

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217677Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 138207

MEETING MINUTES

SpringWorks Therapeutics, Inc.
Attention: Candice Durrence, M.S., R.A.C.
Senior Consultant, Regulatory Affairs
Halloran Consulting Group
22 Thomson Place
Boston, MA 02210

Dear Ms. Durrence:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nirogacestat.

We also refer to the teleconference between representatives of your firm and the FDA on August 23, 2022. The purpose of the meeting was to discuss the content and format of the proposed NDA submission for the product nirogacestat.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Autumn Zack-Taylor, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Meeting Minutes

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 23, 2022; 9:00AM-10:00AM EST
Meeting Location: Teleconference

Application Number: IND 138207
Product Name: Nirogacestat (PF-03084014)

Indication: Treatment of adult patients with desmoid tumors
Sponsor Name: SpringWorks Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Autumn Zack-Taylor, M.S.

FDA ATTENDEES

Paul Kluetz, M.D., Supervisory Associate Director, OCE
Steven Lemery, M.D., M.H.S., Director, OOD/DO3
'Lola Fashoyin-Aje, M.D., M.P.H., Deputy Director, OOD/DO3
Jamie Brewer, M.D., Clinical Team Leader (Acting), OOD/DO3
Leslie Doros, M.D., Clinical Team Leader, OOD/DO3
Joyce Cheng, Ph.D., Statistics Team Leader, OB/DBV
Jiaxin Fan, Ph.D., Statistics Reviewer, OB/DBV
Jason Moore, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPII
Hongfei Zhang, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPII
Lars Johannesen, Ph.D., Clinical analyst, Interdisciplinary Review Team for Cardiac Safety Studies, OCHEN/DCN
Matthew Thompson, Ph.D., Nonclinical Team Leader, OOD/DHOT
Alexander Putman, Ph.D., Nonclinical Reviewer, OOD/DHOT
Yasmin Choudhry, M.D., Clinical Outcome Assessment Reviewer, ODES/DCOA
Amy Chung, Senior Regulatory Health Project Manager, OSE/PMS
Autumn Zack-Taylor, M.S., Senior Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES

L. Mary Smith, Ph.D., Chief Development Officer

(b) (4)

Renu Vaish, Senior Vice President, Head of Regulatory Affairs
Candice Durrence, M.S., R.A.C., Senior Consultant, Regulatory Affairs, Halloran Consulting Group
Allison Lim, Pharm.D., Senior Director, Clinical Research

Todd Shearer, Ph.D., Vice President, Clinical Pharmacology
Rex Williams, Ph.D., Associate Director, Clinical Pharmacology

(b) (4)

BACKGROUND

Regulatory

On March 21, 2018, a Type B, Pre-IND/End of Phase 2 (EOP2) meeting was held between the Division of Oncology Products 2 (DOP2) and SpringWorks Therapeutics, Inc. (SpringWorks) to discuss the design and endpoints of Study NIR-DT-301.

On June 7, 2018, nirogacestat received Orphan Drug Designation for the treatment of desmoid tumors (Orphan Drug Designation #18-6365).

On September 28, 2018, SpringWorks submitted an original Investigational New Drug Application (IND) for nirogacestat for the treatment of patients with desmoid tumors. The IND went into effect on October 23, 2018.

On October 26, 2018, a Type C, Guidance meeting was held between DOP2 and SpringWorks to discuss the ongoing development and use of two desmoid tumor patient reported outcome (PRO) instruments: the MSK/DTRF Desmoid Tumor Symptom Scale (DTSS) and the MSK/DTRF Desmoid Tumor Impact Scale (DTIS), as fit-for-purpose tools (b) (4). These instruments include a desmoid tumor symptom assessment and a desmoid tumor impact assessment.

On November 1, 2018, Fast Track designation was granted for the investigation of nirogacestat for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis, to demonstrate a statistically robust and clinically meaningful effect on progression-free survival (PFS) as assessed by blinded independent review, in a randomized, placebo-controlled trial(s).

On April 24, 2019, a Type C, Guidance meeting was held between DOP2 and SpringWorks to discuss the planned interim analysis for Study NIR-DT-301.

On August 28, 2019, SpringWorks was granted Breakthrough Therapy designation for nirogacestat for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis.

On November 21, 2019, a Pre-NDA, Chemistry, Manufacturing and Controls (CMC) meeting was held to discuss certain aspects of the starting materials for manufacture of nirogacestat hydrobromide for the proposed NDA submission.

On July 13, 2020, a Type B, Guidance meeting was held between the Division of Oncology 2 (DO2) and SpringWorks to confirm the studies that will comprise the clinical pharmacology data package for the original nirogacestat NDA submission.

On September 22, 2020, DO2 issued a Type B, Guidance, Written Responses Only providing advice on the proposed Protocol NIR-DT-302 (DeFi Morbidity [DeFi M]).

On November 19, 2020, a Type B, Initial Breakthrough Therapy meeting was scheduled to be held between DO2 and SpringWorks to discuss the multidisciplinary comprehensive strategy of the nirogacestat development program, including planned clinical trials and plans for expediting the manufacturing development. On November 17, 2022, SpringWorks requested cancellation of the November 19, 2020, meeting because the FDA's responses with the November 13, 2020, preliminary comments were clear.

On January 22, 2021, a Type B, Guidance meeting was held between DO2 and SpringWorks to gain alignment on the proposed amendment to Protocol NIR-DT-301 (DeFi), the Statistical Analysis Plan (SAP), and the Psychometric Analysis Plan (PAP).

On January 25, 2021, the IND 138207 application was administratively transferred from DO2 to the Division of Oncology 3 (DO3).

On August 2, 2021, DO3 issued Type B, Guidance, Written Responses Only to discuss various topics in anticipation of the NDA filing for nirogacestat.

An Agreed Initial Pediatric Study Plan was issued on April 25, 2022, with a plan to request a partial waiver for the subset of pediatric patients from birth to less than 24 months of age, and to request a deferral for the submission of results from the pediatric study ARST1921.

Real-time Oncology Review (RTOR) was granted on June 3, 2022. The pre-submission timeline was submitted to NDA 217677 on July 14, 2022, with the first RTOR submission. The final of four submissions are planned for December 2022.

On June 15, 2022, SpringWorks submitted a Type B, Pre-BLA meeting request to gain the Agency's agreement that the top-line efficacy results from Study NIR-DT-301 (DeFi) to support an NDA submission for nirogacestat in the proposed indication and to obtain the Agency's feedback on the content and format of the proposed NDA.

Nonclinical

SpringWorks states that nirogacestat (PF-03084014) is a small molecule inhibitor of gamma secretase. To support the proposed NDA, the nonclinical package includes 3-month repeat-dose toxicity studies in rats and dogs, a full battery of genetic toxicology

studies, and a pilot embryofetal developmental toxicity study in rats. SpringWorks also conducted a 6-month carcinogenicity study in transgenic rasH2 mice.

Clinical

Study NIR-DT-301 (DeFi) is a multicenter, randomized, double-blind, placebo-controlled study designed to compare the efficacy, safety and tolerability of nirogacestat and placebo in adult patients with progressing desmoid tumors (DF)/aggressive fibromatosis (AF). The study consisted of a double-blind and an optional open-label extension (OLE) phase. The study randomized 142 patients (1:1) to nirogacestat 150 mg twice daily administered on 28-day cycles or placebo. Enrollment was stratified by target tumor location (intra-abdominal or extra-abdominal). The primary study endpoint was progression free survival (PFS), and the analysis of PFS included radiographic progression and clinical progression events that were adjudicated by an endpoint adjudication committee (EAC). Radiographic progression was assessed by blinded independent central review (BICR) per Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1. Clinical progression events were 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/AF.

Secondary endpoints included BICR-overall response rate (ORR) per RECIST v1.1, duration of response (DOR), safety, and patient reported outcomes (PRO) measures. Patients were eligible to participate in the OLE phase of the study if they experienced progression on study or if their treatment was ongoing at the end of the of the double-blind phase and if they met the eligibility criteria for the OLE phase.

The study ended April 7, 2022, after 49 of the initially targeted 51 PFS events had occurred. The study met its primary endpoint of PFS with a HR of 0.29 (95% CI: 0.15, 0.55).

	Nirogacestat (N=70)	Placebo (N=72)
Number of patients with event	12 (17%)	37 (51%)
Type of Event:		
Progression	12 (17%)	36 (50%)
Radiographic progression	11 (16%)	30 (42%)
Qualified clinical progression	1 (1%)	6 (8%)
Death before progression	0	1 (1%)
Hazard Ration (95% CI)	0.29 (0.15, 0.55)	
p-value	<0.001	

Source: Table adapted from Meeting Briefing Document (Table 10, Page 42).

Nirogacestat also demonstrated a statistically significant improvement in ORR compared to placebo (41% vs 8%). Of the 24 responders on the nirogacestat arm, 5 experienced a complete response.

In addition, all PROs in the testing hierarchy were statistically significant measuring the mean change from baseline at the pre-specified time point of Cycle 10, including BPI-SF Average Pain Intensity (API) score, Desmoid Tumor Symptom Scale (DTSS) Total Symptom Score, Desmoid Tumor Impact Scale (DTIS) Physical Functioning Domain Score, EORTC QLQ-C30 Global health status/Quality of life (GHS/QoL), EORTC QLQ-C30 Physical Functioning, and EORTC QLQ-C30 Role Functioning.

Grade ≥ 3 treatment emergent adverse events (TEAEs) were reported by 39 patients (57%) in the nirogacestat arm and 11 patients (15%) in the placebo arm. The most frequently reported ($>5\%$) Grade ≥ 3 TEAEs in the nirogacestat arm were diarrhea (16% vs 1%), folliculitis (6% vs 0%), and maculo-papular rash (6% vs 0%). The most common adverse events (AEs) resulting in the discontinuation of study treatment included diarrhea (n=4), premature menopause (n=3), alanine transaminase (ALT) increased (n=3), and aspartate aminotransferase (AST) increased (n=2). Ovarian dysfunction events (including menopause, premature menopause, ovarian failure and amenorrhea) are considered an AE of special interest and were observed in 27 (75%) of women of childbearing potential (WOBCP) who received nirogacestat. Follow up through July 11, 2022, found that 9 patients of the 27 patients experienced resolution of the ovarian dysfunction while on study drug, 11 patients experienced resolution following treatment discontinuation, 5 did not experience resolution but remained in treatment in the OLE, and 2 were lost to follow up.

SpringWorks proposes an Integrated Safety Summary (ISS) data pooling strategy that includes the pivotal study in addition to supportive trials that will produce three data pools: All DT Pool (n=95), All Cancer Mono Pool (n=177), and health volunteer (HV) Pool (n=128).

DISCUSSION

Nonclinical

1. *Does the Agency agree that the summary of nonclinical studies provides sufficient evidence to adequately support review of the NDA?*

FDA Response: SpringWorks's nonclinical program generally appears sufficient to allow review. In the Assessment Aid, provide a statement under *Other Toxicology Studies* on the phototoxic potential of nirogacestat.

Provide an integrated summary using a weight-of-evidence (WOE) approach for reproductive risk assessment. The WOE risk assessment may not rely on

product-specific literature for which SpringWorks does not have right of reference.

A final determination of the adequacy of nonclinical data will be made during review of the original NDA submission.

FDA notes the Real-Time Oncology Review (RTOR) timeline for the Assessment Aid is December 2022 and Module 4 will be submitted end of July/Early August 2022. If a draft of Assessment Aid Section 5 *Nonclinical Pharmacology/Toxicology* is available for pre-submission 2, submit the draft Section 5 with *The Applicant's Position* completed to facilitate FDA review and include any tracked changes in the final submission of the Assessment Aid.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022:

The integrated summary using a WOE approach for the reproductive risk assessment will be provided in 2.4 Nonclinical Overview, which will be submitted in Pre-Submission 2. As requested by the Agency, the Assessment Aid (Section 5 Nonclinical Pharmacology/Toxicology only) will also be included in Pre-Submission 2. No further discussion is needed.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

2. *Does the Agency agree with the waiver request of the 2-year rat carcinogenicity study?*

FDA Response: FDA acknowledges the SpringWorks waiver request.

As discussed in the End of Phase 2 meeting minutes issued March 21, 2018, if the rat carcinogenicity study was warranted, SpringWorks proposed the final study report would be provided post-approval. FDA stated that the proposal may be acceptable and that a 2-year rat carcinogenicity study could be requested as a postmarketing requirement (PMR).

FDA will make a final determination of whether a 2-year rat carcinogenicity study is warranted as a PMR during review of the NDA and will communicate the determination when available.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022:

The 2-year rat carcinogenicity study waiver request will be provided in 1.12.13 Request for Waiver for In Vivo studies, which will be submitted in Pre-Submission 2. No further discussion is needed.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

Clinical

3. *Does the Agency agree with the clinical studies planned for inclusion in the NDA to support the safety and efficacy for nirogacestat in adult patients with desmoid tumors?*

FDA Response: FDA does not object to the proposal.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

4. *SpringWorks believes that the totality of the data (pivotal DeFi study and supportive clinical studies) forms the basis of the submission and review of an NDA for standard approval of nirogacestat for the treatment of adult patients with desmoid tumors (DTs). Does the Agency agree?*

FDA Response: FDA agrees the proposed data package supported by data from the pivotal DeFi study and supportive clinical studies is sufficient to allow for the review of an NDA.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

5. *Does the Agency agree with the Patient-reported Outcomes (PRO) data analyses [REDACTED] (b) (4) ?*

FDA Response: Although the proposed analyses are reasonable and achieved statistical significance at cycle 10, FDA will review the submitted patient-reported outcomes (PRO) data, the PRO statistical analysis plan (SAP), and completed qualitative and quantitative data during the NDA review cycle. At that time, FDA will determine whether the PRO measures are fit-for-purpose for the context of this development program [REDACTED] (b) (4)

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

6. *Does the Agency agree with the content and timeline for the Day 120 Safety Update?*

FDA Response: In general, the proposed content and timeline for the 120-Day Safety Update appear acceptable. The safety update report should focus on new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

7. *Does the Agency agree with the proposed strategy to integrate data from the DeFi and 14-C-0007 studies for inclusion in the ISE ADaM data sets with a narrative description of these integrated studies in 2.7.3 Summary of Clinical Efficacy?*

FDA Response: The proposal for the Integrated Summary of Efficacy (ISE) appears acceptable; however, patients diagnosed with DT in Study A8641014 should also be included in the ISE if they received the proposed dose of nirogacestat.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: SpringWorks will include the 2 desmoid tumor patients who received 150 mg twice daily nirogacestat from Study A8641014 in the ISE. No further discussion is needed.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

8. *Does the Agency agree with the proposed ISS strategy including the plan to integrate data from DeFi, 14-C-0007, and all completed studies in the ISS ADaM data sets?*

FDA Response: FDA does not object to the proposed Integrated Summary of Safety (ISS) strategy.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

9. *Does the Agency agree with the proposed ISS data pooling strategy including three data pools (All DT Pool, All Cancer Mono Pool, and HV Pool) with a focus on the All DT Pool in the narrative portion of 2.7.4 Summary of Clinical Safety?*

FDA Response: FDA does not object to the proposed ISS data pooling strategy; however, in addition to the three proposed data pools, safety data should also be

presented separately for all patients in the three groups that received the dose of nirogacestat submitted for approval.

Furthermore, it is unclear whether data from the 8 patients with T-LBL or ALL should be pooled with the data from patients with desmoid tumors, solid tumors, or breast cancer (these patients may have different exposure and the safety data may be more difficult to interpret).

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: SpringWorks plans to summarize data for each of the three data pools overall and at the dose of nirogacestat submitted for approval (150 mg twice daily). SpringWorks agrees to remove the 8 patients with T-LBL or T-ALL from Study A8641014 in the ISS "All Cancer Mono Pool." No further discussion is needed.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

Biostatistics

10. *Does the Agency agree with the study data standardization plan and the proposed plan to submit CDISC-compliant datasets for the 7 Pfizer legacy supportive studies (A8641001, A8641002, A8641008, A8641014, A8641016, A8641019, and A8641020)?*

FDA Response: FDA does not object to the data standardization plan.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

Clinical Pharmacology

11. *Does the Agency agree with the proposed ECG waveform data submission plan for the concentration-QT analysis?*

FDA Response: FDA agrees; while submission of digital electrocardiogram waveforms is not required to support QT evaluation, it is generally recommended. If digital electrocardiogram (ECG) waveforms are not available, FDA recommends including automatic measurements as provided by the ECG device for sensitivity analysis. With respect to the analysis plan, FDA recommends that the concentration-QT_c assessment is based on studies that cover anticipated therapeutic exposures or higher (A8641014 and NIR-DT-301). Furthermore, the analysis plan should also include by-time central tendency analysis as well as outlier analysis as described in ICH E14. For frequently asked questions and answers for ECG waveform submission and recommendations for

data submission, please refer to the Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT) website, available at:

<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt>.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022:

SpringWorks thanks the Agency for their feedback. The C-QT analysis has been conducted in accordance with the QT Analysis Plan (QTAP) that was previously submitted (SN0118; 16 Jul 2021) and agreed upon by the Agency in the Type B Written Response Only (WRO) Meeting (02 Aug 2021, REF ID: 4834920). The final report for this analysis is currently in preparation and will include summaries of central tendency and categorical outliers from the contributing studies.

SpringWorks seeks clarification regarding the mentioned sensitivity analysis for automatic measurements. Only the 3 clinical studies with digital waveforms (A8641001, A8641002, NIR-DT-103) appear to have contained QT data derived from manual adjudication. The digital waveform XML files from Pfizer studies A8641001 and A8641002 contain the names of clinicians that edited and/or confirmed annotations. In Study NIR-DT-103, SpringWorks contracted a blinded central review for the ECGs from Part 1 and Part 2 of the study that contributed to the C-QT analysis. SpringWorks studies NIR-DT-101 and NIR-DT-102 included ECG interval data obtained from an automatic measurement from the device. Paper ECG waveforms are known to have existed in 2 patient studies (A8641014 and NIR-DT-301); however, they were not centrally archived from the clinical sites. SpringWorks can confirm that the waveforms from study NIR-DT-301 were not subject to blinded central review and, based on available study documentation, the same is assumed for Study A8641014. Therefore, the C-QT analysis that was conducted used a combination of both manually adjudicated and automatic measurements. As QT data are only available from either automatic measurement or from central review within a single study, a sensitivity analysis to evaluate effects related to the interpretation, such as what may be done with a Bland-Altman plot, is not possible. SpringWorks proposes that a sensitivity analysis using the final C-QT model may be conducted to evaluate the impact of reading type on the concentration-related slope when using only the studies containing automatic measurements and only the studies containing manually adjudicated measurements.

Follow-up question to the Agency: Does the Agency agree with SpringWorks' proposal to conduct 2 separate sensitivity analyses to evaluate the impact of reading type on the concentration-related slope with the final C-QT model using (1) studies that used manual adjudication or (2) studies that used automatic measurements?

Discussion during the meeting: FDA recommended that SpringWorks focus the QTc analyses using Studies A8641014 and NIR-DT-301 supplemented by

information from other studies (because Studies A8641014 and NIR-DT-301 are easier to interpret).

SpringWorks believes that Study 103 should also be included as it collected high quality ECGs and administered adequate doses for the assessment. Although patients received itraconazole, SpringWorks does not believe itraconazole caused QTc increases. FDA stated that SpringWorks may provide both analyses (with and without Study 103) in the NDA; SpringWorks can submit a position statement as to why SpringWorks believes that the analysis that includes Study 103 is the appropriate analysis to assess QTc.

FDA stated that the determination for which studies should be used to assess the QTc interval will be a review issue.

12. *Does the Agency agree with the proposed plan to evaluate and support the proposed labeled dose?*

FDA Response: In general, the proposed plan appears acceptable. The adequacy of data/analyses to support the proposed dosing regimen will be assessed during review of the proposed NDA. Refer to the additional clinical pharmacology comments for more details.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

ADDITIONAL COMMENTS

Clinical / Safety

13. The briefing package did not provide a comprehensive assessment of deaths and overall survival on study. While FDA does not expect to see a (survival) benefit given the natural history of the disease, FDA does consider the information from a safety perspective. Please provide this information at or prior to the pre-NDA meeting.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: In Study NIR-DT-301 (DeFi), two deaths were reported that were not submitted as SUSARs; both were considered unrelated to study treatment, and in one, the death occurred more than 30 days after the participant's last dose of study treatment and after the participant's discontinuation from the study, thus it was not considered an event. Brief narratives of these deaths are included below with full narratives planned for inclusion in the DeFi CSR:

- Participant (b) (6) was a 38-year-old male (at the time of informed consent) with a diagnosis of DT including a family history of FAP and

identified APC mutation. The participant was randomized to receive placebo during the double-blind phase of DeFi. On study Day 462, the participant was hospitalized for a scheduled elective exploratory laparotomy, total colectomy with ileorectal anastomosis, and complex wound closure of incisional hernia. On Day 467, the participant underwent temporary ileostomy bag placement due to an observed leak in the connection to the rectum. The participant also had high white blood cell count, low blood pressure, and was having difficulty with rousing from sedation (laboratory values and vital signs not reported). On Day 468, a CT scan of the abdomen, chest, and pelvis showed suspicion for peritonitis and infected fluid in the abdomen and pelvis, which was confirmed to be an anastomotic leakage. Subsequently, the participant underwent an exploratory laparotomy, abdominal washout, resection of ileorectal anastomosis, rectal stump closure, and wound vacuum-assisted closure (VAC) placement. The participant was also intubated and sedated in the surgical intensive care unit for hemodynamic and ventilatory management. On Day 470 a Grade 5 SAE of sepsis was reported which was considered by the Investigator to be unrelated to study treatment and related to complications following surgery.

- Participant (b) (6) was a 51-year-old male (at the time of informed consent) with a diagnosis of DT including a family history of FAP and identified APC mutation. The participant was randomized to receive nirogacestat during the double-blind phase of DeFi. On Day 59, while receiving nirogacestat at 100 mg BID, the participant was diagnosed with Grade 4 spindle cell sarcoma (initially reported as pulmonary nodule), that was an SAE. The event was considered serious and life threatening. An MRI scan showed bilateral pulmonary nodules suggesting a possible metastatic disease, and a computed tomography (CT) scan of the chest, abdomen, and pelvis showed new pulmonary nodules. Other results from the CT scan with intravenous contrast showed an overall interval increase in size and necrosis of the large, complex, infiltrative centrally necrotic pelvic/right thigh mass, with multiple locules of gas within the fluid components, which was likely related to drain placement; similar appearances of mass effect on the right pelvic vessels, with occlusion of the right common iliac artery and common iliac veins; interval increase in soft tissue encasement of the aortic bifurcation; new bilateral pulmonary nodules, concerning for metastatic disease and possibly from prior colon cancer; and increased extensive pelvic osseous destruction. On Day 65, treatment with nirogacestat was discontinued due to clinical progression, with the last dose received on the same day. On Day 66, the participant was hospitalized for the event of spindle cell sarcoma and an event of Grade 3 tumour haemorrhage, that was an SAE and withdrawal AE leading to

discontinuation of nirogacestat as both events supported the clinical progression of disease. On Day 95, the participant was discontinued from the study due to clinical progression. On the same day, the participant started treatment with pazopanib 800 mg QD as treatment for the event of spindle cell sarcoma. On Day 108, the participant died due to multi-organ failure. The participant's death due to multi-organ failure was not reported as an event because it occurred more than 30 days after the participant's last dose of study treatment and after the participant's discontinuation from the study. The Investigator assessed the events of spindle cell sarcoma and tumour hemorrhage as not related to the study treatment nirogacestat.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

14. An important review issue will involve the uncertainty regarding the natural history of ovarian dysfunction given the limited number of patients exposed to nirogacestat to-date and the natural history of desmoid tumors which may necessitate years (or decades) of therapy. In addition to discussion of this event in product labeling, SpringWorks should develop a proposal to further study ovarian dysfunction in the post-market setting, and this proposal should be submitted with the original NDA submission for review. This further investigation should be sufficient to characterize and describe ovarian dysfunction over long-term use (and if applicable, sequelae of ovarian dysfunction such osteopenia/osteoporosis [e.g., DEXA scans]).

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: SpringWorks commits to developing a proposal to further study ovarian dysfunction in the post-market setting and this proposal will be submitted in the NDA. No further discussion is needed.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

15. FDA will also consider whether long term safety data should be systematically collected to characterize other adverse events during the review of the NDA.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

16. In the NDA, provide an up-to-date summary of known growth abnormality adverse events in patients with skeletal immaturity across SpringWorks trials or trials conducted by other sponsors.

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: SpringWorks has requested this data from Children's Oncology Group (COG), sponsor of pediatric study ARST1921, which will be submitted in the NDA, if available. In addition, SpringWorks will provide relevant data from its Compassionate Use Program (CUP) in the NDA.

Discussion during the meeting: FDA acknowledged SpringWorks Therapeutics, Inc.'s response; there was no further discussion of this item during the meeting.

Clinical / Efficacy

17. In addition to the information requested in FDA's Addition Comment #13, please also provide analyses of efficacy in the subgroups of patients with known beta-catenin mutations versus known familial adenomatous polyposis (FAP).

SpringWorks Therapeutics, Inc. response received via email on August 12, 2022: In 2.7.3 Summary of Clinical Efficacy, SpringWorks plans to include a subgroup analysis of efficacy for each of the following subgroups related to genetic mutations:

- History of familial adenomatous polyposis (FAP),
- Presence of CTNNB1 mutation, or
- Presence of Adenomatous Polyposis Coli (APC) mutation

Each of these analyses will be performed comparing participants receiving nirogacestat versus placebo.

Follow-up question to the Agency: Please confirm if the proposed analyses are acceptable or if the Agency is requesting an analysis among participants receiving nirogacestat with a CTNNB1 mutation versus participants receiving nirogacestat with an APC mutation / history of FAP?

Discussion during the meeting: The proposed analyses are acceptable.

Clinical Pharmacology

18. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: <https://www.fda.gov/media/74346/download>). Consider strategies to enhance clarity, readability, and comprehension of this information for health

care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

19. Address the following questions in the Summary of Clinical Pharmacology:
- a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support the marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - b. What are the exposure-response relationships for efficacy, safety, and biomarkers?
 - c. What is the effect of nirogacestat on the QT/QTc interval?
 - d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendations with regard to meals or meal types.
 - f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA's response; there was no further discussion of this item during the meeting.

20. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
- a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.

- c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
- Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
- d. Submit the following for the population pharmacokinetic analysis reports:
- Standard model diagnostic plots.
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines available at:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- e. Submit the following information and data to support the population pharmacokinetic analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation.
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population.

Refer to the following FDA documents of “Guidance for Industry” for greater details regarding the above recommendations:

- [Population Pharmacokinetics](#)
 - [Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications](#)
 - [Pharmacometric Data and Models Submission Guidelines](#)
- g. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
- h. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in the laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in the adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Discussion during the meeting: SpringWorks Therapeutics, Inc. acknowledged FDA’s response; there was no further discussion of this item during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application were discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- It was concluded that a REMS is not necessary for FDA to file the application.
- Major components of the application are expected to be submitted with the

original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

FDA acknowledges that the Agreed Initial Pediatric Study Plan - Agreement letter for nirogacestat for the treatment of desmoid tumors, has been finalized and issued on April 25, 2022.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA**,

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www.fda.gov

ANDA, BLA, Master File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁰

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹¹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹²

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

19 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹⁰ <https://www.fda.gov/media/85061/download>

¹¹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹² <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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/

AUTUMN D ZACK-TAYLOR
08/23/2022 11:40:25 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 138207
Request Receipt Date	July 3, 2019
Product	Nirogacestat
Indication	Treatment of progressing desmoid tumors
Drug Class/Mechanism of Action	Small molecule inhibitor of gamma-secretase
Sponsor	SpringWorks
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	August 30, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a clinical review: **REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

The sponsor proposes the following indication: Nirogacestat is indicated for the treatment of progressing desmoid tumors.

The division proposes the following indication: Nirogacestat is indicated for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis.

Reviewer note: The sponsor revised the indication in alignment with the division request, with formal submission of this revised indication to the IND on August 23, 2019.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

YES NO

3. Was the BTDR submitted to a PIND?

YES NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? YES NO

If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES, the BTDR is adequate and sufficiently complete to permit a substantive review
 - Undetermined
 - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
 - i. Only animal/nonclinical data submitted as evidence
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

¹ For a definition of serious and life threatening see Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Background

Desmoid tumors are rare, benign but locally invasive tumors which generally arise in the extremities or the abdomen. These tumors may be sporadic and associated with somatic *CTNNB1* mutations, or with a germline mutation of APC as in a variety of syndromes including Familial Adenomatous Polyposis (FAP). The natural history of these tumors is varied, with patients experiencing both progression and regression. Desmoid tumors can cause significant morbidity and occasional mortality due to infiltration or mass effect on adjacent vital structures. Morbidity from abdominal tumors may include complications due to compression or obstruction of the ureters, bowel, or blood vessels. Extremity tumors may cause pain, decreased range of motion, swelling, or potentially require amputation.

Given the variable natural history of these tumors, a “wait-and-see,” conservative approach is commonly used to determine if therapy is needed. Recurrence after surgical resection is common, and thus is no longer considered standard, especially in cases where negative margins cannot be achieved without compromising functional outcomes. Radiation may be considered in lieu of surgery or as an adjuvant treatment but is rarely administered given the potential for secondary malignancies in young patients. There is no standard of care for the systemic treatment of desmoid tumors, and there are no FDA-approved therapies for the treatment of desmoid tumors. The combination of methotrexate and vinblastine has demonstrated prolonged progression-free survival and symptom palliation, and anthracycline-based regimens are reported as having an objective response rate of approximately 50% in small uncontrolled studies (that may have used different response criteria). Clinical studies have also investigated the use of other therapies such as tyrosine kinase inhibitors or antiestrogens. A table of prior studies in patients with desmoid tumors was provided by the sponsor and is copied below:

Table 1: Therapies for Advanced Desmoid Tumors

Treatment	Study	N	Population	% ORR (evaluable patients)	#CR	#PR	Median PFS (M)	Duration of treatment (range)	Reference	Tolerability
Chemotherapy										
Doxorubicin, dacarbazine	R	12	Relapsed	67% (6/9)	2	4	96	NR	Patel 1993	
Pegylated doxorubicin	R	12	Progressive/recurrent	36% (4/11)	0	4	NR	36 mo	Constantinidou 2009	55% pts required dose reduction
Meth/Vin	Phase 2	30	Primary/recurrent	40% (12/30)	0	12	10 years; 65%	~12 mo	Azzarelli 2001	Granulocytopenia most commonly reported and pts stopping therapy at <20 courses were more likely to progress
Meth/Vin	Phase 2	27	Not amenable to surgery	19%	1	4	16	40 wks (10 to 52 wks)	Skapek 2007	Pediatric population, 38% had disease progression on study
Meth/Vin	Phase 2	12	Symptomatic	50%	4	2	NR	Min 16 wks	Weiss 1999	Minimal neurotoxicity in 16% pts
Meth + Vin/vinorelbine	R	75	Progressing	48%	1	35	75	(median duration) 14 mo	Palassini 2017	8 pts discontinued due to toxicity
Tyrosine Kinase Inhibitors (TKIs)										
Imatinib (800 mg/d)	Phase 2	37	Progressing	19%	0	7	18	434 days (14-749)	Kasper 2017	Median response duration of 413 days
Imatinib (800 mg/d)	Phase 2	19	Refractory	16%	0	3	11	NR	Heinrich 2006	Heavily pre-treated population. Dose reductions were frequent for GI, dermatological and hematological
Imatinib (400 mg/d)	Phase 2	36	Progressing	9%	0	3	25	12 mo (1-35)	Penel 2011	50% of pts stopped therapy before 1 yr
Imatinib (200 - 600mg/d)	Phase 2	51	Not amenable to surgery	6%	0	3	NR	NR	Chugh 2010	Pts >10 yrs
Sorafenib (400 mg/d)	R	79	Progressive or symptomatic	18	0	11	48	13.6 mo	Munhoz 2016	20% discontinued due to toxicity
Sorafenib (400 mg/d)	R	26	First or progressive	25	0	6	NR	NR	Gounder 2011	
Sorafenib (400 mg/d)	Phase 3	87	Progressive/symptomatic	33% (sor) vs 20 (PBO)	1	15	Not met	NR	Gounder 2018	20% discontinuation due to toxicity

Treatment	Study	N	Population	% ORR (evaluable patients)	#CR	#PR	Median PFS (M)	Duration of treatment (range)	Reference	Tolerability
Sunitinib (37.5 mg)	Phase 2	19	Advanced	26%	0	5	NR	6 mo (1-47)	Jo 2014	G3/4 neutropenia (33%), diarrhea (5%) and hand-foot syndrome (5%)
NSAIDs, Anti-Hormonals and Combos										
Sulindac (300 mg)	R	14	NR	57%	3	7	NR	NR	Tsukada 1992	
Sulindac (300 mg) + tamoxifen (120 mg)	R	25	First line	24%	0	4	NR	NR	Hansmann 2004	
Sulindac (300 mg) + tamoxifen (3 mg/kg)	Phase 2	59	Recurrent	8	1	4	11 mo	12 mo	Skapek 2013	
Toremifene (180 mg)	R	44	Progressing	25%	0	11	NR	NR	Fiore 2015	
Tamoxifen	R	32	Progressing/refractory	3	0	1	10	316 days (33-997 days)	Libertini, 2018	

CR = complete response, Meth = methotrexate, mo or M = month; N = number; NR = not reported; ORR = objective response rate (CR + PR); PFS = progression free survival; PR = partial response; pts = patients; wk = weeks R = retrospective; Vin = vinblastine

Relevant Regulatory History

On March 21, 2018, DOP2 met with SpringWorks via teleconference for a pre-IND/ End of phase 2 meeting. FDA noted that PFS may be an acceptable primary endpoint to support registration in an adequately designed trial with sufficient follow-up. Approval based on PFS would depend on an overall favorable risk-benefit assessment considering the effects of nirogacestat on secondary endpoints and on safety. DOP2 requested that SpringWorks provide justification for the assumption that patients receiving placebo would have a median progression-free survival of 8 months. DOP2 also recommended that SpringWorks consider the patient population that is likely to support a favorable risk-benefit assessment following review of the study results, including the percent of tumor growth required for eligibility.

FDA noted that allowing cross-over could cause inadvertent unblinding and difficulty in interpreting patient reported outcomes but noted that it was SpringWorks's decision whether or not to allow crossover. FDA also provided preliminary advice regarding the assessment of patient reported outcomes, which was the subject of a subsequent meeting held on October 15, 2018.

IND 138207 was submitted on September 28, 2018. The IND-opening study, Study NIR-DT-301 is a multi-center, randomized, double-blind placebo-controlled study of nirogacestat versus placebo in adult patients with progressive desmoid tumors or deep fibromatosis. Randomization is stratified based on site, with favorable location (abdominal wall, breast, intraabdominal and lower limb) or unfavorable location (chest wall, head and neck and upper limb). The primary objective of the ongoing randomized study is to determine the efficacy of nirogacestat in adult patients with progressing desmoid tumors/deep fibromatosis as defined by progression-free survival based on blinded, central, independent review of response as determined by RECIST v1.1. Following completion of the double-blind phase, after observation of at least 51 progression events, the study will convert to an optional open-label extension (OLE) phase. The study will enroll patients who are ≥ 18 years old with either 1) newly-diagnosed, progressing desmoid tumor/desmoid fibromatosis (DT/DF) not amenable to surgical resection or radiation therapy, 2) recurrent DT/DF following CR to initial therapy or 3) preexisting DT/DF which has demonstrated progression after initial therapy.

Fast Track designation was granted on November 1, 2018 for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis, to demonstrate a statistically robust and clinically meaningful effect on progression-free survival (PFS) as assessed by blinded independent review, in a randomized, placebo-controlled trial(s).

FDA has had two preliminary Breakthrough Designation Request Advice meetings with SpringWorks, most recently on May 24, 2019. DOP2 indicated support for submission of a BTDR in a population of previously treated patients.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

SpringWorks considers durable overall response rate (ORR) to be a clinically meaningful endpoint supporting the BTDR. The data for ORR in Study A8641014 and NCI Study 14-C-0007 is based on investigator-assessed response by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and 1.1, respectively. The ongoing randomized, double-blind, placebo-controlled study designed to support registration has an endpoint of progression-free survival.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RECIST would provide preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint. It is premature at this time to determine if durable ORR could serve as the basis for approval in desmoid tumors. DOP2 would have to consider the effect size on ORR in a condition where the tumor can occasionally shrink in the absence of therapy, and DOP2 would have to consider the toxicity of treatment. Furthermore, it might be difficult to put duration of response in context because desmoid tumors can be slow growing.

Because desmoid tumors generally do not metastasize, and because they are slow growing, conducting a trial with OS as an endpoint would not likely be feasible. Nevertheless, progressive desmoid tumors can be symptomatic, and demonstration of a significant improvement in PFS based on blinded, central, independent review in a randomized study may be considered as benefit to patients, depending on the magnitude of the treatment effect. Improvement in patient reported outcomes could strengthen an application as would a favorable toxicity profile (given the potentially long natural history of desmoid tumors).

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable; see above.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved therapies for desmoid tumors. Therapies used in practice include chemotherapy (methotrexate/vinblastine, doxorubicin, dacarbazine), tyrosine kinase inhibitors (imatinib, sorafenib, sunitinib), and other therapies (tamoxifen, sulindac with tamoxifen, toremifene). Response rates for these therapies range from 9 – 67%, although sorafenib demonstrated an improvement in PFS (0.13; 95% CI, 0.05 to 0.31; P<0.001) in a randomized controlled trial versus placebo that was published in late 2018 (Gounder et al., NEJM). Many of these studies are extremely small, the population defined was variable, and the studies may have used different response criteria. Duration of response is inconsistently reported. See Table 1 above for a complete listing as provided by the sponsor.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

There have been no prior breakthrough therapy designation requests for desmoid tumor.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

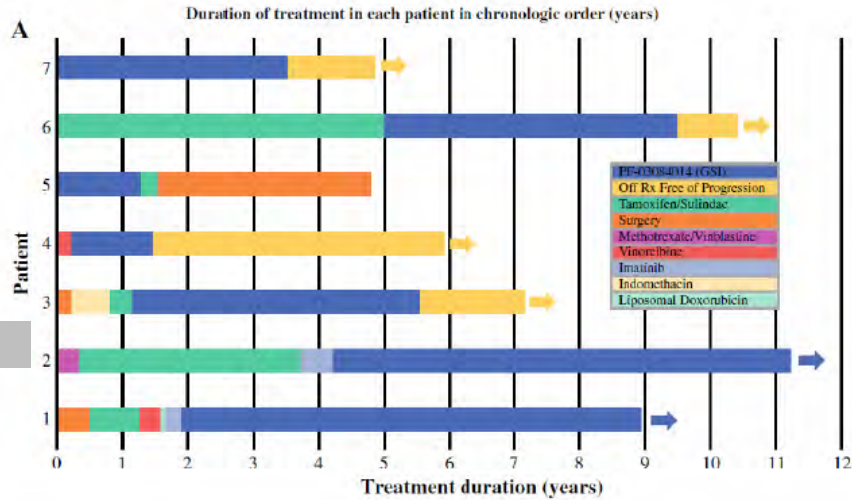
Table 2: Studies supporting the BTDR

Study ID/ Design	Population/N	ORR (95% CI)	DOR	Other
A8641014 Dose escalation and expansion study	N=9 (7 evaluable for response) Progression, prior therapy not required	55.6% (5/ 9) Reported as 71.4% (29.0, 96.3%) 5 PR	DOR 48 – 73+ months 4 patients off therapy free of progression for 11 – 53+ months	Mean time to response 11.9 months (95% CI 2.5 – 21.4 months) No responders developed progression, censored at data cut-off
NCI Study 14-C-007 Single arm, open-label, activity-estimating study	Recurrent, refractory, progressive desmoid tumors that had failed prior therapy OR were not amenable to surgery N=17 (16 evaluable for response)	5/17 (29%) 5 PR, 11 SD	25 – 48 months 3/5 remain on study	Responses occurred at 8.4 – 24.5 months Improvement in sx by MDASI occurred earlier (cycle 2+) than responses Responses included patients with APC (n=1), CTTNB1 (n=3) mutations and no mutation (n=1)

Study A8641014 was a multi-center, open-label dose-escalation and expansion study of nirogacestat in patients with advanced solid tumors (n=64). Nine patients with desmoid tumor enrolled, seven of which were evaluable for response. Villalobos, et al (Annals of Surgical Oncology, 2018) reported the long-term follow-up of the seven desmoid patients from Study A8641014. Two patients received nirogacestat as first-line therapy. Patients received 0 – 4 prior systemic therapies. Responders received 0 – 4 prior systemic therapies; one patient who responded had no prior systemic therapy. The prior therapies by patient are displayed in the graph below:

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 2: Duration of treatment in each patient in chronologic order (years)-Study A6841014 (Villalobos, 2018)



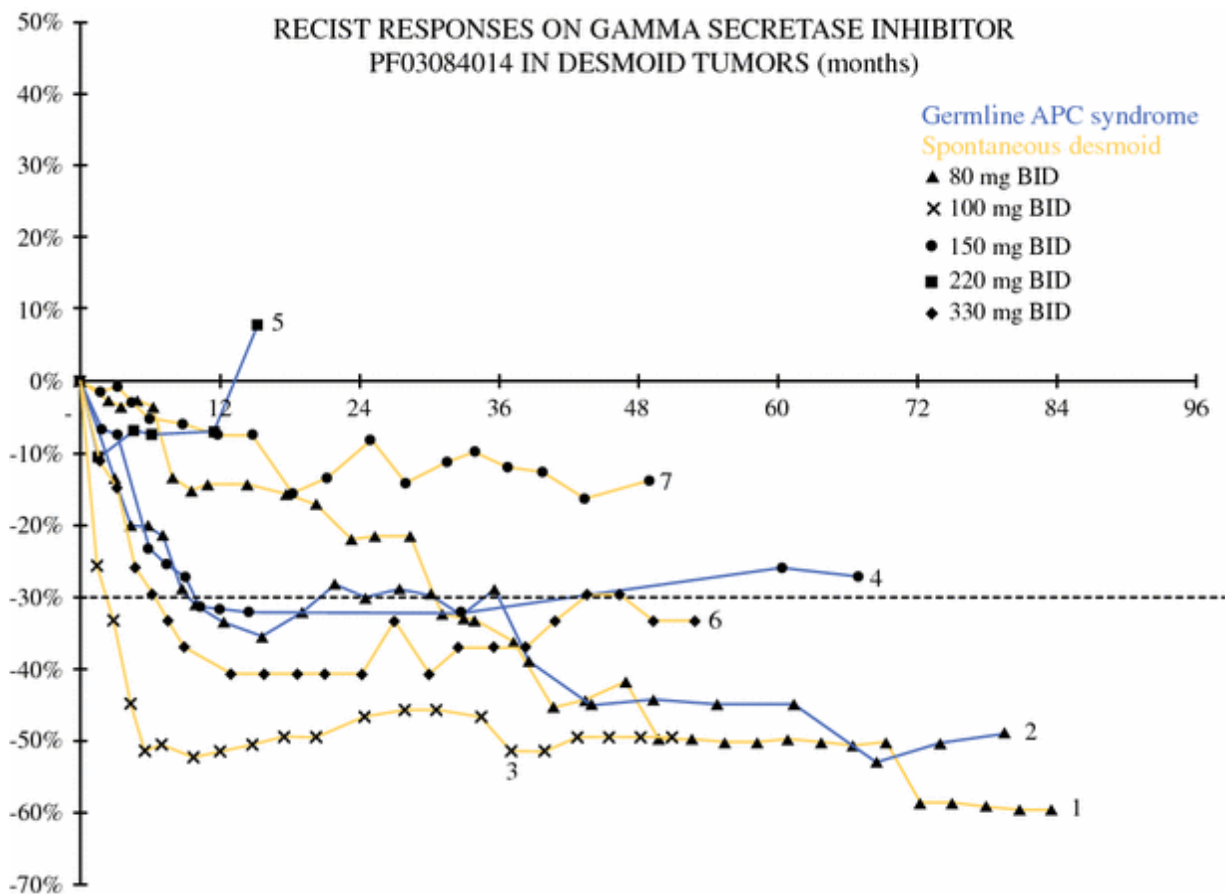
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Patient# - dose	Regimen / Clinical Benefit in Weeks					
	1st regimen	2nd regimen	3rd regimen	4th regimen	5th regimen	6th regimen
7 - 150mg BID	GSI (48 weeks)	Off therapy w/o progression (69 weeks)				
6 - 150mg BID	Tam/Sulindac (200 weeks)	GSI (234 weeks)	Off therapy w/o progression (48 weeks)			
5 - 220mg BID	GSI (69 weeks)	Tam/sulindac (14 weeks)	Surgery (170 weeks)			
4 - 150mg BID	Vinorelbine (12 weeks)	GSI (66 weeks)	Off therapy w/o progression (231 weeks)			
3 - 100mg BID	Surgery (12 weeks)	Indomethacin (30 weeks)	Tam/sulindac (17 weeks)	GSI (229 weeks)	Off therapy w/o progression (84 weeks)	
2 - 80mg BID	MTX/Vinorelbine (17 weeks)	Tam/sulindac (176 weeks)	Imatinib (25 weeks)	GSI (305 weeks)		
1 - 80mg BID	Surgery (26 weeks)	Tam/sulindac (39 weeks)	Vinorelbine (17 weeks)	Liposomal Doxorubicin (3 weeks)	Imatinib (13 weeks)	GSI (156 weeks)

Arrows to the right indicate patients who are still free of a new intervention, either on (blue) or off (yellow) therapy. The table displays the clinical benefit in weeks of each therapy and the color-coded regimen used. Abbreviations: GSI, gamma secretase inhibitor (nirogacestat); BID, twice daily, MTX methotrexate; Tam, tamoxifen

The most common treatment-related adverse events (AEs) were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite. The following spider plot is copied from the 2018 publication of follow-up data for the seven evaluable desmoid tumor patients (Villalobos, 2018):

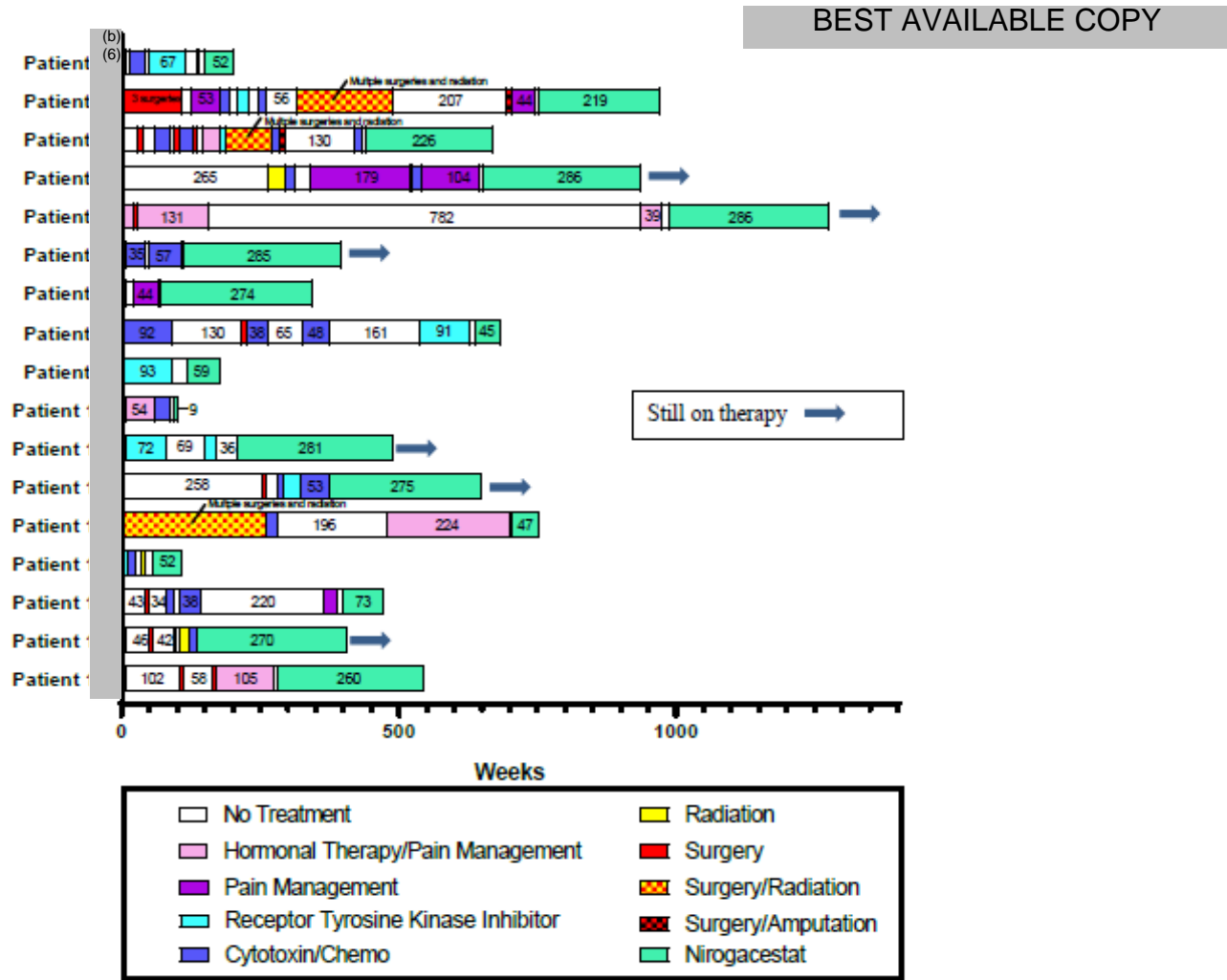


NCI Study 14-C-007 was an investigator-sponsored, single-arm, open-label, activity-estimating study of nirogacestat in patients with progressive desmoid tumors. Seventeen patients received nirogacestat 150 mg BID continuously in 3-week cycles. Fifteen patients had mutations in APC or CTNNB1 genes. Patients were required to have disease which progressed following at least one line of standard therapy. The sponsor states that patients enrolled progressed following one to nine prior lines of therapy that included wait-and-see, surgery, chemotherapy, radiation, tyrosine kinase inhibitors, hormonal therapy and pain management. If one excludes ‘wait and see,’ local therapy, and pain management, patients received 1 - 7 lines of prior therapy.

Responses were reported in 5 patients (29%). Response duration has ranged from 25 – 48 months and occurred at 8.4 – 24.5 months. The investigators reported symptomatic improvement preceding clinical response, though detailed data regarding symptomatic improvement is not provided in the BTDR. Figure 3 below, extracted from the BTDR, provides a visual representation of prior therapy duration and the duration of treatment with nirogacestat on Study 14-C-007.

The safety profile in Study 14-C-007 was consistent with prior experience. Four patients required dose reductions or discontinuation due to adverse events: persistent Grade 2 nausea and diarrhea (n=2), and Grade 2 maculopapular rash (n=1), urticaria (n=1, required discontinuation). The only Grade 3 adverse event was hypophosphatemia (n=8).

Figure 3: Duration of treatment in each patient in chronologic order (years)-NCI Study [Data as of June 30, 2019]



b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.

The sponsor was asked to provide a hypothesis for the different response rates observed between the two studies supporting BTDR. The sponsor proposed that the differences in the response rates between the two studies could potentially be explained by several factors such as the following:

- The small desmoid cohort in Study A8641014

- Patients in Study A8641014 were not required to have progressing disease at disease at study entry, unlike patients in NCI Study 14-C-007
- In NCI Study 14-C-007, seven of the 17 patients stopped treatment within 18 months without progression, six of whom withdrew from the study due to patient choice. After discussion with the investigators, these patients did not want to travel to NCI for further treatment. Of the seven patients who withdrew early, many of them had tumor size reductions, and therefore may have stopped therapy prior to achieving a PR. Of the five patients achieving a PR, three did not achieve a PR until at least 22 months on treatment.

12. Division's recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

The data provided indicate that patients with previously-treated, unresectable progressive desmoid tumors have demonstrated durable responses to nirogacestat. Patients with desmoid tumors have no approved treatment options; available treatment options have variable response rates and many are associated with significant toxicity. Although the natural history of desmoid tumors is variable, with some patients demonstrating stable disease or even regression in the absence of treatment, patients with progressive tumors can experience significant morbidity as well as decreased survival.

Combining the trials, the most conservative estimate of response using the ITT population of all patients would be 38% (10 of 26). Based on the available data, it appears patients are able to remain on treatment for long periods. SpringWorks proposes the indication of progressing desmoid tumors in their request for breakthrough designation, but the majority of the response data provided is in patients who have been previously-treated. Therefore, this reviewer suggests that the BTDR be granted with a revised indication: for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor has met with FDA in a pre-IND meeting and subsequent meetings to discuss the study intended to support registration of nirogacestat for the treatment of patients with desmoid tumors. The study is currently ongoing. The division will continue to interact with the sponsor as needed as development progresses.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

Villalobos, V. M., et al. (2018). "Long-Term Follow-Up of Desmoid Fibromatosis Treated with PF-03084014, an Oral Gamma Secretase Inhibitor." **25**(3): 768-775.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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/

DIANA L BRADFORD
08/26/2019 03:04:05 PM

SUZANNE G DEMKO
08/26/2019 03:11:32 PM

STEVEN J LEMERY
08/26/2019 03:31:39 PM



PIND 138207

MEETING MINUTES

SpringWorks Subsidiary 2, PBC
Attention: Candice Durrence, M.S., R.A.C.
Regulatory Affairs Consultant, Halloran Consulting Group
266 Summer Street, 8th Floor
Boston MA 02210

Dear Ms. Durrence:

Please refer to your Pre-Investigational New Drug Application (PIND) file for nirogacestat.

We also refer to the meeting between representatives of your firm and the FDA on March 21, 2018. The purpose of the meeting was to the available nonclinical data package and the proposed study design of the planned Phase 3 protocol.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND, End of Phase 2
Meeting Date and Time: March 21, 2018, 9:00 AM-10:00 AM
Meeting Location: Teleconference
Application Number: PIND 138207
Product Name: Nirogacestat
Indication: Desmoid tumors
Sponsor/Applicant Name: SpringWorks Subsidiary 2, PBC
Meeting Chair: Steven Lemery, M.D.
Meeting Recorder: Nataliya Fesenko, Pharm.D.

FDA ATTENDEES

Steven Lemery, M.D., Associate Division Director, OHOP/DOP2
Suzanne Demko, PA-C, Clinical Team Leader, CDER/OHOP/DOP2
Diana Bradford, M.D., Clinical Reviewer CDER/OHOP/DOP2
Whitney Helms, Ph.D., Nonclinical Team Leader, CDER/OHOP/DHOT
Anwar Goheer, Ph.D., Nonclinical Reviewer, CDER/OHOP/DHOT
Denise Casey, M.D., Clinical Reviewer CDER/OHOP/DOP2
Dhananjay Marathe, Ph.D., CDER/OTS/OCP/DPM
Paul Kluetz M.D., Associate Director for Clinical Science, CDER/OHOP/OCE
Selena Daniels, Pharm.D., M.S., COA Team Lead, CDER/OMPT
Nataliya Fesenko, Pharm.D., Regulatory Project Manager, CDER/OHOP/DOP2

SPONSOR ATTENDEES

Steve Squinto, Acting Head R&D, SpringWorks
Mary Smith, VP, Clinical R&D, SpringWorks
(b) (4) Biostatistician, (b) (4)
Candice Durrence, Regulatory Affairs Consultant, Halloran Consulting Group
(b) (4) Regulatory Strategy Consultant, (b) (4)
(b) (4) Clinical Pharmacology/ Early Clinical Development
Consultant, (b) (4)

BACKGROUND

On January 26, 2018, FDA received a Pre-IND, End-of-Phase 2 Meeting Request from SpringWorks Therapeutics for nirogacestat for the treatment of desmoid tumors. This submission

(b) (4)

The purpose and objectives of the requested meeting are to obtain feedback regarding

- the adequacy of the current nonclinical data package to support conducting the pivotal clinical trial and submission of the NDA for nirogacestat in the treatment of desmoid tumors;
- the proposed study design of the planned trial, including primary and secondary endpoints, the use of a new desmoid tumor-specific patient reported outcome (PRO) tool, tumor volume assessment by MRI, and cardiovascular safety monitoring;
- the size of the anticipated safety database to support NDA submission;
- the eligibility of nirogacestat for fast track designation.

Nonclinical:

Nirogacestat (PF-03084014) is a small molecule, reversible, noncompetitive inhibitor of γ -secretase (GS). GS is composed of a catalytic subunit (presenilin-1 or presenilin-2) and accessory subunits (Pen-2, Aph1, and nicastrin). GS activity is required for Notch signaling. SpringWorks has completed pharmacology, safety pharmacology, and in vitro genotoxicity studies, as well as GLP-compliant toxicological studies of up to 3 months in both rats and dogs. SpringWorks is planning to perform an in vivo micronucleus test and embryo-fetal development studies (in 2 species unless there is clear evidence of teratogenicity in a pilot study in rats) concurrently with the clinical trial intended to support registration for the treatment of patients with desmoid tumors.

Clinical

Desmoid tumors are rare, benign but locally invasive tumors which generally arise in the extremities or in the abdomen. These tumors may be sporadic and associated with somatic *CTNNB1* mutations, or associated with a germline mutation of APC as in a variety of syndromes including Familial Adenomatous Polyposis (FAP). Desmoid tumors can cause significant morbidity and occasional mortality due to infiltration or mass effect on adjacent vital structures. The natural history of these tumors is varied, with patients experiencing both progression and regression. Morbidity from abdominal tumors may include complications due to compression or obstruction of the ureters, bowel, or blood vessels. Extremity tumors may cause pain, decreased range of motion, swelling, or potentially require amputation.

Given the variable natural history of these tumors, a “wait-and-see,” conservative approach is commonly used to determine if therapy is needed. Recurrence after surgical resection is common, and thus is no longer considered standard, especially in cases where negative margins cannot be achieved without compromising functional outcomes. Radiation may be considered in lieu of surgery or as an adjuvant treatment, but is rarely administered given the potential for secondary malignancies in young patients. There is no standard of care for the systemic

treatment of desmoid tumors, and there are no FDA-approved therapies for the treatment of desmoid tumors. The combination of methotrexate and vinblastine has demonstrated prolonged progression-free survival and symptom palliation, and anthracycline-based regimens are reported as having an objective response rate of approximately 50%. Clinical studies have also investigated the use of other therapies such as tyrosine kinase inhibitors or antiestrogens.

The following table is adapted from the submission to include additional information and reported results from additional studies of targeted therapies. Publications studying populations <20 patients were excluded from this table.

Author, year	Design/ endpoint	Agent	Population	Results
Kasper et al, 2017	Phase II study/ progression arrest rate (PAR) at 6 months	Imatinib 800 mg daily (patients switched to nilotinib at progression)	38 adult patients that demonstrated RECIST v1.0 progression within last 6 months	Imatinib (n=38) • PAR at 6 months 65% (45% at 24 months) • OS 100% at 24 months • ORR 19% Nilotinib (n=8): • PAR at 3 months 88%
Penel et al, 2011	Phase II/ stable disease at 3 months	Imatinib 400 mg/day	40 patients with relapsed or refractory desmoid tumors	• Response rate 12%, CR 3% (n=1), PR 9% (n=3) • Stable disease in 83% • Median PFS 25 months
Azzarelli et al, 2001	Phase II study/ response rate	Vinblastine 6mg/m ² + methotrexate 50 mg/m ² weekly	30 adult patients with advanced, inoperable aggressive fibromatosis	• Response rate 40% (n=12), all PR • No patients progressed during treatment (median time on treatment 12 months)
Skapek et al, 2007	Phase II study/ PR >50% shrinkage, MR >25%≤50% shrinkage, PD >25% increase in	Vinblastine 5mg/m ² /dose, Methotrexate 30 mg/m ² /dose weekly for 26 weeks, then every other week for 26 weeks	28 pediatric patients (ages 1mo. – 18 years) with newly-diagnosed desmoid-type fibromatosis not amenable	• Response rate 31% (n=8), CR (n=1), PR (n=4), MR (n=3) • For patients who progressed after stopping treatment, median time to progression after stopping therapy

	product of perpendicular dimensions		to radiation or surgery, or with recurrent disease	(n=8) was 15.9 months
Systematic Review (Janinis et al, 2003) of anti-inflammatory ad anti-estrogenic therapies				
Anti-inflammatories	• Sulindac, 200 - 400 mg/day • Indomethacin 75 - 300 mg/day • Colchicine 3 mg/day		Patients with recurrent or primary aggressive fibromatosis, ages 21 - 76	• Variable response rate/ case reports of single responders
Anti-estrogens	• Tamoxifen 20 – 160 mg/day (± sulindac, diclofenac, or megace) • Toremifene 200 mg/day • Megace 500 mg/day		Patients with aggressive fibromatosis, ages 1 – 70, from single arm trials and case reports	• Variable responses, response durations 7 months – 8 years

PR = partial response, MR= moderate response, CR = complete response, PD=progressive disease

Nirogacestat has been studied in three dose finding/PK clinical trials conducted in healthy adult human subjects (Studies A8641001, A8641002, and A8641008). Nirogacestat has also been studied in patients with advanced cancers either as monotherapy or in combination with other agents (Studies A8641014A, A8641016, A8641019 and A8641020). In addition, nirogacestat has been studied in patients with desmoid tumors, in the following studies:

- **Study A8641014:** A Phase 1 trial of PF-03084014 in patients with advanced solid tumor malignancy and relapsed or refractory acute T-cell lymphoblastic leukemia or lymphoblastic lymphoma
 - Five of seven (71%) patients with desmoid tumor demonstrated a partial response. The median time to response of the 5 responders was 8.5 months, and, as reported by Villalobos et al, all patients who experienced a PR continued to maintain responses between 48 to >73 months on study (median duration of response not reached, range 1.7 to 69.2 months).
 - The maximum tolerated dose (MTD) was determined to be 220 mg twice daily and the recommended dose (RP2D) was 150 mg twice daily.
 - The most common treatment-related adverse events (AEs) were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite.

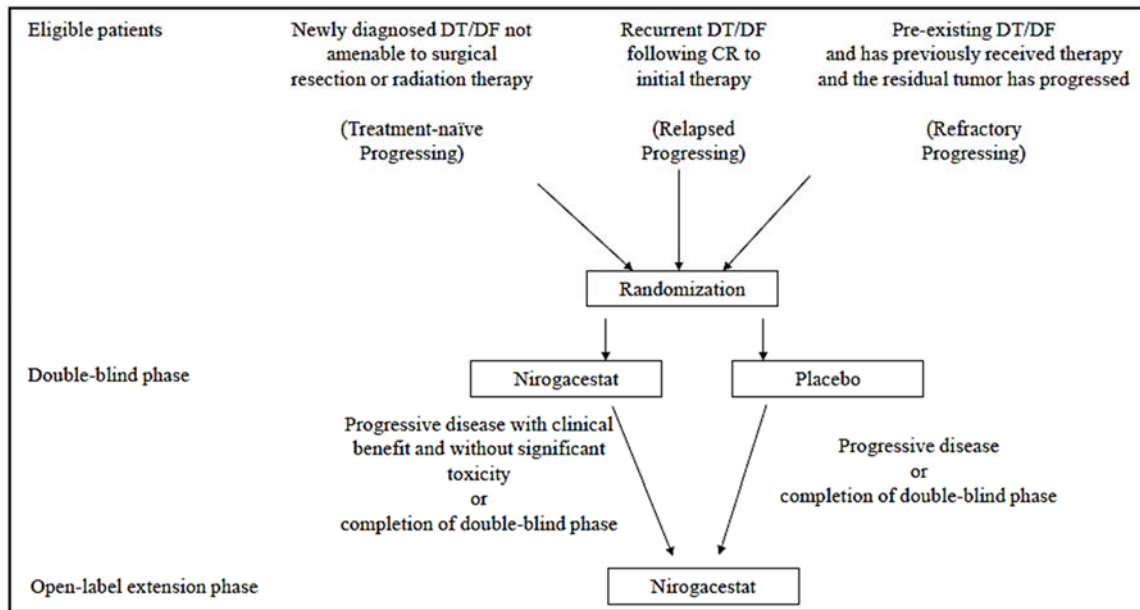
- **Study WI180798:** A Phase II trial of the gamma secretase inhibitor, PF-03084014, in patients with desmoid tumors
 - This was an investigator-initiated study conducted by the NCI under IND 119796.
 - Seventeen patients received nirogacestat 150 mg twice daily continuously in 3-week cycles. Fifteen patients had mutations in APC or CTNNB1 genes.
 - Twenty-nine percent (29%, 5/17) of patients demonstrated a partial response, and all remained on study for at least 2 years. No patients progressed on study.
 - The researchers reported that clinical benefit was observed regardless of mutational status of *CTNNB1* or *APC*, and responders as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 included patients with *CTNNB1* mutations (n=3), *APC* mutations (n=1) and no mutation (n=1).
 - Safety findings were consistent with prior reports. Four patients required dose reductions or discontinuation due to adverse events: persistent Grade 2 nausea and diarrhea (n=2), Grade 2 maculopapular rash (n=1), or urticaria (n=1, required discontinuation). The only Grade 3 adverse event was hypophosphatemia (n=8).

Given the infiltrative and asymmetric nature of desmoid tumors, there is concern amongst desmoid tumor experts that RECIST v1.1 criteria may not be the most effective criteria for evaluating response. Studies have reported measurement of the MRI enhancement ratio, and volumetric assessment by MRI. Study WI180798, as reported by Kummar et al, assessed tumor volume changes and found that 10 of 11 patients who had pre- and post-treatment MRI demonstrated tumor volume reduction, compared to 5/17 who demonstrated partial response by RECIST v1.1. The data reported in this publication provides relative tumor volume changes in cubic centimeters, but does not provide the baseline volume of each tumor to assess the proportion of tumor volume this change represents.

Proposed Clinical Study

A protocol synopsis is provided in the meeting package. The proposed clinical trial is a multi-center, international, randomized, double-blind, placebo-controlled study of nirogacestat versus placebo in adult patients with progressive desmoid tumors or deep fibromatosis. Nirogacestat or placebo will be administered orally at 150 mg twice daily administered continuously in 28-day cycles. Following completion of the double-blind phase, after observation of at least 51 progression events, the study will convert to an optional open-label extension (OLE) phase. The study schema is copied from the meeting package below:

Figure 1. Trial Design



CR = complete response; DF = deep fibromatosis; DT = desmoid tumor.

Patients are eligible to enter the OLE phase if 1) they are enrolled in the double-blind phase when the primary PFS analysis has been completed, 2) they are randomized to receive placebo in the double-blind phase and demonstrate progression, or 3) they are randomized to receive nirogacestat and demonstrate progression, but are deriving clinical benefit without significant toxicity.

The primary objective is to determine the efficacy of nirogacestat in adult patients with progressing desmoid tumors/deep fibromatosis as defined by progression-free survival based on blinded, central, independent review of response as determined by RECIST v1.1. The secondary objectives of this trial are:

- To evaluate the safety and tolerability of nirogacestat in adult patients with progressing desmoid tumors/deep fibromatosis as measured by the incidence of adverse events;
- To determine the response rate (CR+PR) of nirogacestat in patients with progressing desmoid tumors/deep fibromatosis;
- To determine the duration of response;
- To compare tumor volume changes measured by magnetic resonance imaging (MRI) in patients with progressing desmoid tumors/deep fibromatosis; and
- To evaluate quality of life as measured by patient-reported outcomes (PROs).

The study will enroll patients who are ≥ 18 years old with either 1) newly-diagnosed, progressing desmoid tumor/desmoid fibromatosis (DT/DF) not amenable to surgical resection or radiation therapy, 2) recurrent DT/DF following CR to initial therapy or 3) has preexisting DT/DF which

has demonstrated progression after initial therapy. All patients must have demonstrated an increase in size by 10% as measured by RECIST v1.1 criteria within the 6-month period prior to signing informed consent. Patients with previous treatment with gamma secretase inhibitors or anti-Notch antibody therapy are excluded. Use of chronic daily non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of DT/DF is not allowed. Patients are not required to have a *CTNNT1* mutation, but archival or new tumor tissue is required for disease confirmation.

Safety evaluations will include weekly physical examinations, vital signs, and laboratory analyses (serum chemistry) during the first cycle of therapy. Subsequent evaluations, including serum hematology and chemistry, physical exam, and ECG will occur at the end of Cycle 3, then every 3 cycles thereafter. Patient-reported outcome (PRO) evaluations will occur at baseline and then every 3 cycles. Patients will be evaluated by imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) at baseline and every 3 cycles thereafter. Tumor volume as measured by MRI will also be assessed at baseline and every 6 cycles thereafter. In the open-label extension phase, patients previously assigned to placebo will have weekly laboratory evaluations for the first cycle, and then every 6 cycles; other patients will have evaluations every 6 cycles. Monthly telephone follow-up will be performed. Patients will remain on study until they experience progression as defined by RECIST v1.1, premature discontinuation for any reason, or death from any cause.

There is currently no validated tool to assess patient-reported outcomes in patients with desmoid tumors. A desmoid tumor PRO was developed by Quintiles and Memorial Sloan Kettering to collect data on improvement in physical symptoms. The PRO has two components: a sign- and symptom-based instrument and an instrument to evaluate the impact on patients' lives. Analysis of PRO data will be a secondary endpoint; the proposed study will be used to validate the tool as an endpoint for future desmoid tumor clinical studies.

The primary endpoint, PFS, will be analyzed for the intent-to-treat (ITT) population and using a one-sided log-rank test to compare the distributions between nirogacestat and placebo. Secondary endpoints will be evaluated in a hierarchical fashion according to the following order: 1) overall response rate, 2) change in tumor volume, 3) patient-reported outcomes, and 4) duration of response. The sample size is based on the PFS endpoint; 94 patients are expected to be enrolled. Assuming a median 8 month PFS for patients taking placebo and a median of 20 months for patients receiving nirogacestat (corresponding to a hazard ratio of 0.4), a total of 51 events will be required to determine superiority to placebo with a power of 90% and 1-sided type I error rate of 0.025.

FDA sent Preliminary Comments to SpringWorks on March 15, 2018.

DISCUSSION

Nonclinical

1. *Does the Agency agree that the desmoid tumor indication is aligned with the scope of ICH S9 and that the proposed nonclinical toxicology studies are the only additional nonclinical studies required to support a nirogacestat NDA submission?*

FDA Response: No, FDA does not agree that the desmoid tumor indication is fully within the scope of ICH S9. While the tumors can cause debilitating disease, they are non-metastatic tumors with slow progression. This is consistent with the principles discussed in the ICH S9 Q and A draft document available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520942.pdf>.

FDA will not require additional general toxicology studies to support a future NDA submission for the proposed patient population; however, SpringWorks will need to conduct additional studies to the ones proposed in the meeting package to support a marketing application. Specifically, SpringWorks will need to include carcinogenicity studies in mice and rats to support an NDA. FDA recommends that SpringWorks submit an SPA for carcinogenicity studies to receive feedback and concurrence on these studies from FDA's Executive Carcinogenicity Assessment Committee (ECAC). For further information on submitting a carcinogenicity SPA, please refer the CDER Guidance for Industry: Carcinogenicity Study Protocol Submission available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078924.pdf>.

In addition, SpringWorks will need to conduct GLP-compliant studies of fertility. The need for post-natal development studies may depend, in part, on the results of the embryo-fetal development studies. If there are clear and significant findings of teratogenicity in one or more species in the embryo-fetal development studies, then a pre- and post-natal development study may not be necessary to support a future NDA for the proposed indication.

SpringWorks' Response to FDA's Preliminary Comment: SpringWorks thanks the Agency for the guidance provided. We would like to further discuss and gain agreement on the nonclinical study types and their timing with respect to the clinical program, as well as the data that will be available at the time of the initial NDA filing. The following nonclinical toxicology studies will be conducted concurrently with the Phase 3 study and submitted in the initial NDA filing (except for the 2-year rat carcinogenicity study):

- In vivo bone marrow micronucleus GLP study in rats
- Preliminary rat embryo fetal developmental (pEFD) toxicity study
 - o Based on the pharmacological mechanism of action, nirogacestat will have embryo toxic effects. Therefore, the pEFD study demonstrating these effects will be conducted in only 1 species. If the pEFD is negative, then a complete study in rats and rabbits will be conducted.
- Rat fertility study treating both males and females prior to mating and through

- Rat pre- and post-natal developmental study will only be conducted if there are no significant teratogenic findings with nirogacestat
- Transgenic mouse 1-month rasH dose range-finding study in the rasH parental strain will be conducted to set doses for the 6-month transgenic carcinogenicity study
 - o As suggested, these data will be included in a SPA to seek FDA's feedback on the 6-month study design.
- Transgenic mouse rasH 6-month carcinogenicity study will be included in the initial NDA
 - o SpringWorks proposes to not conduct the rat 2-year carcinogenicity study if the mouse rasH study demonstrates nirogacestat-induced tumor formation. However, if the rat carcinogenicity study is required, SpringWorks proposes that this study will be ongoing at the time of the initial NDA filing and the final study report will be provided post-approval.

Does the agency agree with the nonclinical toxicology studies outlined above and the timing of those studies to support marketing approval?

Discussion during the Meeting: FDA stated that the proposal may be acceptable. A 2-year rat carcinogenicity study could be requested as a PMR, if necessary, with the understanding that the 6-month carcinogenicity study in rasH transgenic mice would be provided at the time of the NDA submission.

FDA also stated that if the 6-month transgenic mouse carcinogenicity study is positive, then the 2-year rat carcinogenicity study may not be necessary.

2. *Does the Agency agree that the nonclinical toxicology studies completed to date with nirogacestat are sufficient to support the proposed pivotal clinical trial in alignment with the scope of ICH S9?*

FDA Response: Please see FDA's response to Question 1 regarding the applicability of ICH S9 to the proposed patient population. The descriptions of nonclinical studies discussed in the background section of the meeting package appear acceptable to support the initiation of a clinical trial intended to support registration for the treatment of patients with desmoid tumors.

Discussion during the Meeting: SpringWorks acknowledged FDA's comments. There was no further discussion of this item during the meeting.

Clinical

3. *Desmoid tumors are variable-growing, cause high morbidity due to infiltrating or exerting mass effects on vital structures and can be associated with normal life expectancy except in the case of intra-abdominal tumors. Given the nature of these tumors, we propose progression-free survival (PFS) as the primary endpoint for the proposed clinical study. Does the Agency support PFS as the primary endpoint for the proposed pivotal clinical trial to support a NDA submission?*

FDA Response: Progression-free survival may be an adequate primary endpoint to support registration in an adequately designed trial with sufficient follow-up. Approval based on PFS will depend on an overall favorable risk-benefit assessment considering the effects of nirogacestat on secondary endpoints and on safety. In the original IND submission, provide adequate justification for the assumption that patients receiving placebo will have a median progression-free survival of 8 months. Please also see additional comment 10 regarding justification for the acceptability of the proposed study population.

Discussion during the Meeting: SpringWorks acknowledged FDA's comments. There was no further discussion of this item during the meeting.

4. *Mortality from desmoid tumors is observed as a result of local infiltrative growth and tissue invasion, particularly with intra-abdominal disease, but due to the prolonged course of disease, overall survival is not an informative endpoint in desmoid tumors trials. In the proposed Phase 3 clinical study, placebo-treated patients will have the option to enter an open-label extension of the trial to receive nirogacestat upon progression of disease. Does the Agency concur that placebo-treated patients may receive open-label study drug upon meeting the criteria of Response Criteria in Solid Tumors (RECIST) 1.1 defined progression and that this option would not negatively impact the regulatory utility of this clinical trial to support NDA filing?*

FDA Response: Ultimately, it is SpringWorks's decision regarding whether to allow crossover. FDA cannot confirm based on the information in the meeting package if this proposal could impact FDA's ability to assess risk and benefit in an NDA submission. For example, the potential exists for inadvertent un-blinding (due to toxicity or lack thereof) to result in a bias between arms in the assessment of radiographic progression. Although blinded-central review is proposed, there could be differences in off-schedule imaging. Furthermore, substantial informative censoring may occur unless real-time blinded central review is employed. The proposal to allow crossover may also complicate SpringWorks's ability to assess Patient Reported Outcomes (see additional clinical comment #10 below) or toxicity.

For patients originally assigned to receive nirogacestat who are not on continuous therapy between the double-blind and open-label phase, include additional safety evaluations upon re-starting treatment. Also provide additional specific eligibility criteria for patients

permitted to continue nirogacestat following progression (e.g., patients should not have progressive disease that requires surgery to prevent organ dysfunction).

Discussion during the Meeting: SpringWorks acknowledged FDA's comments. There was no further discussion of this item during the meeting.

5. *The desmoid tumor PRO has been developed* [REDACTED] (b) (4)

[REDACTED] *The proposed clinical study would be the first study where this desmoid-specific PRO is utilized. Does the Agency concur that this tool would be acceptable for use as a secondary endpoint in the proposed pivotal clinical trial?*

FDA Response: While FDA agrees that SpringWorks should focus their PRO measurement strategy to collect and separately analyze disease-related symptoms and impacts, there is insufficient evidence to conclude that the proposed desmoid tumor PRO is fit-for-purpose for the context of the drug development program. The Paty et al (2017) abstract provided limited information on the instrument's development history.

To provide more specific advice on the desmoid tumor PRO instruments, provide the following information for FDA review and comment prior to initiating your pivotal study:

- a. Conceptual framework of the instrument
- b. Evidence of content validity (e.g., qualitative research with patients/clinicians) and psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change) obtained for this specific context of use, including final qualitative and quantitative summary reports
- c. Exact copy of the instrument as it will be administered in the pivotal trial (e.g., screen shots of electronic instruments) and any training materials and user manuals
- d. Proposed scoring algorithms with rationale for any weighting of items or response options in the domain scoring and corresponding information on how the instrument's scores will be analyzed as part of an endpoint including what constitutes meaningful score changes and methods to handle missing data

The following are additional comments on the desmoid tumor PRO based on face validity:

- a. In general, FDA agrees with the assessment of worst pain on an 11-point numeric rating scale. SpringWorks will need to provide 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.
- b. While fatigue may be an important concept in this target population, we do not agree that a single item can sufficiently measure fatigue as it is a

multidimensional concept (e.g., physical fatigue, mental fatigue, etc.). If fatigue is an important concept in this patient population, FDA recommends measuring the dimensions of fatigue that are most relevant.

- c. Swelling around the tumor(s) is a sign and not a symptom. Swelling may be best assessed by clinicians rather than patients, particularly, if the tumor(s) are around the abdominal wall or deep in the abdomen, or other areas of the body which are not easily observable by patients.
- d. Muscle weakness may be a challenging concept to measure in this target population. Additionally, patients may not be able to effectively assess muscle weakness on their own. Therefore, we recommend deleting this item.
- e. Because patients may have desmoid tumors in different joints which may restrict different types of movements, we recommend that questions related to functioning in a targeted extremity (i.e., lower extremity or upper extremity) are asked only for patients with tumor involvement in that area to provide meaningful information (e.g., questions related to the upper extremities are asked only for patients with desmoid tumors involved in their upper extremities, etc.). A performance outcome assessment may be an alternative option to assess physical function.
- f. SpringWorks should provide evidence to support measuring both severity and frequency attributes of effects related to reaching up (i.e., above the head) in this target population (how often have you had difficulty with reaching up?; what was your worst difficulty with reaching up?). Furthermore, SpringWorks may consider modifying the item wording and/or response options for impact item 10 (difficulty with reaching up) as the response options are not grammatically and logically consistent with the item stem.
- g. Some of the impact items measure broad concepts (e.g., sleep, fear, etc.) that might be influenced by factors beyond treatment and consequently not sensitive to the treatment effect of nirogacestat. FDA recommends that SpringWorks measure impacts associated with core disease symptoms (e.g., physical function). For impacts that are not associated to core disease symptoms, you may consider measuring for exploratory purposes.

SpringWorks' Response to FDA's Preliminary Comment: SpringWorks thanks the Agency for the thoughtful comments on the desmoid tumor patient reported outcome (PRO) tool. We will evaluate its use as an exploratory endpoint in the Phase 3 trial to collect data in order to determine how the instrument performs in this patient population.

Independent of the desmoid tumor PRO, SpringWorks intends to collect patient-reported outcomes using two PRO tools: the Brief Pain Inventory (BPI) and the MD Anderson Symptom Inventory (MDASI). It has been reported that up to 60% of patients with desmoid tumor suffer from pain, which can be caused by nerve compression or associated with tumor growth (Rigaux 2015).* Therefore, reduction in pain could be considered a clinically meaningful benefit. Importantly, in the Phase 2 nirogacestat study conducted by

the NCI, the MDASI tool was used to measure baseline changes for treated patients. The authors noted improvements in pain and other symptoms in patients with a partial response.

SpringWorks would like to gain clarity on whether the Agency's recommendation of using anchor scales (e.g. Patient Global Impression of Severity [PGI-S] and Patient Global Impression of Change [PGI-C]) to generate a threshold for improvement that represents a meaningful amount of change in the target patient population would apply if the BPI and/or MDASI tools were used in the Phase 3 study.

* Rigaux P, Lefebvre-Kuntz D, Penel N, "SOS Desmoïde". Pain burden in desmoid tumor patients: a survey of the French Advocacy Group SOS Desmoid. Bull Cancer 2015; 102: 213-216.

Discussion during the Meeting: SpringWorks stated that they would continue to work with the developer of the PRO tools.

Additionally, SpringWorks would like clarity on the use of the anchor scales for the PRO tools used in the study. FDA stated that the Agency's comment would apply to any PRO tool if the meaningful change score is not known.

FDA asked SpringWorks to submit the specific versions of the MDASI tool and the BPI tool that will be used in the proposed study. FDA also asked SpringWorks to provide further details on the specific endpoint(s) to be used in the analyses.

FDA stated that a rigorous assessment of PRO data (e.g., as a secondary endpoint) would provide for a stronger case to support clinical benefit. FDA would be open to further discussion of the PRO development strategy in a Type C meeting.

6. *SpringWorks intends to use changes in tumor volume as a secondary endpoint in the pivotal Phase 3 clinical study based on the Phase 2 NCI data. Can the Agency opine on current regulatory thinking regarding use of MRI in measurement of desmoid tumors?*

FDA Response: FDA does not object to SpringWorks's plan to evaluate response using a volumetric MRI assessment as a secondary endpoint to provide supportive clinical information. Both RECIST- and MRI-based assessments should be conducted using independent review masked to treatment assignment.

Additional information should be provided on the reliability and reproducibility of the volumetric assessments in a marketing application. Also provide information regarding the specific response threshold and regarding characteristics of desmoid tumors that make these tumors better assessed using a volumetric assessment. (b) (4)

Discussion during the Meeting: SpringWorks acknowledged FDA's comments. There was no further discussion of this item during the meeting.

7. *Does the Agency agree that the current cardiac safety data and ECG evaluations are sufficient to preclude implementation of extensive cardiac and ECG monitoring in the pivotal Phase 3 study?*

FDA Response: No. The information provided in the briefing package is not sufficient to characterize nirogacestat's effect on the QTc interval. FDA recommends that SpringWorks collect additional ECGs [around Tmax of Cycle 1 (day 8 or Day 15), and periodically thereafter] in all patients in the proposed study. These ECGs (for safety) can be read locally.

A TQT study in healthy subjects or in patients may be necessary to characterize these effects in the intended patient population. Submit a plan to characterize QTc for review.

SpringWorks' Response to FDA's Preliminary Comment: Nirogacestat nonclinical and clinical evaluations indicate a low risk for QT prolongation and pro-arrhythmic potential. While it is recognized that there is not a detailed characterization of QT intervals at many different nirogacestat concentrations, it is important to note that exposures at or above therapeutic levels have not revealed changes compatible with alterations in cardiac tissue conduction.

A QTc study in healthy subjects can be conducted to confirm the absence of QT prolongation at therapeutic and supratherapeutic nirogacestat concentrations. However, results from this study will be restricted to cardiac safety. Alternatively, assessment of potential ECG changes during the Phase 3 study (population PK analysis) offers the opportunity to determine potential cardiac safety assessment (including QT interval changes) at therapeutic concentrations as well as evaluate other potential extrinsic factors that could affect nirogacestat exposures and resultant changes in the therapeutic effect and adverse events.

Does the Agency agree that the inclusion of population PK analysis in the Phase 3 trial will suffice to assess cardiac safety in the target population and will obviate the requirement for a separate TQT study?

Discussion during the Meeting: FDA stated that a QTc analysis with a supratherapeutic dose of nirogacestat is necessary and that assessments in the proposed randomized trial will not suffice. FDA stated that this would likely need to be done in a separate trial with controls, unless this requirement is waived as is discussed in ICH E14. FDA stated that SpringWorks should provide justification for the safety of the proposed dose in the IND submission.

If the assessment of QTc is done in a separate QTc trial, FDA stated that it may reduce the need for additional ECG assessment in the proposed randomized trial (depending on the QTc study outcome).

FDA recommended that SpringWorks submit the proposed QTc study for comment prior to conducting the study.

8. *Does the Agency concur that the proposed single, randomized, placebo-controlled Phase 3 study is appropriately designed to generate adequate data to support traditional NDA approval of nirogacestat for the treatment of desmoid tumors?*

FDA Response: Please be advised that two adequate and well controlled studies are required for licensure. FDA may accept a single pivotal study, however, to support licensure if results show a statistically persuasive effect on a clinically meaningful endpoint that is internally consistent across relevant subgroups. The results of the single pivotal trial should be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products” at <http://www.fda.gov/cder/guidance/index.htm>.

In addition, a minimum safety database of 300-600 patients treated at the dose and regimen intended for labeling would be sufficient to exclude an adverse event rate occurring at a rate of 3%. Any number less than this should be justified in the NDA as adequate to make a risk/benefit determination and provide direction for safe use in product labeling.

Discussion during the Meeting: SpringWorks acknowledged FDA’s comments. There was no further discussion of this item during the meeting.

Regulatory

9. *Does the Agency agree that nirogacestat for the treatment of desmoid tumors meets the eligibility criteria for Fast Track designation?*

FDA Response: FDA agrees that desmoid tumors may be a serious condition with an unmet medical need; however, SpringWorks should describe the patient population for whom systemic therapy is warranted (see comment 10). In the Fast Track designation request, describe how the development program will demonstrate an effect on a serious aspect of the condition. A final determination will be based upon review of the Fast Track designation request submission.

Discussion during the Meeting: SpringWorks acknowledged FDA’s comments. There was no further discussion of this item during the meeting.

Additional comments:

Clinical

10. With regard to the intended population of the study:
 - a. FDA recommends that SpringWorks revise the study to enroll a patient population that is likely to support a favorable risk-benefit assessment following review of the study results. For example, it is unclear if all patients (e.g., patients with low burden of overall disease) who have tumors that grow by 10% or who have recurrence following surgery should be candidates for long-term systemic treatment. Provide justification in the IND regarding the eligibility criteria.
 - b. To facilitate analyses of PRO data [REDACTED] ^{(b) (4)}, FDA recommends that SpringWorks enroll patients with disease-related symptoms. First, palliation is a stronger endpoint in a risk-benefit assessment compared with time to symptom development. Second, allowance of crossover at progression may make time to symptom development uninterpretable because many patients may progress (and crossover) prior to development of symptoms.
 - c. Depending on whether nirogacestat is expected to affect growth, and depending on the risk-benefit assessment of the trial in the specific population (e.g., based on severity of underlying disease), consider inclusion of adolescents age 12 and older. Provide justification in the IND regarding the inclusion or exclusion of adolescent patients.
11. To facilitate analysis of study results (including PRO data), FDA recommends stratification of randomization based on location of disease.
12. In the protocol submitted with the original IND:
 - a. Include an additional safety visit with physical examination and laboratory analyses at 8 weeks.
 - b. Consider collecting data regarding clinical events associated with morbidity in desmoid tumors (e.g., hospitalization for small bowel obstruction, hospital admission for pain, surgery) as supportive data.

Discussion during the Meeting: SpringWorks acknowledged FDA's comments. There was no further discussion of this item during the meeting.

Patient-Reported Outcomes

13. [REDACTED] ^{(b) (4)}

- 
14. General trial design considerations for PRO
- a. Consider limiting the number of assessments to avoid measurement redundancy and respondent burden.
 - b. Optimize the frequency and timing of assessments. Increased assessments early in therapy is important to capture acute toxicity and tolerability and can maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.
 - c. Prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at the time of crossover and early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and included in the analysis dataset.
 - d. Carefully record the use of concomitant medications that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain).
 - e. When appropriate and feasible, FDA recommends electronic data capture using a device with a reminder or alarm function as this tends to facilitate operation, minimize the extent of missing data, and allows for the collection of other important information (e.g., timestamps for data input). Refer to the FDA Guidance for Industry on electronic source data.¹
 - f. If you proceed with electronic data capture, we recommend that SpringWorks perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device.
 - g. FDA also recommends that SpringWorks implement a back-up plan (e.g., web-

¹ Guidance for Industry: Electronic Source Data in Clinical Investigations
(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf>)

or paper-based) in case of any malfunctions with the electronic devices, prior to using the devices in the proposed trial.

- h. PRO instruments will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. Refer to the ISPOR principles for the translation and cultural adaptation process.²
- i. FDA recommends that SpringWorks include multiple anchor scales in the planned clinical trial to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the selected PRO measures. Consider including a static, current patient global impression of severity (or PGI-S) and a patient global impression of change (PGI-C) to generate a threshold for improvement that represents meaningful amount of change in the target patient population. Examples of the PGI-S and PGI-C are as follows:

Patient Global Impression of Severity (PGI-S) Example:

Please choose the response below that best describes the severity of your <SYMPTOM/OVERALL STATUS/ETC> over the past week.

- None
- Mild
- Moderate
- Severe

Patient Global Impression of Change (PGI-C) Example:

Please choose the response below that best describes the overall change in your <SYMPTOM/OVERALL STATUS/ETC> since you started taking the study medication.

- Very much Better
- Moderately Better
- A Little Better
- No Change
- A Little Worse
- Moderately Worse
- Very much Worse

² Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

Discussion during the Meeting: SpringWorks acknowledged FDA’s comments. There was no further discussion of this item during the meeting.

Clinical Pharmacology

15. Specify in the protocol how nirogacestat is given with respect to food intake (e.g., without regard to food).
16. Include a PK sampling plan to collect sparse PK samples for all patients who will receive nirogacestat to allow for population pharmacokinetics and exploratory exposure-response analyses for safety and efficacy in the target population.
17. Submit a meeting request to discuss the clinical pharmacology development plan. Assess the following items to facilitate rational dose selection for efficacy and safety trials and dose adjustment for specific populations:
 - a. Optimal systemic exposure of parent drug and any major active metabolites in the general patient population
 - b. Effect of intrinsic factors (e.g. renal or hepatic impairment, disease, age, sex, body weight) and extrinsic factors (e.g., food, concomitant drugs) on systemic exposure of parent drug and any major active metabolites
 - c. Effect of parent drug and major metabolites on the systemic exposure of concomitant drugs
 - d. Effect of concomitant gastric acid-reducing agents on the pharmacokinetics of the drug, if the drug is less soluble at pH 6.0–6.5 (with a solubility < clinical dose/250 mL) than at pH 1–2
18. Refer to the following FDA documents of “Guidance for Industry” for greater details regarding the above recommendations:
 - a. [*Bioanalytical Method Validation*](#)
 - b. [*Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*](#)
 - c. [*Population Pharmacokinetics*](#)
 - d. [*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*](#)
 - e. [*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*](#)
 - f. [*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*](#)
 - g. [*E14 Clinical Evaluation of QT/QTc*](#)

19. Provide highlighted Clinical Pharmacology information in subsequent relevant meeting and protocol submissions by updating Tables 1 and 2 (as attached). This is a new request, but not a requirement, for all INDs in order to facilitate timely and thorough reviews.

Table 1: Highlights of Clinical Pharmacology

General Information	
Chemical Structure and major physical and chemical properties	- the chemical structure of the compound and MW - Log P, pKa, solubility (in water and in buffers at different pH levels)
Indication (for this IND)	- the proposed indication - other relevant indications under different INDs.
Route and formulation type (for this IND) and formulation strengths	- Oral, IV, SC or local, etc - Tablet, capsule, IV solution, lyophilized powder, etc.
Planned dose levels (for this IND)	- Planned dose levels for this IND - Dose levels for other indication(s)
Mechanism of action (for this indication)	- the proposed mechanism of action for this indication - the proposed mechanism of action for other indication(s)
Dose and AEs	
Therapeutic dose and exposure (for this IND)	- the proposed clinical dosing regimen(s) for this indication - the proposed clinical dosing regimen(s) for other indications - Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose - Mean (%CV) Cmax and AUC at steady state with the maximum proposed clinical dosing regimen
Maximum tolerated dose	- Clinical - non-clinical data

Table 2: Completed /Ongoing/ Planned Clinical Pharmacology Studies:

Study No.	Study Title	Study Objectives	Study subjects	Study Design	Current Status
			N= Age= Gender= Healthy/Disease=		Completed Ongoing Planned

Discussion during the Meeting: SpringWorks acknowledged FDA’s comments. There was no further discussion of this item during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) **within 60 days of this meeting**. The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit ^{(b) (4)} based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. ^{(b) (4)}



NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

SpringWorks' response to FDA's Preliminary Comments

4 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NATALIYA N FESENKO
03/21/2018