CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217677Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 25, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 217677
Product Name, Dosage Form, and Strength:	Ogsiveo (nirogacestat) tablet, 50 mg
Applicant/Sponsor Name:	SpringWorks Therapeutics
TTT ID #:	2022-3189-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 20, 2023 for Ogsiveo. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Ogsiveo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during the late cycle meeting on September 27, 2023 regarding previously printed labels.[a] The revised label and labeling add a barcode with the NDC # encoded. In addition, the labels were revised with "Product of China" to address DHS' requirement for Country of Origin.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Zack-Taylor, A. Late-Cycle meeting minutes for Ogsiveo. Silver Spring (MD): FDA, CDER, DO3 (US); 2023 OCT 09. NDA 217677.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALI MAHMOUD
10/25/2023 11:40:01 AM

ASHLEIGH V LOWERY
10/27/2023 10:30:35 AM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2023014
NDA#/Referenced IND for NDA:	NDA 217677/IND 138207
Applicant:	SpringWorks Therapeutics, Inc.
Established Name/Trade Name:	Nirogacestat
Indication:	Treatment of adult patients with desmoid tumors.
PDUFA Goal Date:	August 25, 2023
Review Division:	Division of Oncology 3
Clinical Reviewer:	Kristen Snyder
Clinical Team Leader (TL)	Leslie Doros
Regulatory Project Manager:	Autumn Zack-Taylor
COA Reviewer/TL:	Selena Daniels, PharmD, PhD
COA Division Director:	David Reasner, PhD
Instruments Reviewed:	1. GOunder/DTRF DEsmoid Symptom Scale (GODDESS) Desmoid Tumor Symptom Scale (DTSS) ☒ Patient-reported outcome (PRO)
	2. GODDESS Desmoid Tumor Impact Scale (DTIS) ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of nirogacestat for the treatment of adult patients with desmoid tumors. The specific COA [redacted] (b) (4) are related to improvement in pain, desmoid tumor-related symptoms, and physical functioning, which are derived from one randomized, double-blind, placebo-controlled, phase 3 clinical

trial (Study NIR-DT-301). [redacted]

The secondary efficacy endpoints [redacted]

- Mean change from baseline at Cycle 10 in Brief Pain Inventory-Short Form (BPI-SF) average pain intensity (API) score (measured by BPI-SF item 3)
- Mean change from baseline at Cycle 10 in Desmoid Tumor Symptom Scale (DTSS) total symptom score (TSS)
- Mean change from baseline at Cycle 10 in Desmoid Tumor Impact Scale (DTIS) Physical Functioning domain score
- Mean change from baseline at Cycle 10 during the double-phase period in the EORTC QLQ-C30 Physical Functioning domain score

The data from Study NIR-DT-301 demonstrated that nirogacestat had statistically significant improvement in the API, DTSS TSS, and DTIS Physical Functioning domain scores compared to placebo between baseline and Cycle 10. However, it is noted that there was a low completion rate for the PRO assessments at the predefined timepoint (i.e., Cycle 10) and an asymmetric completion rate between treatment arms.

Per the Division's request, the subject of this review is related to the DTSS and DTIS-based endpoints. While the DTSS TSS and DTIS Physical Functioning domain measure some important aspects of the patient experience of desmoid tumors, from a COA perspective, there is concern that the data from these instruments [redacted] issues related to comprehensibility of the instrument, insufficient level of symptom and physical functioning impairment at baseline, and missing data.

2 REVIEW CONCLUSIONS

The applicant submitted an evidence dossier for the DTSS and DTIS instruments, as well as a PRO report. These instruments were reviewed for content validity, other measurement properties, and meaningful within-patient change.

Review Summary

- The DTSS TSS and DTIS Physical Functioning domain score measure some important aspects of the patient experience of desmoid tumors.
- A definitive conclusion cannot be made whether the DTSS and DTIS measures are well-understood and interpreted appropriately due to the limited approach used to evaluate participant comprehension (see Key Issues Identified section).
- While the other measurement properties for the DTSS TSS and DTIS Physical Functioning domain scores appear to fall within reasonable and acceptable ranges, the data is difficult to fully interpret due to questions surrounding the comprehensibility of the measures. Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

- It is difficult to estimate the range of change that represents clinically meaningful within-patient score changes in the DTSS TSS and DTIS Physical Functioning domain score due to issues surrounding comprehensibility of the measures; the limitations of the external anchors used for anchor-based analyses (i.e., misalignment of measurement concepts); and missing data at Cycle 10.

Key Issues Identified

Issue 1: Content Validity

- The applicant did not query 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).

- The applicant did not consistently query about recall period across instructions and items.

Issue 2: Data interpretability

- The relevance of some of the items is questionable in participants who may be asymptomatic and/or have mild desmoid tumor symptoms. 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%).

- Minimal change is observed at the item, domain and/or total score level.

- The anchor scales have limitations that impact the interpretability of the results of the anchor-based analyses. Specifically, the concepts measured in the anchor scales are not aligned with the concepts measured in the DTSS TSS and DTIS Physical Functioning domain.

- Missing data at Cycle 10 for both the target instruments and anchor scales. The PRO report submitted showed low and unbalanced differential completion rate between study arms for both DTIS and DTSS from Cycle 4 to Cycle 10.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend that sponsors specify and define symptoms that are relevant and important to patients with desmoid tumors and that are likely to demonstrate meaningful and interpretable changes in the planned clinical trial(s). Sponsors seeking to demonstrate clinical benefit of a therapeutic on a particular set of symptoms and functional impacts should select a sufficiently symptomatic population or otherwise plan for

stratification or appropriate statistical analyses. Additionally, sponsors should provide evidence to support that respondents understand each of the components comprising the measure (e.g., their understanding and interpretation of instructions, items, response options, and recall period in a PRO measure). For assessment of measurement invariance, sponsors should consider more methodologically appropriate differential item functioning (DIF) method(s) to empirically verify the measurement invariance assumption across various tumor location groups, especially for patients with extra- and intra- abdominal tumors. We recommend sponsors consider the scale of measurement of each item's response levels before conducting DIF analyses, and investigate the impact of DIF items at the scale level.

There are also potential methods for designing endpoint(s) with heterogeneous populations. Sponsors should refer to the Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making[1] regarding considerations on constructing a personalized endpoint. A measurement strategy such as a personalized endpoint, may help increase endpoint interpretability.

Sponsors should have a plan in place to collect information or otherwise determine the reason for missing data. We recommend sponsors provide a table summary of missing data including stratification by important subgroups and reasons for missingness to help better understand the extent and impact of missing data. Additionally, for longitudinal data, missingness should be summarized by assessment visit or relevant time points.

Sponsors should submit exact copies of the anchor scales for Agency review and concurrence prior to implementing them in the planned clinical trial(s).

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
There has been previous communication regarding the DTSS and DTIS instruments during the IND stage (IND 138207), which included the following:

- Type B Meeting Minutes dated August 23, 2022 [DARRTS Reference ID: 5034474]
  - Concluded that the submitted patient-reported outcome (PRO) data, the PRO statistical analysis plan (SAP), and completed qualitative and quantitative data will be reviewed during the NDA review cycle. Whether the PRO measures are fit-for-purpose for the context of the development program (b) (4) would be determined during the NDA review cycle.

1 https://www.fda.gov/media/166830/download

- FDA Advice/Information Request Letter dated December 15, 2021 [DARRTS Reference ID: 4905223]
  - Acknowledged submission plan of the final qualitative and quantitative summary reports (including the additional confirmatory factor analyses) to support the proposed scoring algorithm of the DTSS total symptom score.
  - Requested a revised psychometric analysis plan that includes any additional analyses.

- Final Written Response Only (WRO) dated August 2, 2021 [DARRTS Reference ID: Reference ID: 4834920]
  - Provided specific comments on the PRO statistical analysis plan.
  - Reiterated request for full qualitative summary report.
  - Concluded that it was difficult to comment on the appropriateness of the proposed scoring approach due to lack of clarity on the item relevance; noted that alternative scoring may need to be considered if qualitative data does not support the proposed scoring algorithm.
  - Disagreed with assumption of the daily DTSS total symptom score that all symptoms (pain, fatigue, swelling, muscle weakness, and difficulty moving) are equally important and interchangeable for the disease.
  - Disagreed with the confirmatory factor analysis (CFA) conducted to support the proposed scoring algorithm of the daily DTSS total symptom score.
  - Requested justification to support the missing data rule for scoring for the weekly DTSS total symptom score. Additionally, recommended a missing data simulation study to investigate the missing data rule.
  - Disagreed with the daily and weekly DTSS Pain domain scores (i.e., three pain items are highly correlated).
  - Disagreed with the daily and weekly DTIS Physical Functioning domain scores (i.e., inconsistent scoring description in the meeting briefing package, averaging different concept attributes, items are not on the same response scale)
  - Disagreed that the meaningful change thresholds are appropriate for defining improvement on an individual patient level as the COA endpoint definitions are unclear.
  - Reiterated the limitations of the anchor scales (i.e., misaligned measurement concepts) to interpret the target COA endpoints; suggested the use of qualitative methods (e.g., exit interviews) to complement the anchor-based analyses.

- Type B Meeting Minutes dated January 25, 2021 [DARRTS Reference ID: 4735969]
  - Requested the full qualitative summary report in the NDA submission.
  - Identified limitations regarding the selected anchor scales (i.e., recall period and concept measured of the PGIS and PGIC did not correspond with target COA).
  - Provided specific comments on the psychometric analysis plan.

- Type C Meeting Minutes dated April 24, 2019 [DARRTS Reference ID: 4425780]
  - Requested the full qualitative summary report.
  - Requested details on the scoring information for the DTSS.

  - Provided advice on the anchor scales (e.g., administer anchor scales corresponding to each of the target COAs; align measurement concepts of the anchor and target COAs).
  - Requested clarification on type of device that will be used for the home electronic PRO (ePRO) device (e.g., smartphone, tablet).

- Type B Meeting Minutes dated March 21, 2018 [DARRTS Reference ID: 4237478]
  - Concluded that there is insufficient evidence to conclude that the proposed desmoid tumor PRO is fit-for-purpose for the context of the drug development program.
  - Requested evidence to support that patients can discriminate accurately among different pain sensations (e.g., general pain vs. dull pain vs. shooting pain) and interpret these different pain types as distinct concepts.
  - Noted that swelling is a sign and may be best assessed by clinicians rather than patients, particularly, if the tumor(s) are in areas of the body which are not easily observable by patients.
  - Recommended deleting muscle weakness item.
  - Suggested inclusion of a performance outcome assessment as an alternative option to assess physical function.
  - Requested evidence to support measuring both severity and frequency attributes of select concepts.

The materials reviewed for this submission is summarized in Table 1.

Table 1. Materials reviewed

Document	**SDN**	**eCTD#**	**Date Received**
A Randomized, Double-Blind, Placebo-controlled, Phase 3 Trial of Nirogacestat versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF) Patient-Reported Outcome Report	4	0004	10 Nov 2022
Evidence Dossier Summarizing the Development and Measurement Characteristics of the GODDESS Instrument dated November 22, 2022	5	0005	27 Dec 2022
Applicant's Response to FDA Information Request dated March 20, 2023	34	0034	21 April 2023
Applicant's Response to FDA Information Request dated May 17, 2023	48	0046	07 June 2023
	46	0044	31 May 2023
Communications and Reviews	**DARRTS Ref ID**		**Date**
Previous COA Review: C2022218_IND 138207_Choudhry	5045101		14 Sept 2022

Previous COA Review: C2021258_IND 138207_Choudhry	4857978	16 Sept 2021
Previous COA Review: C2021005_IND 138207_Daniels	4822496	30 July 2021
Previous COA Review: C2019032_IND 138207_Choudhry	4445882	16 June 2019
Previous COA Review: C2018234_IND 138207_Choudhry	4368144	11 January 2019
Previous COA Review: C2018046_IND 138207_Choudhry	4238271	09 April 2018

Disease Background:
Desmoid tumors (DT), also referred to as aggressive fibromatosis (AF), are rare, locally aggressive, slow growing soft tissue tumors that can cause severe pain, functional impairment, nerve damage, and bowel obstruction or perforation by infiltrating or exerting mass effects on vital structures. The most common primary tumor sites include abdominal walls, limbs, girdles, and mesenteric areas.

Investigational Product:
Nirogacestat (PF-03084014) is a potent, small molecule, selective, reversible, noncompetitive inhibitor of the gamma-secretase (GS) enzyme. Nirogacestat has been shown to inhibit the Notch pathway by inhibiting GS, which prevents proteolytic cleavage of the Notch intracellular domain leading to downregulation of the Notch target genes, hairy and enhancer of split-1 and C-MYC, resulting in tumor growth inhibition.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Study NIR-DT-301 were adult patients (≥18 years) with histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan. Eligible participants had:

- Treatment naïve, measurably progressing DT/AF that is deemed not amenable to surgery without the risk of significant morbidity; OR
- Recurrent, measurably progressing DT/AF following at least one line of therapy; OR
- Refractory, measurably progressing DT/AF following at least one line of therapy.

A complete list of the inclusion and exclusion criteria is summarized in Section 5.1 of Protocol NIR-DT-301 Amendment 5 dated February 9, 2021.

5.2 Clinical Trial Design

Study NIR-DT-301

Study NIR-DT-301 is a multi-center, randomized, double-blind (DB), placebo-controlled, parallel group, event-driven, phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF.

Approximately 118 eligible participants were planned to be randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio. Randomization was stratified by target tumor(s) location (intra-abdominal or extra-abdominal). If participants had multiple target tumors that were located in the intra- and extra-abdominal locations, they were classified as intra-abdominal.

For the DB treatment period, participants were randomized to study treatment at Cycle 1 Day 1 (C1D1) using interactive response technology and assigned to orally administered 150 mg twice daily (BID) of nirogacestat or placebo, continuously in 28-day cycles.

Participants remained in the DB phase until one of the following occurred:

- The participant experienced death
- Central imaging review determined that the participant had radiographic progressive disease (using RECIST version [v] 1.1).
- The investigator determined the participant was experiencing clinical progression[2].
- The participant prematurely discontinued study treatment for any reason.
- The study was stopped by the sponsor for any reason (note, this study was not stopped by the sponsor).
- The estimated number of PFS events (approximately 51 events) was observed and the primary PFS analysis was completed (based on statistical assumptions, this was anticipated to be approximately 2 years after the first participant was randomized).

5.3 Endpoint Position, Definition, and Assessment Schedule

The placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study NIR-DT-301 is summarized below.

Primary efficacy endpoint

- Progression-free survival, defined as the time from randomization until the date of assessment of progression or death by any cause. Progression was determined radiographically using RECIST v1.1 or clinically as assessed by the investigator.

[2] Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT. If a participant had clinical progression as determined by the investigator, the participant returned to the site for an end-of-treatment (EOT) visit within 14 days of the date of clinical progression and was not eligible to enter the optional open-label extension phase. These participants were discontinued from the study after completing an EOT and follow-up visit.

Secondary efficacy COA endpoints (multiplicity adjusted)

- Mean change from baseline at Cycle 10 in BPI-SF API score (measured by BPI-SF item 3, worst pain)
- Mean change from baseline at Cycle 10 in DTSS total symptom score
- Mean change from baseline at Cycle 10 in DTIS Physical Functioning domain score
- Mean change from baseline at Cycle 10 during the double-phase period in the EORTC QLQ-C30 Physical Functioning domain score
- Mean change from baseline at Cycle 10 during the double-phase period in EORTC QLQ-C30 Role Functioning domain score

Reviewer's comment(s): *The applicant also administered anchor scales* (*i.e., Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) scales), which are discussed further in Section 5.5.6 of this review.*

In Study NIR-DT-301, the patient-reported outcome (PRO) assessments were completed using the home electronic PRO (ePRO) device. The PROs were administered in this order: (1) BPI-SF, (2) DTSS, (3) DTIS, (4) PGI-S scale, and (5) PGI-C scale. The BPI-SF and DTSS were administered for 7 consecutive days prior to the clinic visit. The DTIS, EORTC QLQ-C30, PGIS and PGIC were administered on the last day of the 7-day PRO assessments.

(b) (4)

(b) (4)

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

5.5.1.1 Desmoid Tumor Symptom Scale (DTSS)

The DTSS (Appendix B) is an 11-item PRO instrument designed to assess desmoid tumor symptom severity. Each item is rated on an 11-point numeric rating scale (NRS) ranging from 0 ("None") to 10 ("As bad as you can imagine"). The recall period is the previous 24 hours.

5.5.1.1 Desmoid Tumor Impact Scale (DTIS) Physical Functioning domain

The DTIS Physical Functioning domain (Appendix C) is an 11-item PRO instrument designed to assess desmoid tumor symptom severity. The items are rated on varying response scales (e.g., NRS and verbal rating scale [VRS]). The recall period is the previous 7 days.

5.5.2 Conceptual Framework(s)

The conceptual framework for the DTSS and DTIS-based endpoints is shown in Figures 1 and 2.

Conceptual Framework for the DTSS Total Symptom Score

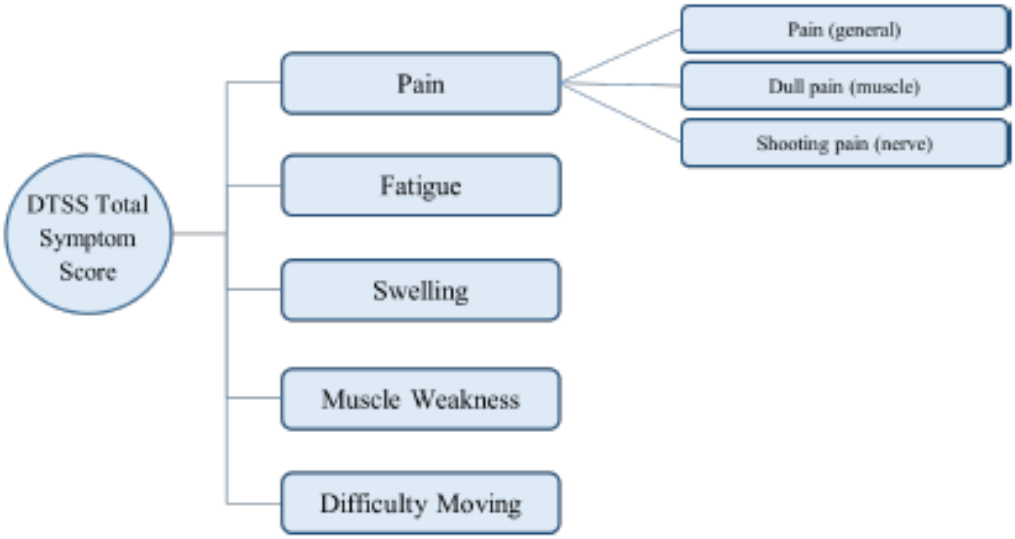
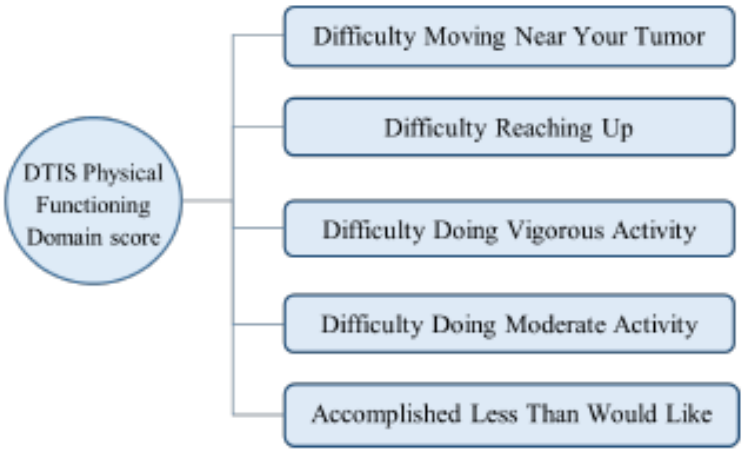


Figure 2. Conceptual Framework for the DTIS Physical Functioning Domain Score



5.5.3 Scoring Algorithm

5.5.3.1 DTSS Total Symptom Score

The DTSS TSS is derived using items 1-7 each day to create a daily average score (range 0-10). Missing data at the item level on a given day are not expected, as all items are administered electronically, and the device requires that all items must be completed by the patient. To calculate the daily score, the mean of the pain items (items 1-3) is taken to produce a mean pain score, thus avoiding overweighting of pain in the TSS. This mean pain score is then averaged with items 4-7 to produce a daily TSS:

$$\frac{\left(\left(\frac{Item\ 1 + Item\ 2 + Item\ 3}{3}\right) + Item\ 4 + Item\ 5 + Item\ 6 + Item\ 7\right)}{5}$$

These daily scores are then averaged over 7 days to produce a weekly symptom score that ranges from 0 to 10, with higher scores representing worse symptoms. This weekly summary score is derived for each patient with enough available data. For this instrument, a common 50% rule was employed meaning that patients need to have at least 4 out of 7 days of daily PRO data to calculate a weekly summary score. The weekly summary score is used in the endpoint analysis. If no weekly summary score is calculable (i.e., missing 4 or more days of data), the participant will have data considered as missing for that time point.

Reviewer's comment(s): *The TSS includes a separate "Pain" subscale consisting of three items (muscle pain, nerve pain, and general pain). This Pain subscale is calculated prior to making a total score." While the "Pain" subscale may be appropriate based on the qualitative data for muscle and nerve pain items, this reviewer questions whether a general pain item is needed as this concept was not elicited in the qualitative interviews. In addition, the three pain items are highly correlated with each other, especially the general pain item and the shooting pain item (Pearson correlation >0.9) at every study time point, indicating the redundancy of the general pain item.*

The Patient-Focused Statistical Scientist (PFSS) group was also consulted for a secondary review of the scoring algorithm. To evaluate the appropriateness of the missing data rule for the TSS, FDA had recommended a missing data simulation study during the IND stage to investigate the impact of number of missing daily scores on the scoring algorithm (see FDA's Type B Written Response Only meeting comments dated 02 Aug 2021). The applicant calculated intra-class correlation coefficient (ICC) of day-to-day variability to justify the missing data rule and the high ICC (> 0.9) indicated low daily fluctuation of the TSS. In addition, the applicant reviewed the daily TSS profile plots of the first 20 patients confirming the low day-to-day variability. However, the low day-to-day variability in TSS may be a patient characteristic and thus may not be generalizable to studies other than NIR-DT-301. Future studies should confirm the results before using the same missing data rule.

Page 40/80 of the PRO evidence dossier dated November 22, 2022 stated "Missing data at the item level on a given day are not expected, as all items are administered electronically, and the device requires that all items must be completed by the patient." Mandatory items with electronically administered measures may result in: (1) a loss of information or (2) misinformation about the subject's symptoms, functioning, and/or impacts. Review of the abandonment rate and careful consideration of patient burden as well as inclusion of questions on item completion in the sponsor's useability and/or cognitive debriefing work is recommended.

5.5.3.2 DTIS Physical Functioning Domain Score

The DTIS Physical Functioning domain score is derived by averaging the scores from items 1, 2, 6, 7, and 8, with a resulting domain score range from 1 to 5, with higher scores representing poorer physical functioning. For missing item-level data, participants would have a missing domain value.

Reviewer's comment(s): *As previously noted in Section 5.5.3.1, the applicant indicated that missing item-level data was not expected as all items were electronically administered, and mandatory. However, it is noted that there was low completion rate for the PRO assessments and an asymmetric completion rate between treatment arms. The applicant did not document the reasons for missing data.*

5.5.4 Content Validity

5.5.4.1 Desmoid Tumor Symptom and Impact Scales

The applicant completed the following instrument development activities to evaluate the content validity of the DTSS and DTIS scales in patients with desmoid tumors:

- A literature review
- Clinician input (clinician interviews)
- Patient input (concept elicitation and cognitive interviews)

A summary of the results for each activity is described below. Refer to the PRO evidence dossier for full details regarding the methodology and results of each activity.

5.5.4.1.1 Targeted literature review

A review of bibliographic databases (including Ovid, PubMed, and PsychInfo) was conducted to:

- identify the most relevant signs and symptoms of desmoid tumor and their impact on patients living with desmoid tumor
- develop a preliminary conceptual model to visualize this experience.
- identify existing disease-specific PRO instruments for use in desmoid tumor patient research.

A total of nine (9) relevant peer-reviewed articles were selected, including eight (8) articles that mentioned quality of life, and one (1) that involved PRO data collection. Additionally, patient blogs were searched to identify additional symptoms or impacts reported by patients on public web blogs. Seven (7) patient blogs were included in the literature review and incorporated into the preliminary conceptual model.

The findings of the literature review are summarized as follows:

- While desmoid tumor patients are often asymptomatic, among patients who do experience symptoms the most common is pain / soreness in the location of the tumor. This pain can be localized to the tumor site and/or radiating (e.g., from the hip to the leg).
- Patients experience a wide range of treatment-emergent symptoms from various treatment types (e.g., gastrointestinal problems and constipation, darkening of skin, hair loss, hand foot syndrome).
- Desmoid tumor treatments may reduce patients' ability to do their usual activities, including their ability to participate in social activities and/or their ability to work.
- Patients with desmoid tumor experience emotional impacts due to the nature of the disease. Younger desmoid tumor patients are often surprised to face a major health issue at their age, and may experience high levels of anxiety and stress over treatment decisions and their outcomes.
- Currently, there are no desmoid tumor-specific, patient-reported outcome (PRO) instruments or endpoints.

Reviewer's comment(s): *The preliminary conceptual model (version 1) is shown in Figure 1 of the qualitative report. The final conceptual model is in Appendix A of this review.*

5.5.4.1.2 Clinician interviews

The applicant conducted 60-minute telephone interviews with clinicians (n= 5) to further investigate and identify important and relevant signs, symptoms, and impacts experienced by patients with desmoid tumor from an expert's perspective, as well as obtain feedback on the preliminary conceptual model.

A total of five clinicians were interviewed. They were all male (n=5, 100%), with the majority based in the United States (n=4, 80.0%) and all with a specialty in soft-tissue sarcoma (n=5, 100.0%). Clinicians were affiliated with the following institutions: Memorial Sloan Kettering Cancer Center, Oklahoma State University Medical Center, MD Anderson Cancer Center, and Fondazione IRCCS Istituto Nazionale dei Tumori.

Reviewer's comment(s): *The applicant did not provide the number of clinicians that were affiliated with the corresponding institution.*

The findings of the clinician interviews are summarized as follows:

- Across the five interviews, clinicians emphasized the importance of categorizing desmoid tumor patients by symptomology and tumor location. Clinicians reported that most patients are asymptomatic.
- Clinicians reported that symptom experience varied in their patients depending on where the tumor was located.
- Clinicians identified pain (n=5), decreased range of motion (n=4) and severe gastrointestinal (GI) issues (n=4) as the most common symptoms associated with desmoid tumor.
    - Pain was considered to be the primary symptom, caused by either the disease or treatment, and had two major types: neuropathic pain and tension-related muscle pain. Pain could either be localized to the tumor location or radiating to different parts of the body.
    - Decreased range of motion was another disease-related symptom that clinicians said often occurs in patients with tumors located in the joint, head or neck region.
    - Familial adenomatous polyposis (FAP)-associated tumor patients can experience GI issues, including: difficulty absorbing food, intestinal obstructions and bowel death. Diarrhea, nausea, weight loss, and getting full easily were also mentioned, but only by one (1) clinician each.
- Stress over making treatment decisions (n=2) and lack of information from healthcare providers (n=2) were identified by clinicians as the most common impacts of desmoid tumor.
- Regarding the preliminary conceptual framework,
    - Clinicians recommended removing fever, lack of energy, and ovarian cysts, as they were considered non-specific to desmoid tumor. They also recommended removing bloody bowel movements, renal/kidney failure, hot flashes, fatigue, chemo brain, and endometriosis, for similar reasons.
    - Clinicians recommended adding stiffness and weakness to the conceptual model, as they said that patients can have muscle stiffness due to limited mobility from a tumor located around the joint, head or neck region and can feel weakness if they have a tumor located in an extremity. Nerve pain, muscle pain, decreased range of motion, stiffness, weakness, swelling, bleeding, infection, and altered body image were also added.

Reviewer's comment(s): *Clinicians described the treatment goal for desmoids as preservation of function and avoidance of over-treatment. Many experts recommended a "wait and see" approach and "do no harm" attitude toward treatment. They reported closely monitoring patients in the quiescent stage and only providing treatment when tumor progression occurred.*

The revised version of the conceptual model (Version 2) can be seen in Figure 2 of the qualitative report. The final version of the conceptual model is in Figure 6 of the qualitative report and is shown in Appendix A of this review.

5.5.4.1.3 Concept elicitation interviews

The applicant conducted 60-minute one-on-one concept elicitation interviews (n= 31) in adult patients (18-75 years) with a confirmed diagnosis of desmoid tumors to:

- Explore and understand the symptoms of adult patients who are living with desmoid tumors, their experience with treatment, and the impact of the disease on their lives
- Determine words and phrases patients use to report symptoms and impacts
- Document the frequency and disturbance associated with the symptoms and impacts

Reviewer's comment(s): *The evidence dossier describes that the interviews were via "a call" but does not specify the specific mode (e.g., telephone, Zoom, etc.).*

The findings of the qualitative reanalysis are summarized as follows:

- A total of 31 adults with desmoid tumors (with and without FAP) were interviewed. The majority of the participants were female (n= 24/31, 77.4%) with a mean age of 44 years (standard deviation [SD]: 13; range: 20- 68 years) and at least some college education (n= 29/31, 93.5%). The participants were predominantly symptomatic (n= 26/31, 83.9%) with FAP tumor type (n= 26/31, 83.9%). Approximately one-fourth of the participants (n= 8/31, 25.8%) had tumors in the intra-abdominal area. Other tumor sites included: joint/extremity, abdominal wall, head/neck and other.

  Reviewer's comment(s): *Racial/ethnicity was not reported for the qualitative sample. As such, this reviewer cannot comment on the diversity and representativeness of the qualitative sample.*

- The symptoms most frequently mentioned by the participants were disfigurement / altered appearance (n= 25/31, 80.6%), nerve pain (n= 22/31, 71.0%), and decreased range of motion (n= 21/31, 67.7%). Other commonly mentioned symptoms included muscle pain (n= 20/31, 64.5%), fatigue (n= 20/31, 64.5%), nausea (n= 18/31, 58.1%) and hair thinning (n= 18/31, 58.1%).

  Reviewer's comment(s): *This reviewer does not agree that decreased range of motion should be classified as a symptom.*

- Participants rated the level of disturbance of their symptoms on an 11-point numeric rating scale (0= Not disturbing at all, 10= Extremely disturbing). The highest rated symptoms (i.e., most disturbing symptoms) by at least two participants were mouth sores (median score of 8.5), hand-foot syndrome (median score of 8.0), vomiting (median score of 7) and muscle pain (median score of 6.75).

- The impacts most frequently mentioned by the participants were fear (n= 26/31, 83.9%), difficulty sleeping (n= 24/31, 77.4%), concern about lack of knowledge among health professionals (n= 23/31, 74.2%), anxiety (n= 22/31, 71.0%), and ongoing medical uncertainty (n= 22/31, 71.0%). Other impacts reported included inability to do daily activities (n= 20/31, 64.5%).

- Participants rated the level of disturbance of their impacts on an 11-point numeric rating scale (0= Not disturbing at all, 10= Extremely disturbing). The highest rated symptoms (i.e., most disturbing impacts) by at least two participants were stress / difficulty over making treatment decisions (median score of 10), concern for other family members (median score of 7.0), and difficulty sleeping (median score of 6.75).

Reviewer's comment(s):
The relevance of some of the symptoms included in the DTSS may be questionable. Specifically, muscle weakness (n= 12/31, 38.7%) and swelling (n= 6/31, 19.4%). Based on the qualitative report, these concepts were not spontaneously elicited by the participants but rather probed by the interviewer. Additionally, the participants were queried about weakness in general and not specifically on muscle weakness.

The qualitative report did not provide details regarding participant comprehension and/or relevancy of the measures. As such, the FDA submitted an information request (IR) dated May 17, 2023 seeking additional detail to further evaluate the content validity of the measures. In response to the IR, the applicant indicated that the original coding of the qualitative data could not be located and they had to recode the qualitative data from existing transcripts. Note that the recoded data is not in complete alignment of the original data reported in the qualitative report, but is similar.

Based on the recoded data, it appears that most of the concepts measured in the DTSS total symptom score were spontaneously reported by participants, with the exception of swelling (spontaneously reported: n= 1/31; 3%). Note that muscle weakness was not explicitly called out in the recoded data. These findings are similar to the original data reported in the qualitative report. Regarding the pain experience, participants spontaneously reported muscle pain (n= 19/31, 61%) and nerve pain (n= 16/31, 52%). General pain was not a concept that was reported by participants.

5.5.4.1.4 Cognitive interviews

The applicant conducted telephone and web-enabled interviews (n= 15) in three waves[3] in adults diagnosed with desmoid tumor to:

- Assess patient understanding of the instructions, items, and response scales of the DTSS and DTIS and
- Revise the instructions, items, and response scales, if necessary, to improve patient comprehension.

The findings of the qualitative reanalysis are summarized as follows:

- A total of 15 adults with desmoid tumors (with and without FAP) were interviewed. The majority of the participants were female (n= 11/15; 73%) with the mean age of 45 years (SD = 12; median= 46 years; range: 29 –69 years) and at least some college education (n= 14/15, 93.3%). The participants were predominantly symptomatic (n= 14/15, 93.3%) with

[3] The interviewer and study team discussed the findings from each interview after the first and second sets ("waves") of interviews (n=5 each) and made changes to the DTSS and DTIS, as needed. An iterated set of items were tested in the third wave of patient interviews (n=5).

non-FAP recurring tumor type (n= 8/15, 53.3%). Over one-third of the participants (had tumors in the joints/extremities (n= 5/15, 33.3%) and abdominal wall (n= 5/15, 33.3%). Other tumor sites included intra-abdominal, head/neck and other.

- The following changes were made after wave 1:
  - An item added in the DTSS on "swelling in other areas" to test in addition to the item on "swelling around your tumor(s)"
  - Instructions for DTIS modified
  - A frequency scale was to test for the frequency-type items in the DTIS
  - Specific revisions made to the DTSS and DTIS are shown in Tables 19 and 20 of the qualitative report.

- The following changes were made after wave 2:
  - The attribution factor to desmoid tumor was removed in the DTSS instructions.
  - The items measuring "zapping pain", "muscle ache", "throbbing pain", "worn out", and "difficulty sleeping" were deleted from the DTSS due to their irrelevancy to desmoid or redundancy with similar questions.
  - An item added in the DTSS to test "swelling in other areas" in addition to "swelling around your tumor(s)"
  - Examples in the item on "moderate activities" in the DTIS was modified to reflect examples suggested by participants.
  - The wording in some DTSS and DTIS items were revised for clarity and congruency to other questions.
  - Some of the NRS for the frequency items in the DTIS was revised to include the preferred VRS.
  - Specific revisions made to the DTSS and DTIS are shown in Tables 21 and 22 of the qualitative report.

- The following changes were made after wave 3:
  - The "tiredness" item in the DTSS was deleted due to its redundancy with the "fatigue" item.
  - The test question of general "weakness" in the DTSS was deleted as it was less preferred.
  - Specific revisions made to the DTSS are shown in Table 23 of the qualitative report.

Reviewer's comment(s):
Based on the recoded data, it appears that most participants (>70%) understood the instrument instructions and items and found the items to be relevant.

Regarding participant comprehension of the response options, the applicant stated that "queries about understanding and appropriateness were made only consistently at time of first appearance of the option type (i.e., DTSS Item 1 (n= 13) and DTIS item 1 (n= 14)) given that the same response scales were used throughout the two documents." For these two items, the majority of participants (>85%) understood the response options and found the response options appropriate. This reviewer does not completely agree with this surrogate approach to evaluate comprehension and relevancy of the instruments' response options, as it provides limited information. It is unclear as

to whether the response options are optimal and/or appropriate for all measurement concepts. For example, the item on "difficulty moving" is rated on a 0-10 NRS ranging from "None" to "As bad as you can imagine" and corresponds to intensity versus difficulty.

Regarding participant comprehension of the response options, the applicant stated that they did not consistently query about recall period across instructions and items. In the 16 cases where responses to DTSS recall periods were collected, 15 responses (94%) reflected understanding of recall period and 13 responses (81%) reflected appropriateness of recall period. In the 14 cases where responses to DTIS recall periods were collected, 14 responses (100%) reflected understanding of recall period and 11 responses (79%) reflected appropriateness of recall period.

This reviewer cannot make a definitive conclusion whether the DTSS and DTIS measures are well-understood due to the limited approach used to evaluate participant comprehension.

5.5.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the DTSS using blinded data (i.e., pooled across treatment arms) from Study NIR-DT-301.

The intent-to-treat population (ITT, i.e., all participants who were enrolled and randomized to study treatment (nirogacestat) or placebo) in Study NIR-DT-301 were used to evaluate the measurement properties of the DTSS and DTIS measures. Timepoints for most analyses were baseline, Cycle 4, and Cycle 7, with analyses to evaluate what is meaningful change conducted using data from Cycle 10. The focus of the sections below is on the DTSS TSS and the DTIS Physical Functioning domain score, as these are the scores used as the basis for multiplicity-controlled endpoints (b) (4).

The ITT population included 142 patients of which 109 had extra-abdominal tumors and 33 had intra-abdominal tumors. The majority of the sample were White (n= 118/142, 83.1%), female (n= 92/142, 64.8%) with mean age of 37.2 (standard deviation: 13.62; range: 18 ─ 76 years). Similar ages were observed for patients in the intra-abdominal and extra-abdominal tumor groups. More male patients (n=19, 57.6%) had intra-abdominal tumors than female (n=14, 42.4%) whereas more female (71.6%) patients had extra-abdominal tumors.

A summary of the psychometric findings for the DTSS TSS and the DTIS Physical Functioning domain score is provided below. For more details on the methodology and results of these analyses, refer to the "Psychometric Analysis Report: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF)" version 1.0 dated January 26, 2022.

Reviewer's comment(s): *This reviewer notes that the psychometric data is difficult to fully interpret due to questions surrounding the comprehensibility of the measures. Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.*

5.5.5.1 Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score

5.5.5.1.1 Item-level descriptive statistics

- A completion rate between 63.1 to 89.4% from Day 1 to 7 at Screening was observed with slightly higher rate of 68.8 to 93.6% from Day 1 to 7 at Baseline. For Post-Baseline timepoints, completion rate remained high at Cycle 2 with 80.7 to 85.7%, then dropped at Cycles 4, 7, and 10. At Cycle 10, 54 to 69% of the patients completed diary entries for each day. As Cycle 10 had exactly 100 patients, these percentages represent a total of 54 to 69 patients.

Reviewer's comment(s): *Note that the applicant selected Cycle 10 as the predefined timepoint for PRO assessment to allow adequate time for a treatment response to be observed.*

- ≥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%).

- Inter-item correlations among DTSS TSS items ranged from 0.4 to 0.9. The three items relating to pain (Item 1 with Items 2 and 3) showed high correlations (r >0.9).

Reviewer's comment(s): *The applicant states that "Although high correlations were observed between items measuring different aspects of pain, these were conceptually similar in the construct they attempted to measure (pain) and as such were expected to correlate highly. It is not recommended that the items are removed, as each measures a different aspect of pain. Instead, the scoring algorithm can, in part, account for some of these potential overlaps by creating a separate "Pain" subscale from these three items prior to making a total score."*

A "Pain" subscale may be appropriate based on the qualitative data for muscle and nerve pain items. However, this reviewer questions whether a general pain item is needed as this concept was not elicited in the qualitative interviews.

- The median change scores from baseline to Cycle 10 in the DTSS TSS are shown in Table 2 (shown on next page).

Table 2. Summary of median DTSS TSS scores at item-level at baseline, Cycle 10, and change from baseline in Study NIR-DT-301.

	DTSS items	Treatment	Baseline			Cycle 10			Change from baseline		
			n	Median	Mean (SD)	n	Median	Mean (SD)	n	Median	Mean (SD)
1	Pain (general)	Nirogacestat	70	3.9	4.1 (2.8)	40	1.0	1.8 (2.3)	40	-2.3	-2.2 (2.3)
		Placebo	71	4.1	4.2 (2.9)	32	4.9	4.4 (3.0)	32	0.0	0.0 (2.4)
2	Pain (dull)	Nirogacestat	70	2.8	3.1 (2.3)	40	0.8	1.4 (1.6)	40	-1.6	-1.7 (1.9)
		Placebo	71	3.3	3.4 (2.6)	32	3.5	3.7 (2.7)	32	0.0	0.2 (2.1)
3	Pain (shooting)	Nirogacestat	70	3.2	3.7 (2.9)	40	0.1	1.1 (1.9)	40	-2.4	-2.6 (2.7)
		Placebo	71	3.3	3.9 (3.2)	32	3.9	4.1 (3.1)	32	0.0	0.2 (2.4)
4	Fatigue	Nirogacestat	70	2.9	3.3 (2.8)	40	2.3	2.7 (2.3)	40	-0.1	-0.5 (2.3)
		Placebo	71	3.0	3.1 (2.7)	32	3.0	3.7 (2.8)	32	0.3	0.3 (1.9)
5	Swelling	Nirogacestat	70	2.7	3.1 (2.7)	40	1.2	1.6 (2.1)	40	-1.2	-1.6 (2.1)
		Placebo	71	2.2	3.0 (2.8)	32	2.8	3.9 (3.3)	32	0.5	0.6 (2.4)
6	Muscle weakness	Nirogacestat	70	2.4	2.8 (2.6)	40	1.0	1.7 (2.1)	40	-1.1	-1.4 (1.9)
		Placebo	71	2.4	3.4 (2.9)	32	3.6	4.2 (3.1)	32	1.0	0.8 (2.4)
7	Difficulty moving	Nirogacestat	70	3.6	3.8 (2.6)	40	1.0	1.7 (2.1)	40	-2.2	-2.1 (1.8)
		Placebo	71	3.7	4.1 (3.2)	32	4.6	4.6 (3.1)	32	0.0	0.2 (2.3)
	Total Symptom Score	Nirogacestat	70	3.3	3.4 (2.4)	40	1.3	1.9 (2.0)	40	-1.5	-1.5 (1.6)
		Placebo	71	3.3	3.6 (2.6)	32	3.9	4.2 (2.7)	32	0.3	0.4 (1.9)

Reviewer's comment(s): *The observed change in the TSS does not seem to be driven by select DTSS items. However, this reviewer notes that there is minimal change observed in the individual items comprising the DTSS TSS. Further, there is missing data at Cycle 10.*

5.5.5.1.2 Dimensionality

- The fit statistics for the different confirmatory factor analysis (CFA) models were:
  - Unidimensional model: Comparative fit index (CFI) = 0.84, Tucker Lewis Index (TLI) = 0.80, Root Mean Square Error of Approximation (RMSEA) = 0.063, and Standardized Root Mean Residual (SRMR) = 0.09
  - Unidimensional model (Items 1-7): CFI = 0.85, TLI = 0.78, RMSEA = 0.085, and SRMR = 0.058
  - Bifactor model (one domain): CFI = 0.98, TLI = 0.95, RMSEA = 0.039, and SRMR = 0.026
  - Bifactor model (two domains): CFI = 1.00, TLI = 0.99, RMSEA = 0.015, and SRMR = 0.011
  - Unidimensional model (Average pain + Items 4-7): CFI = 0.95, TLI = 0.89, RMSEA = 0.060, and SRMR = 0.035

Reviewer's comment(s): *The FDA did not agree with the applicant's initial confirmatory factor analysis (CFA) models to support the proposed scoring algorithm. During the IND phase, the FDA provided advice that if the scoring algorithm is based on the use of a pseudo pain item (i.e., treating the mean of the first three pain item scores as a single item score), then the CFA model(s) should be fitted using a single pseudo pain item score, as opposed to including all three pain*

item scores in the model(s). The applicant was recommended to fit a unidimensional CFA model with the latent factor loading onto the pseudo pain item and the rest of the DTSS TSS items. In discussion with the PFSS group, the unidimensional model based on FDA's recommendations indicates good fit.

- The factor loadings of the general factor for TSS (bifactor model) ranged from 0.73 to 0.92.

  Reviewer's comment(s): *The applicant did not provide factor loadings for the unidimensional model with the pseudo pain item.*

  The applicant should consider exploring an alternative TSS excluding DTSS item 7 ("difficulty moving") as this is not a DT symptom, but rather an impact associated with DTs. DTSS item 1 (general pain) may be another item to exclude as general pain may be capturing some of the concepts in the other pain items, given the high correlations. Further, pain in general was not elicited in the concept elicitation interviews.

5.5.5.1.3 Differential Item Functioning (DIF)

- Participants with extra-abdominal tumor and those with abdominal or intra-abdominal tumors were shown to respond differently to the items in the DTSS TSS ($1.5 \leq$ delta Mantel-Haenszel (ΔM-H) for all items, except item 9 ($1 \leq \Delta$M-H <1.5)).

  Reviewer's comment(s): *The PFSS group was consulted for a secondary review of the DIF analyses. Based on the DIF effect size cutoff values[4] used by the applicant (large: $1.5 \leq \Delta$M-H; moderate: $1 \leq \Delta$M-H <1.5, small ΔM-H<1), most of the items exhibit large DIF, indicating that participants with extra-abdominal tumor and those with intra-abdominal tumor responded differently to all items contributing to TSS scores even if participants' underlying DT symptom level remain the same. However, results of the applicant's DIF analyses are uninterpretable due to several methodological limitations. Future studies should investigate DIF and the impact of DIF on DTSS TSS using more appropriate methods. The PFSS group identified the following methodological issues for future considerations:*

  i. *DIF analyses should take into account the item level scale of measurement. The applicant dichotomized the 11-point NRS DTSS item score into binary responses before conducting DIF analyses. Future study should conduct DIF analyses by treating item responses as continuous variables.*
  ii. *The applicant used an external anchor item, PGIS, to match patients with extra- and intra-abdominal tumors. The appropriateness of using PGIS as the matching variable for DIF analyses is questionable especially given that results identified large number of DIF items. Future studies should conduct DIF analyses using different anchoring schemes with the item purification method.*

[4] The applicant used the educational testing service DIF classification system. See also https://files.eric.ed.gov/fulltext/EJ1109842.pdf

iii. *To avoid the inflated Type I error rate of detecting a DIF item due to the multiple testing procedure, adjustment for multiple comparisons (e.g., Benjamini-Hochberg adjustments) should be considered by future studies.*
iv. *The gold standard of Education Testing Service (ETS) DIF classification system (see footnote 4) may not be applicable to PRO data collected in clinical trials. Further investigation on the influence of DIF items on score reporting should be conducted.*

5.5.5.1.4 Reliability

- For assessment of internal consistency reliability, the Cronbach's coefficient alpha ranged from 0.93 to 0.95 over time (at Baseline and at Cycles 4 and 7).

- For assessment of test-retest reliability[5], the intra class coefficients (ICC) ranged from 0.98 to 0.99 over time (Screening to Baseline, Baseline to Cycle 2, and Cycle 3 to Cycle 4).

5.5.5.1.5 Validity

- For assessment of convergent validity, the DTSS TSS correlated moderately to highly with measures of pain (r= 0.70 – 0.80), physical functioning (r= -0.71), and global health (r= -0.55) but did not correlate well with conceptually different measures (e.g., QLQ-C30 appetite loss and nausea/vomiting scales).
- For assessment of known-groups validity, the mean DTSS TSS observed across the baseline response categories of the PGIS (None, Mild, Moderate, and Severe) increased with increasing severity (mean scores ranged from 0.40 to 5.96). Similarly, the mean DTSS TSS increased over baseline Eastern Cooperative Oncology Group (ECOG) Performance Status response categories of 0, 1, and 2. These results were similar at Baseline, Cycle 4, and Cycle 7.

  Reviewer's comment(s): *This reviewer notes that the response scale for the ECOG Performance Status ranges from 0 to 5. The results show that the DTSS TSS may differentiate between 0 to 1 response categories. The remaining response categories had low sample sizes (i.e., response category 2), or no patients (i.e., response categories 3, 4, and 5), reporting the other levels. As such it is difficult to interpret the data using the ECOG Performance Status scale as a reference measure. Further, it is unknown whether the different response categories of the ECOG Performance Status correspond to clinically distinct groups of physical functioning.*

5.5.5.1.6 Responsiveness

- For assessment of responsiveness, the mean change difference (from Baseline to Cycle 4) between groups of patients specified as improved, stable, or worsened

[5] Stable participants were defined the following ways: (1) All participants who had the same Patient Global Impression of Severity (PGIS) score at Screening (test) and at Baseline (retest), (2) All participants who had the same PGIS score at Baseline (test) and Cycle 2 (retest), (3) All participants who had the same PGIS score between Cycles 3 (test) and 4 (retest)

followed the hypothesized pattern, with patients who reported improvement on the PGIS also showing improvement on DTSS TSS scores in most cases.

Reviewer's comment(s): *Generally, for assessment of responsiveness, sponsors should provide the distribution of change on the target instrument by change on each anchor by providing descriptive statistics for improvement in the target instrument for each level of categorical improvement in the anchors [N (total number), mean, median, standard deviation, range, and confidence intervals]. This applicant did conduct this analysis; however, it was conducted as part of the anchor-based analyses (refer to Section 5.5.6). The distribution-based method (i.e., effect size) provides supportive evidence of responsiveness.*

5.5.5.2 Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score

5.5.5.2.1 Item-level descriptive statistics

- Completion rates of 85.8% at Screening and 92.9% at Baseline were observed. For post-baseline timepoints, the completion rate at Cycle 2 was 81.4%, then dropped at Cycles 4 and 7 with 62.6 and 67.0%, respectively.

- ≥20% of participants endorsed the least severe response category (i.e., participants reported "None" regarding their level of physical functioning) for the majority of the items in the DTIS Physical Functioning domain (n= 7/9, 77.8%).

- Low correlations were observed (r <0.4) for DTIS items 10, 12, 13, 14, 15, and 16. Moderate correlations were observed among DTIS items 1, 2, 6, 7, and 8.

- The median change scores from baseline to Cycle 10 in the DTIS Physical Functioning domain score are shown in Table 3.

Table 3. Summary of median DTIS Physical Functioning domain scores at item-level at baseline, Cycle 10, and change from baseline in Study NIR-DT-301.

	DTIS items	Treatment	Baseline			Cycle 10			Change from baseline		
			n	Median	Mean (SD)	n	Median	Mean (SD)	n	Median	Mean (SD)
1	Difficulty moving near tumor	Nirogacestat	70	3.0	3.2 (1.2)	39	2.0	2.2 (1.3)	39	-1.0	-1.1 (1.1)
		Placebo	70	3.0	3.0 (1.4)	28	4.0	3.4 (1.4)	28	0.0	0.3 (0.81)
2	Difficulty reaching up	Nirogacestat	70	2.0	2.1 (1.3)	39	1.0	1.6 (1.1)	39	0.0	-0.5 (0.85)
		Placebo	70	2.0	2.3 (1.4)	28	1.0	2.1 (1.5)	28	0.0	0.1 (0.66)
6	Difficulty doing vigorous activity	Nirogacestat	70	3.5	3.4 (1.5)	39	2.0	2.3 (1.5)	39	-1.0	-0.8 (1.3)
		Placebo	70	4.0	3.2 (1.5)	28	4.0	3.5 (1.6)	28	0.0	0.2 (0.83)
7	Difficulty doing moderate activity	Nirogacestat	70	2.5	2.4 (1.4)	39	1.0	1.6 (0.99)	39	0.0	-0.7 (1.1)
		Placebo	70	2.0	2.4 (1.3)	28	2.5	2.5 (1.4)	28	0.0	0.1 (0.71)
8	Accomplished less than would like	Nirogacestat	70	2.0	2.7 (1.4)	39	2.0	2.0 (1.2)	39	-1.0	-0.6 (0.96)
		Placebo	70	2.5	2.6 (1.4)	28	3.0	3.0 (1.5)	28	0.0	0.4 (1.1)
	Physical Functioning domain score	Nirogacestat	70	2.7	2.8 (1.1)	39	1.6	1.9 (1.1)	39	-0.6	-0.8 (0.81)
		Placebo	70	2.8	2.7 (1.2)	28	3.0	2.9 (1.2)	28	0.2	0.2 (0.53)

Reviewer's comment(s): *The observed change in the DTIS Physical Functioning domain score does not seem to be driven by select DTIS items. However, this reviewer notes that there is minimal change observed in the individual items comprising the DTIS Physical Functioning domain score. Further, there is missing data at Cycle 10.*

5.5.5.2.2 Dimensionality

- The fit statistics for the different confirmatory factor analysis (CFA) models were:
  - Unidimensional model: CFI = 0.86, TLI = 0.84, RMSEA = 0.15, and SRMR = 0.14
  - Unidimensional model (items 1-8): CFI = 0.96, TLI = 0.95, RMSEA = 0.23, and SRMR = 0.09
  - Bifactor model: CFI = 0.96, TLI = 0.95, RMSEA = 0.085, and SRMR = 0.05
  - Bifactor model (exclude items 10 and 11): CFI = 0.97, TLI = 0.95, RMSEA = 0.08, and SRMR = 0.06

- The factor loadings for the Physical Functioning domain ranged from 0.76 to 0.95.

5.5.5.2.3 Differential Item Functioning (DIF)

- Participants with extra-abdominal tumor and those with abdominal or intra-abdominal tumors were shown to respond differently to most of the items in the DTIS Physical Functioning domain (items 1, 2, and 10: $1.5 \leq \Delta$M-H; items 7 and 8 ($1 \leq \Delta$M-H <1.5)). The only item not affected was DTIS item 6 (performing vigorous activities).

  Reviewer's comment(s): *Results of the applicant's DIF analyses are uninterpretable due to several methodological limitations identified in Section 5.5.5.1.3. Future studies should investigate DIF and the impact of DIF on DTIS physical functioning domain.*

5.5.5.2.4 Reliability

- For assessment of internal consistency reliability, the Cronbach's coefficient alpha ranged from 0.90 to 0.93 over time (at Baseline and at Cycles 4 and 7).

- For assessment of test-retest reliability[6], the ICCs ranged from 0.91 to 0.94 over time (Screening to Baseline, Baseline to Cycle 2, and Cycle 3 to Cycle 4).

5.5.5.2.1 Validity

- For assessment of convergent validity, the DTIS Physical Functioning domain was most correlated with other measures of physical functioning (r= -0.69 ─ -0.88) and least correlated with conceptually different domains (e.g., QLQ-C30 Cognitive functioning and Emotional functioning scales) as hypothesized.

[6] Stable participants were defined the following ways: (1) All participants who had the same PGIS score at Screening (test) and at Baseline (retest), (2) All participants who had the same PGIS score at Baseline (test) and Cycle 2 (retest), (3) All participants who had the same PGIS score between Cycles 3 (test) and 4 (retest)

- For assessment of known-groups validity, the mean DTIS Physical Functioning domain score observed across the baseline response categories of the PGIS (None, Mild, Moderate, and Severe) increased with increasing severity (mean scores ranged from 0.36 to 2.88). Similarly, the mean DTSS TSS increased over baseline ECOG Performance Status response categories of 0, 1, and 2. These results were similar at Baseline, Cycle 4, and Cycle 7.

Reviewer's comment(s): *This reviewer notes the same limitations of the ECOG Performance Status measure as identified in Section 5.5.5.1.5 of this review.*

5.5.5.2.2 Responsiveness

- For assessment of responsiveness, the mean change difference (from Baseline to Cycle 4) between groups of patients specified as improved, stable, or worsened followed the hypothesized pattern, with patients who reported improvement on the PGIS also showing improvement on DTIS Physical Functioning domain scores in most cases.

Reviewer's comment(s): *This reviewer notes similar comments as identified in Section 5.5.5.1.6 for the assessment of responsiveness for the DTSS TSS.*

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

5.5.6.1 DTSS TSS and DTIS Physical Functioning Domain Score

The applicant proposed that a 1.4-point and 0.8-point reduction in the DTSS TSS and DTIS Physical Functioning domain score, respectively, is a meaningful within-patient score change. Accordingly, the applicant performed the following analyses to support the proposed threshold range for meaningful within-patient change in the DTSS TSS using data from Study NIR-DT-301:

- Anchor-based analyses
- Distribution-based analyses

Note this review does not provide an in-depth review of the evaluation of meaningful change in the DTSS TSS and DTIS Physical Functioning domain score as it is difficult to estimate the range of change that represents clinically meaningful within-patient score changes in these measures due to issues surrounding comprehensibility of the measures; the limitations of the external anchors used for anchor-based analyses (i.e., misalignment of measurement concepts); and missing data at Cycle 10.

5.5.6.1.1 Anchor-based analyses

Tables 4 and 5 (shown on next two pages) summarizes the anchors utilized by the applicant and their corresponding target COA. Copies of the anchor scales are in Appendix D.

Table 4. Summary of Anchor Scales for DTSS TSS

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Timing of COA Endpoint (target/anchor)
DTSS TSS ("badness" of worst symptom)	PGIS (symptom severity)	5-point VRS: None, Mild, Moderate, Severe	Previous 24 hours/ Previous 7 days	Cycle 10/Cycle 10
	PGIC (overall status)	7-point VRS: Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, Very much worse	Previous 24 hours/ Since start of study	Cycle 10/Cycle 10
	ECOG-PS (daily living abilities)	6-point VRS: 6-point VRS: Fully active, able to carry on all pre-disease performance without restriction, Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; Dead	Previous 24 hours/Current state	Cycle 10/Cycle 10
	EORTC QLQ-C30 item 29 (overall health)	Very Poor (1) - Excellent (7)	Previous 24 hours/ Previous 7 days	Cycle 10/Cycle 10
	EORTC QLQ-C30 item 30 (overall quality of life)	Very Poor (1) - Excellent (7)	Previous 24 hours/ Previous 7 days	Cycle 10/Cycle 10

DTSS TSS = Desmoid Tumor Symptom Scale Total Symptom Score; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PGIS = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change

Table 5. Summary of Anchor Scales for DTIS Physical Functioning domain score

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Timing of COA Endpoint (target/anchor)
DTIS Physical Functioning domain score (difficulty with daily activity)	PGIS (symptom severity)	4-point VRS: None, Mild, Moderate, Severe	Previous 7 days/ Previous 7 days	Cycle 10/Cycle 10
	PGIC (overall status)	7-point VRS: Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, Very much worse	Previous 7 days/ Since start of study	Cycle 10/Cycle 10
	ECOG-PS (daily living abilities)	6-point VRS: 6-point VRS: Fully active, able to carry on all pre-disease performance without restriction, Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; Dead	Previous 7 days/	Cycle 10/Cycle 10
	EORTC QLQ-C30 item 29 (overall health)	Very Poor (1) - Excellent (7)	Previous 7 days/ Previous 7 days	Cycle 10/Cycle 10
	EORTC QLQ-C30 item 30 (overall quality of life)	Very Poor (1) - Excellent (7)	Previous 7 days/ Previous 7 days	Cycle 10/Cycle 10

DTIS = Desmoid Tumor Impact Scale; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PGIS = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change

Reviewer's comment(s):

As previously communicated in the IND, there is concern regarding the adequacy of the applicant's selected anchor scales. This reviewer notes the following limitations of the anchor scales which impacts interpretability of the results from the anchor-based analyses:

- *The PGIS scale measures the concept of "symptom severity," rather than the concept being measured in the DTIS Physical Function domain (e.g., impacts on daily activities).*
- *The PGIC scale measures the concept of "overall status" rather than the concept being measured in the target PRO instruments.*
- *While ECOG-PS measures daily living abilities, it is from the perspective of a clinician rather than the patient.*
- *The EORTC QLQ-C30 items 29 and 30 measures the concept of "overall health" and "overall quality of life" rather than the concept being measured in the DTIS Physical Function domain (e.g., impacts on daily activities).*

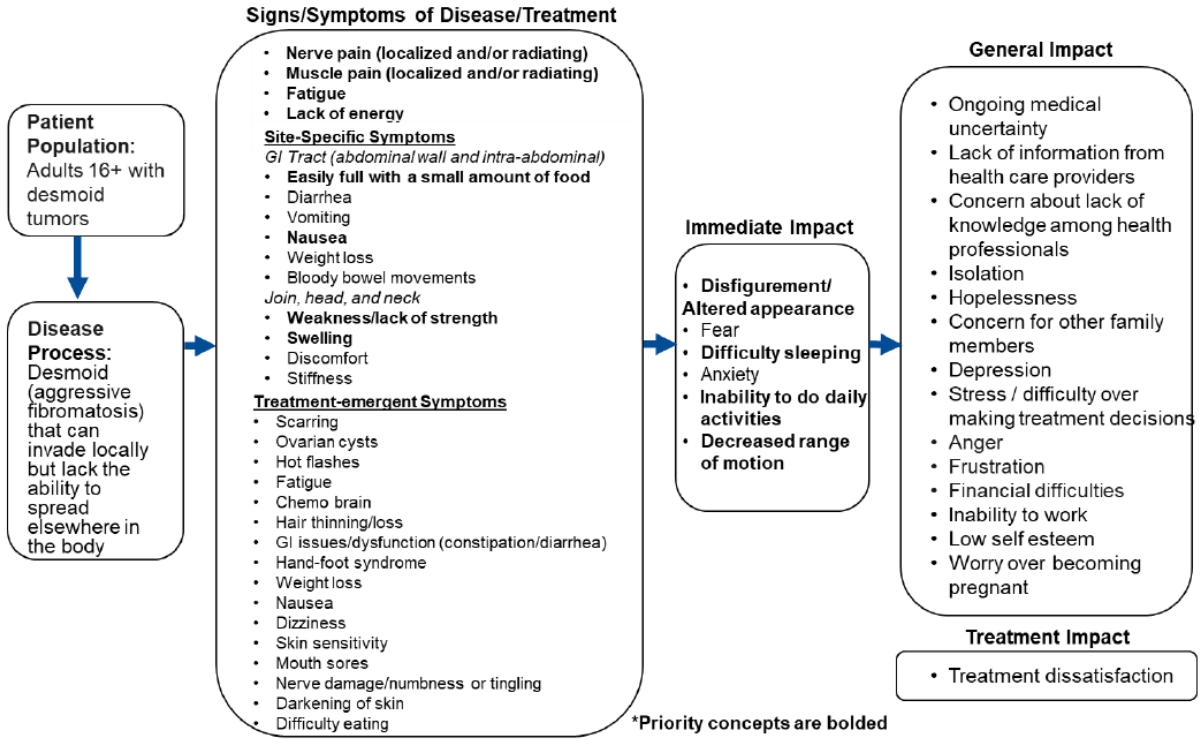
While the recall period of the PGI-S appears misaligned with the DTSS TSS as a score, the endpoint defined for the DTSS TSS is averaged over 7 days and aligns with the recall period of the anchor scales.

6. APPENDICES

Appendix A: Final Conceptual Model
Appendix B: Desmoid Tumor Symptom Scale (DTSS)
Appendix C: Desmoid Tumor Impact Scale (DTIS)
Appendix D: Copies of Anchor Scales

Appendix A: Final Conceptual Model

Figure 6. Desmoid tumor conceptual model (final version)



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SELENA R DANIELS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 8, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 217677
Product Name, Dosage Form, and Strength:	Ogsiveo (nirogacestat) tablet, 50 mg
Applicant/Sponsor Name:	SpringWorks Therapeutics
TTT ID #:	2022-3189-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 31, 2023 for Ogsiveo. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Ogsiveo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Mahmoud, S. Label and Labeling Review for Ogsiveo (NDA 217677). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 03. TTT ID No.: 2022-3189.

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/s/

SALI MAHMOUD
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ASHLEIGH V LOWERY
09/21/2023 03:02:30 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 15, 2023

To: Autumn Zack-Taylor, MS, Regulatory Project Manager, Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, DO3

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ogsiveo™ (nirogacestat) tablets, for oral use

NDA: 217677

Background: In response to DO3's consult request dated January 4, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for Ogsiveo™ (nirogacestat) tablets, for oral use (Ogsiveo).

PI/PPI: OPDP's review of the proposed PI is based on the draft labeling accessed from DO3's SharePoint on September 15, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on September 13, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on August 31, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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REBECCA A FALTER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 13, 2023
To:	Autumn Zack-Taylor, MS Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	OGSIVEO (nirogacestat)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 217677
Applicant:	SpringWorks Therapeutics, Inc.

1 INTRODUCTION

On December 27, 2022, SpringWorks Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217677, a New Molecular Entity (NME), with proposed indication for the treatment of adult patients with desmoid tumors.

On May 26, 2023, the Applicant submitted a major amendment to the application; therefore, the Agency extended the goal date by three months in order to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on January 4, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OGSIVEO (nirogacestat) tablets.

2 MATERIAL REVIEWED

- Draft OGSIVEO (nirogacestat) tablets PPI received on December 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 6, 2023.
- Draft OGSIVEO (nirogacestat) tablets Prescribing Information (PI) received on December 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 6, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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REBECCA A FALTER
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LASHAWN M GRIFFITHS
09/13/2023 01:31:47 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Urology, Obstetrics, and Gynecology

Consultative Review

Date:	August 1, 2023
To:	The Division of Oncology 3
From:	Ioanna Comstock, MD Medical Officer, DUOG **Through:** Gerald Willett, MD Clinical Team Leader, DUOG **Through:** Audrey Gassman, MD Deputy Director, DUOG
Product Name:	Nirogacestat
Subject:	Assessment of ovarian toxicity in premenopausal females
Application Type/Number:	NDA 217677
Applicant/Sponsor:	SpringWorks Therapeutics, Inc.

Introduction

This review documents DUOG's response to a consultative request from the Division of Oncology 3 (DO3) to assess a potential ovarian toxicity signal associated with the use of nirogacestat in premenopausal females for the treatment of desmoid tumor.

Nirogacestat is a potent, small molecule, selective, reversible, noncompetitive inhibitor of gamma secretase (GS) involved in Notch signaling activation that can drive the proliferation of a wide range of tumors. The Sponsor is submitting this NDA for the approved use of nirogacestat for the treatment of desmoid tumor in adults.

During the pivotal Phase 3 study (Study NIR-DT-301), a potential ovarian toxicity signal was identified early in study after 3 participants were reported as having "premature menopause". A protocol amendment was submitted to further investigate this signal with the identification of ovarian dysfunction (OD) as an adverse event of special interest (AESI). This potential for ovarian toxicity was the basis of this consult.

After review of the available safety data on ovarian toxicity, we recommend that the Applicant conduct a Postmarketing Requirement (PMR). For recommendations on the protocol for the PMR, refer to the comments provided at the end of this consult review.

Background

Desmoid tumor is a rare, monoclonal, fibroblastic proliferation that arises in the deep soft tissues. Although it lacks the capacity for metastasis, a desmoid tumor is locally aggressive and has a high rate of recurrence even after complete resection. Tumor-related destruction of vital structures and/or organs can be fatal, particularly when these tumors arise in patients with familial adenomatous polyposis (FAP).

Desmoid tumors are rare; they account for approximately 0.03 percent of all neoplasms and fewer than 3 percent of all soft tissue tumors. The estimated incidence in the general population is five to six cases per million population per year.[1] Desmoid tumors are slightly more common in females than in males with a peak age of 30-40 years.[2] Approximately 5-10% of cases arise in the context of FAP.[2]

Although desmoid tumors can develop at virtually any body site, three main anatomic sites are commonly described. These include: trunk/extremity, abdominal wall, and intra-abdominal (bowel and mesentery) locations. In patients with FAP, intra-abdominal desmoids predominate. In non-FAP-associated cases, the most involved areas are the shoulder girdle, hip-buttock region, and the extremities, where the location is usually deep in the muscles or along fascial planes. Most desmoid tumors present as a deeply seated painless or minimally painful mass with a history of slow growth. Clinical manifestations of intra-abdominal desmoid tumors can include nausea, early satiety, intestinal obstruction, and bowel ischemia.

The anatomic site of the desmoid tumor is the major factor that impacts management. Because of their locally aggressive behavior and tendency to relapse, multimodality treatment is often required for these tumors and is best delivered within the context of a multidisciplinary team specializing in sarcoma treatment.

Desmoids have an unpredictable clinical course, and close observation is the preferred strategy for stable, asymptomatic primary or recurrent desmoids, particularly if resection would entail major morbidity. Consensus-based guidelines from the National

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[1] Penel N, et al. Management of desmoid tumours: a nationwide survey of labelled reference centre networks in France. Eur J Cancer 2016;58:90-6.

[2] Kasper B, et al. Desmoid tumors – clinical features and treatment options for advanced disease. The Oncologist 2011;16:682-93.

Comprehensive Cancer Network (NCCN) suggest observation as a primary therapeutic option for patients with desmoid tumors that are potentially resectable but asymptomatic, non-life threatening, and not causing significant impairment, and includes observation as an option for tumors that are unresectable or if surgery would lead to unacceptable morbidity.[3] Surgical management of an extra-abdominal or abdominal wall desmoid is indicated for symptomatic patients, and for those with progressively enlarging tumors irrespective of symptoms, if there is imminent risk to adjacent structures or if the tumor creates cosmetic concerns.

For situations where the desmoid tumor is causing significant symptoms, systemic therapy, surgery, and radiation therapy should all be considered as potential treatment options. Radiation therapy is an effective primary therapeutic option for patients with abdominal and extra-abdominal desmoids who are not good surgical candidates, those who decline surgery, and those for whom surgical morbidity would be excessive.

The intra-abdominal desmoids that develop in patients with FAP are often unresectable because they diffusely infiltrate the mesentery, encase vessels and/or organs, and are often multiple in number. Morbidity after attempted resection, which often necessitates removal of part of the small intestine, is substantial and includes bowel ischemia, adhesions and resultant obstruction and fistula formation. For these patients, initial systemic therapy is often preferred as an alternative to surgery. Options for systemic therapy include noncytotoxic therapy (an NSAID, tamoxifen), targeted therapy with imatinib, or cytotoxic chemotherapy.

Regulatory History

The development program for nirogacestat for treatment of desmoid tumor was carried out under investigational new drug (IND) 138207. Early in the conduct of the pivotal efficacy trial (Study NIR-DT-301), OD emerged as an AESI for nirogacestat based on three subjects who were reported to experience “premature menopause.” The Applicant submitted Protocol Amendment 3 on January 27, 2020 to further evaluate this ovarian toxicity signal. The Applicant included available gynecological and serum reproductive hormone data on subjects who experienced OD in their NDA submitted on December 27, 2022.

In a consult request dated January 10, 2023, DO3 sought DUOG’s input on the potential for ovarian toxicity associated with nirogacestat. After preliminary review of the NDA submission, DUOG requested clarification regarding the ovarian dysfunction adverse events and additional case narratives for OD events identified in the safety population that were not included in the original submission in an Information Request Letter on February 22, 2023. The Applicant provided additional information to assist the Division in interpretation of the ovarian toxicity signal associated with nirogacestat use. Upon

[3] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls

further review, DUOG determined that there were significant limitations to interpreting the ovarian dysfunction data submitted with the NDA application. DUOG recommends that the Applicant conducts a separate study to further investigate the risk of ovarian toxicity in the post-market setting. Further recommendations for the study design of the post-marketing requirement are provided at the end of this consult review.

Nonclinical Information Submitted in NDA 217677

In the nonclinical evaluation of nirogacestat, the following female reproductive findings are highlighted in the submission package for NDA 217677:

> *Nonclinical studies for nirogacestat in mice, rats and dogs revealed the following findings:*
>
> - *Oocyte mineralization*
> - *Ovarian cysts and altered estrous cyclicity*
> - *Ovarian atrophy that occurred due to decreases in the number of corpora lutea and developing follicles. The remaining follicles in the ovary included primordial and early-stage primary follicles but lacked antral follicles.*
>
> *The Sponsor concluded that "the histopathologic observations in animals suggest that GS inhibition is affecting follicular development rather than ovarian tissue integrity, as evident of ovarian atrophy due to preventing formation of antral follicles and no indication of necrosis."*
>
> *Evidence of embryo/fetal toxicity was noted in reproductive toxicity studies. In the embryo fetal developmental toxicity study in rats, nirogacestat administration induced significant embryo loss, early resorptions and decreased fetal weights in surviving embryos.*

DUOG sought input from the Division of Pharmacology-Toxicology for the Division of Urology, Obstetrics and Gynecology (DPT-DUOG) which reviewed relevant nonclinical reproductive data submitted by the Applicant. DPT-DUOG opined that the nonclinical results raise concerns about nirogacestat having an adverse effect on the ovulatory cycle in animals. It is unclear whether it is a direct effect on the ovary itself, or if the effect is an endocrinologic disruption of the hypothalamic pituitary ovarian (HPO) axis. Additionally, it is unclear whether or not this ovarian dysfunction is reversible.

Based on their review of the nonclinical data available for nirogacestat, DPT-DUOG concluded that additional nonclinical studies are unnecessary to further investigate the ovarian toxicity effect of nirogacestat. They agree with DUOG that the Applicant should

conduct a separate post-marketing study to further investigate the risk of ovarian toxicity in premenopausal females.[4]

Study NIR-DT-301

Study Design - Overview

Study NIR-DT-301 was the pivotal trial used to support efficacy of nirogacestat for the treatment of desmoid tumor in adults. This study was a phase 3, randomized, double-blind, placebo-controlled study evaluating the effectiveness and safety and tolerability of nirogacestat in adult patients with progressing desmoid tumor. This study consisted of 2 phases: a double-blind phase and an optional open-label extension (OLE) phase.

Eligible subjects received oral nirogacestat at a dose of 150 mg BID continuously in 28-day cycles. Subjects 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. Enrolled subjects remained in the double-blind phase until death, disease progression, discontinuation from study treatment for any reason, or the estimated number of progression events were observed, and the primary progression-free survival (PFS) analysis was completed.

Subjects were eligible to enter the optional OLE phase if they were enrolled in the double-blind phase when the primary PFS analysis was completed, or they met the criteria of progressive disease as defined by response evaluation criteria in solid tumors (RECIST v1.1). During the OLE phase, all subjects received nirogacestat 150 mg BID and remained in the study until death, radiographic progressive disease per RECIST v1.1, clinical progression, premature discontinuation, end of study, qualification for Continued Access Plan, or nirogacestat becomes commercially available.

Enrollment Criteria

Key inclusion criteria:

1. Participants ≥ 18 years of age with histologically confirmed desmoid tumor (by local pathologist prior to informed consent) that progressed by ≥ 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.
2. Were treatment naïve or recurrent or refractory to treatment with measurably progressing desmoid tumor.
3. Had Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Had a desmoid tumor where continued progressive disease did not result in immediate significant risk to the participant and had adequate organ and bone marrow function.

Efficacy

Primary endpoint:

[4] Internal communication with Dr. Kimberly Hatfield on May 2, 2023.

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 occurred 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.

Patient Disposition

A total of 142 participants were randomized, with 141 participants receiving study treatment (nirogacestat or placebo) in the double-blind phase. The following table summarizes the demographics of enrolled subjects:

Table 1. Demographics of Intent to Treat 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[b], 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)

	Nirogacestat (N = 70)	Placebo (N = 72)	Total (N = 142)
Ethnicity, n (%)			
Non-Hispanic or Latino	67 (96)	55 (76)	122 (86)
Hispanic or Latino	1 (1)	9 (13)	10 (7)
Unknown	0	3 (4)	3 (2)
Not reported	2 (3)	5 (7)	7 (5)
Age at informed consent (years)			
n	70	72	142
Mean (SD)	37.5 (14.43)	37.0 (12.89)	37.2 (13.62)
Median (Q1, Q3)	33.5 (26, 50)	34.5 (28, 44)	34.0 (27, 46)
Min, max	18, 73	18, 76	18, 76

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.
Error! Reference source not found. Percentages were based on the number of female participants.
Error! Reference source not found. Percentages were based on the number of female participants of childbearing potential.

Ovarian Toxicity Associated with Nirogacestat Use

Ovarian dysfunction (OD) emerged as an AESI for nirogacestat based on observations made early in the conduct of Study NIR-DT-301. After three subjects were reported to experience “premature menopause”, the Applicant submitted Protocol Amendment 3 on January 27, 2020 to evaluate this risk. Within this amended protocol, the Applicant added assessment of serum hormone levels (FSH, LH, estradiol, progesterone, AMH, TSH, and prolactin), obtaining a menstrual history at baseline, and dose modifications for premature menopause/primary ovarian insufficiency. The Applicant included these additional assessments only in patients who were considered “women of childbearing potential” defined as “women that were considered fertile following menarche and until becoming post-menopausal unless permanently sterile and sexually active”.

OD was unavailable as a preferred term (PT) or in MedDRA v24.1, OD was defined narrowly by PTs of ovarian failure, premature menopause, amenorrhea, and menopause. Investigators reported verbatim terms of premature menopause, premature ovarian failure, primary ovarian insufficiency, primary ovarian failure, and amenorrhea to describe events consistent with ovarian dysfunction including menstrual irregularities, cessation of menses (amenorrhea), and hormonal changes including increased FSH/LH and decreased estradiol/AMH. The amended 2020 protocol did not prespecify criteria

for the standardization of definitions of these PTs but rather deferred this to individual investigator's assessment.

On page 71 of the Summary of Clinical Safety (Module 2.7.4) in this NDA submission, the Applicant stated the following regarding OD adverse events in the safety population:

> *"The majority of WOCBP (women of childbearing potential) receiving nirogacestat 150 mg BID in the NIR-DT-301 study reported OD (27 of 36 WOCBP [75%]) as compared to 0 of 37 WOCBP receiving placebo (Table ISS.19.5). OD events resolved in all WOCBP who reported events of OD and discontinued study treatment for any reason with available follow-up data (n = 11; 100%) and also in the majority of participants (n = 9 of 14; 64%) remaining on study treatment with nirogacestat. Two WOCBP who reported OD were lost to follow-up following the discontinuation of study treatment and as such follow-up information is not available for these participants (NIR-DT-301 CSR Figure 17). 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."*

The Applicant concluded from the nonclinical and clinical results that, "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."

DUOG Review of Ovarian Toxicity Data

DUOG reviewed the safety data related to ovarian toxicity submitted in the initial NDA submission, clarifying information and additional case narratives included in the Applicant's IR letter response, and from the 120-day Safety Update. While adverse event data on ovarian toxicity from the clinical trials in premenopausal females with desmoid tumor treated with nirogacestat were included in the case narratives submitted in the NDA, there were significant limitations to interpretability of the clinical data. These limitations include the following:

1. <u>Female population characteristics</u>
    a. The Applicant did not assess all premenopausal subjects in their OD analysis but rather limited this evaluation to those subjects who were of "childbearing potential."
    b. Several subjects had prior exposure to systemic chemotherapy and/or radiation therapy that confound the impact that nirogacestat has on ovarian function. Furthermore, a subset of premenopausal subjects had reported a history of irregular menses prior to nirogacestat exposure.
    c. It is unclear how frequently subjects were questioned regarding their menstrual cycle regularity and the date of their last menstrual period during treatment raising issues of recall bias.
2. <u>Serum reproductive hormone level measurements</u>

a. Serum reproductive hormone measurements were drawn at random days in a given menstrual cycle. It is difficult to interpret serum hormone levels that are drawn on days of the menstrual cycle that are not within the early follicular phase (e.g., cycle day 3) unless they are clearly in the menopausal range.
b. There was no standardization of hormonal assays used in the study, even within the same subject. Different hormonal assays may have different levels of detection and quantification which affects interpretability.
c. Several subjects had missing laboratory values (e.g., serum AMH).

3. Definitions of adverse events
    a. The amended clinical protocol for Study NIR-DT-301 did not predefine criteria for the definition of Preferred Terms (e.g., amenorrhea, premature menopause, ovarian failure, primary ovarian insufficiency) and allowed investigators to make individual assessments of subjects experiencing ovarian toxicity AEs (termed ovulatory dysfunction by the Applicant).
    b. PTs related to premature menopause, primary ovarian insufficiency (POI)/premature menopause/ovarian failure indicate a permanent state without recovery and require demonstration of persistent amenorrhea to confirm the diagnosis. These PTs should not be used to describe potentially reversible drug-induced ovarian toxicity AEs.
4. Resolution of adverse events
    a. Criteria were not predefined to indicate recovery or reversibility of ovarian toxicity. Several case narratives describe a subject "recovery" solely based on return of a single vaginal bleeding episode without measurement of serum reproductive hormone levels.

In summary, the DUOG clinical reviewers are unable to clearly define the incidence and severity of clinical ovarian toxicity during nirogacestat treatment. We are also unable to determine the degree of effect on ovulation/menstrual function and the reversibility of these adverse events on ovarian function in premenopausal women using nirogacestat.

DUOG review team's recommendations to DO3 reviewers:

The DUOG reviewers believe that the reproductive safety data represents a safety signal in females of reproductive potential. However, the totality of the safety data is unclear (and not appropriately collected), and we are unable to conclude whether premenopausal subjects will have menstrual irregularity and/or have issues with return to fertility or not. As written, we believe the information in the proposed warning is not accurate and is interpretable by treating physicians. We recommend instead that the following should be included in the WARNINGS AND PRECAUTIONS section regarding ovarian toxicity:

Female reproductive function and fertility may be impaired in patients being treated with OGSIVEO. (b) (4) Development of infertility may depend on factors including the duration of therapy and the state of gonadal function at the time of treatment. (b) (4) Advise patients on the potential risks for ovarian toxicity (b) (4) before initiating treatment with OGSIVEO *[see Use in Specific Populations (8.3)]*. Monitor patients for changes in menstrual cycle regularity and/or the development of symptoms of estrogen deficiency including hot flashes, night sweats, and vaginal dryness.

DUOG also recommends to further assess this signal of ovarian toxicity that the Applicant conduct a post-marketing, prospective, open-label, single-arm clinical trial in adult premenopausal females with desmoid tumor to assess the ovarian toxicity signal after a minimum of 12 months of nirogacestat treatment as a postmarketing requirement (PMR). The purpose of this ovarian toxicity PMR is to: 1) characterize the incidence and severity of ovarian toxicity associated with nirogacestat use for a minimum of 12 months and 2) assess recovery in ovarian function for up to 12 to 24 months following either treatment discontinuation of nirogacestat or until resolution while on continued treatment.

DUOG provides the following recommendations and comments regarding a future ovarian toxicity PMR for DO3's consideration:

1. **Enroll premenopausal females with pathologically confirmed desmoid tumors < 50 years of age at baseline in your PMR trial to assess the risk ovarian toxicity associated with nirogacestat use, not just subjects you consider to be of childbearing potential. Premenopausal status should be determined at screening defined as: serum E2 > 30 pg/mL, a serum FSH < 40 IU/L, and the presence of a menstrual period within the 12 months prior to study entry. Females are considered to be post-menopausal when one of the following criteria is met:**
    a. **twelve (12) months of spontaneous amenorrhea**
    b. **six (6) months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL**
    c. **six (6) weeks postsurgical bilateral oophorectomy with or without hysterectomy**
2. **Enroll premenopausal females with a history of ovulatory dysfunction (e.g., ovulatory dysfunction due to hypothyroidism, hyperprolactinemia, polycystic ovarian syndrome, etc.). However, it is important to ensure documentation of these conditions at enrollment. Ensure all females should have a complete gynecologic history, including cycle regularity and documentation of last menstrual period, serum TSH and prolactin.**

3. **Ensure collection of gynecologic history including child-bearing potential - history of hysterectomy, history of bilateral salpingectomy or tubal ligation, prior attempts at pregnancy and/or Assisted Reproductive Technology procedures, use of hormonal contraceptives, and hormonal therapy.**

4. **Collect standardized clinical and laboratory measurements of ovarian function in all subjects in this trial. We recommend collection of menstrual data (e.g., menstrual regularity) and serum reproductive hormone measurements [serum follicle-stimulating hormone (FSH), estradiol (E2) and anti-Mullerian hormone (AMH) levels] at baseline (prior to nirogacestat administration), at regular intervals during treatment (e.g., at the completion of months 1, 6 and 12 of treatment), at the end of treatment, and at intervals during post-treatment (e.g., 12 – 24 months post treatment) or during continued treatment until resolution, if possible. While we acknowledge that timing of lab collection is difficult in patients who are oligomenorrheic or become amenorrheic, effort should be made to obtain these lab values on Day 3 in female subjects who report regular menses for accurate interpretation.**

5. **Assessment of serum reproductive hormone levels (i.e., serum FSH and E2) should be performed on Day 3 to 5 of the withdrawal bleed.**

6. **Exclude females who take any medication that could potentially confound results of ovarian function assessment (e.g., hormonal contraceptives, GnRH analogs). Females who are anovulatory and require routine progestin withdrawal bleeds to prevent endometrial hyperplasia (e.g., progestin administration for 7-10 days) may be enrolled, however.**

7. **Propose a plan to: 1) accurately collect menstrual data (e.g., monthly telephone visits) and; 2) collect reproductive adverse events related to vaginal and menstrual bleeding that will mitigate recall error.**

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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AUDREY L GASSMAN
08/02/2023 11:01:30 AM

Clinical Inspection Summary

Date	July 26, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	May Tun Saung, MD, Medical Officer Leslie Doros, MD, Team Leader (CDTL) Steven Lemery, MD, Division Director Division of Oncology 3 (DO3), Office of Oncology Products
NDA #	NDA 217677
Applicant	SpringWorks Therapeutics, Inc.
Drug	Nirogacestat (Ogsiveo)
NME (Yes/No)	Yes
Therapeutic Classification	Gamma secretase inhibitor
Proposed Indication(s)	Treatment of adults with desmoid tumors
Consultation Request Date	January 27, 2023
Summary Goal Date	July 28, 2023
Action Goal Date	August 25, 2023 (extension to November 25, 2023)
PDUFA Date	August 27, 2023 (extension to November 27, 2023, due to major amendment received on May 26. 2023)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study NIR-DT-301 were submitted to the Agency in support of New Drug Application (NDA 217677) for nirogacestat the treatment of adults with desmoid tumors. Three clinical investigators, Drs. Brian Van Tine (site # 06), Mrinal Gounder (site # 17), and Priscilla Merriam (site # 22), as well as the imaging Contract Research Organization (CRO) (b) (4) and the Sponsor, SpringWorks Therapeutics Inc., were inspected.

As previously communicated to the Division, the inspection of the imaging CRO, (b) (4) revealed discrepancies in the sum of target tumor measurements between the blinded, independent reads and the data listings submitted to the FDA by the sponsor. The inspection also determined that the discrepancies occurred at the sponsor's site, prior to the submission to the Agency. OSI were therefore concerned with the reliability of the efficacy data reported in the NIR-DT-301 Clinical Study Report (CSR) version 1.0, dated October 14, 2022, and the associated efficacy tables, listings, and figures. OSI communicated immediately the finding of discrepancies to the ORA inspector who was concurrently inspecting the Sponsor.

During the sponsor inspection, the Sponsor was asked to address the finding of discrepancies discovered at the imaging CRO inspection. The Sponsor acknowledged the discrepancies and initiated an internal investigation. It was determined that the root cause of discrepancies was a programming error by the Sponsor and the CRO responsible for the Statistical Analysis ([redacted]), which added measurements of new lesions into the sum of target tumors. This programming error resulted in incorrect sum of target tumor measurements for seven subjects out of 142 total enrolled in the NIR-DT-301 trial. The Sponsor subsequently submitted a corrective and preventative action (CAPA) plan, as well as an Amendment to the CSR (NDA supporting document # 41, May 19, 2023) with the corrections in the sum of target tumor measurements for these seven subjects, and the associated efficacy tables, listings, and figures (NDA supporting document # 39, May 5, 2023). The review division is currently reviewing the Amendment.

Inspections of the CIs, Drs. Van Tine, Gounder, and Merriam revealed no discrepancies or regulatory violations. Based on these inspections, Study NIR-DT-301 appear to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO appear acceptable in support of the proposed indication.

II. BACKGROUND

SpringWorks Therapeutics, Incorporated (SpringWorks) submitted NDA 217677 seeking approval for nirogacestat for use in the treatment of adults desmoid tumors.

Study NIR-DT-301 was a multi-center, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy, safety, and tolerability of nirogacestat in adult participants with progressing desmoid tumors. Eligible subjects were randomly assigned in a 1:1 ratio to receive either nirogacestat administered orally or placebo. The primary efficacy endpoint of NIR-DT-301 study was progression-free survival (PFS) assessed by central imaging review. Key secondary endpoints were objective response rate (ORR) and duration of response (DoR).

Efficacy data from 142 randomized subjects (70 in the nirogacestat arm and 72 in the placebo arm) were submitted to support the current NDA. Subjects were to sign the informed consent form before any study-specific procedures were to be performed. Imaging assessments were to be performed at baseline, with 28 weeks prior to, or on Cycle 1, Day 1 (C1D1), then every 3 cycles starting at cycle 4, until progressive disease, death, end of study treatment. All scans were to be submitted to [redacted], where blinded central imaging review was performed.

Study NIR-DT-301 was ongoing at the time of NDA submission. The first subject was randomized on May 15, 2019. The data cut-off date for NIR-DT-301 was April 7, 2022. Subjects were randomized across 52 clinical sites across 7 countries (Belgium, Canada, Germany, Italy, Netherlands, United Kingdom, and the United States). A total of 90 subjects were enrolled at 28 sites in US.

Drs. Brian Van Tine (site # 06), Mrinal Gounder (site # 17), and Priscilla Merriam (site # 22), as well as the Sponsor, SpringWorks Therapeutics Inc., and the imaging CRO, (b) (4) were inspected.

III. RESULTS (by site):

1. **Dr. Brian Van Tine (Site # 06)**
   660 S. Euclid, CB 8056
   St. Louis, MO 63110

   Inspection dates: March 6 – Marth 8, 2023

   Dr. Van Tine was inspected as a routine PDUFA inspection for Study NIR-DT-301. Dr. Van Tine was previously inspected in March 2016.

   At the time of the inspection, the site screened 8 subjects and enrolled 5 subjects in the study. Four subjects had discontinued from the study: 2 subjects completed protocol treatment and follow-up (ID # (b) (6) and # (b) (6)), 1 withdrew consent (ID # (b) (6)), and 1 subject (ID # (b) (6)) had died due to multi-organ failure associated with the underlying malignancy, and one subject remained on study.

   Source records for all subjects were reviewed. Records reviewed included, informed consent forms, medical histories, inclusion and exclusion criteria, randomization and blinding investigational drug administration, adverse events reporting, concomitant medications, protocol deviations, and subject dispositions. Records were compared with data listing tables submitted to the NDA and no discrepancies were noted.

   All subjects had imaging scans performed at protocol specified timepoints and scans were submitted to imaging CRO for central assessment of disease response and progression for determination of the primary and secondary efficacy endpoints.

   Additional records reviewed include, but were not limited to, site's overall adherence to the study protocols, IRB approval letters and correspondence, delegation of authority logs, monitoring reports, financial disclosure reports, electronic case report forms, drug accountability records, site staff training records and responsibility logs.

   Based on the results of the inspection, data generated at Dr. Van Tine's site appear acceptable in support of the proposed indication in the NDA.

2. **Dr. Mrinal Gounder (Site # 17)**
   300 East 66th St. Floor 12
   New York, NY 10065

   Inspection dates: February 21 thru March 3rd, 2023

Dr. Gounder was inspected as a routine PDUFA inspection for Study NIR-DT-301. Dr. Gounder was previously inspected in September 2019.

At the time of the inspection, the site had screened 17 and enrolled 14 subjects in the study. Of the 14 subjects, 2 discontinued treatment due to disease progression and 3 due to lack of clinical efficacy, 2 subjects withdrew consent, and 1 subject discontinued study treatment due to an AE of ovarian insufficiency (ID # (b) (6)). Six subjects remain on treatment.

Source records for all 14 subjects were reviewed and compared with line listings submitted to the NDA. Records reviewed for informed consent documents, eligibility criteria, adverse events reporting, subject treatment, protocol deviations, laboratory reports, and concomitant medications.

All imaging scans were performed according to the protocol specified timepoints and were submitted to the imaging CRO for central assessment of disease response and progression for determination of the efficacy endpoints.

Additional records reviewed during the inspection included, but not limited to, IRB approval letters and communication, monitoring logs, electronic medical records, financial disclosure forms, staff training records, and drug accountability.

Based on the results of the inspection, the NIR-DT-301 study data generated at Dr. Gounder's site appear acceptable in support of the proposed indication in the NDA.

3. Dr. Priscilla Merriam (Site # 22)
Dana Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215

Inspection dates: February 21 thru February 24, 2023

Dr. Merriam was inspected as a routine PDUFA inspection for Study NIR-DT-301. This was the first FDA inspection for this investigator.

At the time of the inspection, the site screened 6 subjects and enrolled 5 subjects in the study. One subject withdrew consent prior to initiation of study (ID # (b) (6)), 2 discontinued study treatment due to toxicity during the double-blind phase (ID # (b) (6) and # (b) (6)), 1 subject had progressed during the double-blind phase and was enrolled in the open-label phase (ID # (b) (6)), and 1 subject was on active treatment (ID # (b) (6)).

Source records for all 5 subjects enrolled at the site were reviewed. The inspection covered informed consent forms, physician notes regarding screening, eligibility criteria, progress notes, adverse events, laboratory reports, concomitant medications, and protocol deviations.

Additional records reviewed included, but were not limited to ethics committee approvals, monitoring procedures and documents, drug accountability records, staff qualifications and training.

Based on the results of the inspection, data generated at Dr. Merriam's site appear acceptable in support of the proposed indication in the NDA.

4. (b) (4) (Imaging CRO)

Inspection dates: (b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study NIR-DT-301. The firm was previously inspected in (b) (4).

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study NIR-DT-301. Records reviewed included imaging source data, overview of electronic systems, written agreements, meeting minutes, standard operating procedures (SOPs), manuals, and training records.

Tumor response data from 141 randomized subjects who received at least one dose of study drug in NIR-DT-301 were reviewed. In addition, for the 35 subjects reported as having experienced a complete response (CR) or partial response (PR), the inspection reviewed the sum of target tumor measurements as well as the tumor response. All CR and PR tumor responses were confirmed by imaging at least 4 weeks after initial documentation.

The inspection observed discrepancies between the sum of target tumor measurements in (b) (4) database and the listings submitted to the FDA in 5 subjects: ID # (b) (6) (cycle 16 and cycle 19), ID # (b) (6) (cycle 13 thru cycle 34), ID # (b) (6) (cycle 13 and 19), ID # (b) (6) (cycle 16 thru cycle 34), ID # (b) (6) (cycle 13). See discussion of the Sponsor inspection below for 2 additional subjects identified by the Sponsor.

Specifically, in the case of the above subjects, measurements of new lesions were added to the sum of target tumors, contrary to the RECIST 1.1 guidelines and the Imaging Central Review Manual (new lesions were *not* to be added to the sum but signify progressive disease). A review of datasets transferred from (b) (4) to the Sponsor indicated that the revised tumor measurements (adding the new lesion measurements in the above-mentioned cases) occurred at the Sponsor's site, prior to the submission to the Agency (refer to Table 1 below).

This information was relayed to the FDA inspector conducting the inspection of

SpringWorks for further evaluation. Please refer to the section below for the summary of the Sponsor inspection for the root cause of the data discrepancy and the corrective actions taken.

(b) (4) assessment, procedures in performing image analysis, compliance with the Imaging Review Charter, clinical protocol, and appropriate regulations appeared to be adequate. The imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the NDA.

5. SpringWorks Therapeutics, Inc. (Sponsor)
100 Washington Blvd.
Stamford, CT 06902

Inspection dates: March 20 thru March 31, 2023

SpringWorks was inspected as data audit and surveillance inspection for Study NIR-DT-301. This was the first FDA inspection for this firm.

Documents reviewed during the inspection included: NIR-DT-301 study documents, study plans, charters, data collection and handling procedures, safety reporting and handling, selection of clinical site investigators and monitors, form FDA 1572s, financial disclosures, data monitoring committee activities, investigational product disposition, and contract with research organizations. The inspection also reviewed the source central imaging data from (b) (4), datasets, and TLFs submitted to the Agency by the Sponsor.

During the inspection, the Sponsor was asked to address the discrepancies in the sum of target tumor measurements between the blinded, central reader at (b) (4) and the listings SpringWorks submitted to the FDA that were identified at by the FDA inspector at the imaging CRO inspection.

SpringWorks acknowledged the discrepancies observed by the FDA inspector at (b) (4) and initiated an internal investigation to identify the root cause of the error. In addition to the discrepancies identified by FDA during the inspection of (b) (4) (Subject IDs # (b) (6)), two additional subjects (IDs (b) (6)) were identified by SpringWorks to have discrepancies in the sum of target tumors during the re-evaluation of the data. The list of subjects and tumor measurement discrepancies is shown in the following table.

Discrepancies Observed Between [redacted] (Imaging CRO) Reader's Database and Line Listings (per Sponsor's Report)

			[redacted] Database (transferred to the Sponsor)		Line Listing Submitted to the NDA
Subject #	Cycle #	Reader	Blinded Central Reader Sum of Target Tumors (mm)	Blinded Central Reader New Tumor Size (mm)	Sponsor's Calculated Sum of Target Tumors (mm)
[redacted]	7	B	36.2	15.1	51.3
	10	B	32.1	26.5	58.6
	13	B	31.2	27.5	58.8
	16	B	32.6	29.6	62.2
	19	B	35.3	34.6	69.9
	16	A	50.4	40.3	90.7
	19	A	34.4	40.2	74.6
	13	A	40.2	41.3	81.5
	13	A	193.2	48.1	241.3
	16	A	177.5	51	228.5
	19	A	192.6	53.7	246.3
	22	A	177.9	40	217.9
	25	A	185.9	41.3	227.2
	28	A	191.6	33.3	224.9
	31	A	174.4	37.6	212
	34	A	171.4	22.8	194.2
	13	A	23.5	22.5	46
	19	A	0	15.9	15.9
	16	A	16	13.7	29.7
	19	A	15.4	14.8	30.2
	22	A	14	16.6	30.6
	25	A	13.4	16.1	29.5
	28	A	14	17.8	31.8
	31	A	11.6	12.3	23.9
	34	A	13.1	12.9	26
	7	A	89.7	74.5	164.2

It appears that, when new tumors were identified, their measurements were incorrectly added to the sum of target tumor measurements, resulting in errors in the line listings submitted to the FDA. SpringWorks stated that the cause of the discrepancies was due to a programming error in the ADaM ADTR (tumor results) data set SUMLRA and SUMLRB parameters and acknowledged that according to the Statistical Analysis Plan, new tumors should not be included in the calculation of the sum of the target tumor diameters. The inclusion of the new lesions in the sum of target tumor calculations was introduced in error by [redacted] the CRO responsible for statistical analysis and development of SDTM and ADaM datasets for NIR-DT-301 study.

At the time of the inspection close-out, SpringWorks stated that the programming error had not yet been resolved and revalidation for all output contributing to the NIR-DT-301 protocol Clinical Study Report listings were ongoing.

Reviewer's comment: Incorrect tumor measurements from 7 subjects enrolled in the NIR-DT-301 study resulted in errors in the reporting of efficacy results. The findings suggest that the efficacy data reported in the NIR-DT-301 CSR may be unreliable. SpringWorks initiated an investigation into the observed data discrepancies and opened a CAPA plan. These actions were ongoing at the time of the close-out of the inspection. SpringWorks committed to submitting any corrected datasets and update the CSR to the NDA upon completion of the review. The review division was made aware of the inspection findings during the inspection.

Post-inspection action: Additional discrepancies were identified by SpringWorks during the re-validation of the statistical analysis package and review of the derived variables and parameters in all analysis datasets used for the table, listing and figures included in the CSR.

An addendum to the CSR with revised datasets, tables, listings, and figures was submitted to the FDA on May 5, and May 19, 2023, and is currently under review by the division.

In addition to the discrepancies described above, the inspection observed deficiencies in financial disclosure and conflict of interest reporting by the Sponsor, namely:

- There were three investigators who served on the steering committee for study NIR-DT-301 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 he received > $ 25,000 on her financial disclosure form (FDF) and the other investigators listed no monetary stipend on their FDF. The Sponsor reported no financial disclosures for any investigator or sub-investigator involved in the study on their Form FDA 3454.

- (b) (6): CI for site # (b) (6), disclosed (b) (6) for the Sponsor (receiving < $ 25,000). Her service (b) (6) was not disclosed by the Sponsor.

Reviewer's comment:
In addition to the failure to disclose the above financial interest and conflict of interest (COI), the inspection revealed that the Sponsor did not have a procedure in place for evaluation of such conflicts. SpringWorks stated that the firm would consider expanding their existing financial disclosure procedure to include capturing conflict of interest and updating their financial disclosure process. Notwithstanding the sponsor's failure to disclose the COI, the value of compensation is unlikely to impact on the efficacy outcome of the study given the relatively small number of subjects enrolled at each site (site # (b) (6), enrolled (b) (6) subjects, site # (b) (6), (b) (6) subjects, site # (b) (6), (b) (6) subjects, and site # (b) (6), (b) (6) subjects) and that the primary efficacy measure of the study was determined by blinded, central review.

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DARRTS: NDA 217677
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OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217677
Submission Number	5
Submission Date	12/24/2022
Date Consult Received	1/10/2023
Drug Name	Ogisevo (Nirogacestat)
Indication	Treatment of adult patients with desmoid tumors (DTs)
Therapeutic Dose	150 mg BID
Clinical Division	DO3
Protocol Review	Previous IRT reviews dated 07/01/2020, 11/03/2020, and 07/28/2021

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 1/10/2023 regarding the sponsor's QTc evaluation report. We reviewed the following materials:

- Study report A8641014 (NDA 217677 / eCTD 0002; link);
- Study report NIR-DT-103 (NDA 217677 / eCTD 0004; link);
- Study report NIR-DT-301 (NDA 217677 / eCTD 0004; link);
- Sponsor's Concentration-QT Analysis report (NDA217677/SDN5);
- Proposed Labeling (NDA217677/SDN5);
- Previous IRT under IND 138207 review dated 03/12/2018; 07/01/2020; 11/03/2020; 07/28/2021; 07/27/2022; 08/24/2022 in DARRTS; and
- Highlights of clinical pharmacology and cardiac safety (NDA 217677 / eCTD 0005; Table 20).

1 SUMMARY

Nirogacestat does not cause large mean increases (i.e., 20 msec) in the QTc interval at therapeutic exposures with 150 mg BID. Without a positive control or large exposure margin, we are reluctant to conclude that nirogacestat has no effect on the QTc interval (E14 Q&A 6.1).

The clinical studies used for this alternative QT assessment were A8641014 and NIR-DT-103. Study A8641014 was an open-label, non-randomized, phase 1, multiple dose-finding study in patients with advanced solid tumor malignancies, and patients with relapsed or refractory T-ALL/LBL. Study NIR-DT-103 was a single dose phase 1, single-center, single sequence crossover study to compare the pharmacokinetics, safety, and tolerability of nirogacestat alone or co-administered with rifampin (Part 1) or itraconazole

(Part 2) and to determine the effects of nirogacestat on the pharmacokinetics of total dabigatran etexilate (Part 3) in healthy adult male subjects. The high doses of 220 mg BID and 330 mg BID tested in study A8641014 covered the high clinical exposure scenario (CYP3A4 inhibition). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that nirogacestat is associated with large mean increases in the QTcF interval (section 4.5). The findings of the primary analysis are further supported by by-time (section 4.3) and categorical analyses (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario is when nirogacestat is co-administered with strong CYP3A4 inhibitors resulting in up to ~2.5-fold increase in Cmax (section 3.1)
• The high doses tested were 220 mg BID for 21 days in 10 subjects and 330 mg for 1 day in 3 subjects and for 15 days in 1 subject (Table 3). The 220 mg BID dose in 10 subjects provided geometric mean Cmax of 1667 ng/ml which covers high clinical Cmax.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔQTcF</td><td>Nirogacestat 150 mg</td><td>675</td><td>0.8</td><td>(-1.8 to 3.3)</td></tr>
<tr><td>ΔQTcF</td><td>Nirogacestat 150 mg</td><td>1687.5</td><td>2.2</td><td>(-2.9 to 7.3)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated nonclinical risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0005 (link) from the CS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology (b) (4) [redacted] *At the recommended OGSIVEO dose, a mean increase in the QTc interval > 20 ms was not observed.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Nirogacestat is a gamma secretase inhibitor that is proposed for the treatment of desmoid tumors in adults. The proposed daily dose is 150 mg BID. (b) (4) [redacted]

The sponsor initially proposed that the available nonclinical (hERG and in vivo) and clinical data (studies A8641001, A8641002, A8641014) supported conclusion of low risk for QTc prolongation. However, insufficient information was provided to support adequate review (DARRTS 03/12/2018). In 2020, the sponsor proposed to use study NIR-DT-103 to characterize the QTc effects. We did not agree with the design of NIR-DT-103 as the design did not allow for demonstrating assay sensitivity due to design limitations (i.e., moxifloxacin in periods 1 and 2 only) and the highest dose was not expected to provide a sufficiently high exposure to support waiving the requirement for a separate positive control (DARRTS 07/01/2020).

A pooled concentration-QTc analysis, based on high-quality ECGs from studies A8641001, A8641002, A861014, NIR-DT-101, NIR-DT-102, NIR-DT-103, and NIR-DT-301 was later proposed, which looked overall acceptable to exclude 20 msec mean QTc prolongation (DARRTS 11/03/2020; 07/28/2021).

In 2022, the sponsor requested input on submission of ECG waveforms as ECG waveforms could not be acquired for studies A8641014 and NIR-DT-301 and only paper

ECGs were available for NIR-DT-101 and NIR-DT-102. We responded that while it was not required to submit ECG waveforms, that it was generally recommended to support review and that we recommended inclusion of automatic measurements as a sensitivity analysis. We also recommended that the QT assessment was focused on studies covering anticipated therapeutic exposure in patients or higher (i.e., A8641014 or NIR-DT-301) and that the by-time and categorical analysis was also recommended (DARRTS 07/27/2022).

The sponsor provided additional information about the ECG collection noting that not all studies had digital ECGs and proposed to address the requested sensitivity analysis by assessing the impact of only including studies with automatic ECG measurements on the concentration-QTc relationship. The interpretability of the proposed sensitivity analysis is unclear as there are other confounding factors, which are not controlled. Moreover, based on the additional clarification of variation in ECG collection between studies we recommended that the sponsor focuses the QT evaluation on studies where the anticipated therapeutic exposures were reached (i.e., A8641014 and NIR-DT-301) and high-quality ECGs were collected at or near therapeutic exposures (i.e., NIR-DT-103). (DARRTS 08/24/2022)

In the current submission, the sponsor is proposing to assess the QT interval based on a pooled concentration-QTc analysis (see Table 2). The pooled studies vary in exposure coverage and not all studies covered clinical exposure, study population, inclusion of placebo, ECG and PK collection/analysis and we therefore do not agree with the proposed pool. See section 3.2.3 for additional comments on the sponsor's pooled concentration-QTc analysis.

Table 2 summarizes the studies pooled by the sponsor for assessment of QT effects of nirogacestat. The table also includes bioanalytical centers (PK sites) where PK samples were analyzed using the different methods developed by the bioanalytical centers. The submitted reports do not indicate that the sponsor conducted inter-laboratory cross-validation of the bioanalytical methods at the different centers. Nevertheless, based on comparable geometric mean Cmax after the first dose of nirogacestat 150 mg between study A8641014 (gCmax = 1092 ng/mL (95%CI = 794 - 1502), PK site = (b) (4)) and study NIR-DT-103 – Part 1 (gCmax = 881 ng/mL (95%CI = 724 - 1072), PK site = (b) (4)), an assumption can be made that the bioanalytical centers would give same results for the same PK sample. In study NIR-DT-301, the observed geometric mean Cmax after the first 150 mg dose was 536 ng/mL (95%CI = 444 - 646) which is considerably lower than that observed in study A8641014 and study NIR-DT-103 – Part 1. The reason for these inter-study PK differences is not known but can be attributed to pathophysiological differences or differences in study conduct; study A8641014 was in patients with Advanced Solid Tumor Malignancy and T-Cell Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma while study NIR-DT-301 was in patients with Desmoid Tumors/Aggressive Fibromatosis. Since the intended patient population is patients with DT, we estimated Cmax,ss based on NIR-DT-301 (see Table 3).

Among the studies pooled by the sponsor for assessment of QT effects (See Table 2), study A8641014 covers above therapeutic exposure and NIR-DT-103 has exposures close to therapeutic but includes high-quality ECGs and was therefore considered as the primary studies for analysis. We did not include studies NIR-DT-101 and NIR-DT-102 in

our analysis due to the absence of high-quality ECGs and limited exposure margin. Study NIR-DT-301 was also not included because only average data was provided, and no ECG waveforms were available to support analysis. Our analysis is therefore based on studies A8641014 and NIR-DT-103, which are analyzed separately as the data could not be pooled due to differences in ECG collection and analysis and study population.

We analyzed the data using concentration-QTc analysis as the primary analysis independently by study. By-time and categorical analysis was performed by study as supportive analysis. Lastly, while NIR-DT-301 was not included in the quantitative analysis, the study was still included in the safety analysis.

Table 2: Summary of studies

Study (Population)	Design	Pbo	Digital ECGs	ECG reading	PK site	Dose: Cmax (ng/mL)	ECG/PK
A8641001 (HV)	SAD	Y	Y	Semi	Pfizer	120 mg: 338	Pre-dose, 1, 2, 4, 8, 12, 24, 36 and 48 h post-dose
A8641002 (HV)	MAD	Y	Y	Semi	(b) (4)	95 mg QD: 460	Part 1: D1: Pre-dose, 1, 4, 8, and 12h D2: Pre-dose Days 4,7: Pre-dose and 1 h Day 14: Pre-dose, 1, 4, 8, 12 and 24 h last dose Part 2: D1,4,7: Pre-dose, 1h C1D1: Pre-dose, 1 h C1D15: 1h C1D21: Pre-dose, 1, 4, 24, 48 and 96 h C2 to 8D1: Pre-dose (Escalating/Expand-S) and 1 h (all)
A8641014 (Patients)	OL, non-randomized dose-finding	N	N	Auto	(b) (4)	150 mg BID: 1246	
NIR-DT-101 (HV)	Mass balance	N	N	Auto	(b) (4)	150 mg: 822	Pre-dose and at 1, 2, 4, 8, 24, 48, 168, 312, and 432 h
NIR-DT-102 (HV)	ADME Absolute BA	N	N	Auto	(b) (4)	150 mg: 827	Pre-dose and at 1, 4, 8, 24, 48, 168, and 312 h
NIR-DT-103 – Part 1 (HV)	Single sequence, 2 period, XO DDI study	N	Y	Semi	(b) (4)	150 mg: 876	D1,8,16: Predose, 1, 4, 8, 12 h.
NIR-DT-103 – Part 2 (HV)	Single sequence, 2 period, XO DDI study	N	Y	Semi	(b) (4)	100 mg: 438 100 mg + itraconazole: 1090	D1 (Placebo): Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h

							D2/15 (100 mg): Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose D14 (Itraconazole): Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h
NIR-DT-301 (Patients)	Placebo-controlled, P3 study	Y	N	Auto	(b) (4)	150 mg BID: 675[a]	C1D1/8: Pre-dose and 1h C2D28: Through C4D1 and ever 3 cycle thereafter: Through

Source: Summary of Clin Pharm (Table 18); QT evaluation Checklist; Concentration-QTc Analysis Report (Appendix 1). [a]This value is estimated from observed geometric mean Cmax of 536 ng/mL after first dose of 150 mg in patient with Desmoid tumor and accumulation ratio of 1.26 calculated from geometric Cmax values on days 1 and 14 in healthy subjects receiving 7 mg BID.

3.1.1 Clinical pharmacology

The exposure margin of the highest tested dose in QT assessment over estimated high clinical exposure in subjects with Desmoid Tumor is about 1-fold (Table 3)

Table 3: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	150 mg BID, oral tablets, in patients with Desmoid tumors (Study NIR-DT-301)	675 ng/mL ($C_{max,ss}$)[a]
Sponsor's High clinical exposure scenario	[c]2.5-fold increase with strong CYP3A4 inhibition	1687.5 ng/mL
Highest dose in QT assessment	220 mg BID for 21 days (n=10) and 330 mg BID for 15 days (n = 1) in patients with solid tumor (Study A8641014)	1667.2 ng/mL[b]
C_{max} Ratio	1667.2 / 1687.5 = 0.99	

[a]This value is estimated from observed geometric mean Cmax of 536 ng/mL after first dose of 150 mg in patients with Desmoid tumor and accumulation ratio of 1.26 calculated from geometric Cmax values on days 1 and 14 in healthy subjects receiving 7 mg BID (Based POPPK dataset for Study A8641002). [b] This geometric mean Cmax was calculated by the reviewer using study A8641014 data provided in the QTPK dataset. Geometric mean Cmax for 10 subjects on 220 mg BID on day 21 was 1667.2 ng/mL. Geometric mean Cmax for 3 subjects on 330 mg BID on day 1 was 1892 ng/mL. One subject on 330 mg BID until day 15 had Cmax of 1660 ng/mL. [c]Source is summary of clinical pharmacology studies, section 2.2.5, page 13/91

3.1.2 Nonclinical Safety Pharmacology Assessments

The in vitro effects of nirogacestat on the hERG channel current expressed in HEK293 cells were assessed at concentrations of 0.3, 1, 3, and 10 µM (181008.TQV). Under the conditions of this GLP study, the IC50 for the inhibitory effect of nirogacestat on hERG potassium current was 1.0 µM. This concentration is 98-fold over the human free geometric mean Cmax of 4.98 ng/mL (10.2 nM) after administration of 150 mg BID as observed in Study A8641014. The in vitro effects of the M283 metabolite (PF-03015273)

on the hERG channel current expressed in HEK293 cells were assessed at concentrations of 0.37, 1.11, 3.33, 10.0, and 30.0 µM (200324). Under the conditions of this non-Good Laboratory Practice (nonGLP) study, the IC50 for the inhibitory effect of the M283 metabolite on hERG potassium current was > 30 µM (maximum inhibition at 30 µM was 11%). M283 is a prominent metabolite but did not exceed 10% of total radioactivity in a human mass balance study (NIR-DT-102) and it does not appear to interact with hERG. Therefore, nirogacestat exhibits minimal risk of QT prolongation in humans through direct inhibition of the hERG channel at the proposed clinical nirogacestat dose of 150 mg BID.

Reviewer's Comment: *The observed IC50 for nirogacestat in study 181008.TQV was 1.0 uM (n_h: 1.2). Based on the high clinical Cmax in Table 1 (Total Cmax: 1687.5 ng/mL; MW: 651.48 g/mol; PB: 99%; Free: 25.9 nM) the hERG safety margin for nirogacestat is ~38x suggesting a possibility for hERG induced QTc prolongation.*

The cardiovascular effects of nirogacestat were assessed in male Beagle dogs implanted with telemetry devices using a single-dose crossover design (Report 06GR083). Nirogacestat was administered orally to dogs at 2, 80, or 500 mg/kg. During the 23-hour postdose observation period, no statistically significant changes in heart rate, blood pressure, or electrocardiogram (ECG) parameters were observed. Based on the outcome of this GLP study, nirogacestat does not adversely affect cardiovascular function in male dogs.

Reviewer's Comment: *Study 06GR083 was a 4 by 4 Latin square design with a sample size of four and a washout period of 7 days. Dogs were fasted overnight and fed at ~6 h post-dose. ECG data were collected on each day starting ~1 h pre-dose and ending ~24 h following administration of vehicle or placebo. ECG data was summarized in 15-minute means and subsequently binned into three periods (1-6 h post-dose; 7-14 h post-dose; 14-24 h post-dose). Data collected for dosing to 1 h and feeding to 1 h post-feed were excluded. Individual QT correction was done based on vehicle treatment data (1 min averages) using a linear model. PK was collected at 6 h post-dose in all treatment groups. Originally, the study included four three dose groups (2, 80, and 500 mg/kg), however, an additional treatment period of 80 mg/kg in the last period was added to obtain a complete PK (i.e., predose and 1, 2, 4, 6, 12, and 24 h post-dose) profile due to consistent emesis observed with administration of 500 mg/kg. The observed Cmax at 80 mg/kg was 518 ng/mL at 6 h post-dose the exposure for 80 mg/kg was similar to the 500 mg/kg group (i.e., 500 mg/kg: 134 ng/mL; 80 mg/kg: 102 ng/mL). Protein binding was similar between dogs and humans and the concentrations at the highest dose in the in vivo QT study that was not associated with emesis (80 mg/kg) was sub-therapeutic.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

Not applicable.

Reviewer's comment: *The sponsor didn't conduct by-time analysis.*

3.2.1.1 Assay Sensitivity

Not applicable.

Reviewer's comment: *The study had no placebo, positive control, and the exposure margin over high clinical Cmax was only 1-fold. Due to the lack of assay sensitivity, nirogacestat QT effects were evaluated using an alternative QT assessment pathway (i.e., ICH E14 Q&A 6.1).*

3.2.1.1.1 QT Bias Assessment

Not applicable.

Reviewer's comment: *Could not be performed as digital ECGs were not available for all studies.*

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or >60 msec over baseline).

Reviewer's comment: *The sponsor didn't conduct categorical analysis for HR, PR and QRS. For QTc in study A8641014, more treatment doses (i.e., 10 mg BID, 65 mg BID, 75 mg BID, 110 mg BID, or 125 mg BID) are included since the subjects who were assigned to a dose group (20 mg BID, 40 mg BID, 80 mg BID, 100 mg BID, 130 mg BID, 150 mg BID, 220 mg BID or 330 mg BID) might dose varied along the treatment period. In addition, the sponsor's results seem slightly different from the reviewer's results since 3 subjects (*(b) (6) *with the treatment of 80 mg BID and* (b) (6) *with the treatment of 220 mg BID) who had QTcF >500 msec or >60 msec over baseline in the reviewer's results. For subjects* (b) (6)*, there is no serum concentration. For subject* (b) (6)*, the minute difference between ECG and serum concentration is 11 minutes and 13 minutes at Hour 1 and Hour 4, respectively. However, the sponsor only included paired concentration and QT measurements in their analysis. An ECG and serum concentration was considered paired if taken within 10 minutes of each other, except for pre-dose, which utilized the time of the ECG and a concentration of 0 (as long as both were taken prior to the administration of study medication). Thus, these 3 subjects are not included in the sponsor's analysis. For QTc in study NIR-DT-103, the sponsor's results are similar to the reviewer's results. Please see section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The sponsor pooled PK and ECG data from 7 studies (Studies A8641001, A8641002, A8641014, NIR-DT-101, NIR-DT-102, NIR-DT-103, and NIR-DT-301) and analyzed the data using a customized model. In brief, the customized modelling involved building a baseline QTcF model (based on data from placebo treated subjects) followed by evaluation of impact of different covariates on QTcF during nirogacestat treatment. The evaluated covariates included food intake, sex (male vs female), age, concomitant medications, itraconazole concentrations, and nirogacestat concentrations. The sponsor's final model is presented in equation 1. The analysis included all subjects who had at least one paired concentration and QTcF interval.

$$QTcF_{abs} = \theta + \eta + \alpha$$

$$QTcF = \left(QTcF_{abs} \times e^{(SLPSEX*SEX)} \times \left(\frac{Age}{37}\right)^{SLPAGE} \right) + SLPNIRO \times CONC$$

Equation 1. Concentration – QTcF model equation. QTCFabs is the estimated baseline QTcF (θ) with additive random IIV (η and α), SEX is 0 for male and 1 for female, AGE is individual subject age in years (centered on the median of 37 years), CONC is the nirogacestat concentration in ng/mL, SLPSEX and SLPAGE are the estimated effects of female sex and age on baseline QTcF, respectively, and SLPNIRO is the nirogacestat concentration-related slope on QTcF

Source: Sponsor's Concentration-QT Analysis Report, page 30/225

The sponsor predicted ΔQTcF at selected concentrations (therapeutic and 2-fold therapeutic concentrations). Based on this analysis, the mean ΔQTcF and 90% CI were below 10 msec for each concentration of interest in the Desmoid Tumor patient population, including at 2-fold of Cmax,ss with strong CYP3A4 inhibition.

Reviewer's comment: *We have concerns about the pooled data analysis for the following reason(s):*

1. *Pooling of heterogenous studies may conceal the true concentration - QT effect. The pooled studies differed in several aspects including, methods of ECG acquisition and measurements, data collection schedules, concomitant medications, disease status with different disease pathophysiology, relative food intake schedules, study sites with different study conducts, and different nirogacestat exposures. The sponsor addressed heterogeneity by conducting sensitivity analysis. But despite the sensitivity analysis, the sponsor did not set a clear criterion to select their final model.*

The reviewers developed separate concentration-vs ΔQTcF models for studies NIR-DT-103 and A8641014 (See section 4.5). The findings from the 2 separate models indicate that over the exposure range, a C-QTc relationship was not detected. These findings are consistent with those reported by the sponsor.

3.2.4 Safety Analysis

Study 103 (Part 1):
No deaths, serious AEs, or AEs that resulted in discontinuation were observed.

Study 1014 (cutoff of January 9th, 2013):
There were 5 deaths, 30 patients experienced a serious AE and 14 patients discontinued due to an AE.

Study 301 (double-blind period):
There was 1 death in the placebo arm, without any deaths in the nirogacestat arm. Fourteen patients (20%) in the nirogacestat arm reported a serious AE compared to 8 (11%) in the placebo arm. Sixteen (23%) and 2 (3%) of patients in the nirogacestat and placebo arms discontinued due to an AE.

ISS Safety population:
In total, 12 patients were identified in the ISS datasets to have non-serious MedDRA PTs under the SMQ for "Torsade de pointes/QT prolongation", including 10 patients with an AE of QT prolongation and one who experienced syncope.

There were also 1 patient who experienced syncope and 1 patient who experienced ventricular tachycardia during periods without nirogacestat exposure (i.e., 1 on placebo and 1 during itraconazole).

Reviewer's comment: *Independent analysis of the safety-population using the ISS dataset and our customized AE query produced similar results. That is, 14 patients with a treatment-emergent AE (8: QT prolongation; 2 Seizure; 1: Syncope; 2: Pre-syncope; Ventricular tachycardia). This includes one pre-syncope and ventricular tachycardia that was observed during placebo and itraconazole treatment periods, respectively. Of these subjects, there were 2 subjects without QTcF measurements and none of the remaining 12 had any QTcF measurements above 480 msec. Furthermore, none of the treatment-emergent AEs were serious and the maximum severity was grade 1 or 2 for the majority (11/14) with no worse than grade 3.*

There were three patients with prolonged QTcF (i.e., QTcF >500 msec or ΔQTcF >60 msec) described in section 4.4.1. Two of the patients had prolonged QTc at isolated visits with most of the remaining QTcF measurements below 480 msec. The last patient had a significantly prolonged QTcF at the last ECG collected on day 11 (1 day after last treatment) of 669 msec (baseline: 414 msec) with all other QTcF measurements on day 1 of 392 – 403 msec.

Overall, there were few QTcF outliers at isolated time-points and the few treatment-emergent AEs that were observed where in the absence of QTc prolongation and generally of mild severity.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Study NIR-DT-103 (Part 1):
ECGs were collected digitally and overread by readers blinded to treatment, but not to time. To address potential concerns over lack of blinding to time, we performed sensitivity analysis using automatic measurements, which resulted in similar results to the overread measurements and the overread measurements are therefore presented in the review.

Study A8641014:
Digital ECGs were not available and paper ECGs were not available for submission. Automatic ECG measurements as provided by the ECG devices at the clinical sites were used for all analysis.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG from Cycle 1 Day 1, Cycle 1 Day 15 to Cycle 1 Day 21 for study A8641014 and Part 1 Day 1 for study NIR-DT-103. For study A8641014, few measurements (less than 10) were collected at most visits after Cycle 1 since each subject might have varied visits. For study NIR-DT-103, Part 1 was prematurely terminated at the end of Period 1 due to a safety concern with rifampin so only Day 1 ECG data was collected. For part 2, the dose of nirogacestat was lower (100 mg) and while there is data when administered with itraconazole that data is difficult to interpret without having a separate itraconazole arm.

The statistical reviewer evaluated the ΔQTcF effect using descriptive parametric statistics.

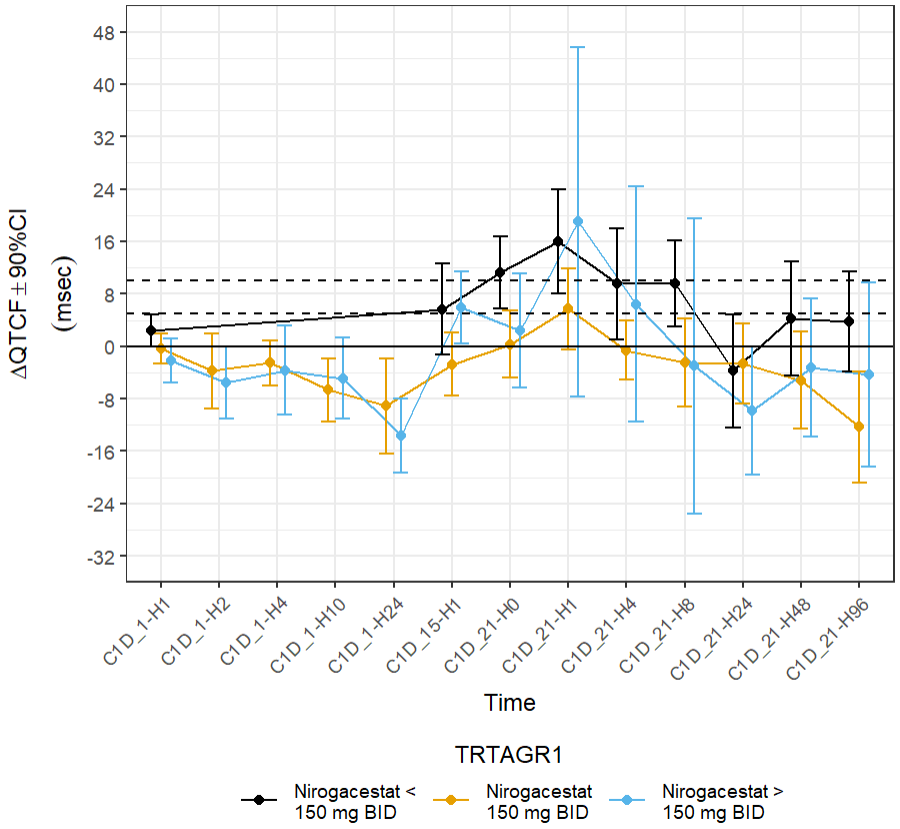
4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups in Study A8641014 and the treatment of Nirogacestat 150 mg in Study NIR-DT-103. The ΔQTcF values by treatment, visit, and time in two studies are shown in Table 4.

An increase in ΔQTcF (i.e., upper bound > 10 msec) was observed for all treatment arms in Study A8641014 at the Cycle 1 Day 21 visits, but not at prior or subsequent visits. In contrast, no increase was observed in NIR-DT-103. The observed increase in Study A8641014 does not appear to be concentration (section 4.5.1) or dose-dependent and could be due to increased variability in this study. For example, in the Nirogacestat >150 mg arm, which had a smaller sample size compared to the other arms, the confidence is wide particularly at Cycle 1 Day 21. At this visit, the subject, (b) (6), experienced QTcF values of 608.3 msec and 532 msec with a change from baseline to be 160 msec and 83.7 msec at Hour 1 and Hour 4 on Cycle 1 Day 21, respectively. The increase in variability in study A8461014 could be due to lack of digitally collected ECGs, which were automatically read (section 4.2).

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

A8641014



NIR-DT-103

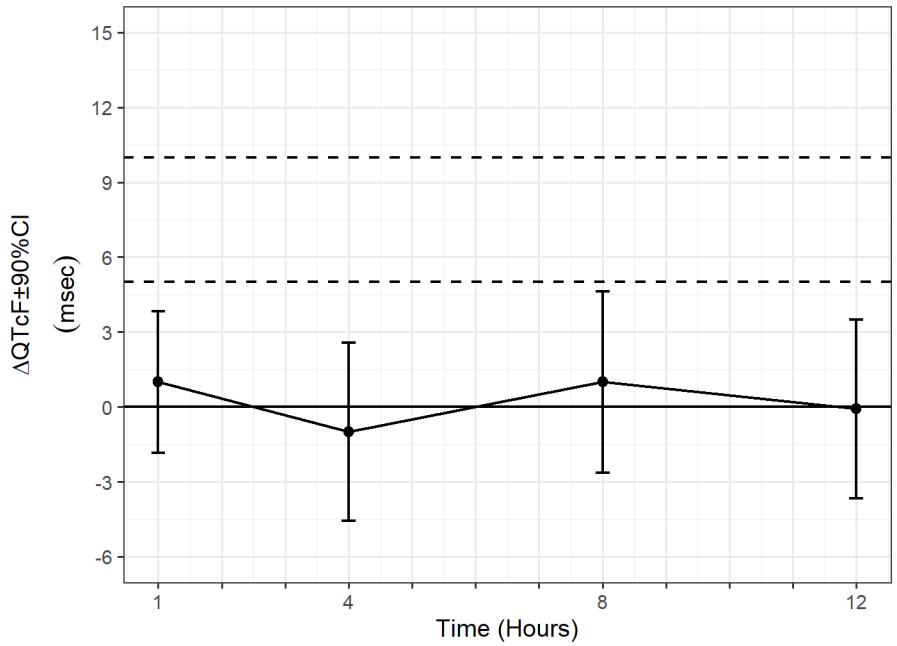


Table 4. Point Estimates and the 90% CIs Corresponding to the Upper Bounds for ΔQTcF by Visit and Time

Study	Actual Treatment	Visit	N	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
A8641014	Nirogacestat < 150 mg BID	C1D_1	21	1.0	2.4	(-0.0 to 4.9)
	Nirogacestat < 150 mg BID	C1D_15	17	1.0	5.6	(-1.3 to 12.6)
	Nirogacestat < 150 mg BID	C1D_21	15	1.0	15.9	(8.0 to 23.9)
	Nirogacestat 150 mg BID	C1D_1	31	1.0	-0.3	(-2.6 to 2.0)
	Nirogacestat 150 mg BID	C1D_15	23	1.0	-2.7	(-7.5 to 2.0)
	Nirogacestat 150 mg BID	C1D_21	20	1.0	5.7	(-0.4 to 11.9)
	Nirogacestat > 150 mg BID	C1D_1	7	4.0	-3.7	(-10.5 to 3.1)
	Nirogacestat > 150 mg BID	C1D_15	13	1.0	5.9	(0.4 to 11.4)
	Nirogacestat > 150 mg BID	C1D_21	11	1.0	19.0	(-7.6 to 45.6)
NIR-DT-103	Nirogacestat 150 mg		25	8.0	1.0	(-2.6 to 4.6)

4.3.1.1 Assay Sensitivity

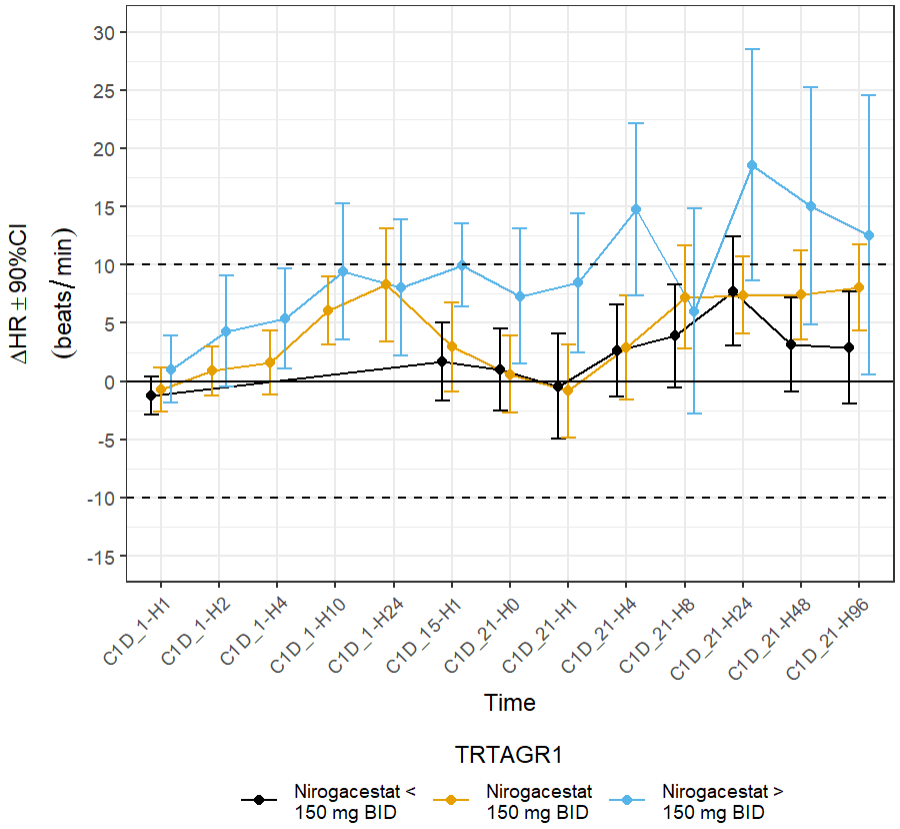
Not applicable.

4.3.2 HR

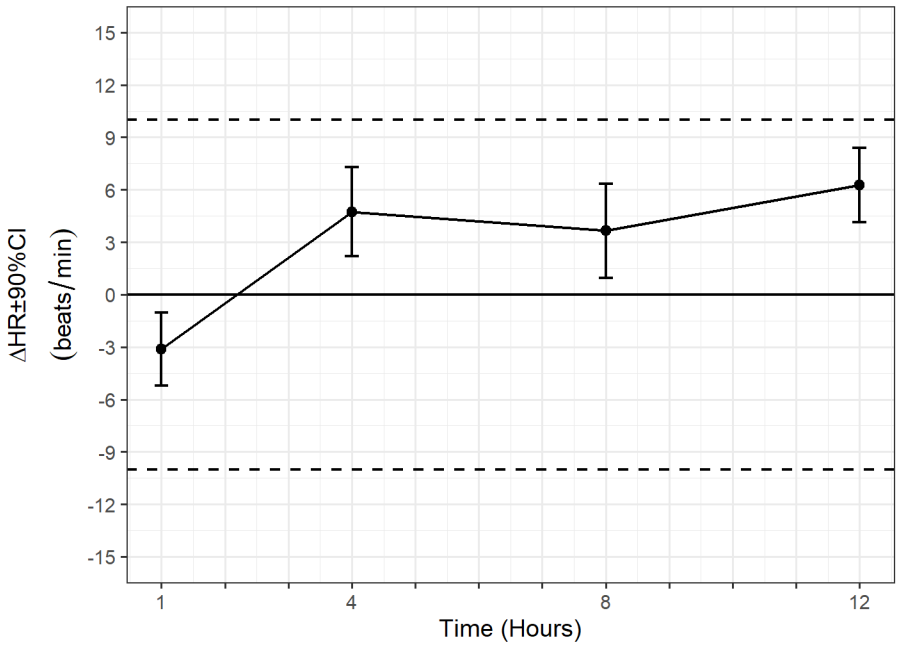
Figure 2 displays the time profile of ΔHR for different treatment groups in Study A8641014 and the treatment of Nirogacestat 150 mg in Study NIR-DT-103.

Figure 2: Mean and 90% CI of ΔHR Time-course

A8641014



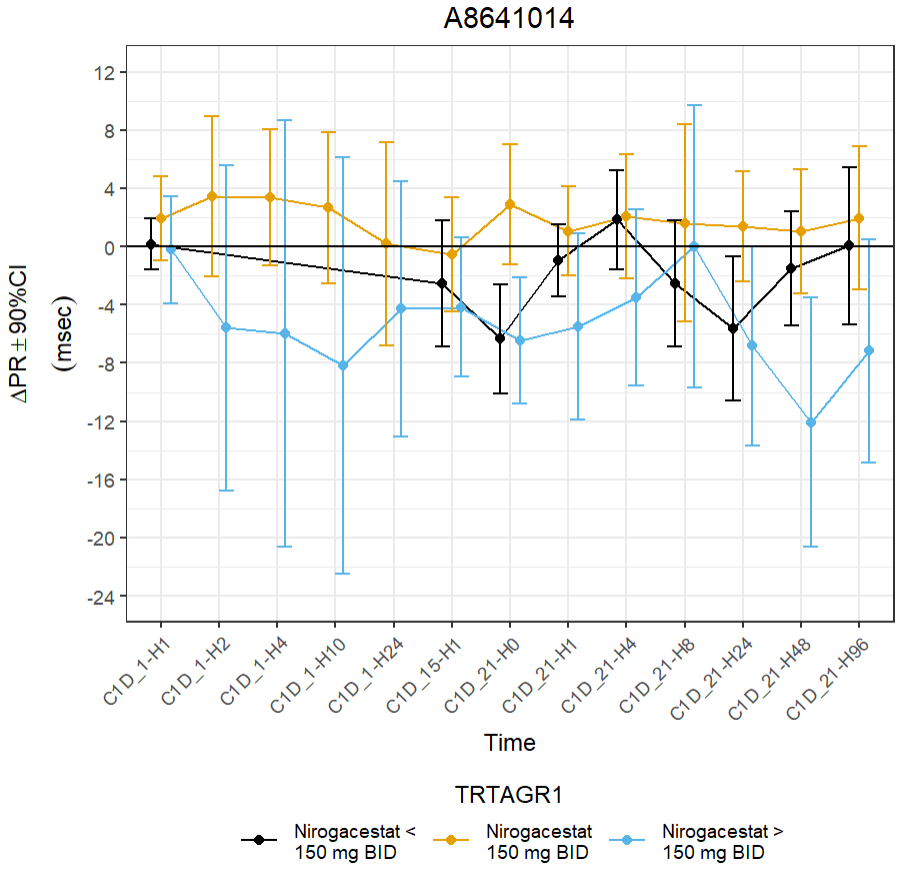
NIR-DT-103



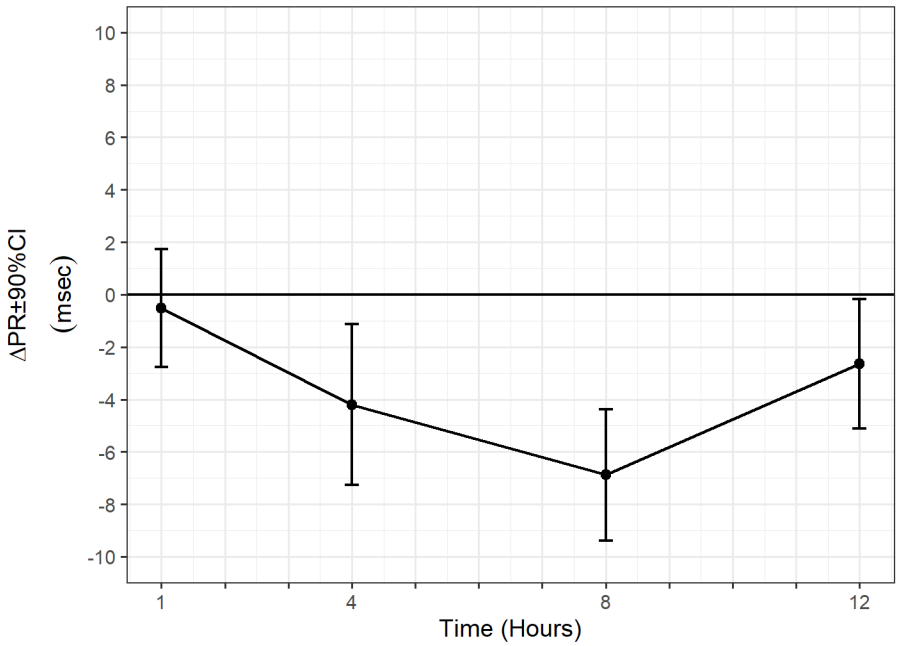
4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups in Study A8641014 and the treatment of Nirogacestat 150 mg in Study NIR-DT-103.

Figure 3: Mean and 90% CI of ΔPR Time-course



NIR-DT-103

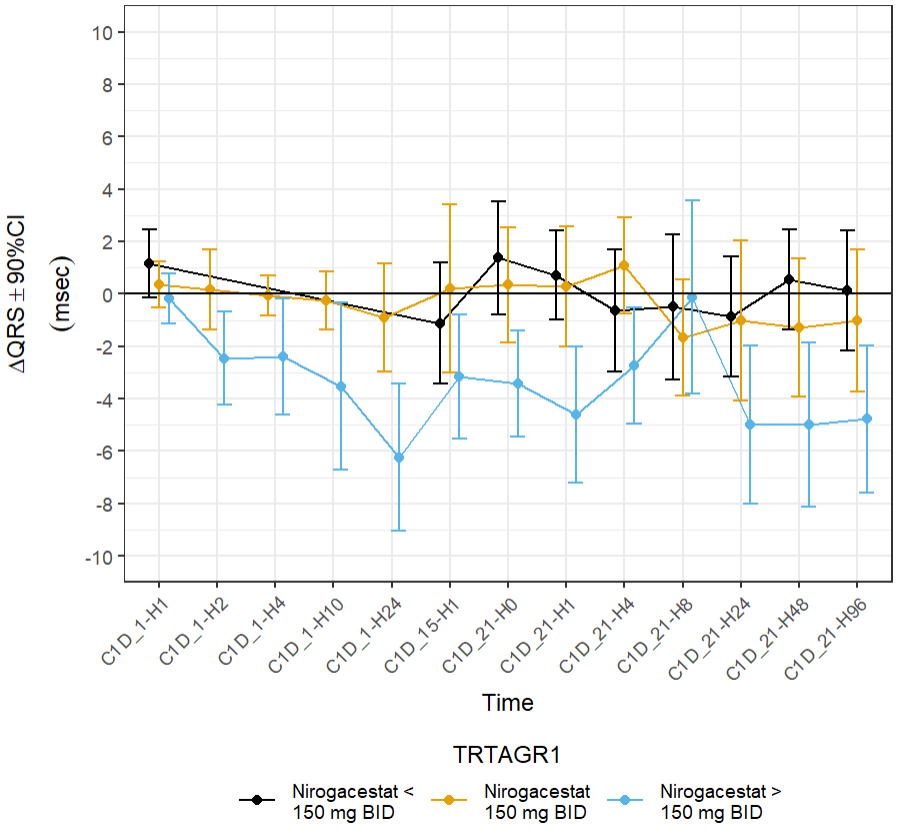


4.3.4 QRS

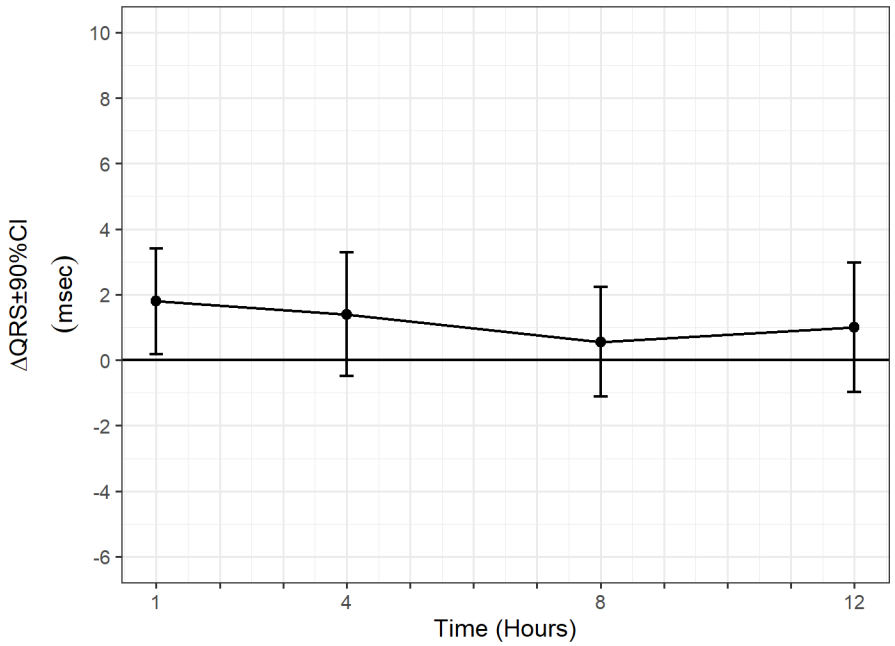
Figure 4 displays the time profile of ΔQRS for different treatment groups in Study A8641014 and the treatment of Nirogacestat 150 mg in Study NIR-DT-103.

Figure 4: Mean and 90% CI of ΔQRS Time-course

A8641014



NIR-DT-103



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 5 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec with a change from baseline >60 msec.

For the treatment of Nirogacestat <150 mg BID and Nirogacestat >150 mg BID in Study A8641014, there were 3subjects ([(b) (6)] with the treatment of 80 mg BID and [(b) (6)] with the treatment of 220 mg BID) who experienced QTcF values >500 msec with a change from baseline >60 msec.

There were no subjects who experienced QTcF >450 msec in Study NIR-DT-103.

Table 5. Categorical Analysis for QTcF (maximum)

Study	Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
A8641014	Nirogacestat < 150 mg BID	22	483	18 (81.8%)	424 (87.8%)	2 (9.1%)	56 (11.6%)	1 (4.5%)	2 (0.4%)	1 (4.5%)	1 (0.2%)
	Nirogacestat 150 mg BID	31	494	22 (71.0%)	446 (90.3%)	8 (25.8%)	46 (9.3%)	1 (3.2%)	2 (0.4%)	0 (0%)	0 (0%)
	Nirogacestat > 150 mg BID	19	299	15 (78.9%)	287 (96.0%)	2 (10.5%)	9 (3.0%)	0 (0%)	0 (0%)	2 (10.5%)	3 (1.0%)
NIR-DT-103	Nirogacestat 150 mg	25	100	25 (100.0%)	100 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 6 lists the categorical analysis results for ΔQTcF (<30 msec, >30 and <60, and >60 msec). For the treatment of Nirogacestat <150 mg BID and Nirogacestat >150 mg BID in Study A8641014, there were 3 subjects ([(b) (6)] with the treatment of 80 mg BID and [(b) (6)] with the treatment of 220 mg BID) who experienced ΔQTcF values >60 msec. There were no subjects who experienced ΔQTcF >60 msec in Study NIR-DT-103.

Table 6. Categorical Analysis for ΔQTcF (maximum)

Study	Actual Treatment	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
A8641014	Nirogacestat < 150 mg BID	22	483	16 (72.7%)	460 (95.2%)	5 (22.7%)	22 (4.6%)	1 (4.5%)	1 (0.2%)
	Nirogacestat 150 mg BID	31	494	30 (96.8%)	493 (99.8%)	1 (3.2%)	1 (0.2%)	0 (0%)	0 (0%)
	Nirogacestat > 150 mg BID	19	299	15 (78.9%)	293 (98.0%)	2 (10.5%)	3 (1.0%)	2 (10.5%)	3 (1.0%)
NIR-DT-103	Nirogacestat 150 mg	25	100	25 (100.0%)	100 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.4.2 HR

Table 7 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). For the treatment of Nirogacestat <150 mg BID, Nirogacestat 150 mg BID, and Nirogacestat >150 mg BID in Study A8641014, there were 4, 9, and 4 subjects who experienced HR values >100 beats/min, respectively.

There were no subjects who experienced HR >100 beats/min in Study NIR-DT-103.

Table 7. Categorical Analysis for HR (maximum)

Study	Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
A8641014	Nirogacestat < 150 mg BID	22	483	18 (81.8%)	475 (98.3%)	4 (18.2%)	8 (1.7%)
	Nirogacestat 150 mg BID	31	494	22 (71.0%)	474 (96.0%)	9 (29.0%)	20 (4.0%)
	Nirogacestat > 150 mg BID	19	299	15 (78.9%)	284 (95.0%)	4 (21.1%)	15 (5.0%)
NIR-DT-103	Nirogacestat 150 mg	25	100	25 (100.0%)	100 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

There were no subjects who experienced PR values >220 msec with 25% increase over baseline in both studies.

4.4.4 QRS

There were no subjects who experienced QRS values >120 msec with 25% increase over baseline in both studies.

4.5 EXPOSURE-RESPONSE ANALYSIS

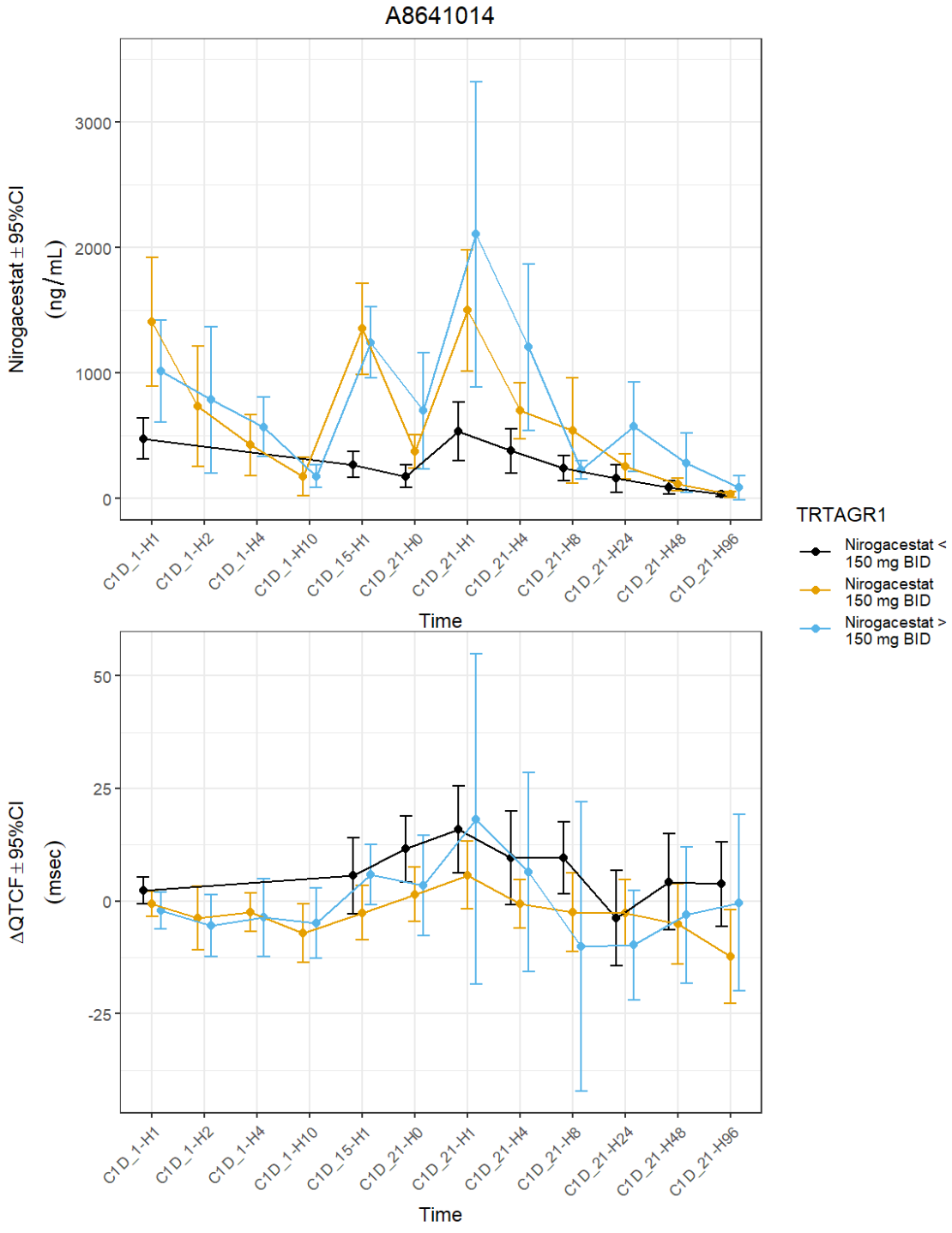
Separate exposure-response analyses were conducted for studies A8641014 and NIR-DIT-103. Each analysis included all subjects with baseline and at a least one post-baseline ECG, with time-matched PK from Cycle 1 Day 1, Cycle 1 Day 15 to Cycle 1 Day 21 for study A8641014 and Part 1 Day 1 for study NIR-DT-103, please see section 4.3 for additional details.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. As described in section 4.3.1, the figure shows absence of dose-dependent ΔQTcF and wide 95% CI at some time points due to high data variability and small sample size. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

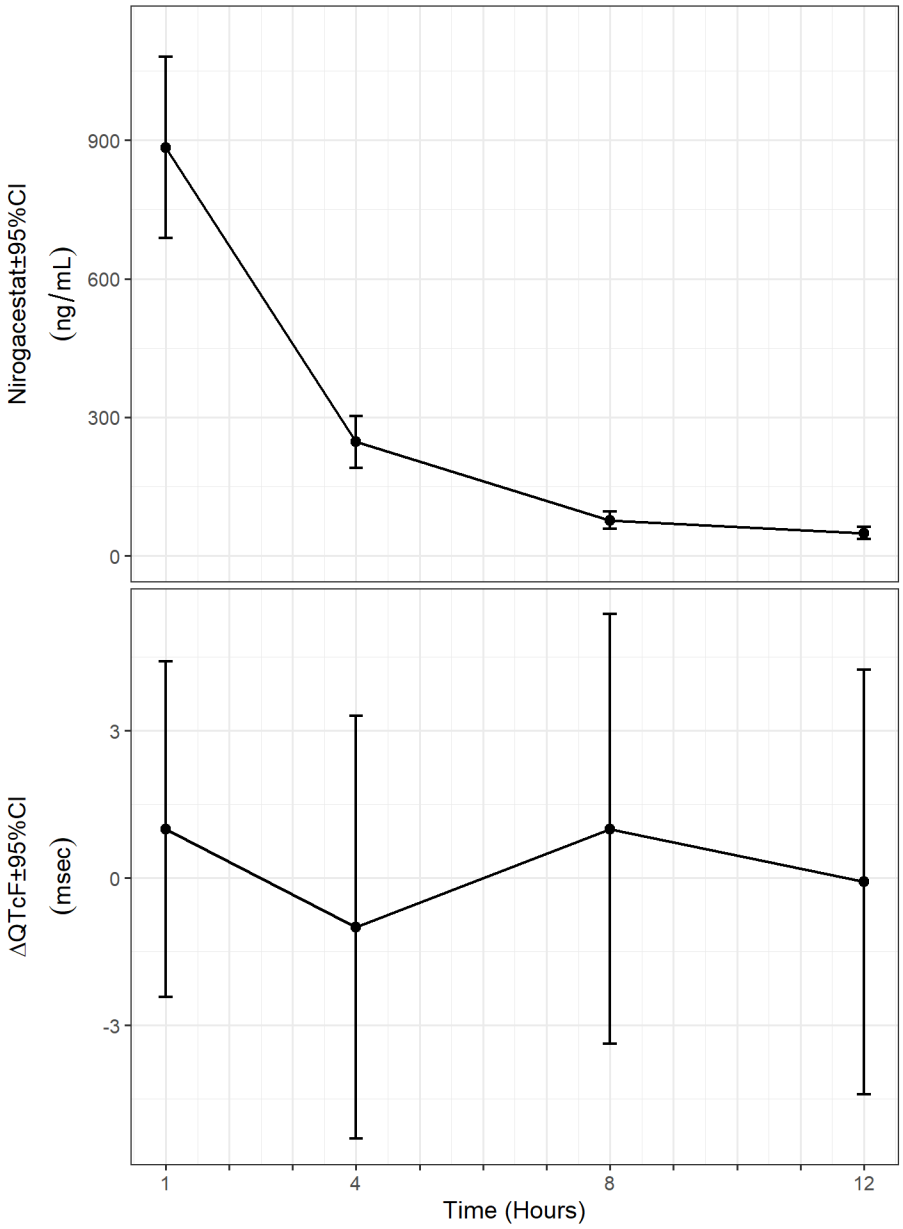
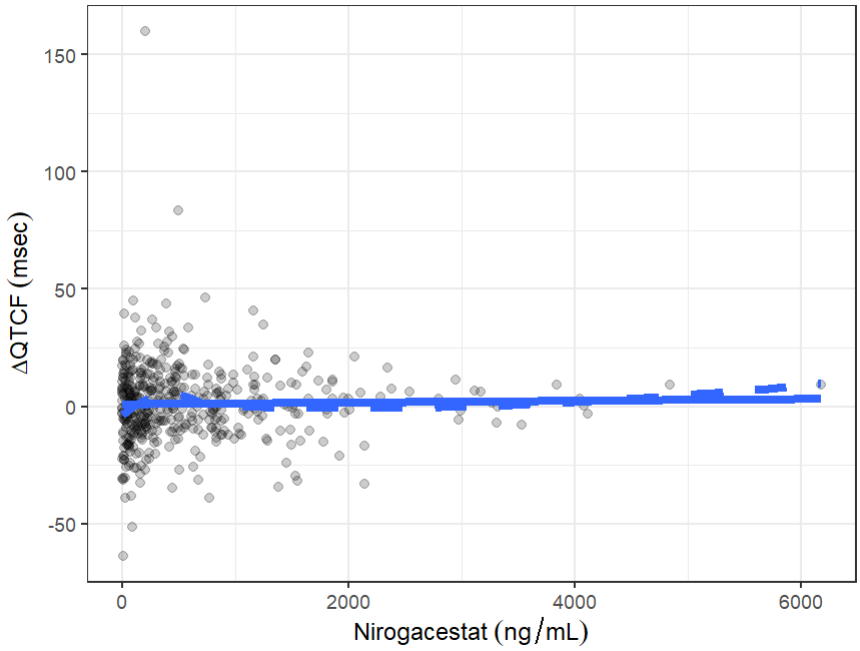
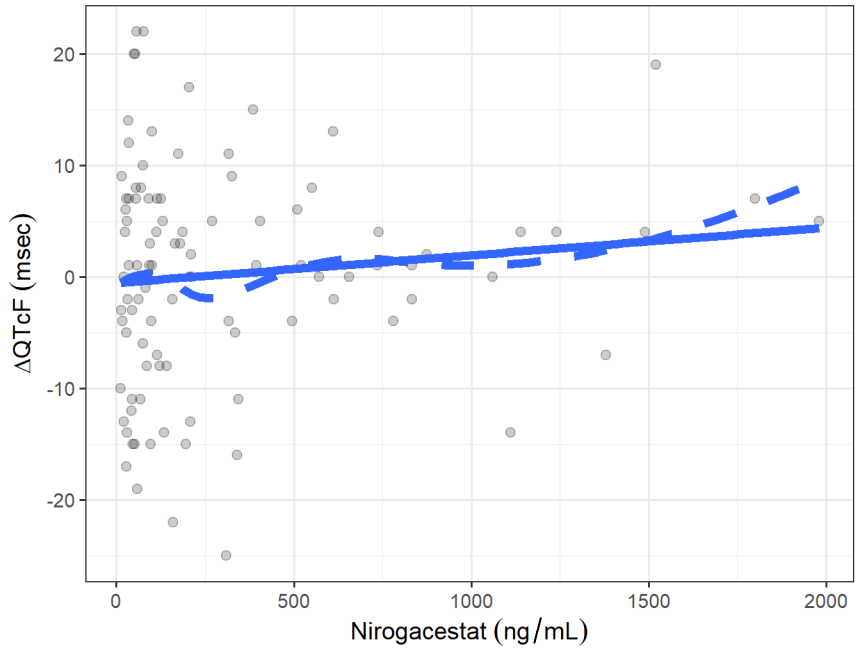


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship

A8641014



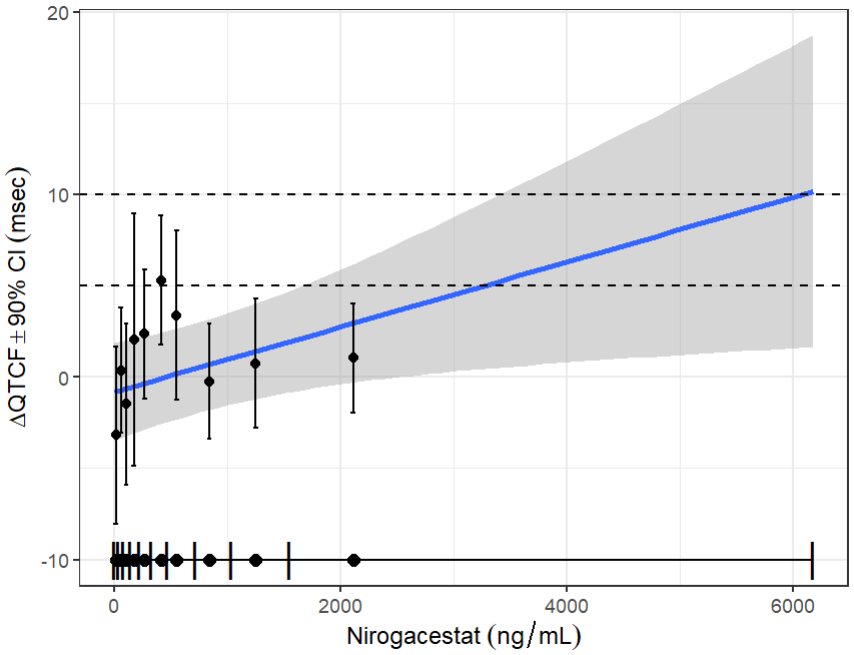
NIR-DT-103



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7 with similar results for the two studies. Predictions from the concentration-QTcF model are provided in Table 8 based on study NIR-DT-103 because that study had high-quality ECGs.

Figure 7: Goodness-of-fit Plot for QTcF

A8641014



NIR-DT-103

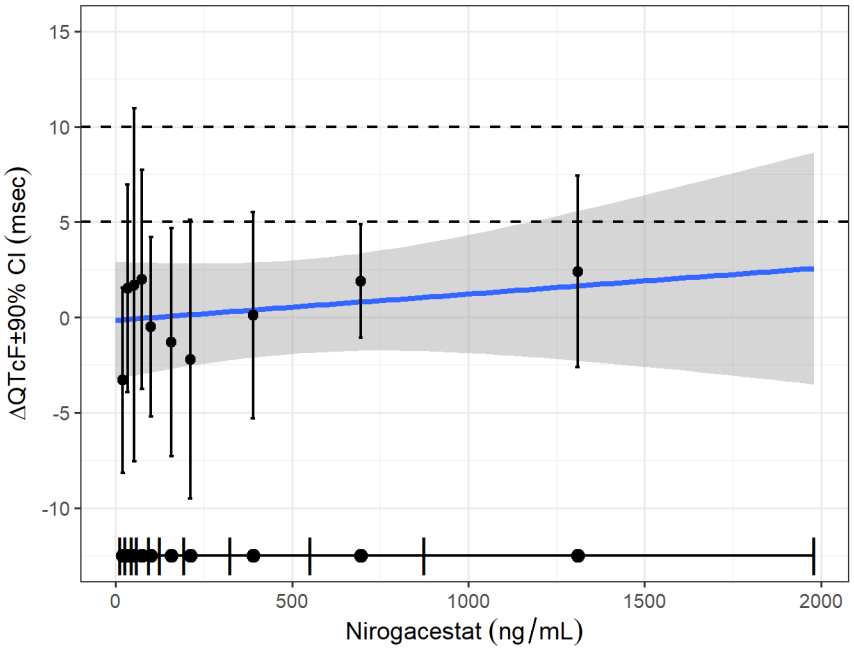


Table 8. Predictions from Concentration-QTcF Model developed using PK/ECG data from study NIR-DT-103

Study	Actual Treatment	Nirogacestat (ng/mL)	ΔQTcF (msec)	90.0% CI (msec)
NIR-DT-103	Nirogacestat 150 mg (Estimated steady state Cmax)	675	0.8	(-1.8 to 3.3)
NIR-DT-103	Nirogacestat 150 mg (Estimated high clinical Cmax)	1687.5	2.2	(-2.9 to 7.3)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 31, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 217677
Product Name, Dosage Form, and Strength:	Ogsiveo (nirogacestat) tablet, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	SpringWorks Therapeutics
FDA Received Date:	December 27, 2022; March 17, 2023
TTT ID #:	2022-3189
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ogsiveo (nirogacestat) tablet, the Division of Oncology 3 (DO3) requested that we review the proposed Ogsiveo prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E—NA
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), Patient information, container labels, and carton labeling for Ogsiveo to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI, Patient information, and the proposed container label and carton labeling. We provide our recommendations to DO3 in section 4.1 and to Springworks Therapeutics in section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

The Ogsiveo PI, Patient Information, Container label and Carton Labeling can be improved for clarity and safety.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Highlights of Prescribing information

    a. To Dosage and Administration section clarify that the 150 mg dose is "(3 tablets)" to emphasize the quantity of tablets required per dose

    b. Add the following statements to facilitate the retrieval of pertinent information and align with Full Prescribing Information
        i. "See Full Prescribing Information for dosing modifications due to adverse events (2.2) or drug-interactions (2.3)"
        ii. "Avoid starfruit, Seville oranges, grapefruit, and juice of these fruits when taking OGSIVEO (2.3)"
        iii. "Continue treatment until disease progression or unacceptable toxicity."

2. Full Prescribing Information

    a. Dosage and Administration Section

        i. To simplify, delete (b) (4) and revise to "3 tablets" to clarify the quantity required per dose.

        ii. To the modified dose of 100 mg, add "(2 tablets)"

3. How Supplied/Storage and Handling Section

    a. Add statement "Keep out of reach of children" to match the carton and container labeling.

B. Patient Information

1. This statement (b) (4) can be deleted as there is no such section in the Patient Information.

4.2 RECOMMENDATIONS FOR SPRINGWORKS THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Revise (b) (4) on the side panel to "Recommended Dosage: See Prescribing Information" for consistency with the prescribing information.

2. As currently presented, the format for the expiration date is MM/YYYY. Confirm if you intend to use numerical or alphabetical characters to represent the month.

FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[a]

B. Container Labels

1. The linear barcode is missing on the Ogsiveo Container label. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).[b] Ensure there is sufficient blank space surrounding the barcode to allow the barcode to be scanned correctly in accordance with 21 CFR 201.25(c)(i).

[a] Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers | FDA

[b] Guidance: Bar Code Label Requirements Questions and Answers, August 2011

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ogsiveo received on December 27, 2022 from SpringWorks Therapeutics.

Table 2. Relevant Product Information for Ogsiveo	
Initial Approval Date	NA
Active Ingredient	nirogacestat
Indication	OGSIVEO is a gamma secretase inhibitor indicated for the treatment of adults with desmoid tumors.
Route of Administration	Oral
Dosage Form	tablet
Strength	50 mg
Dose and Frequency	150 mg by mouth twice daily
How Supplied	OGSIVEO is supplied as orange, film-coated 50 mg tablets. Each 50 mg tablet is debossed with a "50" on one face. Nirogacestat is available in bottles of (b) (4) 180 tablets (NDC # 82448-050-18).
Storage	Store at 20°C-25°C (68°F-77°F). Excursions permitted between 15°C-30°C (59°F-86°F).
Container Closure	Child resistant, (b) (4) opaque push-lock closures.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 17, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, nirogacestat. Our search identified no previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Ogsiveo labels and labeling submitted by SpringWorks Therapeutics.

- Container label received on December 27, 2022
- Carton labeling received on December 27, 2022
- Prescribing Information (Image not shown) received on December 27, 2022, available from \\CDSESUB1\EVSPROD\nda217677\0005\m1\us\ogsiveo-final-fpi-v0-3-dec-9.docx

F.2 Label and Labeling Images

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical consultation

From:	Stephen Voss M.D., Clinical Reviewer, OCHEN/DGE
Through:	Shannon Sullivan M.D., Clinical Team Lead, OCHEN/DGE
To:	Kristen Snyder M.D., Clinical Reviewer for Safety, OCE/DO3
	Autumn Zack-Taylor MS, SRPM, OCE/DO3
Subject:	Potential skeletal toxicity of nirogacestat therapy for desmoid tumors (NDA 217677)

Background:

Desmoid tumors (DTs), also known as aggressive fibromatosis, are a rare subtype of soft tissue sarcoma which are slow growing and do not metastasize but may cause significant morbidity by local invasion. DTs may present at any age beginning at birth and are most common in young adults; about 5-10% of cases are in pediatric patients. The clinical course of DTs is highly variable and treatment is individualized; patients with evidence of progression or worsening symptoms may undergo surgery and/or radiation, but recurrence is common. There are no FDA approved treatments.

Nirogacestat (Ogsiveo) is an oral inhibitor of gamma secretase (GS), an enzyme required for the Notch signaling pathway, which has been implicated in the pathogenesis of multiple tumor types, including DTs. Based on adult studies, NDA 217677 was recently submitted by the Applicant (SpringWorks Therapeutics) for the treatment of DTs in adults. A pediatric study (see below) is ongoing and the results are planned to be submitted post-approval, as described in an agreed iPSP (IND 138207, 04/25/22). Because Notch and gamma secretase play key roles in the early development of multiple organ systems, the iPSP includes a planned request for waiver of studies in patients <24 months of age.

In toxicology studies, growth plate changes in the femorotibial joints of rats (increased physeal cartilage thickening and retention of the hypertrophic zone) were seen with nirogacestat and also with avagacestat, another GS inhibitor. Such effects may be related to interactions of Notch signaling with Wnt components, specifically β-catenin; effects of Notch and Wnt in regulating chondrogenesis; and/or the role of GS in angiogenesis.

DGE is requested to review the potential for skeletal growth issues with nirogacestat in skeletally immature children and provide guidance on appropriate monitoring in future pediatric studies.

Pediatric clinical experience

Study ARST1921, the first pediatric study of nirogacestat, is being conducted by the Children's Oncology Group (COG) under IND (b) (4) in collaboration with the NDA Applicant. This is a single-arm efficacy and safety study of nirogacestat monotherapy in children and adolescents ages >24 months to <18 years with progressing DTs that are deemed not amenable to surgery.

Patients are treated with open label nirogacestat 90 mg/m^2 BID, which is estimated to be equivalent to the adult dose of 150 mg BID. Treatment continues until there is evidence of tumor progression or unacceptable toxicity. Patients are to be followed for 2 years to evaluate the 2-year progression-free survival (PFS) rate.

Per the original protocol submitted on 10/22/19, height and weight are measured at the beginning of each 4-week treatment cycle; there are no detailed instructions pertaining to these measurements. Tanner stage is recorded every 6 cycles (i.e., every 24 weeks). Because of the growth plate abnormalities seen in nonclinical studies, plain AP radiograph of bilateral proximal tibial growth plates is obtained at baseline and, if growth plates are open, repeated every 24 weeks. Patients with evidence of growth plate thickening or other changes are to undergo further evaluation including knee MRI and, according to investigator judgment, orthopedic consultation, more frequent x-ray follow-up and/or discontinuation of treatment. Hand/wrist x-rays for bone age assessment are not conducted routinely.

Study enrollment began in Sept 2020. As of July 2022, 26 patients had enrolled out of the planned total of 35 patients. The median age is 14 years (range 2-17 years); 18 patients (69%) are male.

Safety reports were submitted on 07/05/22 and 07/29/22 (to IND (b) (4) regarding a 13-year-old female with DT of the thigh who experienced numerous complications. At baseline (age 11 yrs/ 9 mos), radiographs showed normal open tibial growth plates and there was no limb length discrepancy by scanogram. After 6 treatment cycles, there was abnormal physeal widening bilaterally (radiograph and MRI) and the right leg was 1.5 cm longer than the left. After 5 additional treatment cycles, physeal widening persisted and the leg length discrepancy was 1.9 cm, resulting in treatment discontinuation. Follow-up x-rays 2-4 months later showed resolution of the physeal widening. Eight months after stopping treatment, leg length discrepancy persisted, but the patient had grown 10 cm in height since starting treatment 18 months earlier. The patient also sustained a sports-related left femoral neck fracture during treatment and whole body BMD Z-score (DXA) was borderline low (-1.0). Other potential confounding factors for this patient were prior treatment for the right thigh DT with sorafenib, a tyrosine kinase inhibitor, and other TEAEs including diarrhea, oral mucositis, weight loss and anorexia.

Another subject in study ARST1921, an 11 y/o female, developed hip pain and a slipped capital femoral epiphysis (SCFE) after about 9 months of study treatment. There was no history of injury, and the event was considered possibly related to obesity (a known risk factor for SCFE in

adolescents), but the patient also had abnormal physeal widening, thus a role for nirogacestat could not be ruled out. The patient continued treatment at a reduced dose and remained on treatment one year later.

Because of these reports, Children's Oncology Group reviewed growth plate data from the study. Out of 25 patients treated, 19 had open growth plates at baseline, and 14 of those have had follow-up tibial X-rays after 6-12 months of treatment. Ten of the 14 patients with follow up x-ray data had not developed any growth plate changes. In addition to the two patients described above, two others had asymptomatic changes in the tibial growth plate: a 7 y/o male with interval physeal widening, which improved off treatment after 1 year; and an 11 y/o male with growth plate lucencies, which improved during continued treatment. Except for the patient described above, there have been no additional reports of limb length discrepancy.

Apart from study ARST1921, about 10 pediatric patients have received nirogacestat for DTs in a Compassionate Use Program. Among these, the Applicant identified two patients with relevant events; each of these patients had previously undergone extensive systemic treatment for their DT.

- An 11 y/o male with distal femur fracture was found to have widening of epiphyseal growth plates in the knee (injury site) and shoulder (tumor site) about 5 months after starting treatment with nirogacestat.
- An 11 y/o male experienced pain in the hip about 2 years after starting treatment with nirogacestat and MRI showed evidence of osteonecrosis of the femoral head; treatment was discontinued.

Based on these reports, the Applicant has designated epiphyseal disorder as an important potential risk for pediatric patients, and COG has amended the study ARST1921 protocol as follows, following FDA recommendations:

- Exclusion criteria regarding presence of a non-healing fracture or steroid use were added.
- Tibial X-ray frequency was increased from every 6 cycles to every 3 cycles during the first 12 cycles of treatment, then every 6 cycles thereafter.
- Premature closure of the growth plate was designated as a DLT [defined as female <12 years or male <14 years with fused tibia growth plates, and bone age (wrist) >14 years (female) or >16 years (male), and no history of precocious puberty].
- Retrospective central review of all growth plate imaging is performed.
- Grade 2 fracture or osteonecrosis was designated a DLT.
- Enrollment will be suspended if ≥ 4 bone abnormality events (premature growth plate closure, fracture or osteonecrosis) are observed.
- Additional language about potential bone toxicity was added to the Informed Consent document.

This study is ongoing and, except for the IND safety reports, no clinical data (e.g., height, weight, Tanner stage) have been submitted.

Summary/conclusion

Although the cases described in IND safety reports are possibly confounded by other systemic treatments for DT, the evidence supports an association of nirogacestat with growth plate abnormalities in pediatric patients. The observed radiographic findings of growth plate widening appear to be consistent with effects on physeal cartilage seen in animal studies, and with the role of Notch signaling in chondrogenesis. Potentially, this could result in impaired or disproportionate growth. Of note, one adolescent subject in study ARST1921 developed a leg length discrepancy, although other factors may have contributed, including a hip fracture and the DT tumor mass in the contralateral thigh. Treatment-related growth plate disorders may also lead to increased susceptibility to fractures or osteonecrosis. In addition, bone growth and development could be affected adversely by effects of nirogacestat on ovarian function in adolescents.

The ongoing pediatric study may clarify these safety concerns. Any future pediatric studies will require close monitoring of growth and growth plates. We would recommend that sponsors refer to the draft guidance Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials (Nov. 2022), especially in regard to methodology for height assessments (e.g., use of wall mounted stadiometry, triplicate measurements, etc.).

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