene, APC tumor suppressor gene		
Final Model Parameters		<table><tr><td>Summary</td><td>Acceptability [FDA’s Comments]</td></tr></table>	Summary	Acceptability [FDA’s Comments]
Summary	Acceptability [FDA’s Comments]			

Model Structure	The relationships between nirogacestat exposure and safety endpoints were evaluated as PKPDx or ERR models. The PKPDx model development for OD and FSH used individual parameter estimates from the final PopPK model added to the PKPDx datasets. For the ERR analyses of safety endpoints evaluated by logistic regression, the final PopPK model was used to calculate individual estimates of exposure on the day of onset, as available. For each safety endpoint, nominal steady state exposure was used for participants with no event. Logistic regression models tested covariates on the model intercept only. Covariates were tested in a stepwise forward search at a $p < 0.05$ level of significance. Only covariates that were significant in a univariate search were included in multivariate testing. The treatment effect and exposure-response models were parameterized as follows (shown here including covariate effects): Treatment effect: $\text{Pr}(\text{Response}) = \text{invlogit}(\text{Intercept} + \text{Effect} * I_{\text{nirogacestat}} + b1 * (\text{Cov-median}) + b2_i * I_{\text{Covi}})$ Exposure-response: $\text{Pr}(\text{Response}) = \text{invlogit}(\text{Intercept} + \text{Slope} * \text{Exposure} + b1 * (\text{Cov-median}) + b2_i * I_{\text{Covi}})$ where $I_{\text{nirogacestat}}$ is a binary variable with value 0 for placebo participants and value 1 for nirogacestat treated participants. Effect is the parameter estimate for the treatment effect of nirogacestat over placebo. Exposure is the estimated nominal steady state AUC for each participant treated with nirogacestat and 0 for placebo participants. Slope is the parameter estimate of the slope of exposure-response relationship. For continuous covariates, a slope (b1) was estimated for the median-centered covariate (Cov). For categorical covariates, a separate effect (b2_i) was estimated for each categorical value of the covariate (I_{Covi}). FSH was described with a linear relationship with nirogacestat serum concentration using an indirect response model. The probability of OD was described by a parametric time-to-event model (Gompertz hazard) comprising an effect of nirogacestat treatment on the hazard. Probability of Grade ≥ 3 hypophosphatemia and dose modifications were described by logistic regression. Phosphate maximum reduction from baseline was described with a treatment effect model with an intercept. No ERR could be	Yes. PK/PD models for AEs of interest (FSH and OD) were considered exploratory for reasons detailed in 19.4.3.5 ER review issues.

	identified for any of the other safety endpoints evaluated.	
Model Parameter Estimates	FSH, OD (Table 76), Grade ≥ 3 hypophosphatemia (Table 75), phosphate maximum reduction from baseline (Table 78)	Yes
Model Evaluation	Final PKPDx models were determined based on maximized likelihood (lowest stable OFV), physiological plausibility of parameter values, successful numerical convergence, parameter precision and acceptable VPC.	Yes
Covariates and Clinical Relevance	The following pre-specified covariate-parameter relationships were examined for inclusion: - Population (tumor type) and age for OD; - APC genotype and CTNNB1 genotype for FSH No covariates were found to have a significant impact in either model.	Yes
Simulation for Specific Population	FSH levels were simulated at 100 mg BID and 150 mg BID, though both dose levels were associated with substantial increase in FSH levels.	Model is not considered reliable for simulating the difference in FSH elevation between the two doses.
Visualization of E-R relationships	FSH CFB is plotted over time by dose administered at the time of measurement (Figure 18). CFB in FSH levels are plotted over time and as boxplots by dose administered at the time of measurement (Figure 19). Occurrence of OD is plotted over time by nirogacestat exposure tertiles (Figure 20). Logistic regression relationships for Grade ≥ 3 hypophosphatemia (Figure 21) and dose modifications (Figure 22) in Study NIR-DT-301 only are plotted. Maximum reduction in phosphate is plotted by AUC quartiles (Figure 23).	Yes
Overall Clinical Relevance for ER	FSH linearly increased with nirogacestat serum concentrations in WOCBP. The temporal difference between nirogacestat serum concentrations and FSH changes was described by an indirect response model. A reduction of nirogacestat effect on FSH over time was detected. Although the typical half-life attenuation was 49 weeks, the effect was associated with high variability.	The relationships between exposures and FSH elevation or ovarian dysfunction are inconclusive for reasons detailed in 19.4.3.5 ER review issues.

	• A nirogacestat treatment effect on OD occurrence was observed, which was exposure independent at the evaluated dose range of 80 mg BID to 330 mg BID. The HR for nominal treatment relative to placebo was estimated to be 3.3. • A statistically significant and plausible ERR ($p < 0.05$) was observed for Grade ≥ 3 hypophosphatemia. Compared to treatment, $C_{\max}$ was found to be the best predictor of Grade ≥ 3 hypophosphatemia occurrence. At a 100 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 5.9%. For a 150 mg dose, the probability of a Grade ≥ 3 hypophosphatemia occurrence was calculated to be 6.78%. No ERRs were observed for the other binary safety events. • A treatment effect model with an intercept was found to best describe the relationship of phosphate maximum reduction from baseline and nirogacestat. • Sixty participants were found to have dose modifications during Study NIR-DT-301 or OLE. Nominal nirogacestat exposure at steady state ($C_{\min}$ and AUC) was found to be a significant predictor ($p < 0.05$) of dose modifications. • No ERRs were detected within the range of nirogacestat exposure for the duration of Grade ≥ 3 diarrhea, Grade ≥ 3 hypophosphatemia, Grade ≥ 3 rash, or OD.	A trend of positive E-R relationship was also observed for Grade 3 TEAE.
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	<u>Exposure-Response Relationships</u> (b) (4) <u>Cardiac Electrophysiology</u>	(b) (4) E-R for Grade 3 hypophosphatemia was revised (b) (4)

		(b) (4)

Table 75 Parameter Estimates of the FSH Model

Parameter	Descriptor	Estimate	CI95
θ_3	Proportional Error (ω)	0.559	(0.526 - 0.593)
θ_5	Basal FSH ($mIU mL^{-1}$)	5.02	(4.20 - 5.83)
θ_6	Drug Slope ($mlng^{-1}$)	0.0718	(0.0453 - 0.0982)
θ_7	FSH degradation rate constant ($hours^{-1}$)	0.000485	(0.000394 - 0.000576)
θ_8	Drug effect time-dependent decay ($hours^{-1}$)	8.4e-05	(5.99e-05 - 0.000108)
$\omega_{5.5}$	$\omega_{BasalFSH}^2$	0.354	(0.219 - 0.489)
$\omega_{6.6}$	$\omega_{DrugSlope}^2$	1.17	(0.564 - 1.78)
$\omega_{8.8}$	$\omega_{DrugEffect-decay}^2$	2.16	(0.707 - 3.62)

CI95: 95% confidence interval; ω : standard deviation; ω_X^2 : variance of the IIV of parameter θ_X .

Table 76 Parameter Estimates of the OD Model

Parameter	Descriptor	Estimate	CI95
θ_1	Gompertz rate (/day)	0.0025	(0.000941 - 0.00405)
θ_2	Gompertz shape (—)	-0.00659	(-0.00868 - -0.00449)
θ_3	Treatment arm effect (—)	1.19	(0.510 - 1.88)

CI95: 95% confidence interval

Table 77 Model Parameter Estimates for Grade 3+ Hypophosphatemia

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.07	0.360	-8.54	<0.001
cmax	0.001	0.000243	3.67	<0.001

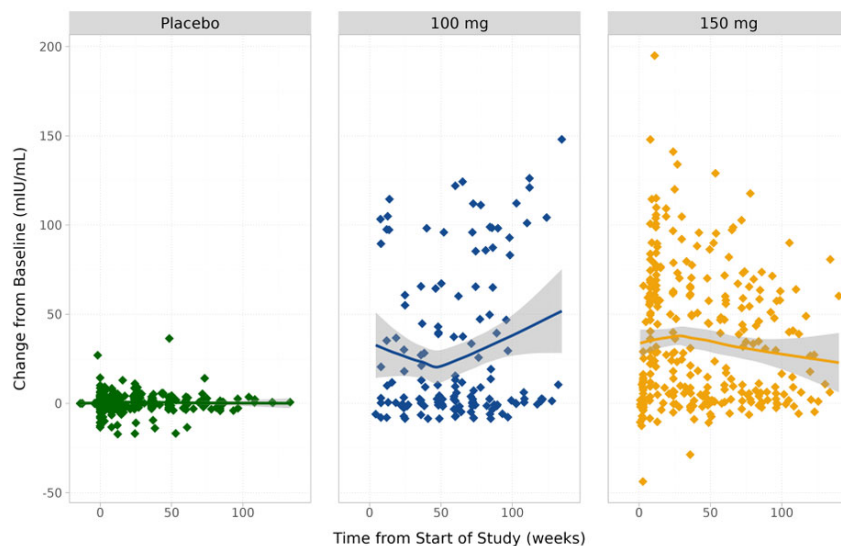
Std.Error: Standard error; **Pr(>|z|):** p-value for the estimated parameter.

Table 78 Model Parameter Estimates for Phosphate Maximum Reduction from Baseline

	Value	Std.Error	t-value	p-value
int	-0.841	0.067	-12.60	<0.001
slope	-0.504	0.084	-6.02	<0.001

Std.Error: Standard Error.

Figure 18 FSH Change from Baseline vs Time, Stratified by Administered Dose



Colored diamonds: Change from baseline of FSH measurements; **Solid lines and shaded areas:** Loess smooth with corresponding 95% confidence interval; **FSH:** Follicle-Stimulating Hormone; subjects randomized to nirogacestat treatment were grouped with placebo prior to first nirogacestat dose.

Figure 19 **FSH vs. Administered Dose**

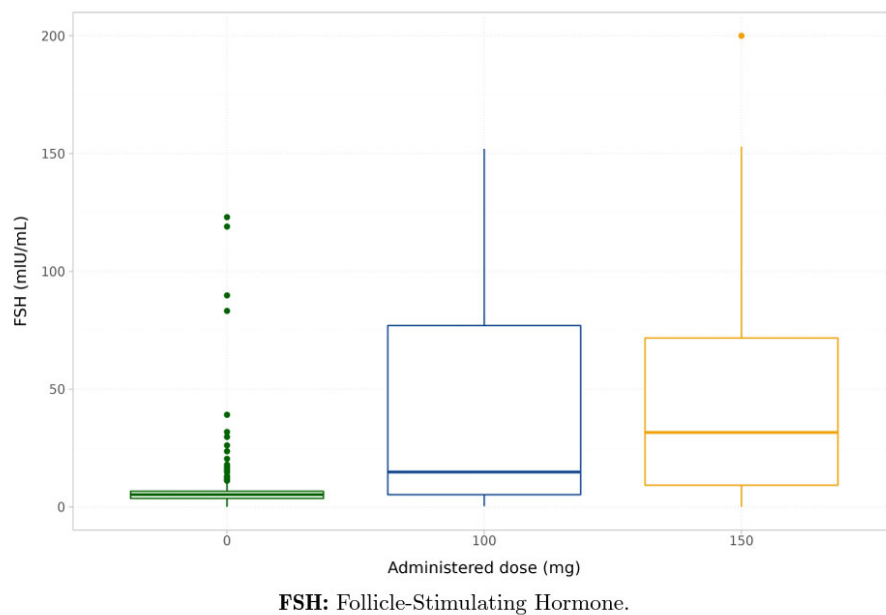
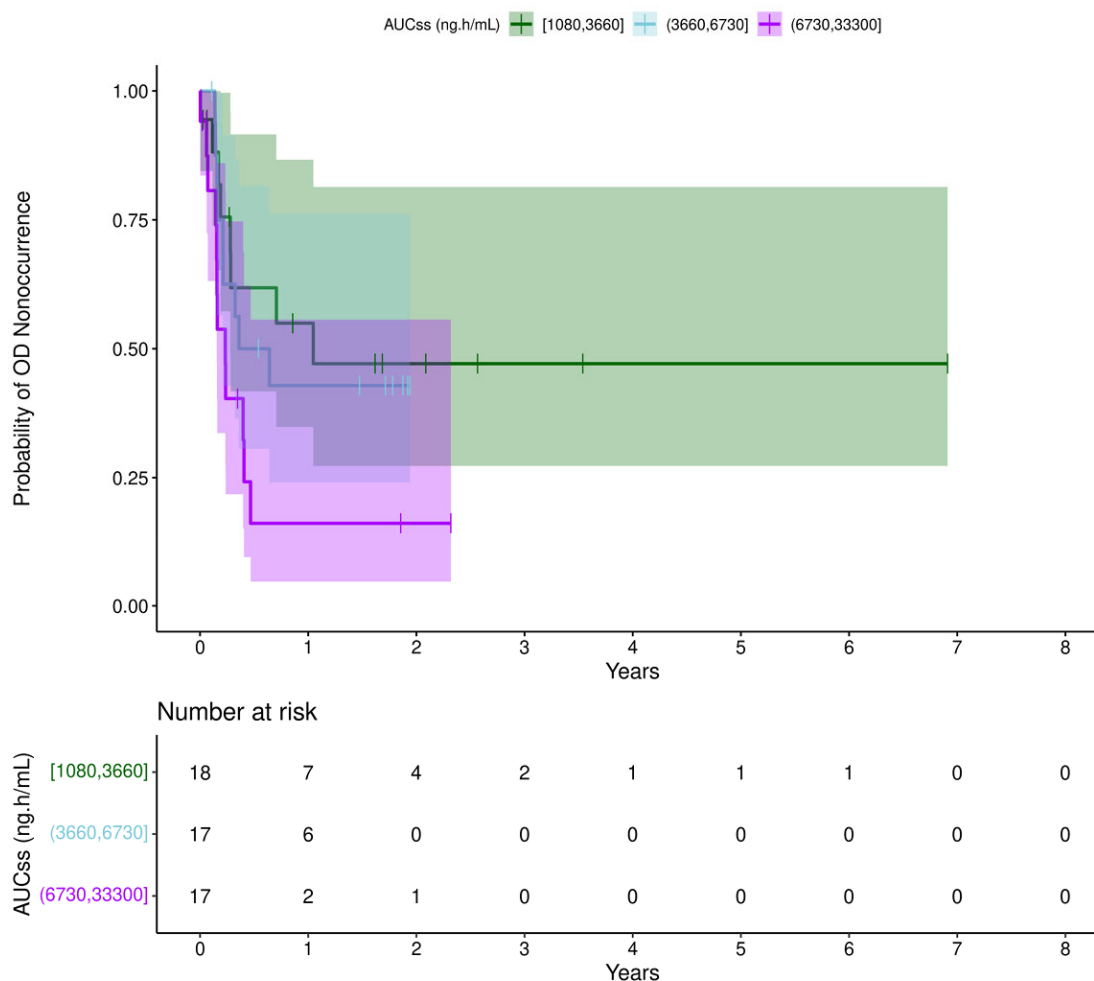
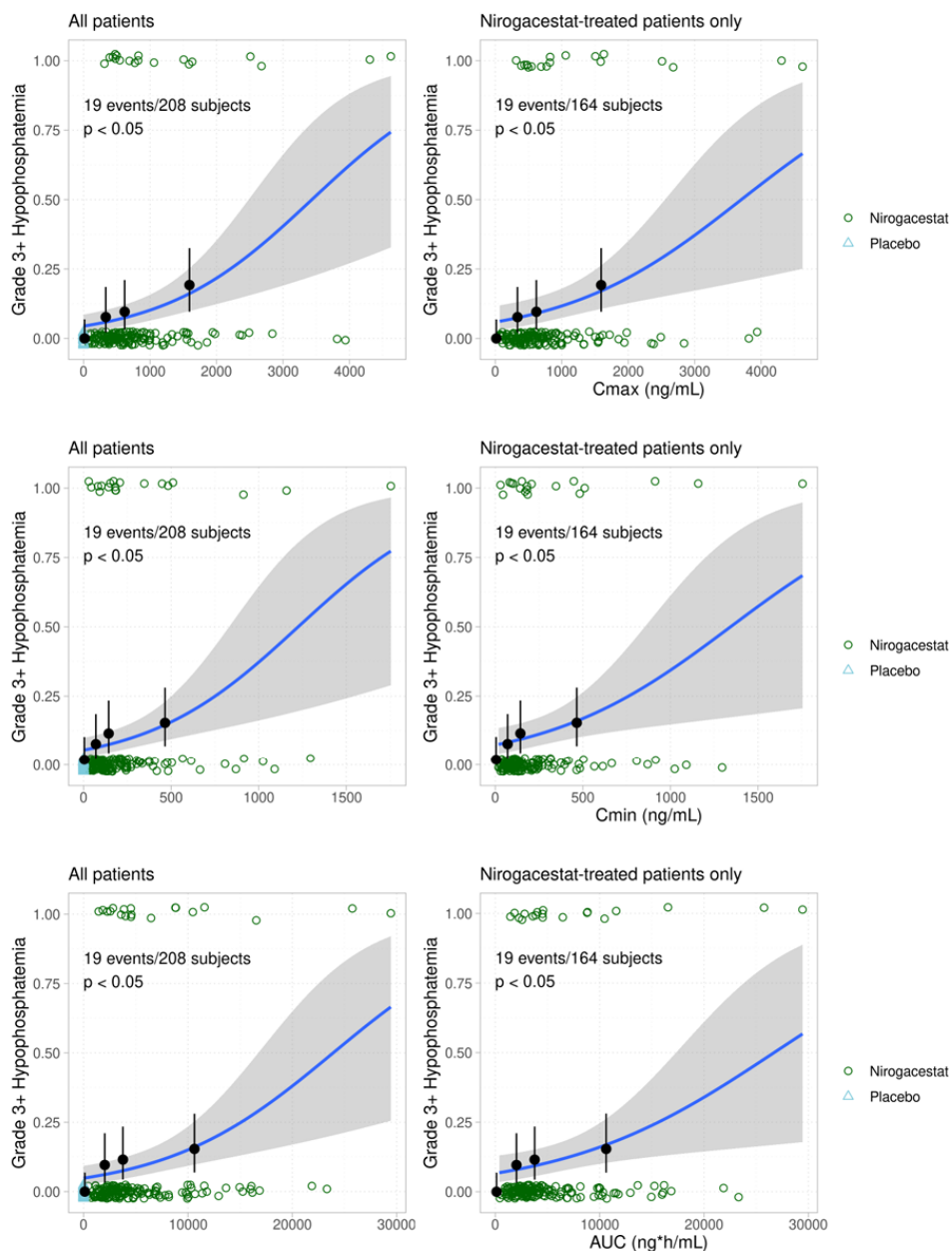


Figure 20 Ovarian Dysfunction vs. Time, Stratified by Nirogacestat Exposure Tertiles



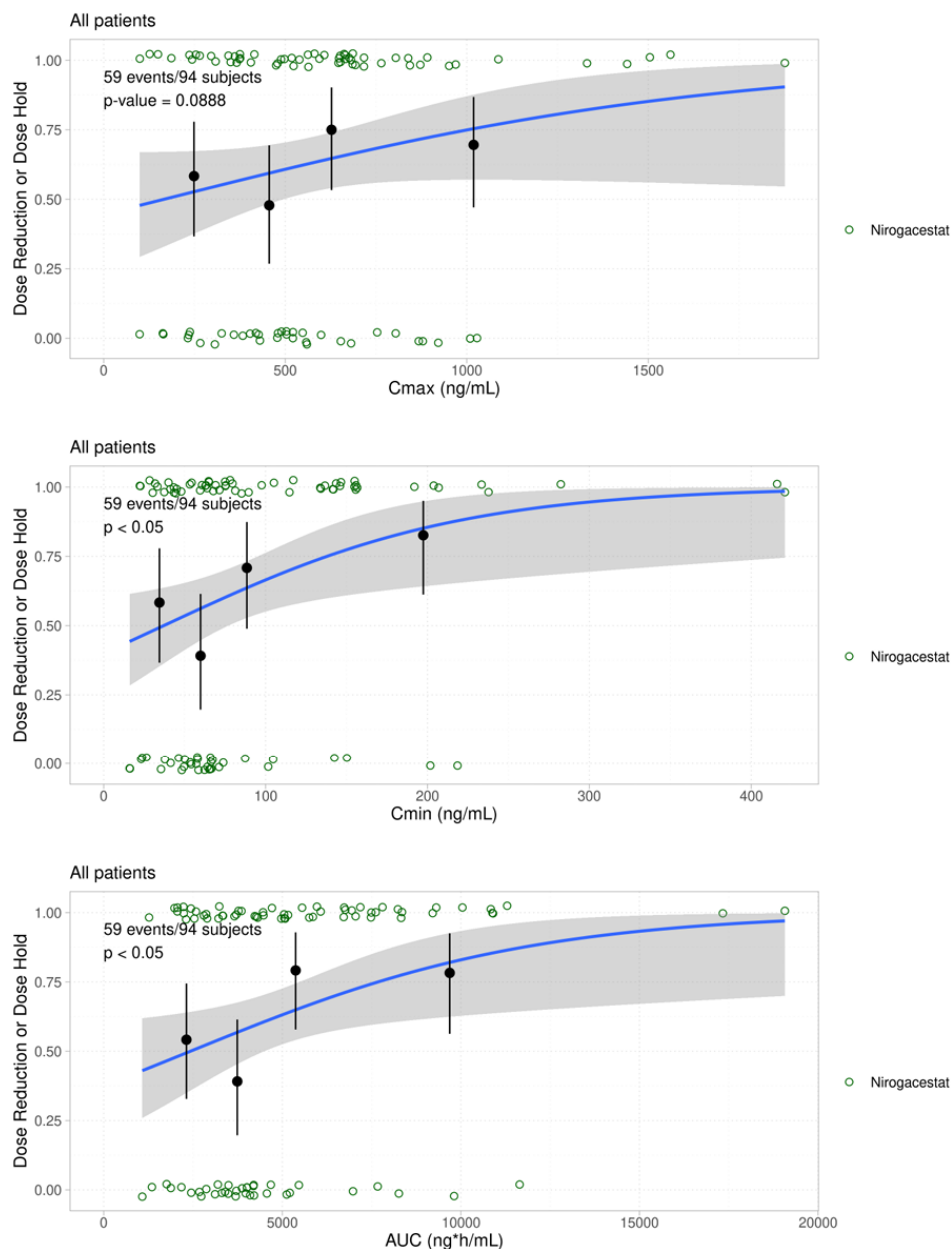
Lines: probability of non-occurrence of OD events; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; exposure tertiles denote AUC_{tau} in ng*h/mL; placebo-treated patients were excluded.

Figure 21 Logistic Regression Relationship for Grade 3+ Hypophosphatemia in All Patients and Nirogacestat-Treated Patients Only



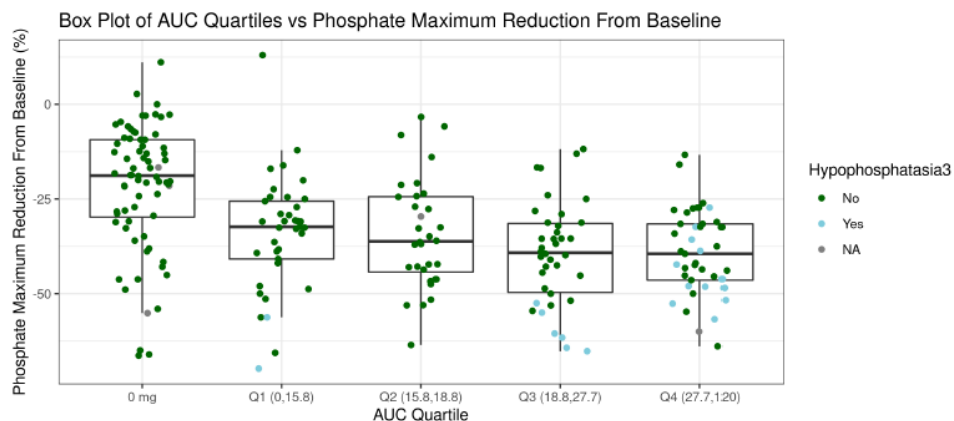
Note: The solid black points represent the mean exposure and event rates in the placebo treated patients or patients stratified by nirogacestat exposure quartile. Vertical black bars represent the 5th to 95th percentile CI on the event rate. The solid blue line indicates the logistic regression model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

Figure 22 Logistic Regression Relationships for Dose Modifications in Nirogacestat-Treated Patients Only in NIR-DT-301



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

Figure 23 **Boxplots of AUC Quartiles in Nirogacestat and Placebo Treated Patients by Phosphate Maximum Reduction in Baseline**



The boxes denote the interquartile range and median, and the whiskers extend to 1.5 times the interquartile range. Qi: Quartile 1,2,3 or 4; AUC: Nominal area under the time-concentration curve at day of onset or steady state; Colored circles: Maximum reduction of baseline per patient, by grade 3+ hypophosphatemia event.

The FDA's Assessment:

FDA verified the Applicant's analysis and in general agreed with the Applicant's position. The PK/PD model for tumor size adequately characterized longitudinal patient data that included two intra-patient doses. The observed longitudinal tumor size data supports that efficacy should not be affected by dose reduction. The PK/PD model was considered reliable to provide further support for the dose reduction. PK/PD models for FSH level and ovarian dysfunction are limited to inform dose modification from safety perspective due to sparse/incongruent data. However, positive E-R relationships for Grade 3 hypophosphatemia was well characterized over the dose range from 20 mg BID to 330 mg BID.

Taken together, the longitudinal tumor PK/PD model, positive ER relationship for dose modification and hypophosphatemia, as well as positive trend in E-R for FSH and Grade 3+ TEAE, suggest benefits in improving safety and tolerability with a lower exposure.

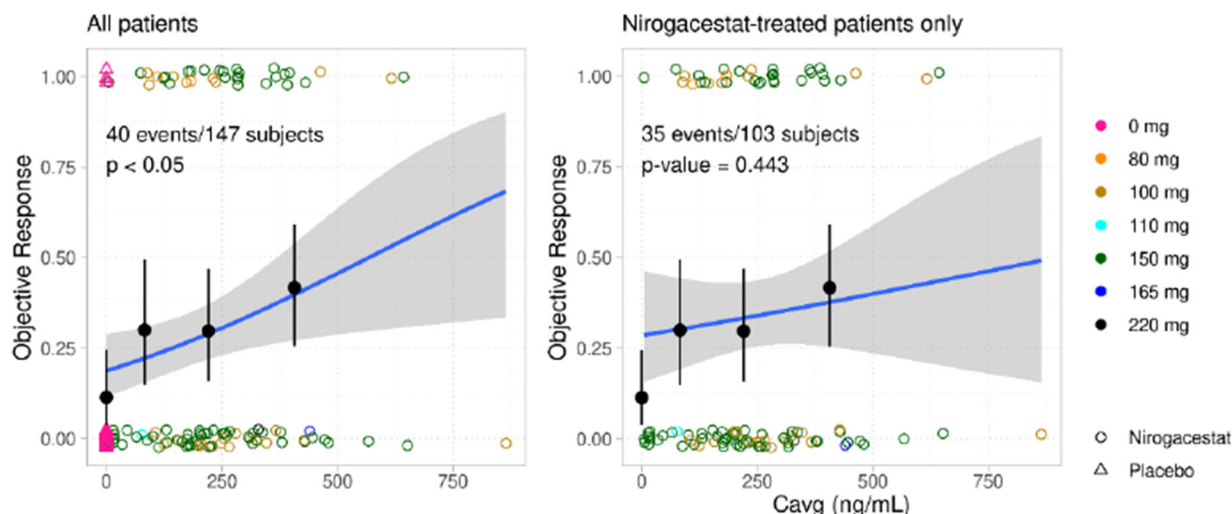
19.4.14. ER Review Issues

E-R for ORR with steady-state exposure

A relatively flat E-R relationship excluding placebo between steady-state exposure and response was observed which could be due to small exposure range for a single dose. Given dose reduction occurred in about half of the patients with DT, the Applicant was asked to perform additional E-R analysis with average exposure till response (for responders) or the end of treatment (for non-responders). Similar to Figure 13, a flat E-R relationship was observed,

suggesting that response was retained despite a lower average exposure due to dose reduction (Figure 24).

Figure 24: Logistic Regression Relationships for Objective Response for Patients with DT and Patients with DT treated with Nirogacestat



Source: Response to FDA IR 07/19/2023 Figure 2.

PK/PD for AEs of interest are considered exploratory or inconclusive

PK/PD model for FSH elevation was described by an indirect response model where the drug effect with a time-dependent decay was parameterized on the generation of FSH. This model is limited due to the sparse sampling and lab collected with no regards to monstrous cycle. As a result, the intra- and inter- individual variabilities of the model are large, and the model does not describe the data well. The exploratory analysis for ovarian dysfunction characterized by FSH level and clinical symptoms is subject to the same issues. The details of these models were thus not provided in this review. Despite the poor model fitness, there was a clear treatment effect on inducing FSH level or ovarian dysfunction. Whether the effect was concentration dependent is inconclusive due to the stated issues.

19.4.15. Reviewer's Independent Analysis

Efficacy does not appear to be affected by dose reduction

Dose modifications in patients with DT with 150 mg daily nirogacestat were primarily due to acute Grade 3+ TEAEs such as diarrhea, rash, and hypophosphatemia. Chronic TEAEs including Grade 2+ premature menopause or primary ovarian insufficiency also led to dose modifications. As shown in Figure 25, a significant proportion of patients had dose reduction as early as 1st cycle and this proportion continued to increase over time.

To assess if efficacy is affected, an exploratory analysis PFS was visualized in patients with dose reduction which was not found to differ from those whose dose was unchanged (Figure 26). In an additional exploratory analysis, tumor shrinkage appeared to correlate with PFS (Figure 27). Tumor size summarized by real-time dose in Study NIR-DT-301 showed comparable slope of tumor size decrease between patients with and without dose reduction.

These results however do not provide information regarding whether the timing of dose reduction affects tumor shrinkage. To visualize temporal relationship between dose reduction and tumor dynamics, patients were further grouped by dose reduction occurring in the following time frames: <12 weeks, 12-<24 weeks, 24-<48 weeks, ≥48 weeks. Considering that tumor size was captured in a time frame for each planned visit and there were nonuniform missing records amongst patients, reviewer used PK/PD model to simulate tumor size every 4 weeks based on patient's individual parameter estimates. The predicted tumor dynamic profiles overlaid with observations for all patients (Figure 28).

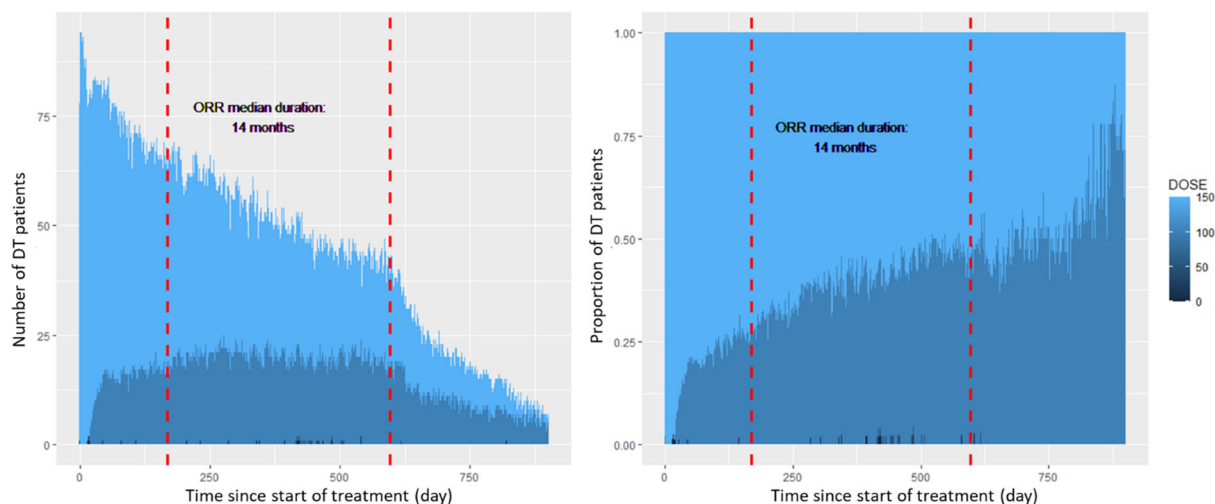
For different dose reduction categories (i.e., <12 weeks, 12-<24 weeks, 24-<48 weeks, ≥48 weeks), the median tumor size reductions over time were summarized. As shown in Figure 29, all groups that were dose reduced to 100 mg had steeper slopes of tumor size reduction compared to the group that stayed on 150 mg. This trend was observed with no regards to the time frame in which dose reduction occurred, suggesting that efficacy was retained with dose reduction including those occurred early. This observation aligns with the modeling results that a treatment effect independent of concentrations was identified as a predictor for tumor dynamics.

Longitudinal PK/PD model for tumor dynamics included two intra-patient doses and thus data were considered robust for evaluating concentration dependent effect on tumor shrinkage in patients with dose reduction. However, one cannot conclude the absence of concentration dependent response in all patients because the analysis of exposure response is determined by the data from patients who underwent dose reduction. These patients could have an increased sensitivity to drug for PK (e.g., high free drug concentrations not reflected by total drug concentrations) and/or PD (e.g., elevated biochemical characteristics) reasons compared to other patients whose dose was unchanged.

Given the very high percentage of protein binding for nirogacestat (99.4%), variability in this percentage may lead to a large difference in free drug concentrations. The possibility of increased free drug in patients with dose reduction could not be verified since it was not measured. To evaluate a potential PD difference, known patient factors were modeled as covariates and none were found statistically significant. For unknown confounding factors, randomized study evaluating two doses is warranted to interrogate the exposure-response relationship. Therefore, the flat exposure response should only be interpreted in the scope of data used to develop the PK/PD model. Although it does not provide conclusive evidence that a lower starting dose could be as effective as the 150 mg BID, the flat ER relationship observed in

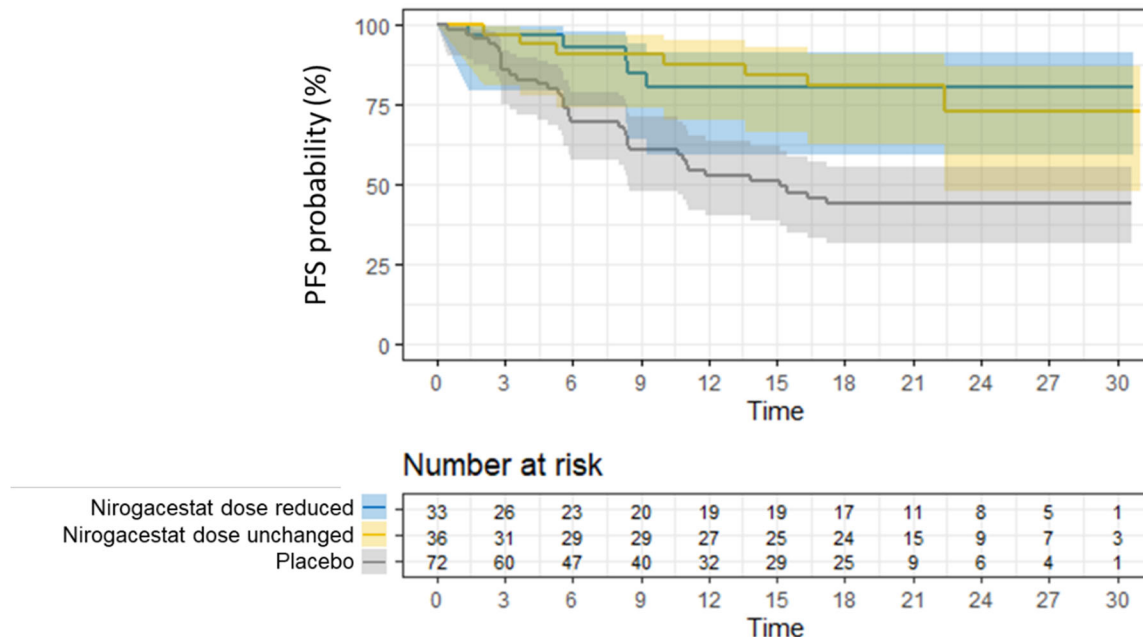
the PK/PD model for tumor size, along with observed data supports maintenance of efficacy in patients who need dose reduction in response to AEs. The onset of AEs may have reflected the possibly increased sensitivity to the drug whether it is attributed to PK and/or PD differences in those patients.

Figure 25: Number and Proportion of Dose Reduction over Time in Patients with DT Treated with Nirogacestat in Study NIR-DT-301



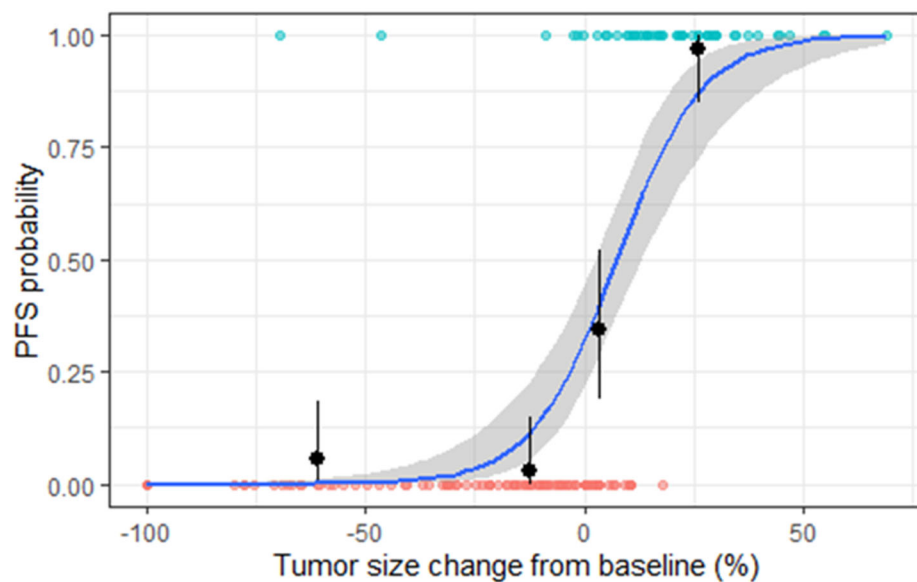
Source: Reviewer's analysis. The time since start of treatment was set to 0 when patients in placebo arm switched to nirogacestat treatment. The vertical lines represent the median onset and duration of response.

Figure 26: PFS by Dose Reduction in Study NIR-DT-301



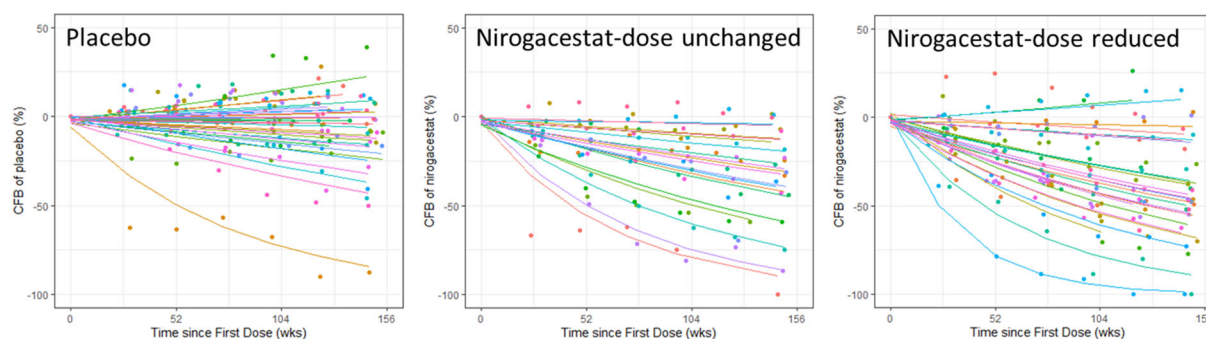
Source: Reviewer's analysis.

Figure 27: Logistic Regression Relationships Between Tumors Size Change from Baseline and PFS in Study NIR-DT-301



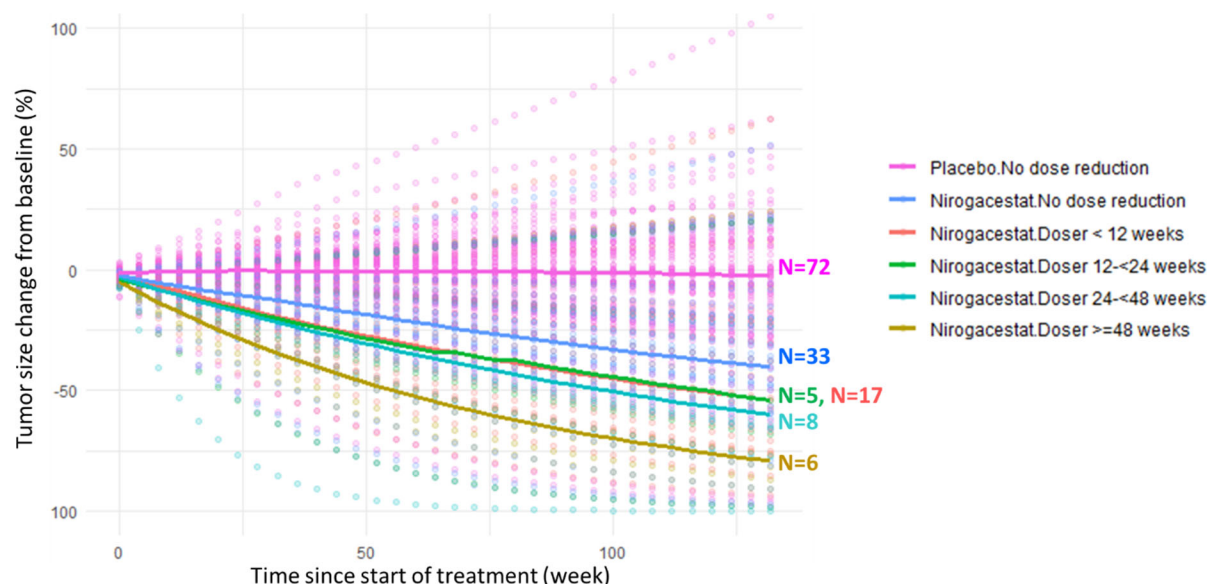
Source: Reviewer's analysis. Tumor size change from baseline at the PFS event or censoring.

Figure 28: RECIST Tumor Size Individual Prediction Overlay with Observation



Source: Reviewer's analysis. CFB: Tumor size change from baseline. Each color dot (observation)/line (individual prediction) represents an individual. Plots were generated for a selected subset of patients who were treated for at least 2 years.

Figure 29: RECIST Tumor Size Dynamics by Dose Reduction at Different Time Frames in Study NIR-DT-301



Source: Reviewer's analysis. Patients with dose reduction included 7 patients who had temporary/intermittent dose reduction.

19.4.16. Overall Benefit-Risk Evaluation based on E-R Analyses

The Applicant's Position:

Exposure-response relationships were explored for several efficacy and safety endpoints using data from Studies A8641014 and NIR-DT-301, and the final model from the PopPK Analysis. An

exposure-response plateau was achieved within the predicted exposure ranges (AUC_{τ} and $C_{\min}$) for the ≥ 100 mg to 150 mg dose range. Reduction in tumor size was independent of nirogacestat exposure within the evaluated dose range, whether it was determined by volumetric MRI (NIR-DT-301 only) or using RECIST (by CT or MRI). Similarly, there was a treatment effect relationship with PFS that was independent of exposure within the evaluated dose ranges. Additional analyses were conducted to explore if a relationship between nirogacestat exposure and objective response could be described; however, exposure was not found to be a significant predictor of duration of response due to low number of participants with loss of response.

A statistically significant relationship was found between exposure and dose modifications. Participants with higher predicted exposures (AUC_{τ} and $C_{\min}$) at steady-state were more likely to have had dose modifications than those with lower steady-state exposures. Given that the majority of dose modifications were due to TEAEs, this relationship may suggest that participants with lower nirogacestat clearance were more likely to experience TEAEs that required a dose modification.

The exposure-response data support a recommended starting dose of 150 mg for all patients with allowance for dose modification based on tolerability to ensure optimal exposure for each individual.

The FDA's Assessment:

FDA agrees.

19.4.17. Physiologically Based Pharmacokinetic Modeling Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK report to support the intended uses.

"Development of a PBPK model for nirogacestat with the Simcyp population-based simulator and subsequent evaluation of DDI liability as a victim and perpetrator of CYP3A4."

The Division of Pharmacometrics has reviewed the PBPK report and supporting modeling files and concluded the followings.

- The nirogacestat model is adequate to predict the nirogacestat PK profiles following a single intravenous dose (0.0435 mg), a single oral dose administration (1, 2.5, 5, 10, 25, 40, 50, 65, 120 and 150 mg), or multiple oral dose administration (7 and 40 mg BID) in healthy subjects

and multiple oral dose administration (20, 40, 80, 100, 130, 150 and 220 mg BID) in cancer patients.

- The nirogacestat model is adequate to predict the effect of itraconazole and ketoconazole (strong CYP3A4 inhibitors) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg or 150 mg BID). Model predicted nirogacestat geometric mean AUC ratio was around 5-7-fold in the presence of itraconazole or ketoconazole in healthy subjects.
- The nirogacestat model is adequate to predict the effect of fluconazole, clarithromycin and erythromycin (moderate CYP3A4 inhibitors) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg or 150 mg BID). Model predicted nirogacestat geometric mean AUC ratio was around 3-fold in the presence of fluconazole, clarithromycin or erythromycin in healthy subjects.
- The nirogacestat model is adequate to predict the effect of cimetidine (a weak CYP3A4 inhibitor) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg or 150 mg BID). Model predicted nirogacestat geometric mean AUC ratio was about 1.4-fold in the presence of cimetidine in healthy subjects.
- The nirogacestat model is adequate to predict the effect of rifampicin (a strong CYP3A4 inducer) and efavirenz (a moderate CYP3A4 inducer) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg or 150 mg BID). The model predicted nirogacestat exposure decreased about 85% and 67% when coadministered with rifampicin and efavirenz, respectively, in healthy subjects.
- The nirogacestat model is adequate to predict the effect of nirogacestat on the PK of midazolam (a sensitive CYP3A4 substrate) following multiple dose administration of nirogacestat (100 mg or 150 mg BID). The model predicted midazolam exposure increased about 100% when coadministered with nirogacestat in healthy subjects.
- The nirogacestat PBPK model is adequate to predict the effect of nirogacestat on the PK of rosiglitazone (a CYP2C8 substrate) and warfarin (a CYP2C9 substrate) following multiple dose administration of nirogacestat (100 mg and 150 mg, BID). Model predicted changes in the exposure of rosiglitazone and warfarin were not considered clinically significant when coadministered with multiple doses of nirogacestat in healthy subjects.
- In vitro study and PBPK modeling efforts suggest that the DDI potential of nirogacestat (100 mg or 150 mg BID) with mephenytoin and omeprazole (CYP2C19 substrates) cannot be excluded.

Applicant's PBPK Modeling Effort

Clinical PK and DDI Data

Study	Description	Note
NIR-DT-102	Mass-balance, IV (0.0435 mg), PO (150 mg)	Model development
A8641002 Part 1, Health subjects	95 mg QD	Model refinement
A8641001, SAD, Health subjects	1, 2.5, 5, 10, 25, 40, 50, 65, 120 mg	Model validation
A8641002 Part 1, Health subjects	7 mg BID, 40 mg QD	Model validation
A8641014, MAD, Patients	20, 40, 80, 100, 130, 150, 220 mg BID	Model validation
NIR-DT-103, Health subjects	Itraconazole 200 mg QD (Day 2-19) + nirogacestat 100 mg on Day 15 ¹	Model validation
A8641002 Part 2, Health subjects	nirogacestat 95 mg QD (Day 2-10) + Midazolam 2 mg on Day 9 ²	Model validation

¹ Co-administration of Itraconazole and nirogacestat resulted in increases in plasma systemic exposure of nirogacestat by approximately 8.2-fold and 2.5-fold for AUCinf and Cmax, respectively; ²Co-administration of nirogacestat 95 mg QD and midazolam 2 mg resulted in increases in plasma systemic exposure of midazolam by approximately 58.9% and 30% for AUCinf and Cmax, respectively.

PBPK software

Simcyp V19 (Simcyp Ltd, UK) was used by the Applicant to develop the PBPK models and assess the DDI liability. The reviewer used the Simcyp V21 for analyses. The simulation results for the PK profiles of nirogacestat and DDI assessment using Simcyp V21 were not significant difference when compared to those generated using Simcyp V19. As a result, the Applicant's simulation results were included in the review.

Model development

PBPK model parameters are listed in Appendix.

The nirogacestat model consisted of a first order absorption model and a whole-body PBPK model. The absorption rate constant (k_a) was estimated to be 2.899 1/h based on the permeability data in MDCK cells. The lag time (T_{lag}) of 0.40 hr was assumed based on gastric emptying time under fasted state.

The $f_{u,gut}$ (unbound fraction in enterocytes) was set to be 1.0. The $P_{eff,man}$ (permeability in man) was predicted to be 6.64×10^{-4} cm/s based on the permeability data in MDCK cells.

The whole-body full PBPK model was used to simulate nirogacestat distribution. The volume of distribution (V_{ss} , 3.55 L/kg) was predicted using Method 2 in Simcyp and subsequently optimized based on the observed nirogacestat PK in healthy subjects using a global K_p scalar of 0.29. The plasma protein binding (f_u) is about 0.4%.

Nirogacestat clearance was estimated to be 13.4 L/h after intravenous administration of nirogacestat in Study NIR-DT-102. CYP3A4 is the primary enzyme responsible for the metabolism of nirogacestat. The f_m CYP3A4 value of 0.857 was estimated based on HLM chemical inhibition data. The rest of the metabolism was assigned as the additional human liver

microsome clearance (14.3%). Renal elimination was not considered in the model because the majority of nirogacestat clearance was attributed to the metabolic elimination, with minimal drug excreted unchanged in urine.

The induction parameter (Indmax and IndC50) values of CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 (b) (4). The KI (8.46 μ M) value for CYP3A4 time-dependent inhibition was optimized based on data in clinical study following multiple dosing of 95 mg QD nirogacestat (study A8641002), and Kinact (4.57 1/h) value for CYP3A4 time-dependent inhibition was obtained from in vitro study (Study 103822). The CYP3A4 competition inhibition parameter value ($K_i=0.04$ mM) applied in the model was refined based on the DDI study results with midazolam (Study A8641002) by the reviewer.

Victim and perpetrator drug models

The default PBPK models of itraconazole, ketoconazole, fluconazole, clarithromycin, erythromycin, cimetidine, rifampicin efavirenz, midazolam, bupropion, rosiglitazone, warfarin, mephenytoin and omeprazole in SimCYP V19 were used without any modification for DDI prediction. Default healthy volunteer population and cancer population in SimCYP V19 were used in simulations.

PBPK model application

The developed PBPK model was used to simulate the DDI for nirogacestat in the following scenarios.

- To predict the effects of itraconazole and ketoconazole (strong CYP3A inhibitors) and fluconazole and clarithromycin (moderate CYP3A inhibitors) and cimetidine (a weak CYP3A4 inhibition) on the PK of nirogacestat.
- To predict the effect of rifampicin (a strong CYP3A inducer) and efavirenz (a moderate CYP3A inducer) on the PK of nirogacestat.
- To predict the effect of nirogacestat on the PK of midazolam (a sensitive CYP3A4 substrate).
- To predict the effect of nirogacestat on the PK of bupropion (a CYP2B6 substrate).
- To predict the effect of nirogacestat on the PK of rosiglitazone (a CYP2C8 substrate) and warfarin (a substrate of CYP2C9).
- To predict the effect of nirogacestat on the PK of mephenytoin and omeprazole (CYP2C19 substrates).

Results

1. Can nirogacestat PBPK model describe nirogacestat PK in healthy subjects?

Yes. Table 79 showed the Applicant's model verification results. The PK profiles after multiple oral doses of 95 mg QD nirogacestat in healthy subjects was used to verify the net auto DDI

effect (TDI and induction on CYP3A4) on the PK of nirogacestat. The in vitro obtained parameter values for mechanism-based inhibition and induction on CYP3A4 were included in the model. The in vitro KI value (reduced by 5-fold) was optimized to capture the nirogacestat PK profile on day 1 and day 14 after multiple oral doses of 95 mg QD nirogacestat in healthy subjects. In general, the model was able to capture the nirogacestat PK profiles following a single or multiple dose administration (Figure 30). The simulated geometric mean AUC and Cmax values for nirogacestat were within 0.7-1.3-fold of the observed values after a single or multiple dose administration in healthy subjects or cancer patients, except for the dose groups where the number of subjects per dose level is less than 8 (Table 79). It was noted that the PK parameters for nirogacestat tended to have substantial inter-subject variability since most geometric CV values are greater than 30% and even approach 100% in some studies. Therefore, considering the limited number of subjects in some dose groups and the significant variability, the Applicant's model is deemed to be acceptable for the purpose of DDI potential evaluation as a victim. The uncertainty associated with the DDI potential evaluation as a perpetrator will be further assessed using sensitivity analyses.

Figure 30: Observed (dots) and simulated (lines) nirogacestat plasma concentration-time profiles following a single dose (A: iv, 0.0435 mg; B: oral, 150 mg), a single ascending oral dose (D: 1, 2.5, 5, 10, 25, 40, 50, 65, and 120 mg), multiple oral doses in healthy subjects (C: 95 mg QD; E 7 mg BID, and 40 mg QD), and multiple oral doses in patients with cancer (F: 25, 40, 80, 100, 130, 150, and 220 mg BID)

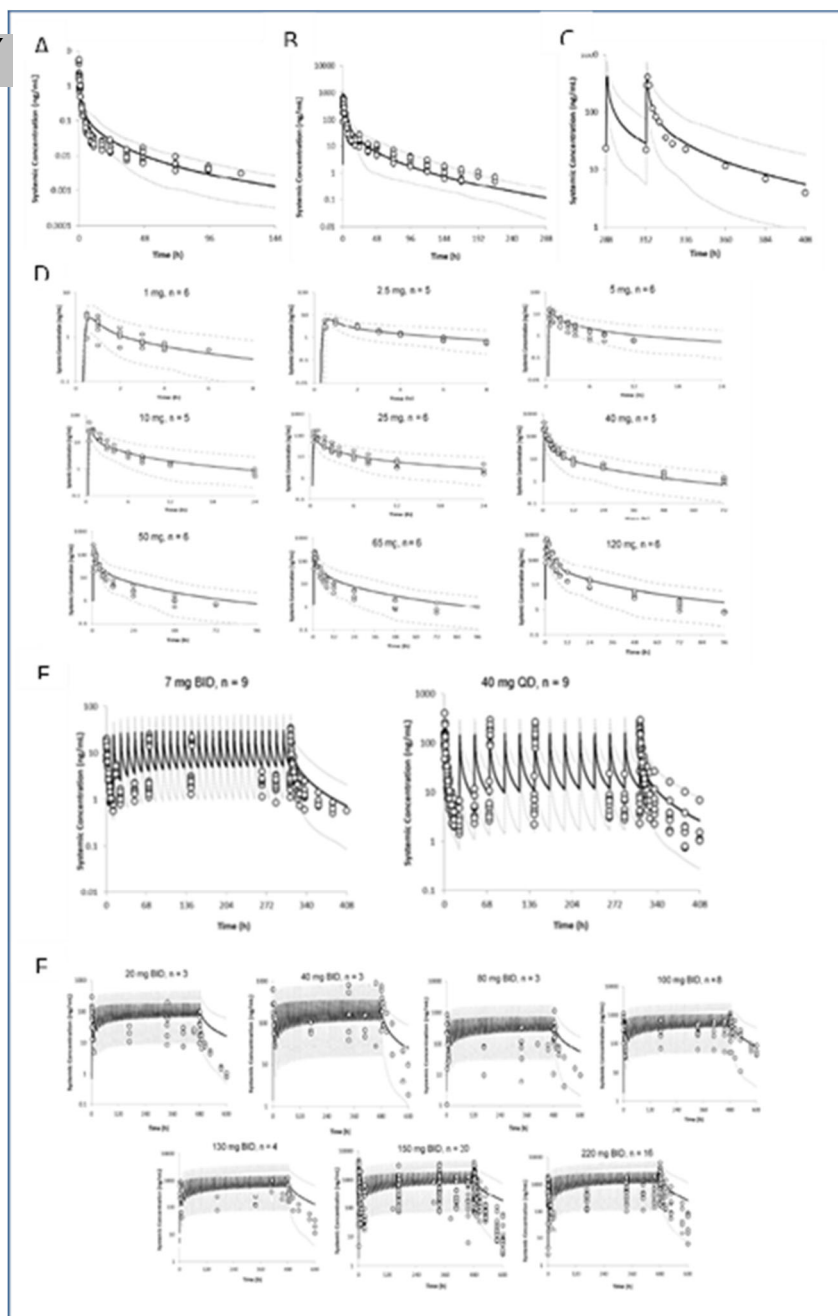


Table 79: Observed and simulated nirogacestat geometric mean PK parameters following single-dose or multiple dose administration of nirogacestat in healthy subjects or patients with cancer.

	Dose	Single dose or Day 1 for multiple doses						Day 14 or 21 for multiple doses ^b						Sources
		Cmax (ng/mL)			AUC ^a (ng*h/mL)			Cmax (ng/mL)			AUC (ng*h/mL)			
		Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	R _{Pred/Obs}	
Model Development Healthy subjects	IV bolus 0.0435 mg, 5 minutes	4.09	3.62	0.88	3.61	3.59	0.99							Study NIR-DT-102
	Oral, 150 mg SD	544	982	1.80	2380	2865	1.20							
	Oral, 95 mg QD N=9	464	315	0.68	1520	1063	0.70	457	436	0.95	1857	1853	1.00	Study A8641002
Model Verification Healthy subjects Single dose	1 mg, N=6	2.48	2.84	1.14	NA	9.24	-							Study A8641001
	2.5 mg, N=5	5.41	6.92	1.28	NA	22.8	-							
	5 mg, N=6	10.4	14.2	1.37	NA	58.7	-							
	10 mg, N=5	32.7	28.7	0.88	117	104	0.89							
	25 mg, N=6	113	72.7	0.64	408	328	0.80							
	40 mg, N=5	241	119	0.49	732	473	0.65							
	50 mg, N=6	145	148	1.02	552	685	1.24							
	65 mg, N=6	194	201	1.03	745	931	1.25							
	120 mg, N=6	393	380	0.97	1800	1823	1.01							
Model Verification Healthy subjects BID	7 mg, N=6	17.9	21.0	1.17	43.3	55.4	1.28	23.1	29.7	1.29	73.1	114	1.56	Study A8641002
	40 mg, N=8	177	126	0.71	471	426	0.91	178	167	0.941	643	737	1.15	
Model Verification Cancer patients BID	20 mg, N=3	163	83.9	0.51	409	274	0.67	64.5	155	2.40	309	745	2.41	Study A8641014
	40 mg, N=3	368	164	0.50	1329	524	0.49	381	297	0.78	2521	1348	0.53	
	80 mg, N=4	230	334	1.45	1649	1143	0.69	313	621	1.98	1572	2955	1.88	
	100 mg, N=8	691	470	0.68	2204	1461	0.66	867	915	1.05	4741	4307	0.91	
	130 mg, N=4	536	615	1.15	2924	1979	0.68	421	1250	2.97	3155	6092	1.93	
	150 mg, N=23	943	745	0.79	3677	2451	0.67	1246	1590	1.28	6430	8142	1.27	
	220 mg, N=16	861	1117	1.30	3593	3624	1.01	1864	2400	1.29	3593	3624	1.01	

a: represents AUCtau for multiple doses or AUCinf for single dose

b: day 14 for 7 and 14 mg BID and 95 mg QD regimen; day 21 for 20, 40, 80, 100, 130, 150 and 220 mg BID regimen

2. Can nirogacestat PBPK model predict its effect on midazolam (a sensitive CYP3A4 substrate) PK following multiple dose administration of nirogacestat (100 mg and 150 mg BID)?

Yes. The nirogacestat mediated combined induction and inhibition effects on CYP3A4 (net inhibition effect) was verified based on the clinical DDI study with midazolam following multiple dose administration of nirogacestat (95 mg QD) (Table 80). The verified model was then used to predict the effect of nirogacestat (100 mg BID and 150 mg BID) on the PK of midazolam. The model predicted about 84% and 107% increase in the exposure of midazolam after coadministration of 100 mg BID and 150 mg BID nirogacestat, respectively, in healthy subjects (Table 80).

3. Can nirogacestat PBPK model predict the effect of itraconazole and ketoconazole (strong CYP3A inhibitors) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg and 150 mg BID) in healthy subjects?

Yes. The contribution of CYP3A4 to the overall clearance of nirogacestat was estimated based on invitro data and verified based on the clinical DDI study data of single dose nirogacestat with itraconazole (Table 80). The verified model was then used to estimate the effect of strong CYP3A4 inhibitors on the PK of multiple dose nirogacestat. The model predicted nirogacestat (100 mg BID and 150 mg BID) exposure increased 7.02, and 6.33-fold and 5.56 and 5.19-fold when coadministered with itraconazole and ketoconazole, respectively, in healthy subjects (Table 80).

4. Can nirogacestat PBPK model predict the effect of fluconazole, clarithromycin and erythromycin (moderate CYP3A inhibitors) and cimetidine (a weak CYP3A4 inhibitor) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg and 150 mg BID) in healthy subjects?

Yes. The contribution of CYP3A4 to the overall clearance of nirogacestat was estimated based on invitro data and verified based on the clinical DDI study data of single dose nirogacestat with itraconazole (Table 80). The verified model was then used to estimate the effect of moderate or weak CYP3A4 inhibitors on the PK of nirogacestat. The model predicted nirogacestat (100 mg BID and 150 mg BID) exposure increased about 3.26 and 3.18-fold, 3.83 and 3.46-fold, 3.00 and 2.73-fold, and 1.40 and 1.40-fold when coadministered with fluconazole, clarithromycin, erythromycin and cimetidine, respectively, in healthy subject.

5. Can nirogacestat PBPK model predict the effect of rifampicin (a strong CYP3A4 inducer) and efavirenz (a moderate CYP3A4 inducer) on the PK of nirogacestat following multiple dose administration of nirogacestat (100 mg and 150 mg BID) in healthy subjects?

Yes. The contribution of CYP3A4 to the overall clearance of nirogacestat was estimated based on invitro data and verified based on the clinical DDI study data of single dose nirogacestat with itraconazole (Table 80). The verified model was then used to estimate the effect of CYP3A4

inducers on the PK of nirogacestat. The model predicted nirogacestat exposure decreased about 85% and 67% when coadministered with rifampicin and efavirenz, respectively, in healthy subjects (Table 80).

6. Can nirogacestat PBPK model predict the effect of nirogacestat on the PK of bupropion (a CYP2B6 substrate) following multiple dose administration of nirogacestat (100 mg BID and 150 mg BID) in healthy subjects?

No. The bupropion substrate models have not been adequately validated; therefore, it cannot be used to evaluate the potential effect of nirogacestat on the PK of CYP2B6 substrate.

7. Can nirogacestat PBPK model predict the effect of nirogacestat on the PK of rosiglitazone (a CYP2C8 substrate) and warfarin (a substrate of CYP2C9) following multiple dose administration of nirogacestat (100 mg BID and 150 mg BID) in healthy subjects?

Yes. In vitro studies indicated that nirogacestat is a CYP2C8 and CYP2C9 inducer with an in vitro determined Indmax and IndC50 values of 11.14 and 2.38 μM for CYP2C8 induction and 12.33 and 4.96 μM for CYP2C9 induction, respectively. The model predicted rosiglitazone and warfarin exposures were not significantly affected by concomitant use of nirogacestat based on in vitro determined enzyme induction parameter values (AUCR~1.00 for both rosiglitazone and warfarin). The Applicant further conducted a sensitivity analysis of nirogacestat Indmax values to assess the effect on the predicted rosiglitazone and warfarin exposure. Due to the uncertainties regarding the in vitro to in vivo extrapolation of the induction parameter, reviewer also conducted additional sensitivity analysis of nirogacestat IndC50 values. The simulated rosiglitazone and warfarin AUC ratios were around 1.0 with 10-fold lower Ind50 values or 10-fold higher Indmax values than the in vitro determined when coadministered with 100 mg BID or 150 mg BID nirogacestat. These results indicated that the induction potential of nirogacestat is low towards CYP2C8 and CYP2C9.

8. Can nirogacestat PBPK model predict the effect of nirogacestat on the PK of mephenytoin and omeprazole (CYP2C19 substrates) following multiple dose administration of nirogacestat (100 mg BID and 150 mg BID) in healthy subjects?

The Applicant used (b) (4) Indmax ((b) (4) and IndC50 ((b) (4) μM) values to assess the effect of nirogacestat on the PK of mephenytoin and omeprazole. In addition, the effect of nirogacestat on the PK of mephenytoin and omeprazole was evaluated using a sensitivity analysis of (b) (4) fold higher nirogacestat Indmax values. These modelling efforts showed a positive induction effect of nirogacestat (b) (4) on the PK of mephenytoin and omeprazole (Table 80). Due to the uncertainties regarding (b) (4) of the induction parameter values, the nirogacestat model was not considered adequate to accurately predict the effect of nirogacestat on the PK of mephenytoin and omeprazole. However, the DDI potential of nirogacestat as a perpetrator with CYP2C19 substrates cannot be excluded.

Table 80 Model Predicted Effects of CYP Modulators on the PK of Nirogacestat and Effects of Nirogacestat on the PK of CYP3A4, CYP2C8, CYP2C9, or CYP2C19 Substrates Following Multiple Dose Administration of 100 mg or 150 mg nirogacestat

		Nirogacestat dose	Observed		Predicted	
			CmaxR	AUCR	CmaxR	AUCR
Model validation	Midazolam 2 mg SD	95 mg QD	1.31	1.59	1.48	1.59
	Itraconazole 200 mg QD	100 mg SD	2.50	8.23	3.25	9.31
Model Application: as a victim	Itraconazole 200 mg QD	100 mg BID			3.76	7.02
		150 mg BID			3.48	6.33
	Ketoconazole 400 mg QD	100 mg BID			3.17	5.56
		150 mg BID			3.03	5.19
	Fluconazole 200 mg QD	100 mg BID			2.24	3.26
		150 mg BID			2.19	3.18
	Clarithromycin 500 mg BID	100 mg BID			2.47	3.83
		150 mg BID			2.31	3.46
	Erythromycin 500 mg TID	100 mg BID			1.86	3.00
		150 mg BID			1.75	2.73
	Cimetidine 400 mg TID	100 mg BID			1.35	1.40
		150 mg BID			1.34	1.40
	Rifampicin 600 mg QD	100 mg BID			0.24	0.13
		150 mg BID			0.29	0.15
	Efavirenz 600 mg QD	100 mg BID			0.53	0.33
		150 mg BID			0.53	0.33
Model Application: as a perpetrator	Midazolam CYP3A4 substrate	100 mg BID			1.66	1.84
		150 mg BID			1.77	2.07
	Mephenytoin CYP2C19 substrate	100 mg BID, Indmax/Indmax*10			(b) (4)	
		150 mg BID, Indmax/Indmax*10				
	Omeprazole CYP2C19 substrate	100 mg BID, Indmax/Indmax*10				
		150 mg BID, Indmax/Indmax*10				

Table 81: Appendix PBPK Model Inputs

Parameter	Value	Note
PhysChem		
Mol Weight (g/mol)	489.6	
log P	4.74	Predicted from ACD Percepta
pKa 1	7.13	
pKa 2	5.77	
B/P	0.55	Study DM2006-03084014-020
fu	0.004	Report 21SPRWP2
Reference Binding Component	AGP	Report 21SPRWP2
Absorption Model	1st order	
fa	0.56	Clinical Study DT-102
ka (1/h)	2.899	Predicted from MDCK data
fu(Gut)	1	Assumed
Q(Gut) (L/h)	16.634	Predicted
Pe _{eff,man} (10 ⁻⁴ cm/s)	6.64	Predicted from MDCK data
Distribution Model	Full PBPK Model	
V _{ss} (L/kg)	3.55	Method 2 predicted
K _p scalar	0.29	Optimized
Elimination		
CL _{IV} (L/h)	13.4	Study NIRDT-102
F _m CYP3A	79.5	DM2006-3084014-19
CL _{int} (μL/min/pmol)	7.33	Retrograde model
fu _{mic}	1	Derived
Additional HLM CL _{int} (μL/min/mg)	241	Retrograde model
CYPs Interaction		
CYP3A4K _i (μM)	0.04	Optimized to recover the DDI data with midazolam
fu _{mic}	0.63	Predicted, [P] 0.1 mg/mL
CYP3A4MBI K _{app} (μM)	8.465	Optimized to recover PK following multiple dosing (95 mg QD)
CYP3A4MBI K _{inact} (1/h)	4.574	Study 103822
MBI fu _{mic}	0.25	Optimized to recover DDI results in Study A8641002
CYP3A4Ind _{max}	35.6	Study XT133045
CYP3A4Ind _{C50} (μM)	3.63	Study XT133045
Other CYPs		
CYP2C8 Ind _{max}	11.14	Study 19SPRWP3
CYP2C8 Ind _{C50} (μM)	2.38	Study 19SPRWP3
CYP2C9 Ind _{max}	12.33	Study 19SPRWP3
CYP2C9 Ind _{C50} (μM)	4.96	Study 19SPRWP3

CYP2C19 Ind _{max}	(b) (4)	
CYP2C19 Ind _{C50} (μM)		

Reference: Summarized from PBPK report

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

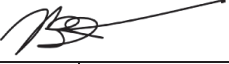
FDA did not conduct additional safety analysis relevant to this Section; see Section 8.2 for FDA's safety analysis.

Signatures NDA 217677

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTION(S) AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Nonclinical Team Leader	Matthew Thompson, PhD, MPH	OOD/DHOT	Section: 5	Select one: ☒ Authored ☒ Approved
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Nonclinical Team Division Director	John Leighton, PhD	OOD/DHOT	Section: 5	Select one: ☐ Authored ☒ Approved
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	Ye Xiong, PhD	OCP/DPM	Sections: 19.4.2, 19.4.3	Select one: ☒ Authored ☐ Approved
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Genomics Team Leader	Jeffrey Kraft, PhD	OCP/DTPM	Section: 6.3.2	Select one: ☒ Authored ☒ Approved
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PBPk Team Leader	Yuching Yang, PhD	OCP/DPM	Section: 19.4.4	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology Division Director	Nam Atiqur (Atik) Rahman, PhD	OCP/DCPII	Sections: 6, 10.4	Select one: ☐ Authored ☒ Approved
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Clinical Team Leader	Leslie Doros, MD	OOD/DO3	Authored: 1, 8.2 Approved: 7, 8, 9-13, 19.2	Select one: ☒ Authored ☒ Approved
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Statistical Reviewer	Ting-Yu Chen, PhD	OB/DBV	Sections: 8.1.1, 8.1.4-8.1.6, 8.3	Select one: ☒ Authored ☐ Approved
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	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2023.10.30 09:39:51 -04'00'			
Division Director (OB)	Shenghui Tang, PhD	OB/DBV	Sections: 8.1.1, 8.1.4-8.1.6, 8.3	Select one: ☐ Authored ☒ Approved
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OSIS Reviewer	Monica Javidnia, PhD	OTS/OSIS/DGDSI	Section: 19.4.1	Select one: ☒ Authored ☐ Approved
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PFSS Reviewer	Weimeng Wang, PhD	OTS/OB/DBIII	Section: 8.1.1.2	Select one: ☒ Authored ☐ Approved
	Signature: Weimeng Wang -S (Affiliate) Digitally signed by Weimeng Wang -S (Affiliate) Date: 2023.11.06 11:12:33 -05'00'			
PFSS Team Leader	Lili Garrard, PhD	OTS/OB/DBIII	Section: 8.1.1.2	Select one: ☐ Authored ☒ Approved
	Signature: Lili Garrard -S Digitally signed by Lili Garrard -S Date: 2023.11.07 11:07:07 -05'00'			
DCOA Deputy Division Director	Selena Daniels, PharmD, PhD	ODES/DCOA	Sections: 1.2, 8.1.1.2	Select one: ☒ Authored ☐ Approved
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DCOA Division Director	David Reasner, PhD	ODES/DCOA	Sections: 1.2, 8.1.1.2	Select one: ☐ Authored ☒ Approved
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Associate Director for Labeling (ADL)	Doris Auth, PharmD	OCE	Section: 11	Select one: ☒ Authored ☐ Approved
	Signature: Doris Auth -S  Digitally signed by Doris Auth -S Date: 2023.11.08 08:44:05 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Leslie Doros, MD	OOD/DO3	Sections: All	Select one: ☐ Authored ☒ Approved
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Division Director (Clinical)	Steven Lemery, MD, MHS	OOD/DO3	Sections: All	Select one: ☐ Authored ☒ Approved
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/s/

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Director, DO3

STEVEN J LEMERY on behalf of LESLIE A DOROS
11/27/2023 01:22:59 PM
Signing as proxy on behalf of Dr. Leslie Doros, CDTL

PAUL G KLUETZ
11/27/2023 02:12:55 PM