A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Nirogacestat Versus Placebo in Adult Patients with Progressing Desmoid Tumors/Aggressive Fibromatosis (DT/AF).

Published: 09-05-2019
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Primary:To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF.Secondary:To evaluate the safety and tolerability of nirogacestat in adult participants with progressing...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55814

Source
ToetsingOnline

Brief title
DeFi study

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign

Synonym
Aggressive Fibromatosis, Desmoid Tumor

Health condition

Desmoid Tumor/Aggressive Fibromatosis

Research involving
Human

Sponsors and support

Primary sponsor: SpringWorks Therapeutics
Source(s) of monetary or material Support: SpringWorks Therapeutics

Intervention

Keyword: Aggressive Fibromatosis, Desmoid Tumor, Nirogacestat, Phase 3

Outcome measures

Primary outcome

PFS defined as the time from randomization until the date of assessment of progression or death by any cause will be determined using Response Evaluation Criteria In Solid Tumors (RECIST) version (v)1.1. The documented date of progression will be determined by an independent, blinded, central radiologic review.

Secondary outcome

Safety endpoints will include incidence of treatment-emergent AEs, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs).

Tolerability will be assessed according to toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0;

Overall response rate, defined as the proportion of participants with CR + PR

assessed by RECIST v1.1 Criteria;

Duration of response for participants whose best response is CR or PR;

Change in tumor volume from baseline as assessed by MRI volumetric;

Symptoms and impacts will be assessed by evaluating change from baseline on the following PROs:

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

-Brief Pain Inventory (BPI) short form;

-Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) short form 10a plus 3 additional items from PROMIS item banks;

-European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC) QLQ-C30.

Study description

Background summary

Desmoid tumors include soft tissue masses arising in any part of the body in different varieties of connective tissue, including muscle and fascia aponeurosis. The most common primary tumor sites include abdominal walls, limbs, girdles, and mesenteric areas. Desmoid tumors infiltrate surrounding structures and spread along plains and muscle, which can lead to severe pain, functional impairment, and more rarely, life-threatening conditions. Despite the benign nature of desmoid tumors, they can behave aggressively, causing significant morbidity, with elevated rates of local recurrence (as high as 60%) despite wide excisions. Mortality is occasionally observed owing to the local aggressive nature of some desmoid tumors that occur in the mesentery.

The NIR-DT-301 Phase 3, double-blind, placebo-controlled study is being conducted to determine the efficacy and safety of nirogacestat in participants with progressing desmoid tumors. A Phase 1 study in patients with solid tumors provided preliminary efficacy, including long-term durable responses and safety of nirogacestat in desmoid participants. These encouraging results lead to a Phase 2 study in participants with progressing desmoid tumors. This study demonstrated that nirogacestat resulted in a 29% response rate, significant tumor shrinkage as measured by magnetic resonance imaging (MRI) and no participants progressing while on therapy. Importantly, participants in the responder group had failed previous systemic therapies (imatinib or sorafenib) indicating a need for alternative therapeutic options for this patient population.

See protocol section 2 (page 24) for an extensive description.

Study objective

Primary:
To determine the efficacy (as defined by progression-free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF.

Secondary:
To evaluate the safety and tolerability of nirogacestat in adult participants with progressing DT/AF as measured by the incidence of adverse events (AEs);

To determine the overall response rate (complete response [CR] + partial response [PR]) of nirogacestat in participants with progressing DT/AF;

To determine the duration of response;

To compare tumor volume changes measured by MRI in participants with progressing DT/AF;

To evaluate desmoid tumor symptoms and impacts using patient-reported outcomes (PROs).

Study design

This is a multi-center, randomized, double-blind, placebo-controlled, event-driven, Phase 3 study to compare the efficacy, safety, and tolerability of nirogacestat and placebo in adult participants with progressing DT/AF. This study will consist of 2 phases, a double-blind and an optional open-label extension (OLE) phase.

Participants will be screened up to 28 days prior to the first dose of study

treatment (nirogacestat or placebo) in the double-blind phase and eligibility will be based on the inclusion and exclusion criteria (See protocol Sections 5.1 and 5.2). Refer to the double-blind schedule of activities (SoA) (Protocol Section 1.3.1) for the required assessments and Table 6 (protocol) for additional details regarding each scheduled study visit.

Intervention

The administration of Nirogacestat (or placebo) every 12 hours, disregarding food. Continuously in 28-day cycles for up to approx. 2 years (if not terminated earlier).

Double-blind phase:
At Cycle 1 Day 1 (baseline), participants will be randomized (stratified by primary tumor location [Protocol Section 6.3.1, page 45) to study treatment (nirogacestat or placebo) in a 1:1 ratio and will receive 150 mg BID of study treatment, continuously in 28-day cycles.

Open-label Phase:
Eligible participants (refer to protocol Sections 6.7.2 and 6.7.3 for OLE eligibility criteria) may enroll in the optional OLE phase to receive 150 mg BID of nirogacestat (open-label study treatment), continuously in 28-day cycles.

Study burden and risks

Participation in this study can take up to approx. 2 years. During this time approx. 15 visits (short to hours long duration) to the study site are required (This is excl. the OLE phase). Besides, during the treatment patients have to complete questionnaires, and have contact with study team over phone/email on a monthly basis. WOCBP also have to complete a pregnancy (urine) test every month. Daily administration of the study drug is a responsibility of the participant.

Approximately 91 participants have received nirogacestat as a single therapy in completed clinical studies for the treatment of advanced tumors of which 9 of these participants had desmoid tumors. The most commonly reported side effects (in approximately 10% or more of the participants) in these completed studies were:
• Diarrhea (57%);
• Nausea (52%);
• Fatigue (41%);
• Vomiting (39%);
• Hypophosphatemia (low level of phosphate in the blood), which may cause muscle weakness, irritability, anxiety, difficulty breathing, and/or, in serious cases, delirium (sudden, severe confusion) and coma (33%);

• Decreased appetite (21%);
• Cough (21%);
• Fever (19%);
• Rash (18%);
• Hypokalemia (low level of potassium in the blood) which may cause fatigue, weakness, muscle cramps, and/or constipation (17%);
• Headache (12%)
• Insomnia (11%);
• Increases in liver enzymes (11%);
• Dry mouth (11%);
• Indigestion (11%);
• Abdominal (stomach) pain (10%); and
• Mouth sores (10%).

A small Phase 2 study was conducted by the National Cancer Institute (NCI) in which 17 participants with desmoid tumor received nirogacestat 150 mg twice a day. The most commonly reported (20% or more) side effects in that study included diarrhea, hypophosphatemia, increases in liver enzymes, nausea, decreased white blood cell count, rash, dry mouth, fatigue, anemia, decreased blood electrolytes (calcium, potassium, and sodium), hot flashes, decreased platelets, irregular menstrual periods, and mouth sores.

However, the results of the nonclinical toxicology and safety pharmacology studies, together with the clinical experience in participants with advanced cancers, support the hypothesis that nirogacestat may represent an important therapeutic approach in patients with desmoid tumors. Thus, the projected benefit/risk balance is considered favorable for further development in this patient population. More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirogacestat may be found in the Investigator*s Brochure.

Also see E9 and E9a.

Contacts

Public
SpringWorks Therapeutics

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Stamford CT 06902
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Scientific
SpringWorks Therapeutics

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Stamford CT 06902
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Participant must be at least 18 years of age at the time of signing the informed consent.
2. Participant has histologically confirmed DT/AF (by local pathologist prior to informed consent) that has progressed by >= 20% as measured by RECIST v1.1 within 12 months of the screening visit scan.
3. Participant has:Treatment naïve, measurably progressing DT/AF that is deemed not amenable to surgery without the risk of significant morbidity; OR
Recurrent, measurably progressing DT/AF at least one line of therapy; OR
Refactory, measurably progressing DT/AF following at least one line of therapy.
4. Participant has a DT/AF tumor where continued progressive disease will not result in
immediate significant risk to the participant.
5. Participant agrees to provide archival or new tumor tissue for re-confirmation of disease.
6. If participant is currently being treated with any therapy for the treatment of
DT/AF, this must have be completed at least 28 days (or 5 half-lives, whichever is longer) prior first dose of study treatment. All toxicities from prior therapy must be resolved to <=Grade 1 or clinical baseline (as measured by NCI Common Terminology Criteria for Adverse Events v5.0).
7. Participants who are receiving chronic nonsteroidal anti-inflammatory drugs (NSAIDs) as
treatment for conditions other than DT/AF must be receiving them prior to the documented DT/AF progressive disease (inclusion criteria 2) for and on a stable

dose for at least 28 days prior to first dose of study treatment.
8. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status <=2
at screening (refer to Section 10.7 for ECOG performance status scale).
9. Participant has adequate organ and bone marrow function as defined by the following
screening laboratory values:
a. Absolute neutrophil count =>1500 cells/µL;
b. Platelets =>100,000µL;
c. Hemoglobin =>9 g/dL;
d. Total bilirubin =<1.5 x upper limit of normal (ULN) (isolated bilirubin >1.5 x ULN
is acceptable if bilirubin is fractionated and direct bilirubin <35%);
e. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvate transaminase) =<2 x ULN; and
f. Serum creatinine =<1.5 x ULN or if creatinine >1.5 x ULN then calculated creatinine clearance must be =>60 mL/min (using the Cockcroft-Gault formula);
10. Participant can swallow tablets and has no gastrointestinal conditions affecting
absorption.
11. Male or Female:
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
a. Male participants are eligible to participate if they agree to the following during the treatment period and for at least 90 days after the last dose of study treatment:
- Refrain from donating or preserving sperm;
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 male condom when having sexual intercourse with women of childbearing potential (WOCBP). An additional form of contraception as described in Section 10.4 should also be used by the female partner, if she is of childbearing potential. Refer to Section 10.4 for definition of WOCBP.
b. 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 Section 10.4 during the treatment period until at least 6 months 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.
- A WOCBP must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the baseline visit prior 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.
12. Capable of giving signed informed consent as described in Section 10.1.3 which includes
compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

1. Participant has known malabsorption syndrome or preexisting gastrointestinal conditions
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.
2. 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; or
- symptomatic pulmonary embolism.
3. Participant has abnormal QT interval corrected by Fridericia*s formula (>450 msec for
male participants, >470 msec for female participants, or >480 msec for participants with
bundle branch block) after electrolytes have been corrected (triplicate ECG readings,
done approximately 2-3 minutes apart and averaged) at screening.
4. Participant is using concomitant medications that are known to prolong the

QT/QTcF interval, including Class Ia (e.g. quinidine, procainamide, disopromide) and class III (e.g. dofetilide, ibutilide, sotalol) antiarrhythmics at the time of informed consent. Non-antiarrhythmic medications which may prolong the QT/QTcF interval are allowed provided the participant does not have additional risk factors for Torsades de Pointes (TdP).
5. Participant has congenital long QT syndrome.
6. Participant has a history of additional risk factors for Torsades de Pointes (TdP) (e.g.,
heart failure, hypokalemia, family history of Long QT Syndrome).
7. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years at the time of informed consent,
except for any locally recurring cancer that has been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast), with no evidence of metastatic disease for 3 years at the time of informed consent.
8. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities
(except for Gilbert's syndrome or asymptomatic gallstones).
9. Participant previously received or is currently receiving therapy with GS inhibitors or
anti-Notch antibody therapy.
10. Participant is currently using any treatment for DT/AF including tyrosine kinase
inhibitors (TKIs), NSAIDs (chronic daily use) or any investigational treatment 28 days
(or 5 half-lives, whichever is longer) prior to the first dose of study treatment.
OR
Participant has started any treatment for DT/AF after the documented DT/AF progressive
disease (inclusion criteria 2).
11. Participant is currently using or anticipates using food or drugs that are known
strong/moderate cytochrome P450 3A4 (CYP3A4) inhibitors, or strong CYP3A inducers within
14 days prior to the first dose of study treatment.
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.
Participation in observational studies may be permitted with prior approval from the medical monitor/sponsor.
13. Participant has a positive human immunodeficiency virus antibody test.
14. Participant has presence of Hepatitis B surface antigen at screening.
15. Participant has a positive Hepatitis C antibody or Hepatitis C ribonucleic acid (RNA) test
result at screening or within 3 months prior to starting study treatment.

16. Participant is unable to tolerate MRI or for whom MRI is contraindicated.
17. Participant with active bacterial, for chronic infection at the time of informed consent and
during the screening period.
18. Participant has experienced other severe acute or chronic medical or psychiatric
conditions, including recent (within 1 year of signing informed consent) or active suicidal
ideation or behavior, or a laboratory abnormality that may increase the risk associated
with study participation or study treatment administration or may interfere with the
interpretation of study results and, in the judgment of the investigator, would make the
participant inappropriate for entry into this study.
19. Participant has known hypersensitivity to the active substance or to any of the excipients
of nirogacestat or placebo (Table 2).
20. Participant is unable to comply with study related procedures (including, but not limited
to, the completion of electronic patient report outcomes (ePROs), or the ePRO questionnaires are not available in the participant*s preferred language)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-11-2019

Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Nirogacestat

Ethics review

Approved WMO Date:	09-05-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-09-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	26-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	01-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-05-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001991-39-NL
ClinicalTrials.gov	NCT03785964
CCMO	NL69411.031.19