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Stanford MEDICINE

Phase 2 Study of Cryoablation and Nirogacestat for Desmoid Tumor

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Single-Center

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Regulatory Information

Study Agent:	Nirogacestat
Other Agent(s):	Cryoablation
IRB of Record:	Administrative Panels on Human Subjects in Medical Research (“Stanford IRB”); Research Compliance Office; Stanford University
IND for this study:	IND 164301
IND Cross-reference:	SpringWorks Therapeutics IND 138207
Funding Source:	SpringWorks Therapeutics

STATEMENT OF COMPLIANCE

SPONSOR-INVESTIGATOR STATEMENT

I have read and agree to the study, as detailed by this protocol document. I am aware of my responsibilities as an Investigator pursuant to the clinical trial protocol, the guidelines of Good Clinical Practice (GCP) [a], the Declaration of Helsinki [b], and the applicable Code of Federal Regulations (CFR) at Title 21 [c] and Title 45 Part 46 [d], as well as my responsibilities as a Sponsor-Investigator and IND-holder under 21 CFR §312 or §812 [c], as a ClinicalTrials.gov Responsible Party under 42 CFR Part 11 [e] as promulgated pursuant to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), and other applicable requirements of the participating institutions including the Stanford Cancer Institute, the Stanford Hospitals and Clinics, Lucile Packard Children's Hospital, and/or the Stanford University Medical Center. I agree to conduct the trial according to these regulations, guidelines, and requirements, and to appropriately direct and assist the participating staff under my authority, and that all staff members are aware of, and trained in, their clinical trial responsibilities.

All key study personnel have completed Human Subjects Protection Training.

Site Principal Investigators are expected to assure that no deviation from, or changes to the protocol, will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) of record, except where necessary to eliminate an immediate hazard(s) to the trial subjects.

Sponsor-Investigator's Name: Nam Bui, M.D.

Name of Site: Stanford Cancer Institute
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Principal Investigator's Signature: _____ **Date**: _____

a. FDA Guidance for Industry: current revision of the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines E6.
b. World Medical Association, Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients.
c. United States Code of Federal Regulations (CFR), Title 21, "Food and Drugs."
d. CFR, Title 45 "Public Welfare;" Part 46 "Protection of Human Subjects."
e. CFR, Title 42 "Public Health;" Part 11 "Clinical Trials Registration and Results Information Submission."

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PROTOCOL SYNOPSIS

Study Title	Phase 2 study of Cryoablation Plus Nirogacestat for Desmoid Tumor
Study Drug and Procedure	Nirogacestat (Ogsiveo™) in combination with cryoablation
Study Description	Single-center, single arm study
Study Phase	Phase 2
Study Purpose	Treatment
Primary Objective	To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy by evaluation of the clinical benefit rate (CBR = CR + PR + SD) at 1 year in subjects with progressive or symptomatic desmoid tumor. Response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
Primary Endpoint	Clinical benefit rate (CR + PR + SD) at 1 year from treatment start with nirogacestat. Response will be assessed according to RECIST v1.1.
Secondary Objective(s)	1. To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy by evaluation of the clinical benefit rate (CBR) at 1 year in subjects with progressive or symptomatic desmoid tumor. Response will be assessed according to the modified RECIST criteria (mRECIST). 2. To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy by evaluation of median disease progression. 3. To assess the effects of cryoablation plus nirogacestat on tumor response (as defined by objective response rate) at 1 year 4. To assess the time to response from the start of treatment with nirogacestat to the first objective tumor response 5. To assess the duration of response from time of response to time of progression 6. To assess safety and tolerability of cryoablation plus nirogacestat in subjects with progressive or symptomatic desmoid tumors
Exploratory Objective	• To evaluate effects of cryoablation plus nirogacestat on quality of life. • To correlate changes during treatment with response using the Nanostring CosMX SMI on biopsy samples.

Secondary Endpoints	1. Clinical benefit rate (CR + PR + SD) at 1 year from treatment start with nirogacestat. Response will be assessed according to mRECIST. 2. Median progression free survival will be determined radiographically using RECIST v1.1, mRECIST and volumetrically (change in tumor volume as assessed by MRI volumetric). 3. Objective response rate at 1 year (RECIST v1.1, mRECIST and MRI volumetric); the percentage of subjects who start study treatment and achieve an objective response (CR or PR), will be calculated. 4. Time to response (RECIST v1.1, mRECIST and MRI volumetric) 5. Duration of response (RECIST v1.1, mRECIST and MRI volumetric) 6. AEs will be tabulated with frequencies and percentages for grade, severity, status, and relationship to study drug or study procedure. Assessment will be from time of consent until 30 days after the last treatment.
Exploratory Endpoint	• Changes from baseline in patient-reported outcomes (EQ-5D-3L)
Indication	Desmoid tumor
Sample Size	Up to 23 enrolled subjects, to achieve 20 evaluable subjects
Eligibility Criteria	Due to length, the Eligibility Criteria are only presented in one instance. Eligible subjects will be subjects ≥ 18 years of age with progressive or symptomatic desmoid tumor that is at least 50% but less than 75% treatable with cryoablation. See Section 3, Subject Selection.
Dose	Nirogacestat 150 mg po BID (150 mg twice-daily) One cycle of treatment = 28 days.
Treatment and Procedural Summary	1. Nirogacestat 150 mg by mouth twice-daily continuously for Cycles 1 through 3. 2. Cryoablation procedure (single session) of one tumor mass between Cycles 3 and 4 of nirogacestat treatment. 3. Continued treatment with nirogacestat for Cycles 4 through 26. Treatment with nirogacestat may continue via this study protocol for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, start of new anticancer therapy (as defined in Sections 5.7.2 and 5.7.3), or one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs. 4. After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

Statistical Considerations	Descriptive statistics (response rate, time to response, progression-free survival). Comparison to historical controls of nirogacestat alone and Stanford-treated cryoablation patients. The primary outcome is clinical benefit rate (CR + PR + SD) at 1 year. We plan to enroll a total of 20 subjects. Assuming a null CBR of ≤ 0.5 versus an alternate CBR of 0.8, we have a maximum statistical power of 100.0% to detect a difference of 0.3 using a one-sided exact test with a type 1 error of 0.05.
Study Duration	Duration of treatment for a subject via this study protocol is up to 24 months (26 cycles of treatment). This study will be complete when the last study data, including follow-up, has been collected, and analysis is complete. The duration of enrollment for this study will be approximately 25 months (including the initial 28-day screening period). Based on the determination of clinical benefit after 12 months' treatment, and 3 months for analysis of the primary endpoint, preliminary results for the primary endpoint are expected to be available approximately 40 months from the start of enrollment. Based on 25 months to completely enroll, and overall individual treatment period of approximately 24 months, the overall period until treatment is complete will be about 49 months from the start of enrollment. The complete final analysis (including primary and secondary analyses and safety assessments) and termination of all study activities is expected to be at about 53 months. Key milestones are as follows. • The per-subject screening period is approximately 28 days. • The duration of enrollment (minus the screening period) is approximately 24 months. • The per-subject primary endpoint (clinical benefit) is assessed after 12 months' treatment. • The per-subject duration of treatment is approximately 24 months (26 cycles of treatment). • Final subject visit is about 30 days after last treatment. • Nominal duration of subject participation is up to about 26 months. • Final study analysis is expected to take about 3 months.
Subject Duration	Approximately 26 months (28-day screening period, approximately 24 months of treatment, and End of Treatment visit about 30 days after last study treatment).

PROTOCOL SCHEMA

Subject Consent

Screening (Day 1 to Day 28):

(Collect archival histology report, EQ-5D-3L questionnaire, ECG, serum pregnancy test, routine labs & scans).

(Collect archival tumor sample if subject opts-in to tissue collection for correlative studies).

(Demographics, medical history, physical exam, vital signs, height, weight, performance status, adverse event [AE] & concomitant medication [conmed] review)

Treatment: 3 cycles of Nirogacestat

1 cycle = 28 days

(Routine labs, urine pregnancy test, and EQ-5D-3L questionnaire every cycle)

(Physical exam, vital signs, weight, performance status evaluation, AE and concomitant medication review every cycle)

(Radiologic imaging [MRI] every 3 cycles = every 12 weeks ± 14 days [ie, before Cycle 4]).

Cryoablation (between Cycles 3 and 4)

(Hold nirogacestat on day of procedure)

(Cryoablation may occur anywhere between Cycles 3 and 4; however, staging scan should be done prior to cryoablation procedure).

(Biopsies will be obtained at the time of cryoablation, if subjects elect to opt-in to tissue collection for correlative studies).

Continued on next page

Continued Treatment with Nirogacestat (Cycle 4 onwards)

Maximum duration of treatment with nirogacestat via this study is 24 months (26 cycles of treatment).

(Routine labs and urine pregnancy test, every cycle for Cycle 4 (C4) through Cycle 6 (C6), then every 3 cycles [ie, C9, C12, C15, C18, C21, C24])

(EQ-5D-3L questionnaire every cycle for Cycles 5 through 9, then every 3 cycles [ie, C12, C15, C18, C21, C24]. There will not be a questionnaire for Cycle 4. For those cycles where subjects are not having an in-person visit (C7 & C8), the EQ-5D-3L questionnaire will be sent to subjects via secure Email or MyHealth Epic message for completion and return via secure Email or MyHealth Epic message).

(Physical exam, vital signs, weight, performance status evaluation, AE and concomitant medication review every cycle for C4 through C6, then every 3 cycles [C9, C12, C15, C18, C21, C24])

(Radiologic imaging [MRI] every 3 cycles = every 12 weeks ± 14 days (i.e., Before C7, C10, C13, C16, C19, C22, C25).

End of Treatment (EOT)

EOT visit 30 days ± 7 days from time of last treatment.

(Routine labs, urine pregnancy test, performance status evaluation, AE and concomitant medication review, imaging)

(Subjects may be seen in person, by video visit or may be contacted by phone. If in-person visit, then physical exams, vital signs, weight, and EQ-5D-3L questionnaire will be done. If a video visit or phone visit is done, then EQ-5D-3L questionnaire will be sent to the subject via secure Email or MyHealth Epic message for the subject to complete and return via secure Email or MyHealth Epic message).

LIST OF ABBREVIATIONS & TERMS

Accrual date	Subject's on-study date (per OnCore)	IRB	Institutional Review Board
AE	Adverse event	IV	Intravenous
AML	Acute myeloid leukemia	KPS	Karnofsky performance status
ALT	Aspartate aminotransferase	LLN	Lower limit of normal
AST	Alanine aminotransferase	LVEF	Left ventricular ejection fraction
BID	*bis in die* (twice-a-day)	MDS	Myelodysplastic syndrome
BSA	Body surface area	NCI	National Cancer Institute
CBC	Complete blood count	Oncore	OnCore Enterprise Research System
CBR	Clinical Benefit Rate	On-study Date	Defined (per OnCore) as date of subject's first research-related procedure, scan, or treatment
CFR	Code of Federal Regulations	OS	Overall survival
CI	Confidence interval	PD	Progressive disease, tumor progression
C_{max}	Maximum concentration of drug	PFS	Progression-free survival
CNS	Central nervous system	PLT	Platelet
CR	Complete response	PR	Partial response
CRF	Case report / record / form	QoL	Quality of life
CTCAE	Common Terminology Criteria for Adverse Events	RECIST	Response evaluation criteria in solid tumors
DLT	Dose-limiting toxicity	RR	Response rate
DSMB	Data Safety Monitoring Board	SAE	Serious adverse event
DSMC	Data Safety Monitoring Committee	SCI	Stanford Cancer Institute
DSMP	Data Safety Monitoring Plan	SD	Stable Disease
ECG	Electrocardiogram	SGOT	Serum glutamic oxaloacetic transaminase
ECOG	Eastern Cooperative Oncology Group	SIN	Subject identification number
EOT	End of Treatment	SRC	Scientific Review Committee
FDA	Food and Drug Administration	Stanford IRB	Administrative Panels on Human Subjects in Medical Research
GCP	Good Clinical Practice	TBI	Total body irradiation
Hgb	Hemoglobin	TLI	Total lymphoid irradiation
HIV	Human immunodeficiency virus	TTP	Time-to-progression
ICH	Int'l Conference on Harmonization	ULN	Upper limit of normal
ICMJE	Int'l Committee of Med Journal Editors	WBC	White blood cell
IND	Investigational New Drug		

INTRODUCTION

1.1. Study Rationale

In this trial, we propose the combination of systemic therapy with nirogacestat and cryoablation to maximize the benefits of both modalities for subjects with growing or symptomatic desmoid tumors. It is hypothesized that the combination will provide long-lasting disease control and a quick time to treatment response.

This phase 2 study will enroll participants ≥ 18 years of age. The pharmacokinetics (PK) and optimal dosing of nirogacestat in younger participants has not been established.

Treatment will consist of a 3-month lead-in period of nirogacestat, followed by cryoablation procedure (single treatment), followed by continued nirogacestat treatment for up to a total of 24 months (maximum 26 cycles of treatment), unless disease progression or one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs. The lead-in period will allow assessment of the response to nirogacestat-alone and potentially lead to improved cryoablation success if there is tumor shrinkage.

In order to assess increased efficacy of combination therapy over single-modality cryoablation, results will be compared to historical data from the Stanford existing cryoablation population treated at Stanford. For these subjects, two-thirds are unable to be completely ablated and most of those patients will have clearly recurrent disease at 6 months. Therefore, we hypothesize that adding on nirogacestat to cryoablation will lead to an 80% clinical benefit rate at 1 year.

Nirogacestat alone has a RECIST response of 29% of patients at a median of 24 months. [1] At 1 year, the ORR was 2 of 17 (12%).

To evaluate effects of cryoablation plus nirogacestat on quality of life (QOL), we will collect patient-reported outcome (PRO) measures using the EQ-5D-3L.

To remain consistent with prior inclusion criteria for desmoid trials, we will only include subjects with growing or symptomatic desmoid tumors. In addition, we will standardize the cryoablation procedure by limiting subjects to 1 cryoablation treatment session at time of intervention and desmoid tumors that can be at least 50% treated with cryoablation but are < 75% cryoablatable.

1.2. Background

1.2.1. Study Disease

Desmoid tumor is a non-metastasizing but locally aggressive neoplasm that can occur anywhere throughout the body. Desmoids are rare with an estimated incidence in the general population of 2 to 4 per million population per year. [2] Affected populations can occur in any age group, most commonly seen between the ages of 15 to 60, with a slight preponderance among women than men. Affected locations can include upper and lower extremities, trunk, head and neck region, abdominal wall, and intra-abdominal. The natural history of desmoid is extremely

variable and there are some tumors that spontaneously regress, some that remain stable for years, and some that have unrelenting growth. Tumors that occur intra-abdominally and are associated with familial adenomatous polyposis (FAP) tend to be multi-focal, more aggressive, and potentially fatal. Under histologic exam, desmoid tumors appear as spindle cells in an abundant fibrous stroma with low cellularity, few mitotic figures, and absent necrosis. Staining for nuclear beta-catenin is commonly seen and a fair amount of desmoids have mutations in Catenin Beta 1 (CTNNB1). Other mutations seen are adenomatous polyposis coli (APC) mutations, which are found in FAP patients.

For growing desmoid tumors, options include surgical resection (which can be morbid and has a high recurrence rate), radiation therapy, systemic therapy [such as chemotherapy or vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs)], and more recently, ablation procedures, such as cryoablation or high intensity focused ultrasound (HIFU). However, each approach has its pros and cons. For radiation therapy, local control rates are excellent, with approximately 80% at 3 years, however, there are potentially devastating albeit rare long-term side effects such as secondary malignancies. [3] For systemic therapy, the time to response is longer (sorafenib trial median of 9 months), and there is associated systemic toxicity. Chemotherapy (doxil, methotrexate/vinblastine) have higher response rates and faster time to response; however, they have more significant side effects than TKIs. For ablation procedures, it may not be technically feasible to totally treat the tumor due to proximity to critical structures such as nerve and skin, there is often a need for multiple treatment sessions. Tumor recurrence or progression is inevitable for tumors that cannot be completely ablated.

1.2.2. Study Agent / Procedures

Systemic therapy with nirogacestat plus cryoablation procedure (single session) in progressive or symptomatic desmoid tumor.

The starting dose of nirogacestat is based on results from a phase 1 dose-finding study (A8641014) in subjects with advanced solid tumors. In this study, a maximum-tolerated dose (MTD) of 220 mg by mouth twice-daily (BID) was established in subjects administered nirogacestat BID continuously for 21 days, and a recommended phase 2 dose (RP2D) of 150 mg by mouth BID was determined from additional subjects with advanced solid tumors enrolled in the expansion cohort of the phase 1 study. [4] The completed randomized phase 3 trial of nirogacestat vs placebo (DeFi Study) also has a starting dose of 150 mg PO BID.

See Section 4 (Study Intervention) and Section 5 (Treatment Plan) for additional information on study agent and procedures. See the nirogacestat Investigator's Brochure[4] and Ogsiveo™ (nirogacestat) package insert[28] for additional information.

1.2.3. Nirogacestat Overview, Indications, and Mechanism of Action

This information is from the nirogacestat Investigator's Brochure. [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

Nirogacestat (PF-03084014) is a potent, small molecule, selective, reversible, non-competitive inhibitor of γ-secretase (GS). Nirogacestat is being investigated for the treatment of desmoid

tumors. The rationale for developing a GS inhibitor in the desmoid tumor indication is supported by evidence that Notch signaling, activated by GS cleavage, is a growth driver in desmoid tumors and contributes to growth and proliferation of a wide range of cell types. An additional potential mechanism of action involving GS inhibition by nirogacestat is the prevention of the release of cytoplasmic β catenin by blocking the proteolytic cleavage of cadherin complexes (Marambaud et al. 2002; Jang et al. 2011). This well conserved feature of cell-cell adhesion is an important factor in the regulation of Wnt signaling. The critical components of this regulation of the Wnt pathway are active in DT. Collectively, these observations support a therapeutically relevant mechanism of nirogacestat mediated GS inhibition that reduces activated Notch and possibly β-catenin signaling resulting in antiproliferative and apoptotic responses.

There is obligatory signaling via the Notch receptor in normal cells, which serves as a key regulator of cell differentiation, proliferation, and apoptosis. Aberrant signaling via the Notch pathway is known to be tumorigenic.

The Notch receptor is comprised of extracellular, transmembrane and intracellular domains. Upon ligand binding, the receptor undergoes a conformational change leading to an initial cleavage event by the A disintegrin and metalloproteinase family of metalloproteinases. This leads to a second cleavage event mediated by the GS enzyme, liberating the notch intracellular domain (NICD). The NICD translocates to the nucleus where it associates with additional proteins involved with the transcriptional regulation of Notch target genes. GS and Notch signaling potentially play important roles in several biologic mechanisms, including tumor growth and survival, endothelial function, angiogenesis and normal stem cell differentiation and development. Activating mutations of the Notch receptor, loss of Notch negative regulators, and indirect activation via other pathways, such as the Ras pathway, lead to increased Notch signaling and NICD-dependent changes in CyclinD1, cMyc, p27 and Hes/Hey gene expression.

1.2.4. Nirogacestat Clinical Trial Experience

This information is from the nirogacestat Investigator's Brochure. [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

Nirogacestat has been studied in 6 completed phase 1 clinical trials conducted in healthy adult human volunteers (studies A8641001, A8641002, A8641008, NIR-DT-101, NIR-DT-102, and NIR-DT103). In these trials, single oral doses of nirogacestat up to 150 mg and multiple doses up to 95 mg (A8641002) once daily for up to 14 days have been administered. Nirogacestat has also been studied in subjects with advanced cancers either as monotherapy or in combination with other agents (Studies A8641014, A8641016, A8641019 and A8641020) utilizing doses from 20 mg to 330 mg BID, continuously. In addition, an investigator-initiated phase 2 study (NCI Study 14-C-007 / WI180798) was conducted with nirogacestat (150 mg BID) in subjects with desmoid tumors. A Phase 3, double-blind, placebo-controlled study (NIR-DT-301) was also conducted with nirogacestat (150 mg BID) in patients with desmoid tumors. The following is a brief summary of the clinical findings from these studies.

Nirogacestat was deemed to be safe and well tolerated after single doses and repeat doses for all dose levels evaluated in healthy volunteers. No maximum-tolerated single or repeat dose

was identified in studies A8641001 and A8641002 respectively, with dose escalation having been terminated due to achievement of the Alzheimer's disease protocol-defined exposure limits.

Adverse events (AEs) across the five healthy volunteer phase 1 trials were generally mild and transient in nature. The most frequently observed AEs were headache, dizziness, and fatigue. In studies with a lumbar puncture (A8641002, Part 2 and A8641008), back pain was also frequently observed. There were no clinically relevant treatment-related changes in vital signs or electrocardiograph endpoints. No clinically important changes were observed in clinical safety laboratory endpoints, including serum chemistry evaluations, hematological profiles, and urinalysis. There were dose-related trends for increases in eosinophils and immature B cell sub-sets observed after administration of nirogacestat 95 mg daily in study A8641002. These observations were interpreted as being potentially indicative of effects of nirogacestat on the Notch receptor.

Evaluation of the nirogacestat pharmacokinetic characteristics indicated that the compound was rapidly absorbed, with median time of occurrence of Cmax (Tmax) values of 0.5 to 1 hour generally observed. Nirogacestat exposure increased with escalating single and repeat doses, with some evidence for greater than dose proportional increases observed across the dose range studied in trials A8641001 and A8641002. The terminal elimination half-life of nirogacestat was approximately 19 hours after single doses and 26 hours after multiple doses. There was evidence that nirogacestat concentrations in cerebrospinal fluid (CSF) may reach equilibrium with unbound serum concentrations at steady-state. Using estimated unbound serum concentrations of nirogacestat (human fraction unbound of 0.004), the average unbound serum concentration at steady-state was comparable to concentrations measured in CSF, indicating potential exposure to the central nervous system.

Administration of nirogacestat resulted in a dose-dependent decrease of mean plasma peptides (Aβ40 and total Aβ) of amyloid precursor protein (APP) between approximately 25% to 40% at nadir, consistent with the compound's mechanistic action as a GS inhibitor. This period of suppression of Aβ formation was followed by a period of rebound potentiation of up to 80% above baseline. In contrast, no significant effects of nirogacestat on CSF Aβ were observed after single doses, using serial CSF sampling methodology, or at 8 hours post-dose following steady state administration. The relative lack of CNS exposure and effects on CSF AB are likely due to the high serum protein binding, which leave insufficient levels of unbound nirogacestat accessible for CNS penetration.

Study A8641014 was a multi-center, open-label, non-randomized, phase 1 dose-finding study in subjects with advanced solid tumor malignancies and subjects with relapsed/refractory acute T-ALL. In the single-agent, dose-finding component of the study, the maximum tolerated dose (MTD) of nirogacestat administered BID continuously for 21 days was estimated to be 220 mg BID in subjects with advanced solid tumors (MTD-S). After definition of the MTD-S at 220 mg BID, additional subjects were enrolled in the study expansion cohort and dosed at 150 or 220 mg BID. The recommended phase 2 dose (RP2D) in subjects with advanced solid tumors

(RP2D-S) was determined to be 150 mg BID by comparing the tolerability, pharmacokinetic and pharmacodynamic profile of nirogacestat at 220 and 150 mg BID.

The MTD in subjects with refractory or relapsed T-ALL/LBL (MTD-L) leukemia was not established, and the study expansion cohort for this subject population was terminated prior to enrollment; consequently, the RP2D in this subject population (RP2D-L) has not been determined.

A total of 64 adult subjects with advanced solid tumor malignancies were enrolled in this study, received study treatment, and have data in the safety database. The most common reason for discontinuation from nirogacestat was objective progression or relapse of disease (32 subjects). Subjects had a mean age of 55.6 years, with about half (31 [48.4%] subjects) being male and most (57 [89.1%] subjects) being white. The most common primary diagnosis was desmoid tumor (9 subjects), with a mean duration since diagnosis of 7.7 years.

All subjects received surgeries and about half of subjects received radiation therapy. The majority (60 [93.8%] subjects) received systemic therapies and more than half (35 [54.7%] subjects) had systemic therapies for > 3 regimens. Of the 64 subjects with solid tumors, 62 experienced at least 1 AE, and 54 experienced at least 1 treatment-related AE (1 subject with a Grade 1 AE of upper respiratory infection was excluded from the analysis due to a database error). The most common (≥ 20% subjects) treatment emergent adverse events (TEAEs), independent of causality, reported in subjects with advanced solid tumors were diarrhea, nausea, fatigue, vomiting, hypophosphatemia, decreased appetite, cough, and rash; all of these events were considered to be treatment related in some subjects. The majority of AEs were considered mild to moderate, but treatment-related Grade 3 hypophosphatemia, diarrhea, and rash were reported in more than 1 subject. The only treatment-related Grade 4 AE was anaphylactic shock reported in 1 subject, an event thought to be related to co-administration of intravenous morphine. No clinically relevant changes in vital signs or electrocardiograph end points were reported. The severe hematology laboratory test abnormalities reported were lymphocytes (absolute) and platelets. The most frequently reported (in more than 1 subject) severe serum chemistry abnormalities were hypophosphatemia, hypokalemia, hyponatremia, and hyperglycemia.

In this study, 5 first-cycle dose-limiting toxicities (DLTs) were observed among the subjects with advanced solid malignancies. The DLTs reported were Grade 4 anaphylactic shock for 1 subject, thought to be related to intravenous morphine (100 mg BID); Grade 3 diarrhea for 2 subjects (150 and 220 mg BID); Grade 3 rash for 1 subject (330 mg BID); and inability to administer 80% of planned dose during Cycle 1 for 1 subject (330 mg BID). Based on the observed DLT, the MTD for subjects with solid tumors was estimated to be 220 mg BID.

Although efficacy was not the primary objective of the dose-finding study, subjects with advanced solid tumors were evaluated for best response according to RECIST 1.0. There were 46 subjects with solid tumors evaluable for response. Overall, objective response (OR) rate (ORR) was 13.0% (95% CI, 4.9 to 26.3) for subjects with solid tumors. 6 subjects had an OR, consisting of 1 complete response (CR) in a subject with thyroid cancer and 5 partial responses (PRs) observed in subjects with desmoid tumors. Of the 7 subjects with desmoid tumors

evaluable for response, 5 subjects (71.4% [95% CI, 29.0-96.3]) achieved PR and 2 subjects achieved stable disease as best overall response (BOR). No complete response, objective progression, symptomatic deterioration or early death were reported in the evaluable desmoid tumor subjects. Overall, ORR was 55.6% (95% CI, 21.2-86.3) for the 9 desmoid tumor subjects. The thyroid subject with CR later had recurrence of disease but was censored at the last disease assessment of CR due to missed tumor assessments.

A total of 8 adult subjects with T-ALL/LBL were enrolled prior to early termination of the study and have data in the clinical database. The dose used in this cohort was 150 mg BID. The most commonly (≥ 20% subjects) reported TEAEs, independent of causality, for subjects with T-ALL/LBL were nausea, vomiting, constipation, diarrhea, dyspepsia, pyrexia, alanine transaminase (ALT) increased, blood bilirubin increased, neuropathy peripheral, and pruritus; these events were considered to be treatment related in some subjects. No clinically relevant changes in vital signs or electrocardiograph end points have been reported.

The most frequently (in more than 3 subjects) reported severe hematology laboratory test abnormalities were platelets and lymphocytes (absolute). The most frequently (in more than 1 subject) reported severe serum chemistry abnormalities were hypophosphatemia and ALT increased.

In this study, 1 first-cycle DLT was observed among the subjects with T-ALL/LBL. The DLT reported was Grade 3 hepatic enzyme abnormal for 1 subject, which was considered possibly treatment related to either study drug, or infection, by the Investigator; this AE met the DLT definition.

Among the 8 subjects with T-ALL/LBL, a complete response was observed in 1 subject with T-ALL. This subject had previously received multiple chemotherapy regimens and also had a relapse following a cord blood transplant. 5 subjects had objective progression as best overall response on study. The best overall response could not be determined in 2 subjects.

Study A8641016 was a phase 1B, open-label, multi-center study of nirogacestat in combination with docetaxel in subjects with metastatic or locally recurrent/advanced triple receptor negative breast cancer (mTNBC). In this study, 29 adult subjects with advanced TNBC were administered nirogacestat 100 mg or 150 mg BID in combination with docetaxel. After utilization of the up-and-down matrix, this study estimated the MTD of this dosing combination to be nirogacestat 100 mg BID + docetaxel 75 mg/m^2. Of the 25 response-evaluable subjects, none had complete response, 4 (16.0%) had confirmed partial response, and 9 (36.0%) had stable disease. The ORR was 16.0% (95% CI, 4.5-36.1). Efficacy evaluation of the combination in this therapeutic setting could not be completed because of the early study termination (unrelated to safety). All subjects experienced TEAEs, with most being Grade 1 and/or 2 in severity. The most common (≥ 20% subjects) TEAEs, independent of causality, were fatigue, neutropenia, nausea, diarrhea, leukopenia, alopecia, anemia, vomiting, mucosal inflammation, headache, hypophosphatemia, rash, constipation, thrombocytopenia, febrile neutropenia, hypokalemia, proteinuria, stomatitis, decreased appetite, hyperglycemia, and hypocalcemia. The majority of AEs were considered to be mild to moderate, but treatment-related severe (Grade 3) hypophosphatemia, diarrhea, pneumonia, nausea, fatigue, febrile neutropenia,

hyponatremia, and white blood cell count decreased have been reported in more than 1 subject; all these were considered as treatment related except for 1 case each of hyponatremia, hypophosphatemia, and diarrhea. The most common (in more than 1 subject) treatment-related Grade 4 AEs were neutropenia, leukopenia, neutrophil count decreased and febrile neutropenia. The Grade 5 AEs included septic shock and disease progression (1 subject each; 3.4% each), among them septic shock was considered as treatment related. No clinically relevant changes in vital signs or electrocardiograph end points have been reported. The most frequent (in more than 1 subject) severe hematology laboratory test abnormalities were lymphocytes (absolute; Grade 3 and 4), neutrophils (absolute, Grade 3 and 4), hemoglobin (Grade 4), and white blood cells (Grade 3 and 4). The most frequently reported (in more than 1 subject) severe serum chemistry abnormalities were hypophosphatemia (6 subjects), hypokalemia (4 subjects), and hyponatremia (2 subjects).

In this study, 6 subjects with advanced TNBC developed first-cycle DLTs. The DLTs reported were Grade 3 diarrhea for 1 subject dosed with nirogacestat 100 mg BID/docetaxel 100 mg/m^2 and for 1 subject dosed at nirogacestat 100 mg BID/docetaxel 75 mg/m^2; Grade 3 dehydration for 1 subject; Grade 3 nausea for 1 subject; Grade 4 febrile neutropenia for 1 subject; and Grade 5 septic shock for 1 subject, all dosed with nirogacestat 150 mg BID/docetaxel 75 mg/m^2.

Study A8641019 was a phase 1/2, open-label, multi-center, randomized clinical trial of nirogacestat in combination with nab-paclitaxel + gemcitabine in subjects with metastatic pancreatic ductal adenocarcinoma (mPDA). This study utilized a starting nirogacestat dose 100 mg BID administered orally in 28-day cycles on a continuous basis, whereas nabpaclitaxel and gemcitabine were administered intravenously at doses of 125 mg/m^2 and 1000 mg/m^2, respectively, on Days 1, 8, and 15 in 28-day cycles.

Due to early termination of the study, only 3 adult subjects with metastatic pancreatic ductal adenocarcinoma (mPDA) were enrolled and received study treatment. All 3 subjects discontinued from treatment (1 subject due to symptomatic deterioration and 2 subjects due to treatment-related AEs) and were also subsequently discontinued from the study (2 subjects due to symptomatic deterioration and 1 subject due to AE related to study drug). The most commonly reported TEAEs independent of causality, (≥ 20% subjects) in this study, were fatigue (3 subjects; 100%), ALT increased, aspartate aminotransferase (AST) increased, nausea, vomiting, anxiety, ascites, blood bilirubin increased, candida infection, chills, cough, decreased appetite, depression, dizziness, failure to thrive, fall, hallucination, hypokalemia, hypophosphatemia, mucosal inflammation, pleural effusion, pulmonary embolism, and rash. The AEs that were considered as treatment-related were ALT increased, AST increased, fatigue, nausea, vomiting, blood bilirubin increased, mucosal inflammation, and rash. No Grade 3-4 treatment-related TEAE were reported with the exception of Grade 3 AST increased occurred in 2 subjects, 1 case each of Grade 3 and Grade 4 ALT increased, and 1 case of Grade 3 vomiting. There were no Grade 5 TEAEs reported in the study. No clinically relevant changes in vital signs or electrocardiograph end points were reported. Grade 3-4 laboratory test abnormalities included: Grade 3 lymphopenia (1 case), Grade 3 AST increased (2 cases), Grade 3 and 4 ALT increased (1 case each).

In this study, 2 first-cycle DLTs were reported among the subjects with mPDA. 1 subject had Grade 3 AST and ALT increased and the second subject had Grade 4 ALT increased and Grade 3 AST increased. The MTD of the combination was not defined due to premature study interruption based on a nirogacestat sponsor portfolio decision.

Overall, 3 subjects were enrolled and received study treatment in the phase 1 portion of Study A8641019. All subjects were off study at the time of the premature study termination. The phase 2 portion of the study was not activated. The primary and secondary objectives of the study were not achieved due to the premature termination of the study. Both of the 2 DLT evaluable subjects were treated at the starting dose of nirogacestat 100 mg BID and had DLTs.

Study A8641020 was a multi-center, open label, single arm phase 2 study of nirogacestat administered as a single agent in the treatment of subjects with advanced mTNBC harboring genomic alterations in Notch receptor (NA+), and in a smaller subset of subjects who test negative for genomic alterations in Notch receptors (NA-).

A total of 19 subjects with advanced TNBC were enrolled in the study and received study treatment (150 mg, BID). The most commonly reported TEAEs (≥ 20% subjects) in this study, regardless of causality, were diarrhea, fatigue, nausea, vomiting, cough, hypophosphatemia, and pyrexia. The majority of AEs were considered mild-to-moderate, and the only treatment related severe (Grade 3) reported in more than 1 subject was hypophosphatemia (4 subjects). No treatment related Grade 4 and Grade 5 AEs were reported. No clinically relevant changes in electrocardiograph end points were reported. The Grade 3 hematology laboratory test abnormalities reported were anemia and lymphopenia. The Grade 3 abnormal serum chemistry values reported in more than 1 subject were hypophosphatemia and hypokalemia.

The study was prematurely terminated based on a nirogacestat sponsor portfolio decision. Due to the early termination of the trial, efficacy analysis of progression free survival (PFS) and overall survival (OS) were not conducted and only reported descriptively.

Study NIR-DT-101 was a phase 1, single-center, open-label, PK, metabolism, mass balance, and safety study of [^{14}C]-nirogacestat following single oral dose administration in healthy male volunteers.

A total of 10 healthy male participants were enrolled in this study and received a single dose of [^{14}C]-nirogacestat 150 mg/5 µCi. A total of 9 subjects experienced TEAEs during this study. All TEAEs were considered Grade 1 or Grade 2 in severity and resolved prior to study completion. A total of 4 subjects experienced TEAEs that required treatment. A total of 4 treatment-related TEAEs were experienced by 4 subjects during this study. Treatment-related headache was reported by 2 subjects. No other treatment-related TEAE was reported by more than 1 subject. There were no deaths, serious adverse events (SAEs), AEs leading to study withdrawal, or action taken with study drug due to AEs during this study.

Study NIR-DT-102 was a phase I, 2-part, open-label study to determine the mass balance recovery, absorption, metabolism, and excretion of [14C]-nirogacestat and the absolute bioavailability of nirogacestat following administration of a single oral dose in healthy male participants.

A total of 12 healthy male participants were enrolled in the study and received a single oral dose of [^{14}C]-nirogacestat (150 mg/5 microcuries) in Part 1 and a single oral dose of nirogacestat 150 mg, followed by a single IV dose of [14C]-NIR 43.5 µg/1 µCi in Part 2. A total of 4 subjects experienced TEAEs during this study, all during Part 2. There were 2 subjects who experienced treatment-related TEAEs. All TEAEs were considered Grade 1 (mild) or Grade 2 (moderate) in severity and resolved prior to completion of the study. No action was taken with study drug due to any of the TEAEs. No subject withdrew from the study due to an AE. There were no deaths or other SAEs during the study.

An investigator-initiated phase 2, open-label, single-center study was sponsored and conducted by the National Cancer Institute (NCI) to evaluate the objective response rate (ORR) after therapy with nirogacestat in subjects with recurrent, refractory, progressive desmoid tumors (Kummar et al., 2017). 17 subjects received daily doses of nirogacestat at the RP2D of 150 mg BID continuously in 3-week cycles. Response to treatment was evaluated at Cycle 1 and every 6 cycles (18 weeks) thereafter by RECIST v1.1. Of the 17 subjects treated in the study, 15 had mutations in APC or CTNNB1 genes. 16 subjects were evaluable for response with 5 (29%) subjects achieving PR after a median of 32 cycles (96 weeks) of nirogacestat. The remaining 11 subjects had a best response of stable disease (SD) and no instances of progressive disease were observed. All but 1 evaluated subject had a measurable regression of tumor volume by MRI. The AE profile was consistent with previous reports (Messersmith, et al., 2015; Kummar et al., 2017) and consisted of all subjects experiencing at least one TEAE with the majority being Grade 1 to 3. The most frequently (≥ 70%) reported TEAEs were diarrhea (88%), headache (76%), hypophosphatemia (76%), AST increased (71%), lymphocyte count decreased (71%), and nausea (71%). A total of 10 (59%) subjects reported Grade 3 treatment-related TEAEs. Eight (47%) subjects reported Grade 3 hypophosphatemia, 1 (6%) subject reported Grade 3 diarrhea, 1 (6%) subject reported Grade 3 fatigue, and 1 subject (6%) reported Grade 3 menstruation irregular. Per the sponsor, the subject that reported the Grade 3 menstruation irregular TEAE was postmenopausal prior to enrolling in the study, and thus this event should not have been reported as a TEAE. A total of 9 (53%) subjects reported at least one SAE including 4 (24%) subjects reporting events considered by the investigator to be related to nirogacestat. No SAE was reported in more than one subject. The 4 SAEs that were considered by the investigator to be related to nirogacestat were blood bilirubin increased, hypersensitivity, squamous cell carcinoma, and vulvovaginal inflammation, which were each reported in a single subject. All related SAEs were reported as Grade 2 severity. A single event of Grade 2 hypersensitivity, considered by the investigator to be possibly related to study treatment, led to the permanent discontinuation of study treatment in one subject. There was one death on study due to a cerebrovascular accident that was assessed by the investigator to be unlikely related to nirogacestat. There were no TEAEs that were considered to be DLTs.

Study NIR-DT-301 was a multi-center, randomized, double-blind, placebo-controlled, parallel arm, Phase 3 study to evaluate the efficacy, safety, and tolerability of nirogacestat in adult patients with progressing DT/aggressive fibromatosis (AF). A total of 142 patients were randomized to study treatment (nirogacestat or placebo) in a 1:1 ratio to receive 150 mg BID of study treatment, continuously in 28-day cycles, or matching placebo. This study consisted of 2

phases: the double-blind phase and the optional open-label extension (OLE) phase, which is still ongoing.

A statistically and clinically significant improvement in the primary endpoint of PFS was observed for nirogacestat over placebo, with a 71% reduction in the risk of disease progression (HR = 0.29 (95% CI: 0.15, 0.55); p <0.001). The probability of being event free at 6-, 12-, and 24 months is consistently higher for nirogacestat as compared to placebo, supporting a sustained clinical benefit over time. Treatment with nirogacestat demonstrated a statistically significant improvement over placebo in ORR (41% vs 8%; P <0.001) with 5 patients reporting a CR in the nirogacestat arm as compared to 0 patients receiving placebo. Clinically meaningful and statistically significant improvements were also observed with all patient-reported outcomes (PROs) included in the testing hierarchy among patients receiving nirogacestat as compared to placebo with significant improvements noted early (beginning at the first post-treatment assessment in Cycle 2) and generally sustained throughout the course of the study (Mease et al. 2011; Osoba et al. 1998). Overall, results from the PRO analyses demonstrate improved quality of life with nirogacestat as compared to placebo.

Nirogacestat had a manageable safety profile and was tolerated by the majority of patients. The frequency of patients that experienced at least 1 TEAE was similar between treatment arms (69 patients [100%] in the nirogacestat arm and 69 patients [96%] in the placebo arm). In the nirogacestat arm, the majority (95%) of TEAEs were Grade 1 or Grade 2. The most frequently reported (> 30% of patients) TEAEs in the nirogacestat arm were diarrhea, nausea, fatigue, hypophosphatemia, and rash maculo-papular. Events of ovarian dysfunction (as defined by the preferred terms of menopause, premature menopause, ovarian failure, and amenorrhea) were also commonly reported in women of childbearing potential (27/36 [75%]) receiving nirogacestat. More Grade ≥ 3 events occurred in the nirogacestat arm compared to placebo; diarrhea had the greatest imbalance in incidence with 16% in the nirogacestat arm vs 1% in placebo. A total of 21 patients (15%) experienced an SAE, including 14 patients (20%) in the nirogacestat arm and 7 patients (10%) in the placebo arm. The only preferred term (PT) reported as serious by > 1 patient in the nirogacestat arm was premature menopause (3 patients). One death occurred; this event of sepsis was in the placebo arm and was considered by the investigator to be unrelated to study treatment. Sixteen (23%) patients receiving nirogacestat had TEAEs leading to study treatment discontinuation; 2 of these 16 patients also had clinical progression as the primary reason for treatment discontinuation and the reported TEAEs were manifestations of the progression. Excluding the discontinuations due to clinical progression, 14 (20%) patients discontinued due to TEAEs. The TEAEs leading to discontinuation of study treatment of > 1 patient in the nirogacestat arm were diarrhea, premature menopause, ALT increased, and AST increased. The overall benefit / risk balance for nirogacestat treatment of adult patients with DTs was favorable, with a substantial reduction in the risk of disease progression, an increase in the objective response rate, and significant and clinically meaningful improvements in pain, DT-specific symptom burden and their impact on patient lives, physical functioning, role functioning, and health-related quality of life, balanced with a manageable safety profile.

1.2.5. Importance of the Clinical Trial

Desmoid tumor (DT) is a rare locally aggressive neoplasm that although does not metastasize, has significant potential for local morbidity. Furthermore, surgical resection is typically difficult due to the infiltrative nature of the disease and the high probability of local recurrence, even if negative margins are obtained. Therefore, new non-invasive treatment options are needed. Cryoablation is an effective non-surgical method for local control of tumor that generally has low morbidity. However, total cryoablation can be difficult for some tumors due to size or location of tumor next to critical structures such as arteries, veins, or nerves. Therefore, adjunctive measures are needed to help control untreated disease after cryoablation.

In this study, a combination of cryoablation plus targeted therapy systemic therapy with nirogacestat are being used to maximize the benefits of both modalities for subjects with progressive or symptomatic desmoid tumors. The addition of nirogacestat to regular medical care cryoablation is being investigated due to nirogacestat being a potent selective, reversible, noncompetitive inhibitor of gamma secretase (GS) an important strategy for therapeutic treatment with promising phase 2 data, and currently being investigated in a phase 3 study.

1.3. Potential Risks and Benefits

1.3.1. Known Potential Risks of Nirogacestat

This information is from the nirogacestat Investigator's Brochure. [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

See also Section 4 (Study Intervention) and Section 7.3 (Potential Adverse Events and Risks), for more detailed risk information.

Contraindications
Nirogacestat is contraindicated in patients with moderate or severe hepatic impairment as per National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG)(total bilirubin > 1.5 x ULN).

Special Warnings and Precautions for Use
To date, important identified risks related to nirogacestat include diarrhea, dermatologic reactions (maculopapular rash, hidradenitis, and folliculitis), ovarian dysfunction, electrolyte abnormalities (hypophosphatemia and hypokalemia), and elevated liver transaminases. Important potential risks include non-melanoma skin cancer, embryo-fetal toxicity, effects on male fertility, and in pediatric patients, epiphyseal disorder.

Fertility, Pregnancy, and Lactation:
Nirogacestat produced embryo toxicity when administered to pregnant rats, and impaired fertility in both male and female rats. In the fertility and early embryo toxicity study in rats, nirogacestat induced significant embryonic loss and decreased fertility in both males and females. In the embryo-fetal developmental study conducted in pregnant rats, nirogacestat induced fetal loss and resorptions. These fetal effects occurred at systemic exposures that are below those that are used in ongoing clinical trials. Additionally, in the repeat dose 1-month and 3-month

toxicology studies in the rat, ovarian atrophy, a decreased number of follicles and asynchrony of the estrous cycle were observed.

Testicular changes in both rats and dogs demonstrated a negative impact on sperm. Based on findings in animals, nirogacestat may impair fertility in females and males of reproductive potential. There are no data in humans, and the effect on potential impairment of, female and male fertility during, and after discontinuation of, treatment with nirogacestat is unknown.

Male and female study participants should be advised of the potential impact on fertility. Women should not donate or harvest their eggs (ova, oocytes) while participating in this research study and for at least 6 months after taking their last dose of study drug. Men should not donate or preserve their sperm for at least 90 days after taking their last dose of study drug.

Events associated with ovarian dysfunction including preferred terms of menopause, ovarian failure, premature menopause, and amenorrhea have been reported in women receiving nirogacestat. It is unknown if events of ovarian dysfunction are reversible after stopping nirogacestat. The effects on long-term fertility are also unknown. Study participants will be counselled regarding fertility preservation (egg or sperm preservation) options prior to starting nirogacestat.

Therefore, nirogacestat should not be used during pregnancy, and if a subject becomes pregnant while receiving this drug, the treatment with nirogacestat should be stopped and the subject should be apprised of the potential hazard to the fetus.

Pregnant women should be excluded from participation in clinical studies with nirogacestat.

Study participants will be counselled to avoid pregnancy while receiving nirogacestat.

Lactation: No studies have been conducted in humans to assess the impact of nirogacestat on milk production, its presence in breast milk and its effects on the breast-fed child. Since drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, breastfeeding women should not receive nirogacestat administration.

Summary of the Most Commonly (≥ 10% of Participants in the Nirogacestat Arm) Reported AEs from Completed Nirogacestat Single Agent Studies in Adult Patients with Cancer (Modified Information from Investigator Brochure)* [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

- Diarrhea
- Fatigue
- Hypophosphatemia
- Cough
- Rash maculo-papular
- Rash
- Headache
- Dry mouth
- Dermatitis acneiform
- Insomnia
- Stomatitis
- Dyspnea
- Anemia
- Constipation
- Upper respiratory tract infection
- Nausea
- Vomiting
- Decreased appetite
- Pyrexia
- Hypokalemia
- Aspartate aminotransferase increased
- Epistaxis
- Alanine aminotransferase increased
- Abdominal pain
- Hot flush
- Arthralgia
- Dry skin
- Dizziness
- Hypertension
- Pruritus

*Data from Single Agent Nirogacestat Studies A8641014, A8641020, 14-C-0007, and NIR-DT-301 (Double-Blind Phase)

Table 1. Adverse Reactions Reported in at Least 15% Patients and at a ≥ 5% Rate in the Nirogacestat Arm Than the Placebo Arm in NIR-DT-301 (Modified Information from Investigator's Brochure)[4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

	Nirogacestat (N=69)		Placebo (N=72)	
Adverse Reaction	**All Grades n (%)**	**Grade 3* n (%)**	**All Grade**	**Grade 3* n (%)**
Reproductive system				
Ovarian dysfunction[a]	27 (75%)	0	0	0
Skin and subcutaneous tissue				
Rash[b]	44 (64%)	4 (6%)	10 (14%)	0
Alopecia	13 (19%)	0	1 (1%)	0
General				
Fatigue	35 (51%)	2 (3%)	26 (36%)	0
Nervous system				

Headache	20 (29%)	0	11 (15%)	0
Respiratory				
Cough	11 (16%)	0	3 (4%)	0
Dyspnea	11 (16%)	0	4 (6%)	0
Infections				
Upper respiratory tract infection[c]	11 (16%)	0	1 (1%)	0
Metabolism				
Hypophosphatemia	29 (42%)	2 (3%)	5 (7%)	0
Investigations				
ALT increased	12 (17%)	2 (3%)	6 (8%)	1 (1%)
AST increased	11 (16%)	2 (3%)	8 (11%)	1 (1%)

*No Grade 4 or 5 adverse reactions were reported in Study NIR-DT-301.
[a]Ovarian dysfunction includes Ovarian failure, Premature menopause, Amenorrhea, and Menopause; the number of women of childbearing potential in each arm is used as the denominator (nirogacestat N=36, placebo N=37).
[b]Rash includes Maculo-papular rash, Dermatitis acneiform, Rash [, Rash erythematous, Rash pruritic, and Rash papular.
[c]Upper respiratory tract infection (URTI) includes URTI, Viral URTI, Acute sinusitis, and Sinusitis

Premature Menopause / Ovarian Dysfunction

- In the Phase 3 Study NIR-DT-301 evaluating nirogacestat in adult patients with progressing desmoid tumors, ovarian dysfunction, which was defined by investigator-reported events of amenorrhea, premature menopause, menopause, and ovarian failure, was observed in 75% (27/36) of women of childbearing potential receiving nirogacestat and none of the 37 women of childbearing potential in the placebo arm. All ovarian dysfunction events were Grade 2. These events resolved in 74% (20/27) of the affected participants, including 64% (9/14) of such participants who remained on nirogacestat treatment and 100% (11/11) of those participants who discontinued treatment for any reason.[27]

Important Side Effect of Nirogacestat Occurring in < 10% of Participants:

- Non-melanoma skin cancer*

*Non-melanoma skin cancer includes Basal cell carcinoma [1 (1%)], Squamous cell carcinoma of skin [2 (1%)], and Squamous cell carcinoma [1 (1%)].

Known Drug Interactions:

Modified information from Investigator's Brochure; See also Section 3.1.3. Lifestyle Considerations, and Section 7.3 Potential Adverse Events and Risks. Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

Cytochrome P450 Inhibitors and Inducers (from Investigator's Brochure) [4]

- Coadministration of nirogacestat with strong or moderate inhibitors of CYP3A4 may increase serum nirogacestat concentrations and should be avoided. The use of

strong or moderate CYP3A4 inhibitors must be stopped at least 14 days prior to first dose of study treatment. If coadministration of strong or moderate CYP3A4 inhibitors is unavoidable, immediately interrupt nirogacestat treatment and remain off nirogacestat for the period of time that the CYP3A4 inhibitor is given. Nirogacestat may be resumed one week after cessation of a strong CYP3A4 inhibitor and immediately following cessation of a moderate CYP3A4 inhibitor.

- Nirogacestat metabolism may be induced when taking strong CYP3A4 inducers resulting in reduced nirogacestat serum concentrations. The use of strong CYP3A4 inducers must be stopped at least 14 days prior to first dose of study treatment. Coadministration of nirogacestat with strong CYP3A4 inducer should be avoided. If a strong CYP3A4 inducer is required, nirogacestat may be interrupted for the period of time that the CYP3A4 inducer is given and may be resumed immediately after cessation of the CYP3A4 inducer. Dose modifications are not recommended if a moderate CYP3A4 inducer is required.

- **Cytochrome P450 Substrates**
  - Nirogacestat is a weak inhibitor of CYP3A4 at therapeutic doses and may increase the exposure of drugs that are metabolized by CYP3A4. Concomitant use of nirogacestat with CYP3A4 substrates that have a narrow therapeutic index should be avoided.
  - Based on the potential for increased exposure on co-administration with nirogacestat, CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If co- administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.
  - Based on physiologically-based pharmacokinetic (PBPK) model predictions, nirogacestat may be a weak-to-moderate inducer of CYP2C19 and may reduce the exposure of drugs that are metabolized by CYP2C19. Therapeutic alternatives to CYP2C19 substrates should be considered as appropriate, however strict avoidance of concomitant use with nirogacestat is not necessary.

- **Other Concomitant Therapy**
  - The effect of nirogacestat on the exposure of hormonal contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various hormonal contraceptives resulting in reduced efficacy. A second method of contraception is required if the subject is using hormonal contraception, as co-administration with nirogacestat may alter the plasma concentrations of hormonal contraceptives resulting in reduced efficacy.
  - Nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Caution should be used when co-administering the nirogacestat with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar. Nirogacestat may also be an inhibitor of P-gp and may increase the exposure of some P-gp substrates like digoxin, dabigatran, and fexofenadine; participants

receiving these medications should be closely monitored, as therapeutic effect and adverse reactions of these medications may be increased.

- Gastric acid reducing agents: Based on the solubility characteristics of nirogacestat, increase of gastric pH may reduce absorption of nirogacestat, although the extent of the effect has not been evaluated in a clinical study. Daily use of gastric acid reducing agents should be avoided. If gastric acid reducers are required, they should be administered 4 hours after administration of nirogacestat.

1.3.2. Known Potential Risks of Study Procedures

- **Cryoablation Risks:** The risks of cryoablation include but are not limited to ecchymosis, edema/swelling, fever, hemorrhage, infection, delayed/non-healing wound, probe site paresthesia, skin burn, and injury to off-target structures. With any procedure there is a small risk of death.

  Based on CRYODESMO-01, Grade 1 and 2 toxicity occurred in 32.8% and 44.5% of subjects, Grade 3-4 toxicity occurred in 22% of subjects, and no Grade 5 toxicity was observed. The most common side effects included: [16]

  - Pain (21.6%)
  - Neural impairment (15.8%)
  - Edema (15.1%)
  - Musculoskeletal impairment (7.9%)
  - Skin burn (5.8%)
  - Increased creatinine kinase (5.8%)
  - Bleeding (2.9%)
  - Fever (0.7%)

- **Biopsy Risks:** The risks of biopsy include but are not limited to ecchymosis, edema/swelling, fever, hemorrhage, infection, delayed/non-healing wound. With any procedure there is a small risk of death.
- **Blood Draw Risks:** Drawing blood from a vein can cause minor pain and bruising at the site where the needle enters. Some people feel dizzy when blood is drawn. Rarely, infection may occur. There is a rare possibility that you will faint while having blood drawn or that nerve damage will occur.
- **Risk of loss of confidentiality:** There is a risk of loss of confidentiality of subject information that is used in this study.
- **Non-Physical Risks:** Subjects' work schedule may be disrupted, or they may be unable to work while on this study because of side effects or the time required for study-related activities.

  Note: Imaging for this study is considered regular medical care.

1.3.3. Known Potential Benefits

We hypothesize that the combination of systemic therapy with nirogacestat and cryoablation will provide longer lasting disease control compared to cryoablation alone and lead to a much quicker time to treatment response and symptom relief than nirogacestat alone. Also, there is no risk of secondary malignancy (in comparison to radiation) and we predict that side effects will be more tolerable than chemotherapy and/or VEGF TKIs.

2. STUDY DESIGN, OBJECTIVES, AND OUTCOMES

2.1. Study Design

2.1.1. Overall Design

The intervention model of this study is **single group.**

2.1.2. Primary Purpose of the Study

Treatment: The primary purpose of this protocol is treatment. Systemic therapy with oral study agent, nirogacestat, will be given for 3 cycles (1 cycle = 28 days) followed by a single cryoablation procedure between Cycles 3 and 4, and then continued nirogacestat for Cycles 4 through 26. Treatment with nirogacestat may continue via this study for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, subject withdraws their consent, start of a new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs.

After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

2.1.3. Study Cohorts / Arms / Groups

One interventional arm.

- Subjects must have progressive (by RECIST criteria over the past 12 months) or symptomatic desmoid tumor (as defined by change in pain regimen or impairment of activities of daily living (ADLs), or at investigator discretion).

Treatment:

- 3-cycle lead-in with systemic therapy with nirogacestat 150 mg po BID, given continuously. 1 cycle of treatment is 28 days.
- Cryoablation procedure (single session) in between Cycles 3 and 4. Hold nirogacestat on day of cryoablation procedure.
- Continued systemic therapy with nirogacestat for Cycles 4 through 26. Treatment with nirogacestat may continue via this study for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, subject withdraws their consent, start of a new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs.
- After 24 months of treatment, if clinically indicated, subjects may transition to commercial nirogacestat supply, once subjects have completed the End of Treatment (EOT) visit and are off study.

Study assessments will be conducted as shown in Section 6.1 (Schedule of Events).

Subject number: Up to 23 enrolled subjects, to achieve 20 evaluable subjects.

2.1.4. Scientific Justification for Study Design

This is a phase 2 study evaluating the addition of a drug (nirogacestat) that has single agent activity, to cryoablation, a well-established therapy for both first-line or salvage treatment of desmoid tumor.

Clinical Benefit Rate at 1 year is chosen as the primary endpoint because this endpoint measures the effect of combining the two modalities of local cryoablation with systemic targeted therapy. The one-year timepoint for assessments was chosen because maintaining response or not progressing from stable disease for 1 year is clinically meaningful for subjects with desmoid tumors. We will also be assessing quality of life (QoL) outcomes to determine if subjects symptomatically benefited from treatment.

2.1.5. Treatment Assignment

- The study is open label.
- Single center
- The interventional model is non-randomized, single group.

2.1.6. Justification for Dose

The starting dose of nirogacestat (150 mg PO BID) is based on results from a phase 1 dose-finding study (A8641014) in subjects with advanced solid tumors. In this study, a maximum tolerated dose (MTD) of 220 mg PO BID was established in subjects administered nirogacestat BID continuously for 21 days, and a recommended phase 2 dose (RP2D) of 150 mg PO BID was determined from additional subjects with advanced solid tumors enrolled in the expansion cohort of the phase 1 study. [4] The completed randomized phase 3 trial of nirogacestat vs placebo in adults with progressing desmoid tumor/aggressive fibromatosis (NIR-DT-301, DeFi Study) also has a starting dose of 150 mg PO BID in the double-blind and open-label extension phase.

2.2. Objectives

2.2.1. Primary Objective

To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy by evaluation of the clinical benefit rate (CR + PR + SD) at 1 year in subjects with progressive or symptomatic desmoid tumor. Response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

2.2.2. Secondary Objectives

- To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy by evaluation of the clinical benefit rate (CBR) at 1 year in subjects with progressive or

symptomatic desmoid tumor. Response will be assessed according to modified RECIST criteria (mRECIST).

- To assess the effects of combination therapy with cryoablation plus nirogacestat on efficacy, by evaluation of median disease progression.
- To assess the effects of cryoablation plus nirogacestat on tumor response (as defined by objective response rate) at 1 year.
- To assess the time to response from the start of treatment with nirogacestat to the first objective tumor response.
- To assess the duration of response from time of response to time of progression.
- To assess safety and tolerability of cryoablation plus nirogacestat in subjects with progressive or symptomatic desmoid tumors.

2.2.3. Exploratory Objective

- To evaluate effects of cryoablation plus nirogacestat on quality of life.
- To correlate changes during treatment with response using the Nanostring CosMX SMI on biopsy samples.

2.3. ClinicalTrials.gov Registration, Outcomes, and Results

This study has been registered on ClinicalTrials.gov, and results will be reported. The US Food and Drug Administration (FDA) has approved nirogacestat (Ogsiveo™) for the treatment of desmoid tumor. The principal investigator of this study has submitted IND 164301 to the FDA. The Visual-ICE Cryoablation System, which will be used to perform cryoablation for this study, has FDA 510(k) clearance. Cryoablation is recognized by National Comprehensive Cancer Network (NCCN) as a viable procedure for desmoid tumor.

2.3.1. Data Sharing Statement

Pursuant to the International Committee of Medical Journal Editors (ICMJE), the following statement, regarding sharing of individual subject data (ie, participant-level data) generated by interventional clinical trials, is provided.

It is not planned that individual participant data, including data dictionaries, will be made publicly available. Individual participant study data judged by the investigator to be pertinent to a participant's understanding of their medical condition and treatment options will be shared with that participant. Otherwise and as such, details of what, or when, or by what mechanism, data and/or documents will be shared, who would share such data, or for what purposes or analyses, are not available or not applicable.

Although not individual participant data, pursuant to the requirements of 42CFR§11.48(a)(5) (if applicable), the final IRB-approved protocol document with statistical analysis will be made available in the ClinicalTrials.gov results record.

2.3.2. Outcome Measures for ClinicalTrials.gov Results Reporting

2.3.2.1. Primary Outcome

- **Primary Outcome Measure Title**: Clinical Benefit per RECIST v1.1

  Description: Clinical benefit (CB) is defined as the number of participants assessed with a complete response (CR), partial response (PR), or stable disease (SD) within 1 year and with no evidence of loss of response nor progression within that year. Response & progression will be assessed according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, as follows:

  RECIST v1.1:

  • CR=Disappearance of all lesions

  • PR=≥30% decrease in diameter of target lesions

  • Progressive disease (PD)=20% increase in diameter of target lesion; progression of non-target lesion; or ≥1 new lesion(s)

  For the overall outcome:

  • SD=Changes not meeting above criteria

  • Overall Response (OR)=CR+PR

  • CB=CR+PR+SD

  The outcome is a number without dispersion.

- **Time Frame**: 1 year
- **Completion of Primary Outcome**: Based on the projected accrual of 20 subjects within 24 months, the last datum for the primary objective / outcome is expected to be obtained approximately 44 months from the time the study opens to accrual.

2.3.2.2. Secondary Outcomes

- **Outcome 2 (Secondary) Title**: Clinical Benefit per mRECIST

  Description: Clinical benefit (CB) is defined as the number of participants assessed with a complete response (CR), partial response (PR), or stable disease (SD) within 1 year and with no evidence of loss of response nor progression within that year. Response & progression will be assessed according to the modified Revised Response Evaluation Criteria in Solid Tumors (mRECIST), as follows.

  mRECIST:

  • CR=Disappearance of intratumoral enhancement

  • PR=≥ 30% decrease in the diameter of target lesion(s)

  • PD=An increase of >20% in the diameter of target lesion.

The outcome is the number of participants alive after 1 year and without PD per mRECIST, a number without dispersion.

Time Frame: 1 year

- **Outcome 3 (Secondary) Title**: Progression-free Survival (PFS)

  Description: Progressive-free survival (PFS) is an assessment of the number of participants at a specific time who remain alive and without tumor progression. Progressive disease (PD) will be assessed according to Revised Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, or, for tumors assessed with MRI enhancement, modified RECIST (mRECIST) defined as follows:

  RECIST v1.1:

  • PD=20% increase in diameter of target lesion; progression of non-target lesion; or ≥1 new lesion(s)

  mRECIST:

  • PD=An increase of >20% in the diameter of target lesion.

  The outcome is the number of participants alive after 1 year and without PD per RECIST or mRECIST, a number without dispersion.

  Time Frame: 1 year

- **Outcome 4 (Secondary) Title: Objective Response**

  Description: Objective response (OR) is defined as the number of participants assessed with a complete response (CR) or partial response (PR) within 1 year and with no evidence of loss of response nor progression within that year. Response & progression will be assessed according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, or, for assessed with MRI enhancement, modified RECIST (mRECIST) as follows:

  RECIST v1.1:

  • CR=Disappearance of all lesions

  • PR=≥30% decrease in diameter of target lesions

  • Progressive disease (PD)=20% increase in diameter of target lesion; progression of non-target lesion; or ≥1 new lesion(s)

  mRECIST:

  • CR=Disappearance of intratumoral enhancement

  • PR=≥ 30% decrease in the diameter of target lesion(s)

  • PD=An increase of >20% in the diameter of target lesion.

For the overall outcome:

• SD=Changes not meeting above criteria

• Overall Response (OR)=CR+PR

• CB=CR+PR+D

The outcome is the number of participants with OR per RECIST or mRECIST within 1 year, a number without dispersion.

Time frame: 1 year

- **Outcome 5 (Secondary) Title: Time-to-Response (TTR)**

Description: Time-to-response (TTR) is an assessment of the length of time from the start of treatment until clinical response (complete response, CR; or partial response, PR) is documented.in accordance with the Revised Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, or, for assessed with MRI enhancement, modified RECIST (mRECIST) defined as follows:`

RECIST v1.1:

• CR=Disappearance of all lesions

• PR=≥30% decrease in diameter of target lesions

• Progressive disease (PD)=20% increase in diameter of target lesion; progression of non-target lesion; or ≥1 new lesion(s)

mRECIST:

• CR=Disappearance of intratumoral enhancement

• PR=≥ 30% decrease in the diameter of target lesion(s)

• PD=An increase of >20% in the diameter of target lesion.

For either:

• SD=Changes not meeting above criteria

The outcome is expressed as the median TTR (by RECIST or mRECIST), with standard deviation.

Time Frame: 1 year

- **Outcome 6 (Secondary) Title: Duration of Response (DoR)**

Description: Duration of response (DoR) is defined as the time from the date of documented disease response (complete response, CR; or partial response, PR) to the date of the first documented disease progression. CR and PR will be assessed according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, or, for assessed with MRI enhancement, modified RECIST (mRECIST) as follows:

RECIST v1.1:

• CR=Disappearance of all lesions

• PR=≥30% decrease in diameter of target lesions

• Progressive disease (PD)=20% increase in diameter of target lesion; progression of non-target lesion; or ≥1 new lesion(s)

mRECIST:

• CR=Disappearance of intratumoral enhancement

• PR=≥ 30% decrease in the diameter of target lesion(s)

• PD=An increase of >20% in the diameter of target lesion.

For both:

• SD=Changes not meeting above criteria

The outcome is expressed as the median DoR, with standard deviation. Participants alive with a clinical response and without progression 24 months after treatment will be censored at that time.

Time Frame: 2 year

- **Outcome 7 (Secondary) Title: Related Adverse Events (AEs)**

  Description: Safety is assessed as the number of adverse events determined by the investigator to be possibly, probably, or definitely related to nirogacestat treatment (ie, drug toxicities). All related events will be collected and reported. Adverse events of Grade 3 (severe) are considered notable and potentially actionable during treatment, while adverse events Grade 1 or 2 are considered routine, with typically little or no change in treatment needed. The outcome will be reported as the number of related adverse events Grade 3 or higher is a number without dispersion.

  Time Frame: 1 year

3. SUBJECT SELECTION

3.1. Eligibility Criteria and Participant Eligibility Checklist

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist which may be extracted from this document for use in screening potential subjects.

The Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist is retained in the subject's record. Screening results will be collectively documented on the Study Participant Log.

Pursuant to Stanford Cancer Institute SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator), the Study Coordinator, and an Independent Reviewer will verify that the subject's eligibility is accurate, complete, and legible in source

records. A description of the eligibility verification process should be included in EPIC or other Electronic Medical Record progress note.

Participant Eligibility Checklist

I. Protocol Information

Protocol Title:	Phase 2 Study of Cryoablation and Nirogacestat for Desmoid Tumor
Study Identifiers:	eProtocol: IRB-67799 Oncore: SARCOMA0061 SpringWorks Therapeutics program / protocol number: NIR-DT-602
Principal Investigator:	Nam Bui, M.D.

II. Subject Information

Subject Initials / Unique ID: /		
Gender	☐ Male	☐ Female

III. Eligibility Criteria

3.1.1. Inclusion Criteria

Prospective Participant Must Meet ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
1. Histologically-confirmed diagnosis of desmoid tumor (DT) that is progressing (by RECIST criteria over the past 12 months) or symptomatic (as defined by change in pain regimen or impairment of activities of daily living (ADLs), or at investigator discretion). **Note: Must have diagnosis of desmoid tumor on pathology report**.	☐	☐	Pathology Date: _____ Progress notes: _____

Prospective Participant Must Meet ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
2. Desmoid tumor is 50 to <75% cryoablatable. Tumors that are 50 to <75% (volume) ablatable in a single session which may be characterized by: a. Proximity (< 1 cm) to critical structures, such as nerves, vessels, bowel, or skin, at risk of injury during ablation, despite hydrodissection, and/or b. Large size (> 100 mL), and/or c. Complex shape, such that parts of the tumor cannot be reached from a single approach or subject position, and/or d. Thin, infiltrative components, where ablation of that portion would damage more normal anatomy than tumor (e.g., tumor extending along a fascial plane between muscles, such that ablation would damage more muscle than tumor volume)	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	
3. If participant is currently being treated with any therapy for the treatment of DT, this must be completed at least 28 days (or 5 half-lives, whichever is shorter) prior to first dose of study treatment. All toxicities from prior therapy must be resolved to ≤ Grade 1 or clinical baseline.	☐	☐	
4. Participants who are receiving chronic nonsteroidal anti-inflammatory drugs (NSAIDs) as treatment for conditions <u>other than</u> DT must be on a stable dose for at least 28 days prior to first dose of study treatment.	☐	☐	
5. Age ≥ 18 years.	☐	☐	
6. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening.	☐	☐	ECOG: _____ Date of ECOG: _____

Prospective Participant Must Meet ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
7. Participant has adequate organ and bone marrow function as defined by the following screening laboratory values:			
a. Absolute neutrophil count ≥ 1500 cells/μL;	☐	☐	ANC: _____
b. Platelets ≥ 100,000μL;	☐	☐	Platelets: _____
c. Hemoglobin ≥ 9 g/dL;	☐	☐	Hb: _____
d. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%);	☐	☐	Total bilirubin: _____
e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) ≤ 2 × ULN; and	☐	☐	AST: _____ ALT: _____
f. Serum creatinine ≤ 1.5 × ULN or if creatinine > 1.5 × ULN then calculated creatinine clearance must be ≥ 60 mL/min (using the Cockcroft-Gault formula)	☐	☐	Creatinine: _____
8. Women of childbearing potential must have a negative serum pregnancy test **at screening.**	☐	☐	Serum pregnancy test: Date: Result:
9. Participant can swallow tablets.	☐	☐	
10. Participant able to have MRI.	☐	☐	
11. Ability to understand and the willingness to personally sign the written IRB-approved informed consent document. **Note that this study does not allow the use of a legally-authorized representative.**	☐	☐	

Prospective Participant Must Meet ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
12. Contraceptive use by men or women should be consistent with the standard that will be used at Stanford regarding the methods of contraception for those participating in clinical studies. **a. Male participants:** Male participants are eligible to participate if they agree to the following during the treatment period and for at least 1 week after the last dose of study treatment: • Refrain from donating or preserving sperm for at least 90 days after the last dose of active study treatment; PLUS either**:** • Be abstinent from sexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent; OR • Must agree to use a male condom when having sexual intercourse with women of childbearing potential (WOCBP). An additional form of contraception as described in Appendix H should also be used by the female partner, if she is of childbearing potential. **Postmenopausal state (not of childbearing potential)** is defined as no menses for 12 months without an alternative medical cause. **b. Female participants:** A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: • Is not of childbearing potential (not WOCBP), OR • Is of childbearing potential but is abstinent or using 1 highly effective contraceptive method, as described in Appendix H during the treatment period and for at least 1 week after the last dose of active study treatment. **A second method of contraception is required if the participant is using hormonal contraception**, as coadministration with nirogacestat may alter the plasma concentrations of hormonal contraceptives resulting in reduced efficacy. Additionally, the participant agrees not to harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 6 months after the last dose of active study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment. • The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.	☐	☐	

3.1.2. Exclusion Criteria

Prospective Participants Must NOT Meet ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
1. Participant previously received or is currently receiving therapy with GS inhibitors or anti-Notch antibody therapy.	☐	☐	
2. Participant is currently using any treatment for DT including tyrosine kinase inhibitors (TKIs), NSAIDS (chronic daily use – except as in inclusion criterion 4) or any investigational treatment 28 days (or 5 half-lives, whichever is longer) prior to the first dose of study treatment.	☐	☐	
3. Participant is currently using or anticipates using food or drugs that are known strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3a inducers within 14 days prior to the first dose of study treatment.	☐	☐	
4. Participant has known hypersensitivity to the active substance or to any of the excipients of nirogacestat.	☐	☐	
5. Participant with active or chronic infection at the time of informed consent and during the screening period.	☐	☐	
6. Participant has known malabsorption syndrome or preexisting gastrointestinal condition that may impair absorption of nirogacestat (e.g., gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.	☐	☐	

Prospective Participants Must NOT Meet ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
7. History of other high-grade malignancy ≤ 2 years previous. Exceptions include prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen; adequately treated basal cell or squamous cell skin cancer; or adequately treated, with curative intent, cancer from which the subject is currently in complete remission per study Principal Investigator's (PI's) judgment. Specific situations can be discussed with study PI.	☐	☐	
8. Participant has experienced any of the following within 6 months of signing informed consent: • Clinically significant cardiac disease (New York Heart Association Class III or IV); • Myocardial infarction • Severe / unstable angina • Coronary / peripheral artery bypass graft • Symptomatic congestive heart failure • Cerebrovascular accident • Transient ischemic attack • Symptomatic pulmonary embolism	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
9. Participant has congenital long QT syndrome.	☐	☐	
10. Participant has a history of additional risk factors for Torsades de pointes (TdP) (e.g., heart failure, hypokalemia, family history of long QT syndrome).	☐	☐	
11. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).	☐	☐	

Prospective Participants Must NOT Meet ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
12. Participant is currently enrolled or was enrolled within 28 days of first dose of study treatment in another clinical study with any investigational drug or device.	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is:

☐ eligible for participation in the study ☐ ineligible for participation in the study

Study Coordinator printed name:	Date:
Signature:	

Investigator printed name:	Date:
Signature:	

Triple-check reviewer printed name:	Date:
Signature:	

3.1.3. Lifestyle Considerations

Nirogacestat may be taken with or without food. Tablets should be swallowed whole and should not be chewed prior to swallowing. Tablets should not be ingested if broken, cracked, or not fully intact. Doses should be taken by mouth TWICE per day, approximately every 12 hours.

If a participant misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the participant should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours have elapsed since the time of schedule administration, the participant should be instructed not to administer the missed dose and to resume study treatment as prescribed.

Participants should not take 2 doses together to “make up” for a missed dose.

If a participant vomits any time after taking a dose, then they must be instructed not to take another dose to “make up” for vomiting, but rather to resume subsequent doses as prescribed.

If a participant inadvertently takes 1 extra dose then the participant should not take the next schedule dose of study treatment.

Delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.

Nirogacestat has not been reported to cause dizziness or hypotension in clinical studies. However, as nirogacestat remains under evaluation, subjects should be instructed that if they experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

Participants should consult their study doctor before taking any new medications, over-the-counter drugs, or supplements.

Concomitant Medications to Avoid:

See also Section 4 (Study Intervention), and Section 5.8 (Concomitant Medications, Procedures, and Supportive Care Guidelines), and Section 7.3 (Potential Adverse Events and Risks).

Please also refer to the current Investigator’s Brochure and the Ogsiveo™ (nirogacestat) package insert for detailed information regarding medications to avoid taking with nirogacestat.

During this study, participants are asked to <u>avoid the following medications, foods, and supplements during their treatment on this study</u>:

- Participants must refrain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, or grapefruit hybrids at least 14 days prior to the first dose of study treatment and throughout the study.
- CYP3A4 substrates with a narrow therapeutic index
- Gastric acid reducing agents

Known Drug Interactions: [4]

- **Cytochrome P450 Inhibitors and Inducers**
  - CYP3A4 inhibitors and inducers
- **Cytochrome 3A4 Substrates**
  - Nirogacestat is a weak inhibitor of CYP3A4 at therapeutic doses and may increase the exposure of drugs that are metabolized by CYP3A4. Concomitant use of nirogacestat with CYP3A4 substrates that have a narrow therapeutic index should be avoided.
  - Based on the potential for increased exposure on coadministration with nirogacestat, CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If coadministration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.
  - Based on physiologically-based pharmacokinetic (PBPK) model predictions, nirogacestat may be a weak-to-moderate inducer of CYP2C19 and may reduce the exposure of drugs that are metabolized by CYP2C19. Therapeutic alternatives to CYP2C19 substrates should be considered as appropriate, however strict avoidance of concomitant use with nirogacestat is not necessary.

Other Concomitant Therapy

- The effect of nirogacestat on the exposure of hormonal contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various hormonal contraceptives resulting in reduced efficacy.
- Non-clinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Therefore, caution should be used when co-administering the study treatment with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar. Non-clinical studies have indicated that nirogacestat may also be an inhibitor of P-gp and may increase the exposure of some P-gp substrates like digoxin, dabigatran, and fexofenadine; participants receiving these medications should be closely monitored, as therapeutic effect and adverse reactions of these medications may be increased.
- Co-administration of gastric acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, etc.) may reduce the absorption of nirogacestat. These drugs should be avoided if possible or, when necessary, administered 4 hours following dosing with nirogacestat.

Anti-Emetic and Anti-Diarrheal Therapy

- The choice of anti-emetic drug(s) and anti-diarrheal drug(s), as well as the duration of treatment, is up to the investigator assuming there is no known or expected drug-drug

interaction (DDI). See Section 5.6 (Dose Modifications; select AE management recommendations, diarrhea).

Prohibited Concomitant Medications and Treatment (while on this study)

- Other investigational cancer therapies
- Anti-cancer surgery
- Definitive radiation (treatment with intent to cure) is not allowed. However, palliative radiation is allowed.
- Strong CYP3A4 inhibitors and strong CYP3A4 inducers are not allowed throughout the study and must be stopped at least 14 days prior to the first dose of study treatment.
    - Because inhibition of CYP3A4 isoenzymes may increase nirogacestat exposure leading to potential increases in toxicities, the use of known strong CYP3A4 inhibitors is not allowed throughout the study and must be stopped at least 14 days prior to the first dose of study treatment.
    - Nirogacestat metabolism may be induced when taking strong CYP3A4 inducers resulting in reduced plasma concentrations. Therefore, co-administration of nirogacestat in combination with strong CYP3A4 inducers is not allowed throughout the study and must be stopped at least 14 days prior to the first dose of study treatment.
- GS inhibitors; anti-notch antibody therapy; and gastric bypass, lap band, or other gastric procedures that would alter absorption.
    - No prior use, therapy or procedure is allowed; and
    - Not allowed throughout the duration of the treatment period.
- Delivery of nirogacestat via nasogastric tube or gastrostomy tube not allowed

If the study subject needs concomitant medications or treatment not allowed while on this study, then the Protocol Director will require the subject to stop study treatment. An EOT visit (and EOT assessments) will be done within 30 days of last treatment ± 7 days. See Section 3.5 (Treatment Period and Duration), Section 5 (Treatment Plan), and Section 6 (Study Procedures and Assessments).

3.1.4. Screen Failures

Participants consent to participate in the clinical trial, but who do not meet 1 or more Eligibility Criteria (Section 3.1) during the screening procedures are considered Screen Failures. Screen Failures will not be considered enrolled subjects, although they **WILL** be tracked on the Screening Log (with reason for ineligibility) and in the OnCore study management system.

Subjects who are screen failures may be rescreened at the discretion of the Stanford Principal Investigator. Potential subjects who are rescreened will be assigned the same sequence number and Oncore subject identifier as for the initial screening.

3.2. Recruitment and Retention Procedures

3.2.1. Recruitment

Potential participants may be identified by the following methods:

- Review of the medical records of new or existing oncology patients for potential subjects who meet eligibility criteria.
- Stanford physicians may refer patients to the study for screening.
    - Participants may be identified for recruitment by referral from Stanford Cancer Center physicians. Recruitment of these subjects will occur at Stanford Cancer Center. One of the study investigators and study coordinator will discuss the study with the participant during a patient visit or with a visit scheduled for the purpose of recruitment to the study.
- External physicians may refer patients to the study for screening.
- Self-referral by subject after viewing study listing on CT.gov or the Stanford Clinical Trials website

This study will be listed on the Stanford Clinical Trials website and ClinicalTrials.gov.

3.2.2. Retention Procedures

No specific retention procedures are planned at this time.

3.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Study participants will provide written informed consent prior to the conduct of any study-specific procedures in accordance with institutional policies. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

If the study subject providing consent is fluent in English, the prospective subject must sign the IRB approved informed consent.

In the event that the study subject is considered or self identifies as “non-English speaking,” and the “Short Form” consent process will be used, the IRB approved English consent form (aka, the “Summary Form”) will be signed by the person obtaining consent (POC) and the witness; and a Short Form in the language of the study subject providing consent will be signed by the subject and the witness.

In the event that the study subject is considered or self identifies as “non-English speaking,” and a fully translated consent form will be used, the prospective study subject must sign the translated informed consent.

3.4. Registration and Enrollment

3.4.1. Subject Registration Procedures

All subjects who provide informed consent for this study will be registered in the Stanford OnCore Enterprise Research System ("OnCore") database within 5 days of the date of their signature on the informed consent document, regardless of the outcome of any eligibility screening. Subject identification numbers (SIN, aka sequence numbers) will be sequentially assigned by the lead site, Stanford Cancer Institute, at the time of registration.

Each subject's assigned subject identification number will be used on all subject specific documentation, including subject specific Case Report Forms (CRFs) and serious adverse event (SAE) forms.

A Study Participant Log will be maintained for all consented / enrolled subjects. The Study Enrollment Log may be physical (i.e., paper) or solely an electronic record, e.g., in OnCore. The Study Enrollment Log will indicate consent date (equivalent to enrollment); subject identification number; screening date; outcome of screening (eligible or not eligible); reason if not eligible; and date of registration of the subject in OnCore, see below.

3.4.2. Subject Enrollment Procedures

For this study, a subject is enrolled on the study when registered in Oncore per Section 3.4.1; has met eligibility per the screening procedures; and has been otherwise accepted into the study.

3.5. Treatment Period and Duration

Treatment may continue via this study protocol for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, start of new anticancer therapy (as defined in Section 5.7.2.), or one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs. After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

3.5.1. Definition of On-study

For the purposes of this study, the "on-study" date for each subject will be considered to be the date that subject receives first interventional treatment. This date may be used as the cut-off criteria for which subjects will or will not be included in results reported to ClinicalTrials.gov.

Note that for the purposes of OnCore subject registration and Stanford IRB Unanticipated Problem reporting, subjects are considered to be study participants when consented.

3.5.2. Definition of Off-treatment

The subject is considered to be off-treatment when the subject is no longer receiving the study agent.

In the absence of treatment delays due to an adverse event(s), treatment may continue with 3 cycles of nirogacestat (1 cycle = 28 days), followed by 1 session of cryoablation in between Cycles 3 and 4 of nirogacestat, followed by continued treatment with nirogacestat alone for Cycles 4 through 26, unless there is disease progression, unacceptable side effects, start of new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 occurs.

3.5.3. Definition of Study Suspension

At a minimum, study suspension is considered to be a pause in accrual of the study. Depending on the nature of the suspension, it may include a pause in treatment or intervention as well.

- Study suspension for administrative reasons.

3.6. Duration of Follow-up

For any subject, the nominal duration of study involvement is up to 26 months.

After completion of last treatment, subjects will be seen within 30 days ± 7 days for End of Treatment visit. If a subject is removed from study due to unacceptable adverse event(s)/ toxicity, that subject will be followed and safety data collected for at least 30 days and until resolution or stabilization of the adverse event, to the extent possible. Subjects that personally withdraw from treatment will be requested to attend a 30-day End of Treatment visit or otherwise receive a follow-up contact, unless specifically countermanded by the subject.

3.7. Subject Study Completion or Termination

3.7.1. Definition of Off-study by Subject Completion

Subjects are considered to have completed the study when any of the following criteria are met:

- Protocol-specified treatment and per protocol follow-up have been completed.
- Females reporting ovarian dysfunction including ovarian failure, menopause, premature menopause and/or amenorrhea have been followed until event resolution or for at least 90 days after discontinuing study treatment.
- Disease progression and per protocol follow-up have been completed.
- Death

3.7.2. Investigator-initiated Discontinuation of Study Treatment

The investigator may require a study subject to discontinue study treatment in the event of one of the following:

- The study subject has disease progression.
- Noncompliance
- The study subject needs treatment not allowed in the study.
- Pregnancy

- The study subject develops an AE that cannot be tolerated or that cannot be controlled with other medication.
- The investigator feels that it is in subject's best interest to stop treatment.
- The study subject is unable to meet study requirements.
- New information about the treatment of desmoid tumor becomes available.

If study therapy is stopped but the study subject allows the physician to submit follow up information, subject will continue to be followed clinically according to the study schedule.

If a subject must be removed from the study, the reason for the study removal and the date the subject was removed will be documented in the subject documentation/Case Report Form (CRF).

3.7.3. Subject-initiated Discontinuation of Study Treatment

Even after a subject agrees to take part in the study, they may stop therapy or withdraw from the study at any time. If the study participant stops treatment but still allows the study physician to submit follow up information (progression and survival information), the subject will continue to be followed clinically according to standard of care. Alternatively, the subject may withdraw consent and choose to have no further interaction regarding the study.

3.8. End of Study (Study Completion)

This study will be complete when the last study data, including follow-up, has been collected, and analysis is complete. The study is anticipated to reach study completion approximately 53 months from the time the study opens to accrual.

- The duration of enrollment for this study will last approximately 24 months.
- It is anticipated that each study subject will be on study for approximately 28 days of screening, approximately 24 months of treatment, and End of Treatment visit approximately 30 days after last treatment.
- Final Study Analysis: The final study analysis is expected to take approximately 3 months and will be started approximately 1 year after the final subject begins treatment.

If a subject is removed from treatment due to unacceptable adverse event(s), that subject will be followed and safety data collected for at least 30 days and until resolution or stabilization of the adverse event, to the extent possible.

Serious adverse events (SAEs) will be followed for 30 days after the last dose of the study drug nirogacestat, or until the SAE(s) is/are resolved or stable, whichever is longer. Pregnancies will be followed until term. See also Sections 5.6, 6.0, 7.2.4, and 7.6.

Subjects are considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in Section 6.1 (Schedule of Events).

Subjects will no longer be followed or subject data collected once the study is complete per this section.

3.8.1. Primary Completion

Primary completion is the date that the final datum is obtained/expected to be obtained for the primary outcome. This is primarily a concept for ClinicalTrials.gov results reporting. The timeframe for primary completion for an individual subject is approximately 12 months from start of treatment. Based on completion of the projected accrual of 20 evaluable subjects within 25 months (including the 28-day screening period), the last datum for the primary objective / outcome is expected to be obtained approximately 37 months from the time the study opens to accrual.

3.8.2. Premature Termination of the Study

This study may be terminated prior to completion. Termination means to stop the study ahead of its planned completion, either by accrual or by time. The reason that may warrant termination include, but are not limited to:

- The study is determined to be non-feasible, including inadequate accrual
- Determination of unexpected, significant, and/or significant risks to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Business decision by the Principal Investigator, institution, or funding source
- Unanticipated circumstances

Written notification will be provided by the investigator to the funding entity and regulatory authorities as appropriate, including the IRB of record.

4. STUDY INTERVENTION

4.1. Investigational Drug

4.1.1. **Nirogacestat (Ogsiveo™)** (Modified information from Investigator's Brochure). Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

4.1.2. **Dose and Administration** [See Section 5 (Treatment Plan) for detailed information on dosing and administration, and Section 3.1.3. (Lifestyle Considerations)].

Doses must be taken by mouth TWICE per day, approximately every 12 hours.

Starting dose: Nirogacestat 150 mg orally twice daily. One cycle of treatment = 28 days.

Nirogacestat will be held on the day of cryoablation.

4.1.3. Regulatory Status of Nirogacestat

Nirogacestat is approved for marketing in the United States. It is indicated for adult patients with progressing desmoid tumors who require systemic treatment. However, combination therapy with cryoablation plus nirogacestat is investigational. Regulatory authorization to conduct this study is pursuant to IND 164301 submitted by Stanford Principal Investigator, Nam Bui, M.D. In addition, SpringWorks Therapeutics has submitted to FDA a Letter of Authorization of Cross-reference to their IND 138207 on behalf of this study.

Treatment with nirogacestat may continue via this study protocol for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, start of new anticancer therapy (as defined in Section 5.7.2), or one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs. After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

Nirogacestat Preparation, Handling, Storage, and Accountability

4.1.3.1. Acquisition and Accountability

SpringWorks Therapeutics will provide nirogacestat (study drug) to the Stanford Investigational Pharmacy for individual participant distribution. The agent will be kept secure per Stanford Investigational Pharmacy SOP.

Nirogacestat will then be requested from the Stanford Investigational Pharmacy.

IP may be dispensed by the Pharmacist or designee per Stanford University standard operating procedure. Study treatment will be dispensed to participants at Cycle 1 Day 1 (Cycles 1 through 6) and then every 3 cycles (ie, Cycle 9, Cycle 12, Cycle 15) during scheduled study visits as described in Section 6.1 (Schedule of Events), or unscheduled visits if study treatment is damaged / lost or a dose modification is necessary. Participants will be instructed to keep their study treatment in the bottles provided and not to transfer it to any other containers.

Nirogacestat drug accountability: Per Stanford Investigational Pharmacy standard operating procedures. Additionally, study subjects will be instructed to bring dispensed IP (used and unused bottles) and study drug diary to each clinic visit. During these visits, clinical research coordinator / PI will perform accountability, reconciliation, and record maintenance.

Institutional guidelines for destruction of investigational product will be followed.

4.1.3.2. Formulation, Appearance, Packaging, and Labeling

The dihydrobromide salt form of nirogacestat (PF-03084014) will be used in this study.

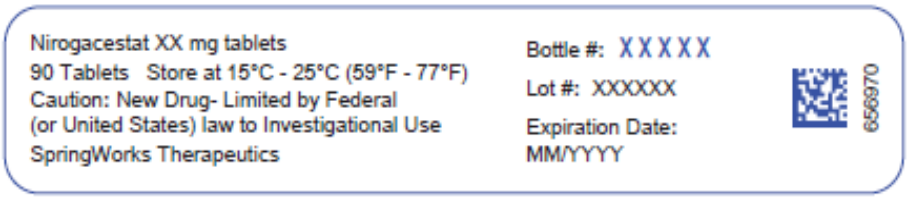
IUPAC name: (S)-2-(((S)-6,8-Difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)amino)-N-(1-(2-methyl-1-(neopentylamino)propan-2-yl)-1H-imidazol-4-yl)pentanamide dihydrobromide.

Table 2. Formulation and Ingredients:

Dose Formulation:	Tablet
Unit Dose Strength:	50 mg
Appearance:	Coated; white to off-white; round
Ingredients:	Nirogacestat (PF-03084014) Opadry QX Film Coated tablets: Macrogol (PEG) polyvinyl alcohol graft copolymer, Talc, Titanium dioxide, GMCC Type 1, Polyvinyl alcohol- part hydrolyzed, Yellow 6 / Sunset Yellow FCF Aluminum lake, iron oxide yellow

Nirogacestat tablets may be uncoated or coated with a non-functional aqueous film coat (Opadry QX). All tablets contain common compendial excipients with appropriate packaging material.

Table 3. Investigational Packaging and Labeling:

Packaging details:	• 90 count bottles
Labeling details	• Sample label: 

4.1.3.3. **Storage and Stability**

Please refer to the current Investigator's Brochure[4] and the Ogsiveo™ (nirogacestat) package insert[28] for detailed information about handling and storage of nirogacestat.

Nirogacestat will be delivered to and managed by Stanford Investigational Drug Services (IDS).

Participants should be instructed to keep their medication at room temperature and avoid storing in a place that experiences heat and cold fluctuation.

4.1.3.4. **Preparation and Handling.**

No special preparation of investigational product is required, as it will be dispensed in sealed bottles.

Handling: Participants should be instructed to keep their medication in the bottles provided and not transfer it to any other containers.

4.1.4. Investigational Agent Supply

The name, mailing address and local contact phone number for the drug supplier is:

Shannon Downs
Associate Director, Medical Research Operations
100 Washington Blvd.
Stamford, CT. 06902
Shannon.Downs@springworkstx.com
Phone: 203-561-3177

4.1.4.1. Investigational Agent Ordering

Nirogacestat will be requested from the Stanford Investigational Pharmacy.

Nirogacestat will be delivered to and managed by the Stanford Investigational Pharmacy.

4.2. Other Procedures: Cryoablation

Cryoablation of the tumor will occur between investigational agent treatment Cycles 3 and 4, and will be performed according to standard procedures. The cryotherapy device will be an FDA-approved cryoablation system used according to its approved labeling within the Stanford University Medical Center.

Prior to the cryoablation procedure, the interventional radiologist will review cross-sectional imaging studies to formulate a treatment plan, including identifying the target lesion appropriate for treatment, the number and type of cryoablation probes needed, and the optimal percutaneous access approach. Subjects will be limited to one cryoablation treatment session at time of intervention for desmoid tumors that can be at least 50% treated with cryoablation but are < 75% cryoablatable; the cryoablation will be subtotal. For lesions that are in close proximity to freeze-sensitive tissues, such as bowel or skin, the cryoablation treatment will be performed with a safe distance (≥ 5 mm) between the edge of the tissue to be frozen (the “iceball”) and the freeze-sensitive tissue.

The cryoablation procedure will be performed with general anesthesia in an MR procedure room. Limited MRI will be obtained, and the desired access site(s) will be marked on the subject’s skin. After sterile preparation of the treatment field and application of local anesthesia, cryoablation probes will be sequentially placed percutaneously into the target lesion using MRI and/or ultrasound guidance. After all cryoablation probes are positioned appropriately, cryoablation will be performed with 1 or more freeze-thaw cycles. Iceball growth will be monitored by MRI. After active thawing, the probes will then be removed and sterile dressings applied. Immediate post-treatment MRI without and with contrast will be obtained.

Cryoablation of the tumor will be performed using standard technique. In brief, a total of 15-30 minutes of freezing time will be administered to the tumor in two or three freeze cycles, separated by 10-30 minutes of active and/or passive thawing using the Visual-ICE Cryoablation System. Care will be taken to avoid off-target ablation of sensitive structures such as bowel and

skin. The procedures will be performed under general anesthesia. The risks of ablation include but are not limited to ecchymosis, edema/swelling, fever, hemorrhage, infection, delayed/non-healing wound, pneumothorax, probe site paresthesia, skin burn, and injury to off-target structures. With any procedure there is a small risk of death. After ablation, the subject can expect discharge to home within 23 hours in most circumstances.

4.2.1. Regulatory Status of Cryoablation

The Visual-ICE Cryoablation System, which will be used to perform cryoablation for this study, has FDA 510(k) clearance.

Cryoablation is recognized by the National Comprehensive Cancer Network (NCCN) as a viable procedure for desmoid tumor.

Intended use:

The Visual-ICE Cryoablation System is intended for cryoablative destruction of tissue during surgical procedures. The Visual-ICE System is indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology, proctology, and urology. The system is designed to destroy tissue by the application of extreme cold temperatures, including prostate and kidney tissue, liver metastases, tumors, skin lesions, and warts.

The Visual-ICE Cryoablation System has the following specific indications:

- Urology (ablation of prostate tissue in cases of prostate cancer and Benign Prostate Hyperplasia "BPH"
- Oncology (ablation of cancerous or malignant tissue and benign tumors, and palliative intervention)
- Dermatology (ablation or freezing of skin cancers and other cutaneous disorders. Destruction of warts or lesions, angiomas, sebaceous hyperplasia, basal cell tumors of the eyelid or canthus area, ulcerated basal cell tumors, dermatofibromas small hemangiomas, mucocele cysts, multiple warts, plantar warts, actinic and seborrheic keratoses, cavernous hemangiomas, perianal condylomata, and palliation of tumors of the skin.)
- Gynecology (ablation of malignant neoplasia or benign dysplasia of the female genitalia)
- General surgery (palliation of tumors of the rectum, hemorrhoids, anal fissures, pilonidal cysts, and recurrent cancerous lesions, ablation of breast fibroadenoma)
- ENT (Palliation of tumors of the oral cavity and ablation of leukoplakia of the mouth)
- Thoracic surgery (ablation of arrhythmic cardiac tissue cancerous lesions)
- Proctology (ablation of benign or malignant growths of the anus or rectum, and hemorrhoids

5. TREATMENT PLAN

5.1. Treatment Assignment

This is an open-label, phase 2 single center study to evaluate the efficacy and safety of cryotherapy and nirogacestat in desmoid tumors.

The interventional model is non-randomized single group.

One interventional arm.

After the subject is determined to be completely eligible to participate in the study, the OnCore sequence number, a unique subject identifier, will be sequentially assigned.

5.2. Treatment Dose

- Nirogacestat 150 mg by mouth twice daily continuously for Cycles 1 through 3.
- Cryoablation procedure (single session) of one tumor mass between Cycles 3 and 4 of nirogacestat treatment. Nirogacestat will be held on the day of cryoablation.
- Continued systemic therapy with nirogacestat for Cycles 4 through 26. Treatment with nirogacestat may continue via this study for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, subject withdraws their consent, start of a new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs.
- After 24 months of treatment, if clinically indicated, subjects may transition to commercial nirogacestat supply, once subjects have completed the End of Treatment (EOT) visit and are off study.

5.3. Treatment Schedule

1 cycle of treatment is 28 days.

Reported adverse events and potential risks are described in Sections 1.3 and 7.3.

Dose modifications are described in Section 5.6.

Systemic therapy with nirogacestat will be given continuously. A single session of cryoablation will be done between Cycles 3 and 4. **Note: Imaging (staging scan) should be done prior to cryoablation procedure.** Nirogacestat will be held on the day of cryoablation. Continued systemic therapy with nirogacestat for Cycles 4 through 26. Treatment with nirogacestat may continue via this study for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, subject withdraws their consent, start of a new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs.

The use of cryoablation for desmoid tumor is considered standard of care. However, for the purposes of this study, the use of nirogacestat in addition to regular medical care cryoablation therapy is considered investigational.

5.4. Treatment Duration

After completion of 3 cycles of treatment with nirogacestat followed by 1 session of cryoablation between Cycles 3 and 4, nirogacestat may continue for Cycles 4 through 26. Treatment with nirogacestat may continue via this study for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, subject withdraws their consent, start of a new anticancer therapy (as defined in Section 5.7.2), or until one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs.

After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

5.5. Subject Medication Diary

Subjects will be provided with a nirogacestat study medication diary. They will be instructed on how to take the study medication and how to fill in their study medication diary. When they return to clinic at each visit, unused study medication and study medication diary will be collected and reviewed by study staff.

Information captured in the diary:

- Subject ID
- Site
- Cycle number
- Assigned nirogacestat dose
- Was the dose changed by the study doctor during the cycle?
- Exact date and time when each dose was taken
- Dose taken (number of tablets taken with each dose)
- Comments (reason for any missed doses, side effects, anything else participant wants to report, etc.)
- Participant signature and date

5.6. Dose Modifications

Adverse event documentation and reporting is described in Section 7.

Dose Modification

Every effort should be made to administer treatment with nirogacestat at 150 mg BID. However, dosing should be interrupted and/or dose reduced for the adverse events (AEs) described in Table 4. For patient safety, treatment may also be modified or held to manage any AE(s), at the PIs discretion.

If a subject experiences an AE as described in Table 4, hold treatment until the AE is resolved to ≤ Grade 1 or baseline.

- If the AE is resolved within 14-21 days, then treatment should be restarted at the reduced dose as described in Table 4.
- If the AE does not resolve to ≤ Grade 1 or baseline after holding treatment for 22 days, decision to resume treatment should be taken very carefully by the treating physician.

Should the same ≥ Grade 3 AE recur at the reduced dose, and the AE is considered related to the treatment, treatment should be permanently discontinued.

Table 4. Dose Modifications

Toxicity (NCI CTCAE)	Intervention
Gastrointestinal Toxicities	
Grade ≥ 3 diarrhea persisting for ≥ 3 days despite maximal medical therapy[1]	Decrease dose to 100 mg BID and/or hold nirogacestat until Grade 1 or baseline.
Grade ≥ 3 nausea persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Grade ≥ 3 vomiting persisting for ≥ 3 days despite maximal medical therapy	Decrease dose to 100 mg BID
Reproductive System Toxicities	
Grade ≥ 2 premature menopause / ovarian dysfunction [1,2]	Decrease dose to 100 mg BID
Other Toxicities	
Grade ≥ 3 skin toxicity [1]	Decrease dose to 100 mg BID
Grade ≥ 3 hypophosphatemia persisting for ≥ 7 days despite maximal replacement therapy and in the absence of symptoms	Decrease dose to 100 mg BID
Any clinically significant Grade ≥ 3 non-hematological toxicities	Decrease dose to 100 mg BID
Grade ≥ 3 hematological toxicities	Decrease dose to 100 mg BID
Anaphylaxis	Permanently discontinue
Grade ≥ 3 allergic reaction	Permanently discontinue
Hepatic toxicities	See below

1 Please see below for recommendations regarding AE management
2 A dose reduction is not required for events of premature menopause / ovarian dysfunction but may be considered for symptomatic participants based on the individual benefit / risk profile. A dose interruption is not required prior to a dose reduction for reproductive system toxicities.

Select Adverse Event Management Recommendations

Diarrhea:

Subjects experiencing diarrhea considered related to nirogacestat should be treated with loperamide. The recommended initial dose is 4 mg followed by 2 mg after each unformed stool

until the diarrhea is controlled, after which the dosage should be reduced to meet individual requirements. Loperamide should be dosed according to the treating physician's medical discretion. Subjects should also receive appropriate fluid and electrolyte replacement as needed.

If diarrhea is Grade ≥ 3 diarrhea and persists ≥ 3 days despite maximal medical therapy, decrease nirogacestat dose to 100 mg BID and/or hold nirogacestat until the diarrhea is resolved to ≤ Grade 1 or baseline.

- If the dose is held and diarrhea resolves within 14 days, then nirogacestat may be restarted at a dose of 100 mg twice daily.
- If the AE does not resolve to ≤ Grade 1 or baseline after holding study treatment for 22 days, nirogacestat may be resumed at a reduced dose of 100 mg twice daily only after careful consideration by the treating physician.

Skin Toxicity / Rash:

Non-acneiform rashes / skin eruptions:

Pruritic eruptions/skin rash and other non-acneiform rash should be treated with a moisturizer such as Cerave or Eucerin or another equivalent product. If symptomatic, a low-potency topical steroid such as betamethasone valerate lotion (0.05%), desonide cream (0.05%), fluocinolone acetonide solution (0.01%), dexamethasone sodium phosphate cream (0.1%), hydrocortisone acetate cream (1%), methylprednisolone acetate cream (0.25%) or equivalent may also be used.

Acneiform rash:

Topical clindamycin (0.1%) gel or lotion applied BID, rather than steroids, is the most helpful for pustular rash. In severe cases, semisynthetic oral tetracyclines such as doxycycline or minocycline may also be useful with appropriate precautions in women of childbearing potential.

Follicular cysts:

Follicular cysts can be associated with disruptions of the gamma secretase and notch signaling pathway which help maintain pilosebaceous gland function. This adverse reaction was observed in a phase 2 study of nirogacestat in desmoid tumor subjects conducted by the National Cancer Institute (O'Sullivan, 2018). [5] If this event is suspected, it is recommended that a dermatology consultation is obtained for appropriate management recommendations.

Premature menopause / Ovarian dysfunction (OD):

Events of early menopause, such as amenorrhea and hot flushes have been commonly reported in women receiving nirogacestat. It is unknown if these symptoms are reversible after stopping nirogacestat. The effects on long-term fertility are also unknown at this moment.

In the Phase 3 DeFi Trial evaluating nirogacestat in adult patients with progressing desmoid tumors, ovarian dysfunction, which was defined by investigator-reported events of amenorrhea, premature menopause, menopause, and ovarian failure, was observed in 75% (27/36) of women of childbearing potential receiving nirogacestat. These events resolved in 74% (20/27)

of the affected participants, including 64% (9/14) of such participants who remained on nirogacestat treatment and 100% (11/11) of those participants who discontinued treatment for any reason.[27]

Consultation with either a reproductive endocrinologist or OB/GYN experienced with ovarian dysfunction may be considered for further information regarding treatment options for OD. For example, symptoms of OD may be treated with:

- Low dose selective serotonin reuptake inhibitors
- Clonidine
- Hormone replacement therapy (HRT): Given the potential impact of hormone fluctuations on desmoid tumors, HRT should be considered on a case-by-case basis in subjects with desmoid tumors.

A dose reduction of nirogacestat to 100 mg twice-daily may also be considered for symptomatic study participants; however, at this time, there is no data to support whether this will result in symptom resolution.

Discontinuation of Treatment (See also Section 3.7)

It may be necessary for a subject to permanently discontinue treatment with nirogacestat.

Reasons for discontinuation of treatment may include:

- Any serious adverse event (SAE), clinically significant AE (refer to QTcF stopping criteria below), severe laboratory abnormality (refer to liver stopping chemistry stopping criteria below), any Grade ≥ 3 hypersensitivity reaction, anaphylaxis, intercurrent illness, or other medical conditions which indicate that continued treatment is not in the best interest of the subject;
- Pregnancy
- Termination of the treatment protocol by the Institutional Review Board (IRB) / Ethics Committee (EC) or the regulatory authority.

Liver Chemistry Stopping Criteria

Discontinuation of treatment for abnormal liver function should be considered when a subject meets one of the conditions outlined in Figure 1 or if it is believed that it is in the best interest of the subject.

- **See also Appendix G: Liver Safety: Suggested Actions and Follow-up Assessments.**

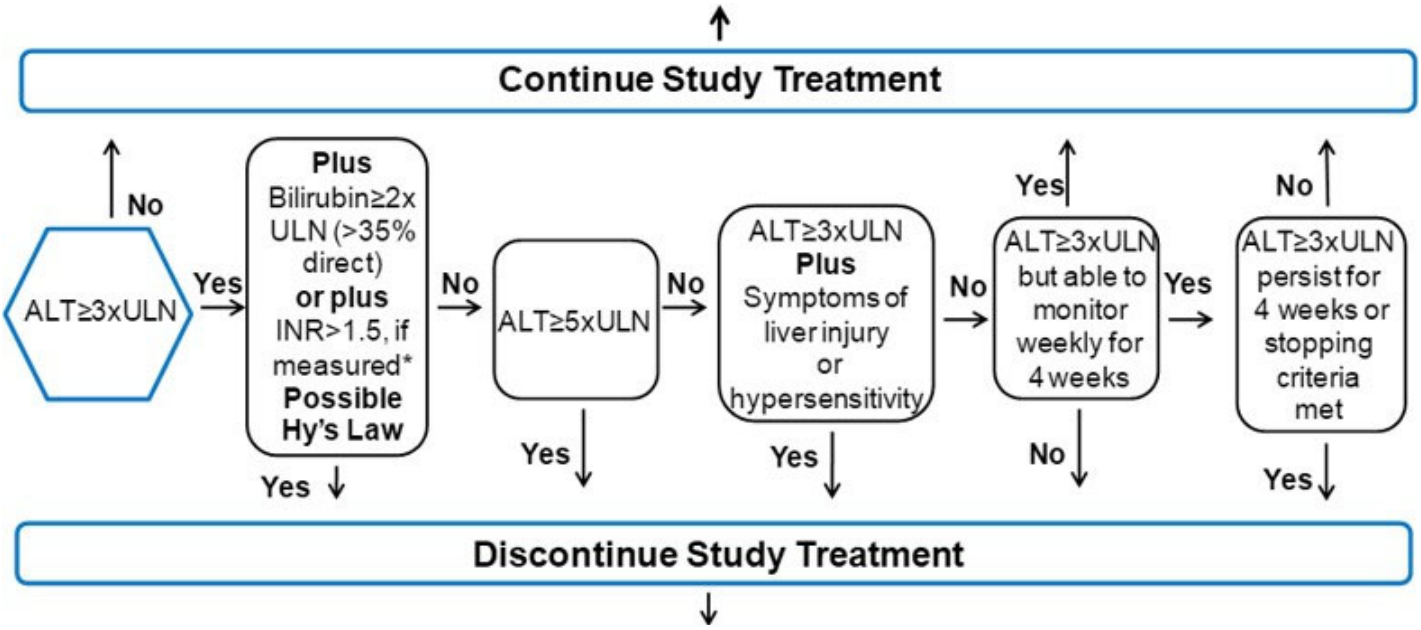


Figure 1. Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm. Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

- **Report as an SAE if adverse event is possible Hy's Law case:**
  ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct) or INR > 1.5, if measured.*

  *INR value not applicable to participants on anticoagulants.

Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

QTcF Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding must be reported as an AE. A participant who meets either bulleted criterion based on ECG readings will be withdrawn from study treatment:

- QTcF > 500 msec
- Change from baseline of QTcF > 60 msec

Table 5 describes discontinuation criteria for participants with underlying bundle branch block.

Table 5. Bundle Branch Block Discontinuation Criteria

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

Pregnancy

A female who becomes pregnant should be withdrawn from treatment with nirogacestat.

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment, and pregnancies will be followed until term. See also Sections 3.8, 6.0, 7.2.4 and 7.6.

If a pregnancy is reported, the investigator must inform SpringWorks within 72 hours of learning of the pregnancy by completing Stanford SAE form and submitting to SpringWorks via email at PV@springworkstx.com.

Abnormal pregnancy outcomes (eg, Spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

5.7. Concomitant Medications, Procedures, and Supportive Care Guidelines

No restrictions on supportive care, except as noted in Section 3.1.3. (Lifestyle Considerations), Section 5.7.1. (Concomitant Medications to Avoid), Section 5.7.2. (Prohibited Concomitant Medications and Procedures), and Section 5.7.3. (Permitted Concomitant Medications).

5.7.1. Concomitant Medications to Avoid

Avoid with nirogacestat:

- CYP3A4 substrates with a narrow therapeutic index
  - Should be avoided if possible, and
  - If co-administration is unavoidable, the subject should be monitored closely for toxicity, and investigator should consider reducing or titrating the dose of the substrate as necessary.
- Gastric acid reducing agents, such as proton pump inhibitors
  - Should be avoided if a reasonable alternative is available; and
  - If administration is necessary, should be administered 4 hours following dosing with nirogacestat.

5.7.2. **Prohibited Concomitant Medications and Procedures.** See also Section 3.1.3. Lifestyle Considerations

- Other investigational anti-cancer therapies
- Anti-cancer surgery
- Definitive radiation (treatment with intent to cure) is not allowed. However, palliative radiation is allowed.
- Strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers are not allowed throughout the study and must be stopped at least 14 days prior to the first dose of study treatment.
- GS inhibitors; Anti-Notch antibody therapy; and Gastric bypass, lap band, or other gastric procedures that would alter absorption.
    - No prior use, therapy or procedure is allowed; and
    - Not allowed throughout the duration of the treatment period.
- Delivery of nirogacestat via nasogastric tube or gastrostomy tube not allowed.

If the study subject needs concomitant medications or treatment not allowed while on this study, then the Protocol Director will require the subject to stop study treatment. An EOT visit (and EOT assessments) will be done within 30 days of last treatment ± 7 days. See Section 3.5 (Treatment Period and Duration), Section 5 (Treatment Plan), and Section 6 (Study Procedures and Assessments).

5.7.3. **Permitted Concomitant Medications**

Permitted medications would include:

- Phosphate supplements:

Nirogacestat has been associated with hypophosphatemia, which may require phosphate supplementation. The choice of phosphate replacement, as well as the duration, is at the investigator's discretion.

- Palliative care:

Medications for the standard management of symptoms or supportive care for the management of the effects of study treatment may be administered at the investigator's discretion, unless they are excluded concomitant medications (Section 5.7.2.).

5.7.4. **Treatment of Overdose**

Overdose

For this study, any dose of study treatment greater than 450 mg daily dose of study treatment within a 24-hour period will be considered an overdose.

In the case of accidental overdosing with nirogacestat:

- Contact the Protocol Director / IND-holder, Dr. Nam Bui, immediately at: nambui@stanford.edu and/or phone 650-498-6000.
- In the event of an overdosage, stop treatment with nirogacestat and initiate general supportive measures. Due to the high level of protein binding, nirogacestat is not expected to be dialyzable in patients with normal serum protein levels.
- Vital functions should be monitored carefully in an appropriate health care facility. Special attention should be given to hematological (complete blood counts with differential) and gastrointestinal functions.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities for at least 4 days.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1. Schedule of Events

Cycle Length: 28 days

Labs, Tests, Procedures, Drug Administration [a]	Screening [b]	Cycles 1–6 [c]	Cycles 7 – 26 [c]	End of Treatment (EOT) [o]
Nirogacestat [c]		X	X	
Cryoablation [d]		X		
Informed consent	X			
Demographics	X			
Medical history	X			
Concomitant medications [e]	X	X	X	X
Physical exam	X	X	X	X
Vital signs	X	X	X	X
Height	X			
Weight	X	X	X	X
Performance status	X	X	X	X
EQ-5D-3L questionnaire [f]	X	X	X	X
CBC w/differential [g]	X	X	X	X
Serum chemistry, magnesium, phosphorus [h]	X	X	X	X
Coagulation (PT, PTT)	X			
β-HCG [i]	X			
Urine pregnancy test [j]		X	X	X
ECG [k]	X			
Adverse event evaluation [L]	X	X	X	X
Tumor measurements [m]	X	X	Tumor measurements at Screening, then every 3 cycles (every 12 weeks ± 14 days) until End of Treatment (EOT) Visit. Subjects who come off treatment for reasons other than progressive disease may have imaging for EOT visit at the discretion of the provider.	
Radiologic evaluation (MRI) [m]	X	X	Radiologic evaluation at Screening, then every 3 cycles (every 12 weeks ± 14 days) until EOT Visit. Subjects who come off treatment for reasons other than progressive disease may have imaging for EOT visit at the discretion of provider. Documentation (radiologic or clinical) must be provided for subjects removed from study for PD.	
Archival histology report [n]	X			

Correlative studies [p]	**X**	**X**		

a. Unless otherwise specified, visits/procedures must occur within ± 3 days of the planned visit date.
b. **Screening procedures must occur within 28 days prior to start of treatment.**
c. **Treatment: Nirogacestat:** 150 mg by mouth twice daily for up to 26 cycles. Subjects will be seen on Day 1 of every cycle (Cycles 1 through 6) and then every 3 cycles thereafter (Cycles 9 through 26). Subjects will have physical exam, vital signs, weight, performance status evaluation, side effect review, concomitant medication review at the time of their visit. Nirogacestat will be dispensed to subjects during scheduled study visits. See also footnote a.
d. **Treatment: Cryoablation:** Cryoablation procedure (single session, 1 tumor mass) may occur anywhere between Cycles 3 and 4; however, imaging (staging scan) should be done prior to cryoablation procedure.
e. Concomitant medications will be recorded from the time the subject signs informed consent and for 30 days after last treatment.
f. EQ-5D-3L questionnaire will be completed by subjects at screening, at Cycles 1 thr 3 and Cycles 5 through 9, then every 3 cycles (Cycles 12 through 26) before any assessments are performed, and at EOT. There will not be a questionnaire for Cycle 4. Questionnaires are attached in Appendices I (English), J (Spanish), K (Simplified Chinese), and L (Vietnamese).
   - Non-in-person visits: For those cycles where participants are not coming to clinic either due to protocol (ie, Cycles 7 & 8) or due to Covid-19 restrictions, participants will be sent the EQ-5D-3L questionnaire via secure Stanford Email or MyHealth Epic message to complete and return via secure Email or MyHealth Epic message.
g. CBC with differential
   - Should be done within 72 hours prior to Day 1 of each cycle (for Cycles 1 through 6)
   - CBC with differential should be every 3 cycles thereafter (Cycles 9, 12, 15, 18, 21, 24) within 7 days prior to Day 1 of the cycle.
   - CBC with differential should be done within 7 days prior to End of Treatment visit.
h. Serum Chemistry (Metabolic comprehensive panel plus magnesium and phosphorus) includes: albumin, alkaline phosphatase, AST, ALT, bicarbonate, BUN, calcium, chloride,CO_2, creatinine, glucose, globulin, potassium, sodium, total bilirubin, total protein, plus magnesium and phosphorus.
   - Laboratory assessments should be done within 72 hours prior to Day 1 of each cycle (for Cycles 1 through 6).
   - Laboratory assessments should be done every 3 cycles thereafter (Cycles 9, 12, 15, 18, 21, 24) within 7 days prior to Day 1 of each cycle.
   - Laboratory assessments should be done within 7 days prior to End of Treatment visit.
i. B-HCG: A serum pregnancy test (women of childbearing potential) will be performed at screening within 28 days prior to start of treatment. This test can be omitted if subject is post-menopausal by history.
j. Urine pregnancy test for women of childbearing potential (this test can be omitted if subject is post-menopausal by history)
   - A urine pregnancy test (should be performed within 72 hours prior to Day 1 of each cycle (for Cycles 1 through 6)
   - Urine pregnancy test should be done every 3 cycles thereafter (Cycles 9, 12, 15, 18, 21, 24) within 7 days prior to Day 1 of the cycle.
   - A urine pregnancy test (women of childbearing potential) should be done within 7 days prior to End of Treatment Visit.
k. Electrocardiogram (ECG): To be done at Screening. Further ECGs are to be performed if indicated.
l. Adverse events (AEs) recorded from the time the subject signs informed consent and for 30 days from the time of last treatment. If removed from study due to unacceptable adverse event(s) toxicity, the subject will be followed & safety data collected for at least 30 days or until resolution or stabilization of the adverse event, to the extent possible. SAEs will be followed for 30 days after the last dose of study treatment, or until the SAE(s) is/are resolved or stable whichever is longer. Females reporting dysfunction including ovarian failure, menopause, premature menopause, and/or amenorrhea, will be tracked until resolution or for at least 90 days after discontinuing study treatment. Pregnancies will be followed until outcome is known. See also Sections 3.8, 5.6, 7.2.4, and 7.6.
m. Radiologic evaluation and tumor measurements should be performed at Screening, then every 3 cycles (ie, every 12 weeks ± 14 days) and End of Treatment visit. Subjects who come off treatment for reasons other than progressive disease may have imaging for EOT visit at the discretion of the provider. MRI scan will be used at screening and at subsequent time points). Imaging must encompass all areas of disease.
n. Archival histology report will be reviewed for verification of diagnosis. Subjects must have a diagnosis of desmoid tumor/desmoid fibromatosis on pathology report.
o. EOT: EOT visit to be done within 30 days of last treatment ± 7 days. Subjects may be seen in person, by video visit, or may be contacted by phone. Routine labs, AE assessment, conmed review, performance status assessment, and imaging will be done. If subject has in-person visit, physical exam will be performed, and vital signs, weight, and performance status will be evaluated. Other assessments to be done at discretion of the treating investigator. If a video visit or phone visit is done, then EQ-5D-3L questionnaire will be sent to the subject via secure Email or MyHealth Epic message for the subject to complete and return via secure Email or MyHealth Epic message.

p. Correlative studies (Optional archival tumor sample and biopsies). If subjects elect to opt-in to correlative studies, archival tumor sample will be requested at screening, and biopsies will be obtained at the time of cryoablation.

6.2. Description of Procedures and Assessments

6.2.1. Efficacy Assessments

Screening tests, examinations, or procedures to be done as part of the study to support the determination of efficacy include:

- Radiologic evaluation and tumor measurements: Imaging must encompass all areas of disease. MRI scan will be used at screening and at subsequent time points.

Assessments (after screening) to support the determination of efficacy include:

- Radiologic evaluation and tumor measurements should be performed at Screening, then every 3 cycles (ie, every 12 weeks ± 14 days), and End of Treatment Visit. MRI scan will be used at screening and at subsequent time points. Imaging must encompass all areas of disease.

6.2.2. Safety and Other Assessments

Screening assessments, including coagulation tests (PT, PTT) and a serum pregnancy test for women of childbearing potential, must occur within 28 days prior to start of treatment. All other laboratory assessments must be done within 72 hours of C1D1. Serum pregnancy test can be omitted if subject is post-menopausal by history.

Women of childbearing potential must agree to use highly effective contraception for the duration of study participation and for at least 1 week after the final dose of study medication. Sexually active males must agree to use highly effective contraception for the duration of study participation and for at least 1 week after the final dose of study medication (see also Appendix H). Women should not donate or harvest their eggs (ova, oocytes) while participating in this research study and for at least 6 months after taking their last dose of study drug. Men should not donate or preserve their sperm for at least 90 days after taking their last dose of study drug.

Screening tests, examinations, or procedures include:

- **Demographics:** Date of birth, sex, race, ethnicity
- **Medical history review:** Review of medical history, including cancer history and other cancer treatments subject has received.
- **Medication review:** Review of any medications subject is taking now or has recently taken, including any over-the-counter medications.
- **Physical exam and vital signs:** A complete physical exam including vital signs (temperature, heart rate, respiratory rate, blood pressure, height, and weight). Height will only be obtained at screening visit.
- **ECOG Performance Status**: Subject will be asked about their ability to perform everyday tasks (see Appendix B. ECOG Performance Status).

- **Blood samples:** Routine laboratory assessments
  - CBC with differential, platelets
  - Serum chemistry: Comprehensive metabolic panel, plus magnesium and phosphorus
  - Coagulation: PT and PTT
- **Research samples:**
  - **Blood sample for research: Pregnancy test: β-HCG**
  - **Tissue sample for research:**
    - **Archival tumor sample** will be requested by pathology, if subjects elect to opt-in to optional tissue collection for correlative studies.
- **EQ-5D-3L Questionnaire:** Subjects' quality of life will be assessed.

  The EQ-5D-3L questionnaire (Appendix I to L) includes questions for following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions.
- **Electrocardiogram (ECG):** At screening ECG, QT interval corrected by Fridericia's formula must not be > 450 msec for male subjects or > 470 msec for female participants, or > 480 msec for participants with bundle branch block after electrolytes have been corrected (Exclusion criteria 9). Further ECGs to be done at discretion of treating investigator.
- **Radiologic evaluation and tumor measurements:** Imaging must encompass all areas of disease.
- **Archival histology report:** Pathology reports will be reviewed for verification of diagnosis. Subjects must have a diagnosis of desmoid tumor on pathology report. Central review, for verification of diagnosis, will not be done.

Enrollment: Subjects must have progressive or symptomatic desmoid tumor.

Subjects will all be assigned to receive the same treatment: systemic therapy with nirogacestat for 3 cycles, followed by 1 session of cryoablation between Cycles 3 and 4, followed by nirogacestat for Cycles 4 through 26.

The duration of enrollment for this study will last approximately 24 months.

Assessments (after screening):

- Unless otherwise specified, visits/procedures must occur within ± 3 days of the planned visit date.
- **Subjects will be seen Day 1 each cycle (C1 through C6) and then Day 1 of every 3 cycles (= approximately every 12 weeks ± 7 days, ie, C9, C12, C15, C18, C21, C24) and have the following assessments.** If an in-person visit is not allowed secondary to Covid-19, then a video visit or contact by phone is allowed.

- Physical exam, vital signs, weight
- EQ-5D-3L Questionnaire: Subjects' quality of life will be assessed at multiple timepoints throughout the study. The EQ-5D-3L questionnaire will be completed at Cycles 1 through 3 and Cycles 5 through 9, then every 3 cycles thereafter (Cycles 12, 15, 18, 21, 24), and at the EOT visit. There will not be a questionnaire for Cycle 4.
  - The questionnaire will be completed at specified study visits before any assessments are performed.
  - Non-in-person visits: For those times where subjects are not coming to clinic for an in-person visit, either due to protocol (ie, Cycles 7 and 8) or due to Covid-19 restrictions, an EQ-5D-3L questionnaire will be emailed to the subjects via secure Stanford Email or MyHealth Epic message for subject completion and return via secure Email or MyHealth Epic message.
  - The EQ-5D-3L questionnaire will then be completed every 3 cycles thereafter (Cycle 12, Cycle 15, etc.), and at the EOT visit). The questionnaire will be completed at each study visit before any assessments are performed.
- Side effect review, concomitant medications review, performance status assessment

- **Laboratory assessments:**
  - **Blood samples will be drawn for routine tests** every cycle within 72 hours prior to Day 1 of Cycles 1 through 6. Blood samples will be drawn for routine tests every 3 cycles thereafter (approximately every 12 weeks) within 7 days prior to D1 of cycle (Cycles 9, 12, 15, 18, 21, 24) and at the End of Treatment visit.
  - **Research-related Laboratory Assessments: Urine pregnancy test** will be done every cycle within 72 hours prior to Day 1 of Cycles 1 through 6. Urine pregnancy test will be done every 3 cycles thereafter (approximately every 12 weeks) within 7 days prior to D1 of cycle (Cycles 9, 12, 15, 18, 21, 24) and at the End of Treatment visit.
- **Tissue samples for research: Optional**
  - **Biopsies** will be obtained at the time of cryoablation (between Cycle 3 and 4) for correlative studies if subjects elect to opt-in to optional tissue collection for correlative studies. Biopsies may be saved for future research.
- **Radiologic evaluation and tumor measurements** should be performed at screening, then every 3 cycles (ie, every 12 weeks ± 14 days), and End of Treatment. MRI scan will be used at screening and at subsequent time points. Imaging must encompass all areas of disease.
- **Adverse events:** Adverse events will be assessed from the time the subject signs consent until 30 days after last treatment. If a subject is removed from study due to unacceptable adverse event(s) toxicity, that subject will be followed and safety data collected for at least 30 days and until resolution or stabilization of the adverse event, to the extent possible.

End of Treatment:

An End of Treatment visit will be done within 30 days of last treatment ± 7 days. Subjects will be followed for safety for 30 days from time of last treatment, except if being monitored for related adverse event.

The following procedures/assessments may be performed at the EOT visit:

- Subjects may be seen in person, by video visit, or may be contacted by phone. If in-person visit, then physical exam, vital signs, weight and EQ-5D-3L questionnaire will be done.
- If a video visit or phone visit is done, then EQ-5D-3L questionnaire will be sent to the subject via secure Email or MyHealth Epic message for the subject to complete and return via secure Email or MyHealth Epic message.
- Vital signs and weight will be done if subject has in-person visit.
- EQ-5D-3L Questionnaire: See above.
- Adverse event assessment
- Review of concomitant medications
- Performance status assessment
- Routine labs
- Urine pregnancy test
- Radiographic evaluation and tumor measurement: Subjects who come off treatment for reasons other than progressive disease may have imaging for EOT visit at the discretion of the provider.
- Other assessments to be done at the discretion of the treating investigator.

Subjects that personally withdraw from treatment will be requested to have a 30-day End of Treatment visit or otherwise receive a follow-up contact, unless specifically countermanded by the subject.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

References for SCI adverse event (AE) policies and practices are provided in Appendix A.

7.1. Adverse Event Definitions

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An adverse event can be any unfavorable and unintended sign or symptom, including abnormal laboratory findings, or disease, that is temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse reaction is any event that is caused by a drug or device, ie, possibly-, probably-, or definitely-related to the use of the drug or device.

Except as otherwise explicitly defined within this section, **this also includes all events of clinical deterioration such as tumor relapse, recurrence, or upstaging, or new cancers**.

Within the scope of this study and protocol, adverse device effects, ie, events that have a serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device may be referred to as “serious adverse events (SAEs).”

Serious adverse events (SAEs) are defined per the FDA definition at 21CFR§312.32(a) and ICH GCP E6. An adverse event is considered "serious" if, in the opinion of the PD, investigator, or sponsor, it results in ANY of the following.

- Death
- Life-threatening adverse event with an **actual and immediate risk of death** [21CFR§312.32(a)]
- In-patient hospitalization or prolongation of existing hospitalization, except planned hospitalization or hospitalization only for study conduct will not be considered SAEs. Note that the per-protocol cryoablation procedure will not be considered an SAE hospitalization, even if the patient stays in the clinic overnight.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Event jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed here

7.2. Classification of Adverse Events

7.2.1. Severity of Event

NCI CTCAE version 5.0 is used to assess the severity of adverse events in this study.

7.2.2. Adverse Event Attribution to Intervention or Study

For this study, all recorded adverse events will be assessed on the basis of whether or not the adverse event was caused by / due to (ie, related) to the study intervention(s). AEs, serious or otherwise, will be attributed by the Principal Investigator or qualified designate to study treatment in accordance with the definitions below.

• **Definitely Related**. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary. • **Probably Related**. There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. • **Potentially / Possibly Related**. There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an adverse event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.	These are treated as **"Related"**
• **Unlikely to be related**. A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments). • **Not Related**. The adverse event is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.	These are treated as **"Not Related"**

In addition, for adverse events determined "Not Related" to the study intervention(s), the Principal Investigator or qualified designate will attribute the event to the study or procedures according to the definitions above. Note that adverse events can be determined related to both the intervention(s) and/or the study / procedures.

7.2.3. Expectedness of Event

The Principal Investigator or qualified designate will also assess all recorded adverse events on basis of event severity, frequency (if applicable/assessable), and the established product risk information described within the product Investigator's Brochure; the FDA-approved product labeling (if an approved agent); and/or this protocol document, as to whether the events are "expected" or "not expected" relative to the study interventions and/or the study / procedures.

Note that unexpected adverse events may have reporting requirements as described elsewhere in this section.

7.2.4. Time Period of Event Assessment and Follow-up

Adverse events will be recorded from the time the subject signs the informed consent form and for 30 days after the last study treatment, except if being monitored for a related adverse event.

If a subject is removed from study due to unacceptable adverse event(s) toxicity, that subject will be followed & safety data collected for at least 30 days and until resolution or stabilization of the adverse event, to the extent possible. All SAEs will be followed for 30 days after the last dose of study treatment, or until the SAE(s) is/are resolved or stable, whichever is longer. Pregnancies will be followed until term. See also Sections 3.8, 5.6, 6.0, and 7.6.

7.3. Potential Adverse Events and Risks

A brief summary of nirogacestat adverse events and risks was described in Section 1.3.1 Known Potential Risks.

In addition to the summary risks described in Section 1.3.1, adverse events described by severity and frequency within the research agent nirogacestat Investigator's Brochure and/or the Ogsiveo™ (nirogacestat) package insert are considered anticipated, ie, not unexpected. Procedural risks described in Section 1.3.1 are considered anticipated.

Cryoablation is widely used within the Stanford Cancer Institute for the treatment of cancer, both as an individual treatment as well as part of a treatment regimen, and its risk profile is well understood as a regular medical care procedure. Risks associated with cryoablation are expected in accordance with the current FDA 510k approval. It is not known if there are additional risks of cryoablation in combination with the study drug, nirogacestat. However, safety is being monitored, as described within this section and within Section 6.2.2 (Safety and Other Assessments). Doses of nirogacestat may be adjusted in response to specific adverse events, as described in Section 5.6 (Dose Modifications).

7.3.1. **Nirogacestat** (Information from Investigator's Brochure) [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

Special Warnings and Precautions for Use

To date, important identified risks related to nirogacestat include diarrhea, dermatologic reactions (maculopapular rash, hidradenitis, and folliculitis), ovarian dysfunction, electrolyte abnormalities (hypophosphatemia and hypokalaemia), and elevated liver transaminases. Important potential risks include non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma), embryo-fetal toxicity, effects on male fertility, and in pediatric patients, epiphyseal disorder.

- **Diarrhea**

  Nonclinical data suggest that inhibition of GS may interfere with the integrity of the lower gastrointestinal tract epithelium and control of intestinal motility. GS inhibition may affect the intestinal tract epithelium (Barker, 2007; Kurokawa, 2020), villus lacteals (Norden, 2021), and enteric nervous system (Willem, 2016; Barrenschee, 2015), and lead to diarrhea.

In the Study NIR-DT-301, diarrhea occurred in 84% of participants who received nirogacestat compared to 35% in participants given placebo. Grade 3 events occurred in 16% of participants; no events of Grade 4+ diarrhea were reported. Participants should be monitored and diarrhea managed according to recommendations in Section 5.6 Dose Modifications.

- **Dermatologic reactions**

  The Notch signaling pathway exerts a crucial role in regulating and maintaining skin homeostasis, orchestrating keratinocyte differentiation at the level of inter-follicular epidermis and hair follicles, and finally working in epithelial barrier formation (Condorelli, et al, 2021). Further, a genetic association between mutations in the GS complex and hidradenitis suppurativa has been described in the literature (Wang 2010; Frew et, 2017). In addition, when GS is inhibited, the outer root sheath cells activate epidermal differentiation which results in the conversion of hair follicles to cysts (Melnik B, Plewig G, 2013).

  Nirogacestat can cause dermatologic reactions including maculopapular rash (32%), hidradenitis (9%), and folliculitis (13%). Participants should be monitored for skin reactions throughout the treatment course and managed as clinically indicated. See Section 5.6 Dose Modifications.

- **Ovarian Dysfunction:**

  Nonclinical data for nirogacestat showed ovarian atrophy with decreased follicular development and no presence of corpora lutea at clinically relevant doses in rats. GS inhibition may interfere with both the angiogenesis needed to support luteal development (Vanorney, et al, 2017) and the cell-to-cell signaling within the thecal cell layer to control luteal development (Hahn, et al, 2005; Zhang C-P, et al, 2011).

  In Study NIR-DT-301, 75% of WOCBP receiving nirogacestat reported events related to OD. The median time to first onset of OD was 8.9 weeks and the median duration of events was 21.3 weeks. These events resolved in 64% of WOCBP with OD who continued taking nirogacestat and in all WOCBP who stopped nirogacestat for any reason. OD events are accompanied by suppression of AMH and estradiol production, and increases in FSH, LH, and progesterone; however, nirogacestat treatment did not appear to result in a prolonged suppression of estradiol. Effects of nirogacestat on fertility are unknown. WOCBP should be advised about the risk of OD before initiating treatment with nirogacestat.

- **Electrolyte Abnormalities:**

  GS inhibition may affect the intestinal tract epithelium (Barker, 2007; Kurokawa, 2020), villus lacteals (Norden, 2021), and enteric nervous system (Willem, 2016; Barrenschee, 2015), and lead to diarrhea, which could in turn lead to loss of electrolytes. In addition, Notch signaling in the nephron is responsible for the maintenance of the balance of epithelial cell type diversity and epithelial repair (Mukherjee, Fogarty, et al, 2019), and

disruption of this balance could lead to altered ability of the kidney to adapt to impaired electrolyte imbalances (Mukherjee, deRiso, et al., 2019).

Electrolyte abnormalities occurred in participants taking nirogacestat in Study NIR-DT-301. This included hypophosphatemia (42%) and hypokalemia (12%). Grade 3 events occurred in 3% and 1% of participants, respectively. Phosphate and potassium levels should be monitored regularly and supplemented as necessary. See also Section 5.6 Dose Modifications.

- **Elevated Liver Transaminases:**

  Effects on hepatic function emerged as an AE of special interest for nirogacestat based on observations of mild hepatic vacuolation in nonclinical studies in rats, and transient transaminase elevations in early clinical studies with nirogacestat.

  ALT or AST elevations occurred in 20% of participants who received nirogacestat in Study NIR-DT-301. Grade 3 ALT or AST elevations (> 5 times ULN) occurred in 3% of participants. The majority of ALT or AST elevations were Grade 1 (> ULN to 3 times ULN), occurred within the first month of treatment, and resolved spontaneously without dose modification. Liver function tests should be monitored regularly. See Section 5.6 Dose Modifications and Section 13.8 Appendix G Liver Safety: Suggested Actions and Follow-up Assessments.

- **Embryo-fetal Toxicity:**

  Based on its mechanism of action and data from animal studies, nirogacestat may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nirogacestat to rats during organogenesis resulted in embryo loss, resorption and decreased fetal weights in surviving embryos, while administration of nirogacestat to rats prior to conception resulted in decreased early embryo-fetal implantation and early embryonic loss. These effects occurred at exposures below those occurring clinically at the recommended dose. Advise patients of the potential risk to a fetus. Advise women of childbearing potential to inform their healthcare provider of a known or suspected pregnancy, and to stop taking nirogacestat if they become pregnant. Advise women of reproductive potential to use effective contraception during treatment with nirogacestat and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with nirogacestat and for 1 week after the last dose. Women should not donate or harvest their eggs (ova, oocytes) while participating in this research study and for at least 6 months after taking their last dose of study drug. Men should not donate or preserve their sperm for at least 90 days after taking their last dose of study drug.

- **Effects on Male Fertility:**

  In the 3-month dog study, changes in the testes include vacuolation of Sertoli cells, degenerative spermatids and loss of spermatocytes and germinal cells were observed. In the treated male rats, a decrease in epididymal weight was noted. Sperm motility was markedly lower at all dose levels, and mean cauda epididymal sperm concentrations

were lower in the 20 and 40 mg/kg/day groups when compared to the control group. In addition, the percentages of morphologically normal sperm in the 20 and 40mg/kg/day groups were lower than the control group.

- **Epiphyseal Disorder:**

  Increased retention of the hypertrophic zone of the growth plate and articular cartilage (sternum and joint) was seen at >20 mg/kg/day in the 1-month study rat study. This change was characterized by minimal to moderate thickening of the hypertrophic zone in the cartilage with pallor and slight vacuolation of the osteocytes in the primary spongiosa. Partial recovery of these effects were evident after discontinuation of nirogacestat. This response is similar to those observed with vascular endothelial growth factor (VEGF) inhibitors. Whether the anti-angiogenic like effects of nirogacestat are mechanism-related (i.e., a result of Notch inhibition or effects on other GS substrates) or are downstream effects on angiogenic growth factor signaling (i.e., VEGF) cannot be determined at this time.

  Events of limb asymmetry, slipped capital femoral epiphysis, epiphyseal disorder, femoral neck fracture, and osteonecrosis of the femoral head have been reported by pediatric patients participating in the nirogacestat compassionate use and the investigator-initiated research program. Routine growth plate monitoring of the tibial growth plate has been included in clinical trials involving participants with open growth plates. Participants with open growth plates being treated with nirogacestat should have their tibial growth plate monitored. Nirogacestat should be discontinued if fracture through an open growth plate or osteonecrosis are observed.

- **Reproductive System Effects:**

  - **Pregnancy:**

    Pregnant women will be excluded from participation in this clinical study with nirogacestat. Study participants will be required to utilize highly effective contraception and avoid pregnancy while receiving nirogacestat. If a subject becomes pregnant while receiving nirogacestat, the treatment with nirogacestat should be stopped, and the subject will be apprised of the potential hazard to the fetus.

    Women of childbearing potential must have a negative pregnancy test prior to starting treatment with nirogacestat and must agree to use a highly effective method of contraception (ie, copper-containing intrauterine device, established use of oral, injected or implanted hormonal method of contraception, or male/female sterilization) while receiving treatment with nirogacestat and for at least 1 week after the last dose of active study treatment. A second method of contraception is required if the female subject is using hormonal contraception, as coadministration with nirogacestat may result in reduced plasma concentrations of hormonal contraceptives and increase the risk of reduced efficacy. See also Appendix H.

If a pregnancy is reported, the investigator will inform SpringWorks within 72 hours of learning of the pregnancy by completing a Stanford SAE form and submitting to Safety (PV@springworkstx.com).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Male subjects must use a condom when having sexual intercourse with a woman of childbearing potential (WOCBP) while receiving treatment with nirogacestat and for at least 1 week after the last dose. An additional form of highly effective contraception should also be used by the female partner, if of childbearing potential.

Women should not donate or harvest their eggs (ova, oocytes) while participating in this research study and for at least 6 months after taking their last dose of study drug. Men should not donate or preserve their sperm for at least 90 days after taking their last dose of study drug.

Lactation: No studies have been conducted in humans to assess the impact of nirogacestat on milk production, its presence in breast milk and its effects on the breast-fed child. Since drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, breastfeeding women should not receive nirogacestat administration.

Effects on Ability to Drive and Use Machines:

The effects on the ability to drive or operate machinery or impairment of mental ability have not been formally studied with nirogacestat. No Grade 3 events that might be associated with an effect on the ability to drive machinery occurred at an incidence of >1% in any single-agent study among all participants receiving any dose of nirogacestat. Based on these data, nirogacestat is not expected to have a clinically significant effect on the ability to drive or operate machinery.

Summary of the Most Commonly (≥ 10% of Participants in the Nirogacestat Arm) Reported AEs from Completed Nirogacestat Single Agent Studies in Adult Patients with Cancer (Modified Information from Investigator's Brochure)* [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

- Diarrhea
- Fatigue
- Hypophosphatemia
- Cough
- Rash maculo-papular
- Rash
- Headache
- Dry mouth
- Dermatitis acneiform
- Nausea
- Vomiting
- Decreased appetite
- Pyrexia
- Hypokalemia
- Aspartate aminotransferase increased
- Epistaxis
- Alanine aminotransferase increased
- Abdominal pain

- Insomnia
- Stomatitis
- Dyspnea
- Anemia
- Constipation
- Upper respiratory tract infection
- Hot flush
- Arthralgia
- Dry skin
- Dizziness
- Hypertension
- Pruritus

*Data from Single Agent Nirogacestat Studies A8641014,A8641020, 14-C-0007, and NIR-DT-301 (Double-Blind Phase).

Table 6. Adverse Reactions Reported in at Least 15% Patients and at a ≥ 5% Rate in the Nirogacestat Arm Than the Placebo Arm in NIR-DT-301 (Modified Information from Investigator's Brochure) [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

	Nirogacestat (N=69)		Placebo (N=72)	
Adverse Reaction	**All Grades n (%)**	**Grade 3* n (%)**	**All Grades**	**Grade 3* n (%)**
Reproductive system				
Ovarian dysfunction[a]	27 (75%)	0	0	0
Skin and subcutaneous tissue				
Rash[b]	44 (64%)	4 (6%)	10 (14%)	0
Alopecia	13 (19%)	0	1 (1%)	0
General				
Fatigue	35 (51%)	2 (3%)	26 (36%)	0
Nervous system				
Headache	20 (29%)	0	11 (15%)	0
Respiratory				
Cough	11 (16%)	0	3 (4%)	0
Dyspnea	11 (16%)	0	4 (6%)	0
Infections				
Upper respiratory tract infection[c]	11 (16%)	0	1 (1%)	0
Metabolism				
Hypophosphatemia	29 (42%)	2 (3%)	5 (7%)	0
Investigations				
ALT increased	12 (17%)	2 (3%)	6 (8%)	1 (1%)
AST increased	11 (16%)	2 (3%)	8 (11%)	1 (1%)

* No Grade 4 or 5 adverse reactions were reported in Study NIR-DT-301.
[a]Ovarian dysfunction includes Ovarian failure, Premature menopause, Amenorrhea, and Menopause; the number of women of childbearing potential in each arm is used as the denominator (nirogacestat N=36, placebo N=37),
[b]Rash includes Maculo-papular rash, Dermatitis acneiform Rash , Rash erythematous , Rash pruritic , and Rash papular .
[c]Upper respiratory tract infection (URTI) includes URTI, Viral URTI, Acute sinusitis, and Sinusitis

Premature Menopause / Ovarian Dysfunction

- In the Phase 3 Study NIR-DT-301 evaluating nirogacestat in adult patients with progressing desmoid tumors, ovarian dysfunction, which was defined by investigator-reported events of amenorrhea, premature menopause, menopause, and ovarian failure, was observed in 75% (27/36) of women of childbearing potential receiving nirogacestat and none of the 37 women of childbearing potential in the placebo arm. All ovarian dysfunction events were Grade 2. These events resolved in 74% (20/27) of the affected participants, including 64% (9/14) of such participants who remained on nirogacestat treatment and 100% (11/11) of those participants who discontinued treatment for any reason.[27]

Important Side Effect of Nirogacestat Occurring in < 10% of Participants:

- Non-melanoma skin cancer*

*Non-melanoma skin cancer includes Basal cell carcinoma [1 (1%)], Squamous cell carcinoma of skin [2 (1%)], and Squamous cell carcinoma [1 (1%)].

Summary of TEAEs in Phase 2 Study of Nirogacestat 150 mg Twice-daily in 17 Subjects with Desmoid Tumors, Study WI180798 (NCT01981551) (Modified Information from Investigator's Brochure). [4] Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

- Most frequently reported TEAEs:
  - Diarrhea (88%)
  - Headache (76%)
  - Hypophosphatemia (76%)
  - AST increased (71%)
  - Lymphocyte count decreased (71%)
  - Nausea (71%)
- Additional reported TEAEs in Study WI80798
  - Diarrhea Grade 3 (1 [6%] subject)
  - Fatigue Grade 3 (1 [6%] subject)
  - Menstruation irregular Grade 3 (1 [6%] subject; subject was postmenopausal prior to enrolling in the study, and per study sponsor this event should not have been reported as a TEAE)
  - Hypophosphatemia Grade 3 (8 [47%] subjects)
- SAEs reported in Study WI80798: 4 SAEs were considered related to nirogacestat by the investigator, and each SAE was reported in a single patient. All were reported as Grade 2 severity. There was one death due to a cerebrovascular accident that was

assessed by the investigator as unlikely related to nirogacestat. There were no TEAEs that were considered to be DLTs.

- Blood bilirubin increased
- Hypersensitivity – led to permanent discontinuation of study treatment in one patient.
- Squamous cell carcinoma
- Vulvovaginal inflammation

Other AEs

- Anaphylactic shock
- Cholecystitis (Reported in ongoing NIR-DT-301 study in less than 1% of study participants)
- Arrhythmia

Table 7. Serious Adverse Drug Reactions for Nirogacestat Considered Expected for Safety Reporting Purposes: Please see Investigator's Brochure Reference Safety Information (RSI) section. The RSI outlines expected serious adverse reactions for regulatory reporting purposes.

Known Drug Interactions:

Modified information from nirogacestat Investigator's Brochure [4]; See also Section 3.1.3. (Lifestyle Considerations), and Section 1.3 (Potential Risks and Benefits), and Appendix F. Please also reference the Ogsiveo™ (nirogacestat) package insert.[28]

- **Cytochrome P450 Inhibitors and Inducers** (from Investigator's Brochure) [4]
  - Coadministration of nirogacestat with strong or moderate inhibitors of CYP3A4 may increase serum nirogacestat concentrations and should be avoided. The use of strong or moderate CYP3A4 inhibitors must be stopped at least 14 days prior to the first dose of study treatment. If coadministration of strong or moderate CYP3A4 inhibitors is unavoidable, immediately interrupt nirogacestat treatment and remain off nirogacestat for the period of time that the CYP3A4 inhibitor is given. Nirogacestat may be resumed one week after cessation of a strong CYP3A4 inhibitor and immediately following cessation of a moderate CYP3A4 inhibitor.
  - Nirogacestat metabolism may be induced when taking strong CYP3A4 inducers resulting in reduced nirogacestat serum concentrations. The use of strong CYP3A4 inducers must be stopped at least 14 days prior to the first dose of study treatment. Co-administration of nirogacestat with strong CYP3A4 inducer should be avoided. If a strong CYP3A4 inducer is required, nirogacestat may be interrupted for the period of time that the CYP3A4 inducer is given and may be resumed immediately after cessation of the CYP3A4 inducer. Dose modifications are not recommended if a moderate CYP3A4 inducer is required.

- **Cytochrome P450 Substrates**
  - Nirogacestat is a weak inhibitor of CYP3A4 at therapeutic doses and may increase the exposure of drugs that are metabolized by CYP3A4. Concomitant use of nirogacestat with CYP3A4 substrates that have a narrow therapeutic index should be avoided.
  - Based on the potential for increased exposure on co administration with nirogacestat, CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If co-administration is unavoidable, the participant should be monitored closely for toxicity and investigator should consider reducing or titrating the dose of the substrate as necessary.
  - Based on physiologically-based pharmacokinetic (PBPK) model predictions, nirogacestat may be a weak-to-moderate inducer of CYP2C19 and may reduce the exposure of drugs that are metabolized by CYP2C19. Therapeutic alternatives to CYP2C19 substrates should be considered as appropriate, however strict avoidance of concomitant use with nirogacestat is not necessary.
- **Other Concomitant Therapy**
  - The effect of nirogacestat on the exposure of hormonal contraceptives has not been evaluated. However, induction of these CYP enzymes has been associated with reduced plasma exposure of various hormonal contraceptives resulting in reduced efficacy.
  - Nirogacestat is a substrate for the drug efflux transporter P-glycoprotein (P-gp). Caution should be used when co-administering the nirogacestat with known P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar. Nirogacestat may also be an inhibitor of P-gp and may increase the exposure of some P-gp substrates like digoxin, dabigatran, and fexofenadine; participants receiving these medications should be closely monitored, as therapeutic effect and adverse reactions of these medications may be increased.
  - Gastric acid reducing agents: Based on the solubility characteristics of nirogacestat, increase of gastric pH may reduce absorption of nirogacestat, although the extent of the effect has not been evaluated in a clinical study. Daily use of gastric acid reducing agents should be avoided. If gastric acid reducers are required, they should be administered 4 hours after administration of nirogacestat.

7.3.2. **Cryoablation**

The risks of ablation include but are not limited to ecchymosis, edema/swelling, fever, hemorrhage, infection, delayed/non-healing wound, pneumothorax, probe site paresthesia, skin burn, and injury to off-target structures. With any procedure there is a small risk of death.

Based on CRYODESMO-01, Grade 1 and 2 toxicity occurred in 32.8% and 44.5% of subjects, Grade 3-4 toxicity occurred in 22% of subjects, and no Grade 5 toxicity was observed. The most common side effects included: [16]

- Pain (21.6%)
- Neural impairment (15.8%)
- Edema (15.1%)
- Musculoskeletal impairment (7.9%)
- Skin burn (5.8%)
- Increased creatinine kinase (5.8%)
- Bleeding (2.9%)
- Fever (0.7%)

7.4. Adverse Event Monitoring and Collection

Untoward medical events experienced by a study subject receiving an interventional drug, device, or procedure, or within **30** days after such treatment, will be considered an adverse event (AE), regardless of whether or not considered drug-related. All events of disease progression or second cancer will be recorded as a serious adverse event (SAE) using the Preferred Term appropriate for the clinical finding.

All adverse events Grade 1 and higher will be collected and recorded as AEs.

In addition, laboratory values without a requirement for intervention, clinical consequence, or outcome will not be considered adverse events, unless deemed serious.

7.4.1. Case Report Forms for Adverse Event Reporting

Both SAEs and non-serious adverse events will be described in source documentation and listed on study-specific Case Report Forms (CRFs or eCRFs).

Adverse events will be recorded in an EPIC smartphrase contained within an EPIC clinic note. This will be transcribed into Oncore database. The information will include the unique subject identifier, event preferred term, CTCAE body system, date of occurrence, date of resolution; and type of resolution. All signs, symptoms, significant laboratory findings, AND diagnoses should be recorded, regardless of relationship, except as described in this document. A single "overarching" diagnosis should not be solely entered as the adverse event term in lieu of the full list of observed signs, symptoms, and significant laboratory findings, which may include the diagnostic preferred term.

Types of resolution are:

- "Resolved," ie, to Grade 0 (or baseline if a pre-existing condition)
- "Continuing" and stable (includes downgrades from a higher grade to a lower grade)
- "Deceased" (due to any cause while on-study)
- Lost-to-follow-up.
- **NOTE**: "Hospitalized" is not an outcome.

Any pre-existing condition that worsens in severity/grade or frequency should be recorded as a new adverse event, except as described in this document.

7.5. Adverse Events of Special Consideration

7.5.1. Second vs Secondary Malignancy

7.5.1.1. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). A second malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly.

7.5.1.2. Secondary Malignancy

In the context of a clinical study, a secondary malignancy is a cancer caused by chemotherapy, radiation, or the investigational agent/intervention. A secondary malignancy is not considered a metastasis of the initial neoplasm, but nonetheless, a secondary malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly. Secondary malignancies are usually described as one of the following:

- Leukemia secondary to oncology chemotherapy [eg, acute myelocytic leukemia (AML)]
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

By definition, secondary malignancies are adverse events that are both serious and related to the research, and should be anticipated to be an Unanticipated Problem (UP) and reported accordingly. If also determined to be related to the study treatment, and not described by the Investigator's Brochure or package insert as known to be associated with the study agent, the secondary malignancies may also necessitate Expedited Reporting to FDA, eg, an IND Safety Report to the IND.

7.5.2. Progressive Disease

Progressive disease will be reported by the clinical signs or symptoms of disease progression. If the event is Grade 5 fatal and signs/symptoms of disease progression are not available / informative for the event, the CTCAE v5.0 preferred term "Disease Progress" may be used.

7.5.3. Other Adverse Events of Special Interest

Adverse events of special interest (AESI) are selected non-serious and serious AEs that must be reported regardless of relationship to study treatment. Refer to Table 8 for the AESIs identified for this study. AESIs will be followed until resolution or return to baseline.

Serious AESIs will be reported to SpringWorks Safety at (PV@springworkstx.com) according to procedures and timeline (Section 7.6)

Non-serious AESIs must be reported to SpringWorks Safety at PV@springworks.com as soon as possible, but no later than 30 calendar days of awareness.

Following medical evaluation, SpringWorks may request study site to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESI; additional events may be identified during the course of the study.

Table 8. Adverse Events of Special Interest

Elevated Liver Enzymes (reported as AESI if Grade ≥ 2, per CTCAE v. 5)
1. AST
2. ALT
3. Alkaline Phosphatase
4. Total bilirubin
Drug Reactions, any Grade
1. Allergic reaction
2. Anaphylaxis
3. (Drug) Hypersensitivity
Ovarian Dysfunction, any Grade[1]
1. Ovarian dysfunction
2. Ovarian Disorder
3. Amenorrhea
4. Oligomenorrhea
5. Premature Menopause
6. Ovarian failure
Non-Melanoma Skin Cancer, any Grade, and Pre-cancerous Skin Lesions, any Grade
1. Basal cell carcinoma
2. Squamous cell carcinoma (of skin)
3. Keratoacanthoma
4. Actinic keratosis

[1] Females reporting AEs / AESIs / SAEs of ovarian dysfunction will have hormone levels assessed every 3 months until event resolution (or for at least 90 days after discontinuing study treatment).

7.6. Adverse Event Reporting

Reportable adverse events, based on relatedness (attribution) to the study agent; expectedness, severity (Grade 1 to 5), seriousness (Yes/No), or any other aspect of the investigation, will be reported as described below.

- Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat; and head congestion should be reported as "upper respiratory infection").

- Serious adverse events (SAEs) per the definition at 21CFR§312.32 will be reported to the sponsor-investigator (IND holder), Dr. Nam Bui, **within 24 hours of the knowledge of the event**.
- SAEs will be reported by the IND-holder to the study drug supplier / funding source SpringWorks on a MedWatch Form FDA 3500A for an SAE initial and follow-up case (as defined later in this Section 3.2) for a 7 day or 15 day expedited report to SpringWorks at the same time of reporting to the regulatory authorities; and submit all SAE initial and follow-up cases that do not qualify for reporting to regulatory authorities as an expedited report to SpringWorks within 30 calendar days from the date of investigator awareness. Reports should be completed and submitted by email to PV@springworkstx.com and/or fax 866-750-4514.
- SAEs will be reported to the SCI Data and Safety Monitoring Committee (DSMC) by submission to CCTO-Safety. The event must be described on either the SCI SAE form (see references in Appendix A), or a study-specific form. If applicable, the Form FDA 3500A (see Section 7.6) for mandatory IND Safety Reports may be substituted. The report will be sent by **secure** email to CCTO-safety@stanford.edu at the time of the **first** notification to any of the drug supplier / funding source, SpringWorks; the IRB of record; or the IND (ie, FDA). The SAE form must be signed by the investigator. CCTO-Safety will process the SAE report into OnCore, and the DSMC will review the event. See the SCI Data Safety and Monitoring Plan (DSMP).
- SAEs per 21CFR§312.32 will be reported by the IND-holder, Dr. Nam Bui, to the IND under which this study is being conducted within 7 days (for a life-threatening or fatal event) or 15 days (for other SAEs) of the IND-holder's determination that the SAE meets the criteria for an IND safety report, ie, the event was serious, unexpected, and at least possibly-related to the study drug [a serious, unexpected, suspected adverse reaction (SUSAR)]. IND Safety Reports will be submitted to the IND using the MedWatch Form FDA 3500A for mandatory reporting.

  Do not send IND Safety Reports to the MedWatch fax number, ie, the number for voluntary post-marketing safety reporting.

  IND Safety Reports will be submitted to either the address specified in the IND Study May Proceed letter, any other address specified by the IND reviewers, or via the Electronic Submissions Gateway (contact CCTO-Regulatory@Stanford.edu for electronic submission assistance).
- All SAEs per protocol will be reported will be reported to the IRB of record in the Continuing Review, and/or the Final Report. IRB reporting format can be as an event line listing (such as the Adverse Event log), or as an aggregate listing or summary (such as an IND Annual Report or SAE listing for ClinicalTrials.gov).

- All **Unanticipated Problem (UPs)** associated with the use of a drug, biologic, or device will be reported as follows.
    - Note that for the purposes of Stanford IRB Unanticipated Problem reporting, subjects are considered to be study participants when consented, ie, events during screening and/or pre-treatment through that subject's official end of study participation may qualify as reportable.
    - To the Stanford IRB, by the Stanford Protocol Director, if an adverse event meets the Stanford IRB's current definition of an Unanticipated Problem (UP) as specified by the IRB document "Events and Information that Require Prompt Reporting to the IRB" (GUI-P13), per the timeframes defined therein. See also Section 9.3 Data and Safety Monitoring Plan. In addition to event triggered expedited UP reports, all UPs should be summarized in the Continuing Review, with, as applicable, a discussion of any change in assessment of risk (ie, different than previously described).
    - To the SCI Data and Safety Monitoring Committee (DSMC), by submission to CCTO-Safety / OnCore as an SAE (see SAE reporting to DSMC above. See also the SCI DSMP).

Serious adverse events (SAEs) will be reported to the IRB of record and to the DSMC in accordance with the applicable guidelines and regulations.

All serious adverse events (SAEs) will be followed for 30 days after the last dose of the study drug nirogacestat, or until the SAE(s) is/are resolved or stable, whichever is longer. Pregnancies will be followed until term. See also Section 3.8, 5.6, 6.0, and 7.2.4.

Adverse events that are serious and unexpected suspected adverse reactions, ie, are possibly, probably, or definitely-related to the study drug nirogacestat will be reported (on a MedWatch 3500A form) to the FDA via IND Safety Report [21CFR§312.32] within 15 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction. The IND annual report will include summaries of the collected AEs, as specified by 21CFR§312.33.

7.7. Adverse Event Records

The investigator will retain adverse event source data, supporting documentation of attribution and seriousness, and copies of official adverse event reports or SAE CRFs, as well as documentation of informal communications (such as telephone calls or emails) in accordance with the current version of Stanford School of Medicine standard operating procedure SOP-005 "Identifying and Reporting Adverse Events" (see references in Appendix A).

7.8. Risk Mitigation

There are no specific risks that are being mitigated by any specific action.

8. CORRELATIVE / SPECIAL STUDIES

8.1.1. Assessment of desmoid tumor response using the Nanostring CosMX SMI

It is intended that subject specimens will be used in correlative studies. If subjects elect to opt-in to optional sample collection, then an archival tumor specimen will be requested at screening, and biopsies will be obtained at the time of cryoablation for correlative studies.

We propose to study the response of desmoid fibromatosis lesions to nirogacestat as part of the Sarcoma00061 trial at Stanford. Pre-existing diagnostic FFPE samples from the same patients will be compared to biopsies post-nirogacestat treated desmoid tumors using the Nanostring CosMX SMI. The post-Nirogacestat samples will be obtained with informed consent at the time of the cryoablation procedure that is part of the trial. This Nanostring tool allows for gene expression levels for 1,000 genes in individual cells on FFPE tissue sections with simultaneous expression of 64 proteins on an adjacent section. The analyzed 1,000 genes are involved in many processes in tumor biology but can also be used to extrapolate to genome-wide expression levels using a tool developed by the group of Aaron Newman at Stanford (Vahid et al. Nature Biotechnology, 2023). With this in-depth analysis we will be able to study the pathways targeted by treatment with Nirogacestat but also changes in the varying allele fraction (VAF) and changes occurring in the tumor microenvironment upon treatment. The findings will be validated by orthogonal technologies such as immunohistochemistry to quantify cells with nuclear beta-catenin expression (for VAF) and through correlation with in-vitro studies on desmoid tumors in the Nusse laboratory.

8.1.2. Collection of Specimens

If subjects elect to opt-in to optional blood and tissue collection for correlative studies:

- Archival tumor sample will be requested from pathology and may be saved for future research.
- Biopsies will be obtained at the time of cryoablation (between Cycle 3 and 4) for correlative studies. Biopsies may be saved for future research.

8.1.3. Handling of Specimens

- Archival tumor sample will be ordered by Dr. Bui's Clinical Research Coordinator (CRC). After deidentification (to the minimum information necessary) of the archival tumor sample by the CRC, the sample will be taken to Dr. Matt van de Rijn's laboratory for analysis.
- Biopsies:
    - Prior to collection: Record the required information (subject identification) on the biopsy specimen containers.
    - Biopsies obtained at the time of cryoablation will be placed in small containers with 10% buffered formalin. Biopsy specimen(s) will then be transferred from the MR

procedure room to Dr. Matt van de Rijn's laboratory, where the specimen(s) will be embedded in paraffin blocks and sections will be cut for H&E staining, immunohistochemistry, and Nanostring SMI analysis. Biopsies will be kept at room temperature for transport to Dr. van de Rijn's laboratory.

- Dr. Bui's clinical research coordinator (CRC) will pick up the samples from the MR procedure room and transport them to Dr. van de Rijn's laboratory.
- A requisition form will be used to document the transfer of the biopsy specimen(s) from the MR procedure room to Dr. Matt van de Rijn's laboratory. The following will be included in the requisition form:
  - Subject study identification number, and other required information per Pathology Laboratory.
  - Name and signature of person picking up biopsy specimen(s) from MR procedure room for transfer to Dr. van de Rijn's laboratory, and date and time of biopsy specimen(s) pick-up.
  - Name and signature of person receiving biopsy specimen(s) at Dr. van de Rijn's laboratory, and date and time biopsy specimen(s) was/were received.

8.1.4. Coding of Specimens for Privacy Protection

At the time of enrollment, each subject will be given a specific confidential study identification number. Specimens will be stored under subject study identification number. The information can be shared with other investigators listed on this protocol. Study data will be maintained in password protected computer files (protected online database). Only research personnel will have access to this information.

9. REGULATORY CONSIDERATIONS AND DATA REPORTING

Treatment may continue via this study protocol for up to 24 months (26 cycles of treatment), unless there is progression of disease, intolerance, start of new anticancer therapy (as defined in Section 5.7.2), or one of the criteria in Section 3.7 (Subject Study Completion or Termination) occurs. After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study.

9.1. Review and Approval of Protocol by IRB and SCI SRC

This protocol, the proposed informed consent, and all forms of information related to the study that will be provided to the subjects (eg, questionnaires, handouts, written instructions, diaries, advertisements used to recruit subjects, etc.) will be submitted to, reviewed, and approved by the SCI Scientific Review Committee (SRC) and the Stanford Administrative Panels on Human Subjects in Medical Research of the Research Compliance Office (ie, the Stanford IRB) prior to initiation of the research. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB of record prior to implementation.

This study will be conducted in accordance with the iteration of the protocol that is currently IRB-approved.

9.2. Protocol Compliance and Deviations

9.2.1. Compliance with the Protocol

No deviation or changes from the procedures and process described by the IRB-approved protocol, except those necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial [eg, change in study monitor(s), change of telephone number(s)], will be knowingly permitted without review and approval by the IRB of record.

9.2.2. Protocol Deviations

Any deviation (or violation) from the IRB-approved protocol, including those that eliminate an immediate hazard or are administrative in nature, will be documented and explained in the study site file. All deviations at the Stanford clinical site that meet the reporting requirements defined in the Stanford University HRPP Policy Guidance "Events and Information that Require Prompt Reporting to the IRB" GUI-P13 with be reported to the Stanford IRB by the Stanford investigator within the defined timeframes. All deviations will reported to the Stanford IRB either annually in the IRB continuing review, or individual as IRB Prompt Reports (within 5 or 10 working days, see GUI-P13).

For all studies monitored by the SCI Data and Safety Monitoring Committee (DSMC) as defined in Section 9.3 Data and Safety Monitoring Plan, all deviations, exceptions, and/or violations of the protocol, as well as deviations, exceptions, and/or violations to applicable IRB policies and overarching regulations, will be reported to the SCI data Safety and Monitoring Committee (DSMC). Accordingly, as the DSMC only reviews reports recorded in OnCore, such events will be promptly submitted in the OnCore record for the study, per the current SCI DSMC SOP.

The principal investigator (PI) will review deviations on a weekly basis with the Clinical Research Coordinator, including a description of the deviation(s), the date the PI became aware of the deviation, the date the deviation was reported to Oncore and whether or not the deviation required prompt reporting to the IRB, the determination of the deviation root cause, and determination if a corrective action plan (CAP) is needed. Weekly review will include discussion of any recurring deviations. Aggregate data will be used to evaluate trends.

9.3. Data and Safety Monitoring Plan

The Principal Investigator is responsible for monitoring the conduct of the study including oversight of safety and protocol compliance. On an ongoing basis, the Principal Investigator will review safety data and identify any changes to the research necessary to ensure the appropriate measures and monitoring necessary for participant safety. In addition to the Principal Investigator's safety monitoring role, the SCI DSMC will conduct data and safety monitoring activities for this study.

9.3.1. Monitoring

In addition to investigator self-monitoring (Section 9.3.1.1), the SCI DSMC will monitor study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, GCP, and SOPs. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC monitoring activities will be communicated to the investigator, who has the responsibility to provide such reports to the IRB of record and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9.3.1.1. Investigator Monitoring

Pursuant to the Guideline for GCP, monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

The Principal Investigator is responsible for self-monitoring the progress of the trial on a continuous basis. Monitoring may be delegated to an appropriately trained individual (local monitor). The local monitor will prepare a report and provide it to the Principal Investigator/IND holder. This report will be filed with study documentation. The PI/IND holder will review the monitoring findings and determine any needed actions. Self-monitoring includes, but is not limited to, those items that will be reviewed during an audit (see also Section 9.5). Critical data will be monitored from 1 out of every 6 study participants, including but not limited to consent, eligibility, safety, and study participant on-treatment and off-treatment dates. Efficacy endpoints will be assessed at the end of the trial once all patients have been on study long enough to reach the primary endpoint. The monitoring will be adequate to assure that the valid consent is obtained and documented; the per-protocol data is collected; records and databases are maintained with adequate and accurate participant case histories; adverse events are reported; clinical protocol is maintained; and the study is conducted according to the established procedures of the IRB.

9.4. Data Management

Source documents for all research data will be retained in accordance with all applicable regulations and institutional requirements for data retention. These materials will be made available for monitoring and/or auditing by SCI DSMC, other monitoring body and/or regulatory agencies.

9.4.1. Data Management Plan

A chart with all of the relevant research subject information will be maintained for each subject by the CRC. Subject paper source records will be kept in a secure location at Stanford University Medical Center. The study data will be transcribed and retained in the Oncore central online database, with password protected access limited to the study team of each clinical site. Clinical site is expected to have and maintain the original source document or record for verification of all research data. Data will be temporarily locked for the primary outcome

assessment after the last subject has completed the timeframe for primary outcome. Final database lock will be once all subjects have completed all study visits.

Source documents include but are not limited to:

- Consent document
- Regulatory documents
- Medical history
- Archival tumor sample pathology report
- Physician notes
- Treatment records
- Laboratory reports
- Any other ancillary reports as required by protocol
- Pharmacy records
- Radiology reports
- Tumor measurements
- Vital signs
- Concomitant medications
- Adverse event assessments
- All other protocol-specified tests and data event assessments
- Questionnaire

The Protocol Director must maintain adequate and accurate participant case histories with observations and other data pertinent to the study. The Protocol Director will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to the IRB.

9.5. Site Documentation and Management

The following information will be maintained by the Principal Investigator:

- Delegation of Authority Log, indicating study role, training date, on-study date (date of first research-related procedure or scan), and off-study date
- Financial Disclosure Forms and updates
- Copies of all correspondence with the IRB of record, including all approval letters and approved template informed consent documents, in chronological order by date.
- Copies of all correspondence with the local Scientific Review Committee, including approval letters, renewals, and other types of communication.
- Study agent accountability log
- Serious adverse event (SAE) log, documenting the subject, date, event, relatedness, follow-up, and outcome, with dates of communication to the IRB of record and Oncore/CCTO-Safety (Stanford site).
- Log of Deviations (ie, excursions from the protocol not authorized by the Stanford investigator and approved by the IRB). The Log of Deviations must be maintained in OnCore.
- Laboratory documentation, including copies of local site CAP and CLIA certificates, State licenses, laboratory director CV and medical license, with laboratory normal values/reference ranges for all labs used in the study.

- Printed, dated copy of roster for IRB of record, for each year of the study.

9.6. FDA Oversight

9.6.1. Investigational New Drug (IND) Application Considerations

This study will be conducted under IND-164301, held by Nam Bui, M.D.

9.6.1.1. Protocol Amendments

The protocol will be conducted at all times according to the current version of the protocol as approved by the IRB of record. IRB-approved protocol versions will be submitted to the IND as a Protocol Amendment: Change in Protocol.

9.6.1.2. IND Reports

Information regarding the progress and status of this study will be submitted to IND-164301, in accordance to the content and format defined at 21CFR§312.32 (Safety Reports) and 312.33 (Annual Reports).

9.6.2. Investigational Device Exemption (IDE) Application Considerations

Exempted Device Investigation

This study describes the use of a device in a study that is considered to not require an Investigational Device Exemption (IDE), as elucidated at 21CFR§812.2(c). This study will be submitted to the IRB of record, and their approval obtained, before the study is initiated.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Plan

This study is an open-label, single-arm, single-center, phase 2 study to assess the efficacy and safety of cryoablation and nirogacestat in desmoid tumors.

10.1.1. Method of Treatment Assignment

The interventional model is non-randomized.

10.2. Study Endpoints and Analyses

10.2.1. Primary Endpoint and Analysis

10.2.1.1. Primary Endpoint

The clinical benefit rate (CBR) is defined as the number and proportion of participants who are assessed with either a complete response (CR), a partial response (PR), or stable disease (SD) prior to 1 year after treatment start and show no evidence of loss of response nor progression

within that year. Response and progression will be assessed according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

10.2.1.2. Primary Analysis Plan

The primary analysis will be the calculation of the clinical benefit rate, (CBR), defined as the percentage of subjects in the analysis population who achieve a complete response (CR), partial response (PR), or stable disease (SD) as measured at 12 months ± 1 month (approximately 1 year) from the start of treatment. CR, PR, and SD are as defined by RECIST v1.1. (See Appendix C RECIST v1.1). The CBR and the two-sided 95% Clopper-Pearson (exact) confidence interval will be calculated.

The analysis population will include all subjects who started nirogacestat and underwent cryoablation. Subjects who withdraw from the study prior to start of treatment or before receiving cryoablation and completing 1 year of treatment will be replaced.

10.2.1.3. Relevant Subset for Primary Objective and Endpoint

Evaluable subjects are those subjects who have received cryoablation therapy and completed 1 year of treatment.

10.2.1.4. Primary Objective and Endpoint Assessment Methods

CBR will be evaluated on the basis of clinical response as measured using imaging by MRI scan and evaluated by RECIST v1.1 (Appendix C). Determination of response will be made by the treating investigator.

10.2.1.5. Measurement Time Points for Primary Objective / Outcome

Imaging will be performed at screening, then every 3 cycles (ie, every 12 weeks ± 14 days) until End of Treatment. MRI scan will be used at screening and at subsequent time points.

10.2.2. Secondary Endpoints and Analysis

10.2.2.1. Clinical Benefit Rate (CBR) assessed by modified RECIST

For tumors with MRI enhancement, CBR will be evaluated on the basis of clinical response as measured using imaging by MRI scan and evaluated by modified RECIST (Appendix D). Determination of response will be made by the treating investigator. Imaging will be performed at screening, then every 3 cycles (ie, every 12 weeks ± 14 days) until End of Treatment. MRI scan will be used at screening and at subsequent time points.

10.2.2.2. Median Progression-free Survival (PFS)

Median progression free survival (PFS) will be measured using imaging by MRI scan and evaluated by RECIST v1.1, mRECIST, and volumetrically (change in tumor volume as assessed by MRI volumetric).

Progression-free survival is defined as the time from start of treatment to date of progression or death due to any cause. If a subject is not known to have progressed or died, then PFS will be censored at the latest date the subject was known to be alive or progression-free (on or before the cut-off date). The PFS distribution will be estimated using the Kaplan-Meier method, and

the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

10.2.2.3. Objective Response Rate (ORR) at 1 year

For the objective response rate (ORR) at 1 year, the percentage of subjects who start study treatment and achieve an objective response (CR or PR) will be calculated. ORR will be measured using imaging by MRI scan and evaluated both RECIST v1.1, mRECIST, and MRI volumetric.

The ORR will be calculated as the proportion of subjects with objective response. The ORR and the two-sided 95% Clopper-Pearson (exact) confidence interval will be calculated.

10.2.2.4. Time to Response (TTR)

Time to response is defined as the time from the start of treatment with nirogacestat to the first objective tumor response (CR or PR), and will be measured using imaging by MRI scan and evaluated by RECIST v1.1, mRECIST, and volumetrically.

The TTR distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

10.2.2.5. Duration of Response (DoR)

Duration of response (DoR) is defined as the time from the date of documented disease response (CR or PR) to the date of the first documented progression, and will be determined using imaging by MRI scan and evaluated by RECIST v1.1, mRECIST, and volumetrically.

Duration of response will be summarized descriptively. If sufficient data are available the distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

Nominal duration of study involvement is 26 months, with last assessment after about 24 months of treatment.

10.2.2.6. Adverse events and safety

Adverse events will be tabulated with frequencies and percentages for grade, severity, status and relationship to study drug or study procedure. The analysis population will include all subjects who have started study treatment. Assessment for safety signals will be from time of consent until 30 days after the last treatment.

10.2.3. Exploratory Endpoints and Analysis

10.2.3.1. Patient-reported outcomes (EQ-5D-3L)

Summary measures (mean, standard deviation, median, interquartile range) of the EQ-5D-3L survey scores will be calculated for each time point during the duration of the study; scores will graphically depicted at each time point. In addition, we will calculate the difference of the scores at the baseline, time of demonstrated clinical benefit rate, and last follow-up date and report summary statistics. Nominal duration of study involvement is 26 months, with last assessment after about 24 months of treatment.

10.3. Interim Analysis

No interim analysis is planned.

10.4. Sample Size

10.4.1. Accrual estimates

Stanford sees approximately 30 to 40 adult subjects annually in the Sarcoma Clinic with desmoid tumor. This study will enroll up to 23 subjects, in order to achieve 20 evaluable subjects. It is estimated that approximately 23 subjects can be enrolled within 24 months at Stanford University.

10.4.2. Sample Size Justification

We calculated power using a one-sample proportion test to determine if a population proportion is significantly different from hypothesized value. We define our hypotheses as:

Null hypothesis (H0) that the proportion is P0 = 0.5

Alternative hypothesis (H1) that the proportion is P1 = 0.8.

To test our hypothesis of clinical improvement:

$$H0: P \leq P0 \text{ vs } H1: P = P1 > P0$$

Our sample size of 20 achieves 100.0% power to detect a difference (P1-P0) of 0.3 using a one-sided exact test at an alpha level of 0.05. The results assume that population proportion under the null hypothesis is 0.5. Power was also computed using the normal approximation method.

10.4.3. Effect Size Justification

The null hypothesis efficacy rate (CBR at 1 year) of 50% at 1 year is based on clinical experience at Stanford where desmoid tumors that are subtotally treated with cryoablation have > 50% chance of recurrence at 1 year; determined using mRECIST.

10.4.4. Criteria for Future Studies

With our total sample size of 20, we will reject the null hypothesis and conclude that the treatment is efficacious if the number of responses is ≥ 11. Otherwise, we will conclude that that the treatment is not promising.

10.5. Descriptive Statistics and Exploratory Data Analysis

Demographic and other baseline data including disease characteristics will be listed and summarized. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, as relevant, will be presented. Additionally, at the time of final analysis, we will separately assess the response to nirogacestat alone in the first 3 cycles. We will describe the ORR of the first 3 months of nirogacestat treatment (CR/PR/SD/PD).

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12. PROTOCOL HISTORY

Version Date *	Change Summary
10 January 2023	Initial SRC approved protocol 10 January 2023
01 February 2023	Protocol was revised to reflect updated Investigator's Brochure Version 7.0. Changes are noted below. • Updated protocol version to 01 February 2023 on title page and footer. • Updated Section 1.2.3. to reflect an additional potential mechanism of action involving GS inhibition by nirogacestat. • Section 1.2.4 Nirogacestat clinical status experience updated to reflect completed and ongoing studies. Additionally updated phase 2 experience with nirogacestat in patients with desmoid tumors to align with interim clinical study report including a more recent data cut (November 2020) than the Kummar 2017 publication on the same study. Added summary of recently completed NIR-DT-301. • Section 1.3.1 Added contraindication of moderate or severe hepatic impairment for completeness. Inclusion criteria already requires participants to have adequate organ function, including adequate liver function. • Section 1.3.1 updated to better reflect the most up-to-date understanding of the current safety profile. Summary of commonly reported AEs from completed nirogacestat single agent studies updated; added information from 14-C-0007 and NIR-DT-301 (double-blind phase). • Known Drug Interactions updated, including Cytochrome P450 inhibitors, inducers, and substrates. See Sections 1.3.1, 3.1.3, 7.3.1, 13.6. • Updated information on gastric acid reducing agents. See Sections 1.3.1, 3.1.3 • Recommended duration of contraception required following treatment with nirogacestat was increased for women of childbearing potential from 90 days to 6 months to align with the NIR-DT-301 protocol. See Sections 3.1, 6.2.2, and 7.3.1. • Updated to current IUPAC name. See Section 4.1.3.2. • Instructions for management of an overdose were updated for clarity and to add more detail around use of dialysis in event of overdose. Specifically, due to the high level of protein binding observed in clinical studies, nirogacestat is not expected to be dialyzable. See Section 5.7.4. • Section 7.3.1 Special Warnings and Precautions for Use updated to better reflect the most up-to-date understanding of the current safety profile. • Section 7.3.1 Special Warnings and Precautions for Use updated regarding nirogacestat effects on ability to drive machines. • Minor administrative changes, such as grammatical changes, spelling corrections,

Version Date *	Change Summary
	minor changes in wording, clarifications, updates to table of contents, and formatting.
28 March 2023	Per FDA comments, protocol was revised to include baseline coagulation studies (PT and PTT) at screening.
28 September 2023 Amendment 1	Protocol was revised as noted below: • Added sub-investigators on title page of protocol. • Corrected Dr. Nam Bui's address on title page of protocol. • Added Dr. Kristen Ganjoo's new address on title page of protocol. • Added NCT number NCT05949099 to title page of protocol. • Added new safety language regarding non-melanoma skin cancer. • Section 1.3 and 7.3.1: Deleted "dyspepsia" from Summary of the Most Commonly (≥ 10% of Participants in the Nirogacestat Arm) Reported AEs from Completed Nirogacestat Single Agent Studies in Adult Patients with Cancer, as it is no longer in IB. • Section 1.3 Other concomitant therapy, Section 3.1.3, and Section 7.3: Deleted statement about nirogacestat induction of CYP3A4, CYP2B6, CYP2C8, CYP2C9 enzymes, as per SpringWorks, clinical evidence does not support 3A4 induction, and the PBPK model did not predict induction effect of 2B6, 2C8, and 2C9. • Added exploratory objective to Synopsis, Section 2.2 (Objectives). New exploratory objective: To correlate changes during treatment with response using the Nanostring CosMX SMI on biopsy samples. • Added correlative studies: Updated Synopsis, Section 6.1 (Schedule of Assessments), Section 6.2 (Description of Procedures and Assessments), Section 8 (Correlative/Special Studies) to add optional archival tumor sample collection and biopsies at time of cryoablation for correlative studies. • Added risks of biopsy to Section 1.3.2 (Potential Risks of Study Procedures). • Deleted Cycle 4 EQ-5D-3L questionnaire. • Updated inclusion criteria #2: Added text "which may be" and "and/or" to indicate that tumors that are 50 to <75% cryoablatable in a single session which may be characterized by: 2 a, and/or b, and/or c, and/or d. • Deleted exclusion criteria #9 and #10, as SpringWorks Therapeutics SWTx c-QT analysis ruled out effect on QT at therapeutic dosing in DT. Per SpringWorks, nirogacestat does have a small relationship, but we do not expect a QT prolongation of greater than 10 msec, even with a potential DDI. • Section 3.1.3 (Lifestyle considerations - prohibited concomitant medications), Section 5.7.2 Prohibited Concomitant Medications and Procedures): Deleted antiarrhythmic medications known to prolong the QT/QTcF interval from

Version Date *	Change Summary
	prohibited concomitant medications. • Section 6.1 (Schedule of Events): Changed pregnancies will be followed until term to Pregnancies will be followed until outcome is known. • Section 7.3 Potential Adverse Events and Risks - Premature Menopause/Ovarian Dysfunction: Information added regarding premature menopause/ovarian dysfunction percentages of occurrence from Phase 3 NIR-DT-301 study. • Section 7.3 Potential Adverse Events and Risks: Added statement to reference the IB RSI for serious adverse drug reactions for nirogacestat considered expected for safety reporting purposes. • Section 7.5.3 Other Adverse Events of Special Interest: SpringWorks is now requiring that non-serious AESIs must be reported to SpringWorks Safety at PV@springworks.com as soon as possible but no later than 30 calendar days of awareness. Previously, the requirement was to report no later than 5 business days of awareness. • Section 7.5.3 Other Adverse Events of Special Interest; Table 8 (Adverse Events of Special Interest) has been updated per safety memo dated 11Aug2023 provided to site by SpringWorks, and ovarian dysfunction recommended follow-up has been updated Table 8 footnote 1, per SpringWorks PV team recommendations. • Increase window for labs (Cycles 1 through 6) from 24 hours prior to day 1 of each cycle to within 72 hours prior to Day 1 of each cycle. • Delete Nirogacestat Study Medication Diary (Appendix F) and reletter subsequent appendices in Section 13 (and also updated appendix letters throughout the protocol). • Minor administrative changes, such as grammatical changes, spelling corrections, minor changes in wording, clarifications, updates to table of contents, and formatting.
15 December 2023 Amendment 2	Protocol was revised to reflect FDA approval of nirogacestat, brand name Ogsiveo™, and also to reflect updated Investigator's Brochure, IB v8. Protocol changes are noted below: • Section 1.2.3: Deleted sentence: Currently, there are no approved therapies for desmoid tumors. • Section 1.2.2: Deleted "ongoing" and added "completed." The completed randomized phase 3 trial of nirogacestat vs placebo (DeFi Study) also has a starting dose of 150 mg PO BID. • Section 2.1.6: Deleted "ongoing" and added "completed." The completed randomized phase 3 trial of nirogacestat vs placebo in adults with progressing

Version Date *	Change Summary
	desmoid tumor/aggressive fibromatosis (NIR DT 301, DeFi Study) also has a starting dose of 150 mg PO BID in the double blind and open label extension phase. • Synopsis, Sections 2.3, 4.1: Add nirogacestat brand name Ogsiveo™. • Section 2.3: Updated to state that the FDA has approved nirogacestat (Ogsiveo™) for the treatment of desmoid tumor. • Synopsis, Sections, 2.1.2, 2.1.3, 3.5, 4.1.3, 5.2, 5.4, 9. : Updated text to state: After 24 months of treatment, if clinically indicated, a subject may transition to commercial nirogacestat supply, once the subject has completed the End of Treatment (EOT) visit and is off study. Deleted compassionate use of nirogacestat, since FDA approval of nirogacestat has been granted. • Section 4.1.1: Deleted compound number and added brand name. • Section 4.1.3: Updated status of nirogacestat to state that it is approved for marketing in the US and is indicated for adult patients with progressing desmoid tumors who require systemic treatment. Combination therapy with cryoablation plus nirogacestat is investigational. • Section 8.1.3 Handling of Specimens. Archival tumor sample will be ordered by Dr. Bui's Clinical Research Coordinator (CRC) instead of being ordered by the Pathology Department. After deidentification to minimum information necessary of the archival tumor sample by the CRC, the sample will be taken to Dr. Matt van de Rijn's laboratory for analysis. • Section 8.1.3 Biopsies: Prior to collection: Deleted text to state subject identification instead of subject study identification number. New text: Record the required information (subject identification) on the biopsy specimen containers. • Section 8.1.3 added "and other required information per Pathology Laboratory," to the information that will be included on the biopsy requisition form. • Throughout protocol added statement to also reference the Ogsiveo™ (nirogacestat) package insert; Sections 1.2, 1.3, 4.1, 7.3. • Section 11: Added Ogsiveo™ (nirogacestat) package insert_version 11/2023. to the reference section. • Sections 3.1, 6.2.2, 7.3.1 were updated to reflect that males must use highly effective contraception for at least 1 week after the last dose of nirogacestat (previously 3 months), and females must use highly effective contraception for at least 1 week after the last dose of nirogacestat (previously 6 months). • Sections 1.3.1, 3.1, 6.2.2, 7.3.1 Added that women should not donate or harvest their eggs (ova, oocytes) while participating in this research study and for at least 6 months after taking their last dose of study drug. Men should not donate or preserve their sperm for at least 90 days after taking their last dose of study drug.

Version Date *	Change Summary
	• Section 11: Investigator's Brochure updated from Version 7.0 December 2023 to IB version 8.0, December 2023. • Minor administrative changes, such as grammatical changes, spelling corrections, minor changes in wording, clarifications, updates to table of contents, and formatting.

09 February 2024
Amendment 3
	Protocol changes are noted below:
	• Updated version date and amendment number
	• Section 2.3. Updated from "will be registered" to "has been registered" New text: This study has been registered on ClinicalTrials.gov, and results will be reported.
	• Updated exclusion criteria #2 to reference inclusion criteria #4 instead of inclusion criteria #3.
	  • New text: 2. Participant is currently using any treatment for DT including tyrosine kinase inhibitors (TKIs), NSAIDS (chronic daily use – except as in inclusion criterion 4) or any investigational treatment 28 days (or 5 half lives, whichever is longer) prior to the first dose of study treatment.
	• Section 5.6: Updated text for clarification purposes.
	  • Old Text: Treatment may also be modified to manange other AEs.
	  • New Text: Fort patient safety, treatment may also be modified or held to manage any AE(s), at the PIs discretion.
	• Update Table 4 regarding Grade ≥ 3 diarrhea and page 59 Select AE management recommendations for Grade ≥ 3 diarrhea so that they are in agreement. New text states that for Grade ≥ 3 diarrhea that persists for ≥ 3 days despite maximal medical therapy, nirogacestat dose should be decreased to 100 mg BID and/or held until AE is Grade 1 or baseline.
	• Pg 59 Select AE management recommendations: Added text: "dose is held and." New text: If the dose is held and diarrhea resolves within 14 days, then nirogacestat may be restarted at a dose of 100 mg twice daily.
	• Minor administrative changes, such as grammatical changes, spelling corrections, changes to correct typographical errors, minor changes in wording, clarifications, updates to table of contents, and formatting.

17 May 2024 Amendment 4	Protocol changes are noted below: • Updated version date and amendment number from 09Feb2024, Amendment 3 to version 17May2024, Amendment 4. • Increase imaging window from +/- 7 days to +/- 14 days to allow flexibility in scheduling cryoablation. Radiologic evaluation and tumor measurements should be performed at Screening, then every 3 cycles (ie, every 12 weeks ± 14 days).

Version Date *	Change Summary
	• Delete Scott Vahradian, PA-C from title page. • Section 6.1 Schedule of Events. Urine pregnancy test: Delete checkmark for screening urine pregnancy test, as serum pregnancy test (B HCG) is done at screening, and urine pregnancy test is done at other specified timepoints. • Section 8.3: Correct section number from 8.3 to Section 9.3, so that it reads "See also Section 9.3 Data and Safety Monitoring Plan." • Minor administrative changes, such as grammatical changes, spelling corrections, minor changes in wording, clarifications, updates to table of contents, and formatting.

* Latest version date should match footer date of the current protocol

13. APPENDICES

13.1. Appendix A. References for Stanford Cancer Institute Policies & Practices

Relevant Stanford Cancer Institute (SCI) process, policies, and documentation include the following.

Standard Operating Procedures (SOPs):

- Stanford School of Medicine standard operating procedure SOP-005 "Identifying and Reporting Adverse Events." This document is available on the Spectrum website.

http://med.stanford.edu/spectrum/b4_research_quality/b4_3_standard_operating_procedures.html.

- SCI Scientific Review Committee (SRC) Policies and Procedures

http://med.stanford.edu/content/dam/sm/cancer/documents/PRMSDocuments/SRC_SOP.pdf.

- Confirmation of Participant Eligibility in Clinical Trials

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/sop/SOP_Participant_Eligibility_Confirmation.pdf.

- SCI Institutional Data and Safety Monitoring Plan.

http://med.stanford.edu/cancer/research/trial-support/dsmc.html.

- SCI Data Management in Clinical Investigations

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/sop/SOP-Data%20Management.pdf.

Logs and Forms:

- The SCI Adverse Event Log (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Adverse%20Event%20Log.pdf.

- SCI Serious Adverse Event Report Form (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/SAE_CRF.pdf.

- Sample Study Participant Log (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Subject_Log_07.29.11.doc.

Guidelines:

- SCI Guideline for Studies Relying on External Central or Single IRBs.

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/NCTN%20Guideline_Studies_Relying_on_External_Central_or_Single_IRBs.pdf.

Current Stanford University IRB policies and procedures:

- Stanford University Human Research Protection Program (HRPP) Policy Manual at:

http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf.

- Stanford University HRPP Policy Guidance Events and Information that Require Prompt Reporting to the IRB GUI-P13 at:

http://humansubjects.stanford.edu/research/documents/Events-Info-Report-to-IRB_GUI03P13.pdf.

- Stanford University HRPP Unanticipated Problem reporting process is defined at Section 3.10, in the Human Research Protection Program (HRPP) Policy Manual

http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf.

Other regulatory documentation and resources

- Contact a Department of Biomedical Data Science (DBDS) biostatistician:

https://redcap.stanford.edu/surveys/?s=7TTM3AELCT.

- The US FDA requirements for adverse event reporting for investigational drugs are defined at 21CFR§312.32(a)

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32.

- The Common Terminology Criteria for Adverse Events (CTCAE) **version 5** are available at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50, see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx OR https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

- The International Conference on Harmonization (ICH) Guideline on Good Clinical Practice (ICH GCP E6r1), including adverse event reporting, is available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

These links may change from time to time, and will be updated in this template as needed. Consult issuing authority as needed.

13.2. Appendix B. ECOG Performance Status [8]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

* Oken M, Creech R, Tormey D, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

13.3. Appendix C. Revised Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[9]

Appendix C: Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228−47.

1. Measurability of tumor at baseline

1.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1. Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be

considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

2. Tumor response evaluation

2.1. Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3).

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

<u>Lymph nodes</u>

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

<u>Target lesions that become 'too small to measure'</u>

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist

that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease).

New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

Table 1 on provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

2.4.2. Missing assessments and non-evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the subject is known.

Best response determination in this trial where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered non-evaluable.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression

should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the case report form (CRF).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

13.4. Appendix D. Modified RECIST (mRECIST)[10]

FORMULA

Responses are defined as the following (RECIST is listed for comparison):

	RECIST	mRECIST
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

https://www.mdcalc.com/modified-response-evaluation-criteria-solid-tumors-mrecist#evidence

Modified RECIST criteria were proposed to address scenarios where treatment did not result in overall tumor shrinkage but did cause intratumoral necrosis, reducing viable tumor. Tumor response after ablation will also include assessment by modified RECIST guidelines to incorporate measurements of viable tumor. Similar to RECIST, target lesions must appear suitable for accurate and repeat measurements, and have a diameter of 1 cm or more, while non-target lesions have diameter < 1 cm. At baseline and follow up imaging, measurement of the longest viable tumor diameter should not include any major intervening areas of necrosis. Multiphasic post-contrast imaging will be available; the radiologist will choose the phase of imaging for measurement that best delineates the viable tumor component. If there are multiple intratumoral areas of enhancing viable tumor surrounded by areas of necrosis within the same target lesion, only the longest viable tumor diameter should be captured, again avoiding the

inclusion of any major intervening areas of necrosis. For evaluation by mRECIST, CR is defined by absence of enhanced areas in target lesions; PR and PD as the same degree of decrease and increase as in the RECIST criteria, with sums of diameters of enhanced areas in target lesions rather than sums of diameters of the whole target lesions size; and SD as neither PR or PD.[11-16]

13.5. Appendix E. Tumor Volume Calculation by MRI

A short-coming of both RECIST and mRECIST is their reliance on measuring single diameters. A more accurate and reproducible approach would utilize both total and viable tumor volumes for comparison of treatment results. For this purpose, T1-weighted fat suppressed post-contrast MR images of the target lesion will be manually segmented on each slice by a radiologist using a free open-source software package (Horos). The total tumor area will be contoured on each slice, as will the total enhancing viable tumor area. The areas of the segmented lesion will be used to calculate the volume of interest for computer-based image analysis by summing areas of the tumor on each slice and multiplying by slice thickness to obtain total tumor volume. For evaluation by MR volumetry, CR is defined by absence of enhanced volume in target lesions; PR and PD as the same degree of decrease and increase as in the RECIST criteria, with volumes of enhanced areas in target lesions rather than sums of diameters of the whole target lesions size; and SD as neither PR or PD.[17]

13.6. Appendix F. Cytochrome P450 3A4 and 3A5 Known Drug Interactions Chart[18]

CYP3A4 and CYP3A5 Substrates		CYP3A4 and CYP3A5 Inhibitors
ANTIHISTAMINES	**NEUROPSYCHIATRIC**	**STRONG INHIBITORS**
astemizole	alprazolam	clarithromycin
chlorpheniramine	diazepam	indinavir
ANTIEMETIC	midazolam	itraconazole
aprepitant	triazolam	ketoconazole
ondansetron	haloperidol	nefazodone
ANESTHESIA/PAIN	aripiprazole	ritonavir
cafergot	buspirone	saquinavir
codeine-N-demethylation	carbamazepine	suboxone
fentanyl	pimozide	telithromycin
levomethadyl acetate (LAAM)	quetiapine	**INTERMEDIATE STRENGTH INHIBITORS**
lidocaine,	risperidone	aprepitant
methadone	trazodone	erythromycin
ANTIBIOTIC/ANTIVIRAL	zaleplon	fluconazole
alfentanil	ziprasidone	grapefruit juice
boceprevir	zolpidem	verapamil
clarithromycin	**ONCOLOGY**	diltiazem
efavirenz	docetaxel	**WEAK INHIBITORS**
erythromycin (not CYP3A5),	gleevec	cimetidine
indinavir	irinotecan	**OTHER POSSIBLE INHIBITORS**
nelfinavir	paclitaxel	amiodarone
nevirapine	romidepsin	boceprevir
quinine	sorafenib	chloramphenicol
ritonavir	sunitinib	ciprofloxacin
saquinavir	torisel	delaviridine
telaprevir	vemurafenib	diethyl-dithiocarbamate
telithromycin.	vincristine	fluvoxamine
CARDIOVASCULAR	**PULMONARY**	gestodene
amlodipine	salmeterol	imatinib
cilostazol	sildenafil	mibefradil
diltiazem	**STEROID**	mifepristone
eplerenone	dexamethasone	norfloxacin
lercanidipine	estradiol	norfluoxetine
nifedipine	hydrocortisone	starfruit
nisoldipine	progesterone	telaprevir
nitrendipine	testosterone	voriconazole
propranolol	**OTHER**	**CYP3A4 and CYP3A5 Inducers**
quinidine (not CYP3A5)	cocaine	barbiturates
verapamil	dapsone	carbamazepine
HMG COA REDUCTASE	dextromethorphan	efavirenz
INHIBITORS	finasteride	glucocorticoids
atorvastatin	finasteride	modafinil
lovastatin simvastatin	nateglinide	nevirapine
simvastatin	dextromethorphan	oxcarbazepine
IMMUNE MODULATORS	finasteride	phenobarbital
cyclosporine	finasteride	phenytoin
sirolimus	nateglinide	pioglitazone
tacrolimus		rifabutin
		St John's Wort
		troglitazone

13.7. Appendix G. Liver Safety: Suggested Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5 × ULN
ALT Increase	ALT ≥ 3 × ULN persists for ≥ 4 weeks
Bilirubin[a,b]	ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin)
INR[b]	ALT ≥ 3 × ULN **and** INR > 1.5, if INR measured
Cannot Monitor	ALT ≥ 3 × ULN and cannot be monitored weekly for 4 weeks
Symptomatic[c]	ALT ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• Immediately discontinue study treatment (nirogacestat) • Complete the SAE eCRF form if the event meets the criteria for an SAE [b] • Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline • Restart/rechallenge is not allowed per protocol and not granted, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments. **If ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT ≥ 3 × ULN AND bilirubin < 2 × ULN and INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hrs.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology [d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2 × ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF page • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF page. **ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN or INR > 1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; HPLC = high performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; SAE = serious adverse event; ULN = upper limit of normal.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

b. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (> 35% direct bilirubin) or ALT ≥ 3xULN and INR > 1.5 may indicate severe liver injury (possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). The INR stated threshold value will not apply to participants receiving anticoagulants.

c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

d. Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

13.8. Appendix H. Contraception Guidance

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods [b] That Have Low User Dependency
Failure rate of < 1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

Highly Effective Methods[b] That Are User Dependent
Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
    - Oral
    - Intravaginal
    - Transdermal
    - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
    - Oral
    - Injectable
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) Barrier methods such as condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

13.9. Appendix I. EQ-5D-3L (English) Questionnaire v1.1

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

SELF-CARE

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

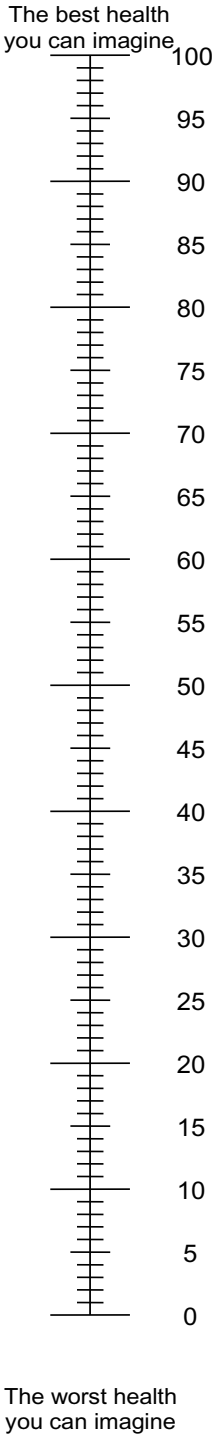
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.10. Appendix J. EQ-5DK3L (Spanish) Questionnaire v1.1

Cuestionario de Salud

Versión en español para los EE. UU.

(Spanish version for the USA)

Marque con una cruz como esta ☒ la afirmación en cada sección que describa mejor su estado de salud en el día de hoy.

Movilidad

No tengo problemas para caminar ❑

Tengo algunos problemas para caminar ❑

Tengo que estar en la cama ❑

Cuidado-Personal

No tengo problemas con el cuidado personal ❑

Tengo algunos problemas para lavarme o vestirme solo/a ❑

Soy incapaz de lavarme o vestirme solo/a ❑

Actividades de <u>Todos los Días</u> *(ej, trabajar, estudiar, hacer tareas domésticas, actividades familiares o realizadas durante el tiempo libre)*

No tengo problemas para realizar mis actividades de todos los días ❑

Tengo algunos problemas para realizar mis actividades de todos los días ❑

Soy incapaz de realizar mis actividades de todos los días ❑

Dolor / Malestar

No tengo dolor ni malestar ❑

Tengo moderado dolor o malestar ❑

Tengo mucho dolor o malestar ❑

Ansiedad / Depresión

No estoy ansioso/a ni deprimido/a ❑

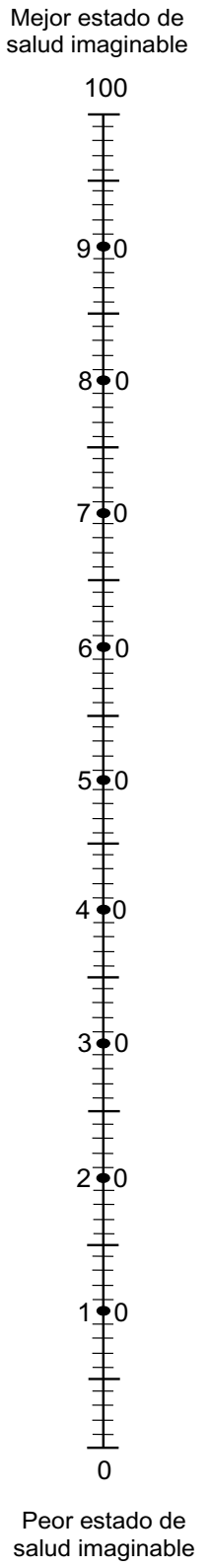
Estoy moderadamente ansioso/a o deprimido/a ❑

Estoy muy ansioso/a o deprimido/a ❑

Para ayudar a la gente a describir lo bueno o malo que es su estado de salud, hemos dibujado una escala parecida a un termómetro en la cual se marca con un 100 el mejor estado de salud que pueda imaginarse, y con un 0 el peor estado de salud que pueda imaginarse.

Por favor, dibuje una línea desde el cuadro que dice “su estado de salud hoy,” hasta el punto en la escala que, en su opinión, indique lo bueno o malo que es su estado de salud en el día de hoy.

Su estado de salud hoy



13.11. Appendix K. EQ-5DK3L (Simplified Chinese) Questionnaire v1.1

健康问卷

供美国地区使用之简体中文版

(Simplified Chinese version for the USA)

请在下列各组选项中，指出哪一项最能反映您今天的健康状况，并在 方格内打勾(✓)。

行动能力

我可以四处走动，没有任何困难 ❑

我行动有些不方便 ❑

我不能下床活动 ❑

自主生活能力

我能自己照顾自己，没有任何困难 ❑

我在洗脸、刷牙、洗澡或穿衣方面有些困难 ❑

我无法自己洗脸、刷牙、洗澡或穿衣 ❑

日常活动 *(如工作，学习，家务事，家庭或休闲活动)*

我能进行日常活动，没有任何困难 ❑

我在进行日常活动方面有些困难 ❑

我无法进行日常活动 ❑

疼痛 / 不舒服

我没有任何疼痛或不舒服 ❑

我觉得中度疼痛或不舒服 ❑

我觉得极度疼痛或不舒服 ❑

焦虑 *(如紧张、担心、不安等等)* **/ 抑郁** *(如做事情缺乏兴趣、没乐趣、提不起精神等等)*

我不觉得焦虑或抑郁 ❑

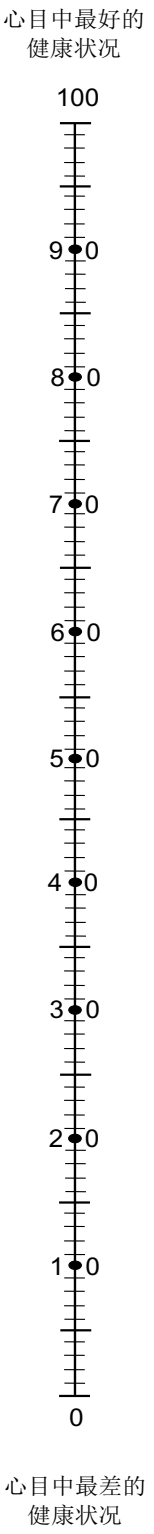
我觉得中度焦虑或抑郁 ❑

我觉得极度焦虑或抑郁 ❑

为了帮助您反映健康状况的好坏，我们画了一个刻度尺(有点像温度计)，在这刻度尺上，100代表您心目中最好的状况，0代表您心目中最差的状况。

请在右边的刻度尺上标出您今天的健康状况。请从以下的黑色方格划一连綫，连到刻度尺上最能代表您今天健康状况好坏的那一点上。

您今天的
健康状况



13.12. Appendix L. EQ-5DK3L (Vietnamese) Questionnaire v1.1

Bảng câu hỏi về sức khỏe

Phiên bản tiếng Việt dùng tại Hoa Kỳ

(Vietnamese version for use in the USA)

(Best available)

Xin anh/chị chỉ rõ tình trạng diễn tả đúng nhất sức khỏe của anh/chị hôm nay bằng cách đánh dấu vào ô tương ứng ở mỗi nhóm bên dưới.

Sự đi lại

Tôi không gặp vấn đề gì khi đi lại ❑

Tôi đi lại hơi khó khăn ❑

Tôi chỉ có thể nằm tại giường ❑

Tự chăm sóc

Tôi không gặp vấn đề gì khi tự chăm sóc bản thân ❑

Tôi gặp một vài vấn đề khi tự tắm rửa hay khi tự mặc quần áo ❑

Tôi không thể tự tắm rửa hay không thể tự mặc quần áo ❑

Sinh hoạt thường lệ *(ví dụ: làm việc, học hành, làm việc nhà, chăm sóc gia đình, vui chơi giải trí)*

Tôi không gặp vấn đề gì khi thực hiện các sinh hoạt thường lệ của tôi ❑

Tôi gặp một vài vấn đề khi thực hiện các sinh hoạt thường lệ của tôi ❑

Tôi không thể thực hiện các sinh hoạt thường lệ của tôi ❑

Đau / khó chịu

Tôi không đau hay không khó chịu ❑

Tôi khá đau hay khá khó chịu ❑

Tôi rất đau hay rất khó chịu ❑

Lo lắng / u sầu

Tôi không lo lắng hay không u sầu ❑

Tôi khá lo lắng hay khá u sầu ❑

Tôi rất lo lắng hay rất u sầu ❑

Nhằm giúp mọi người có thể xác định tình trạng sức khỏe tốt hay xấu, chúng tôi vẽ ra một thang điểm (giống như nhiệt kế). Ở thang điểm này, số điểm 100 tương ứng với tình trạng sức khỏe tốt nhất và 0 tương ứng với tình trạng sức khỏe xấu nhất mà anh/chị có thể hình dung được.

Chúng tôi mong muốn anh/chị chỉ ra trên thang điểm này tình trạng sức khỏe (tốt hay xấu) của mình ngày hôm nay, theo ý của anh/chị. Xin hãy vẽ 1 đường kéo ngang từ ô tô đen bên dưới đến điểm mà anh/chị cho là thích ứng nhất với tình trạng sức khỏe của mình hôm nay.

Tình trạng sức khỏe (tốt hay xấu) của anh/chị ngày hôm nay