



Clinical trial results:

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

Summary

EudraCT number	2018-001991-39
Trial protocol	GB BE NL DE IT
Global end of trial date	17 October 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	NIR-DT-301
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03785964
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 138207

Notes:

Sponsors

Sponsor organisation name	SpringWorks Therapeutics
Sponsor organisation address	100 Washington Blvd, Stamford, United States, CT 06902
Public contact	Clinical Operations, SpringWorks Subsidiary 2, PBC, clinical@springworkstx.com
Scientific contact	Clinical Operations, SpringWorks Subsidiary 2, PBC, clinical@springworkstx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	07 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2022
Global end of trial reached?	Yes
Global end of trial date	17 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to determine the efficacy (as defined by progression free survival [PFS]) of nirogacestat in adult participants with progressing DT/AF.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locales and countries where the study was conducted, and in compliance with Good Clinical Practice Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 90
Worldwide total number of subjects	142
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	136
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study with a total of 52 sites across 7 countries (Belgium, Canada, Germany, Italy, Netherlands, United Kingdom, and United States of America). A total of 201 participants were screened and 142 participants were enrolled and randomised.

Pre-assignment

Screening details:

All eligible participants must have had histologically confirmed Desmoid Tumor /Aggressive Fibromatosis (by local pathologist prior to informed consent) that had progressed by $\geq 20\%$ as measured by Response Evaluation Criteria in Solid Tumors version 1.1 within 12 months of the screening visit scan.

Period 1

Period 1 title	Double-Blind Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Phase - Nirogacestat

Arm description:

Nirogacestat 150 mg twice daily

Arm type	Experimental
Investigational medicinal product name	Nirogacestat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nirogacestat 50 mg tablets (3 tablets; 150 mg) twice daily (BID) orally continuously for 28-day cycles.

Arm title	Double-Blind Phase - Placebo
------------------	------------------------------

Arm description:

Placebo twice daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo 50mg (sugar pill manufactured to mimic nirogacestat 50 mg tablet) (3 tablets) BID orally continuously for 28-day cycles.

Number of subjects in period 1	Double-Blind Phase - Nirogacestat	Double-Blind Phase - Placebo
Started	70	72
Treated (Safety Population)	69	72
Completed	12	35
Not completed	58	37
Adverse event, serious fatal	-	1
Unqualified clinical progression	1	1
Adverse event, non-fatal	14	-
Ongoing (still on treatment)	36	23
Other reason	5	11
Participant non-compliance	1	1
Not treated	1	-

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind Phase - Nirogacestat
Reporting group description: Nirogacestat 150 mg twice daily	
Reporting group title	Double-Blind Phase - Placebo
Reporting group description: Placebo twice daily.	

Reporting group values	Double-Blind Phase - Nirogacestat	Double-Blind Phase - Placebo	Total
Number of subjects	70	72	142
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	67	69	136
From 65-84 years	3	3	6
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	37.5	37.0	
standard deviation	± 14.43	± 12.89	-
Gender categorical			
Units: Subjects			
Female	45	47	92
Male	25	25	50

Subject analysis sets

Subject analysis set title	Intent-to-treat Population - Nirogacestat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat Population consisted of all participants who were enrolled and randomized to study treatment.	
Subject analysis set title	Intent-to-treat Population - Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat Population consisted of all participants who were enrolled and randomized to study treatment.	
Subject analysis set title	Safety Population - Nirogacestat
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Subject analysis set title	Safety Population - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Reporting group values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo	Safety Population - Nirogacestat
Number of subjects	70	72	69
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	67	69	66
From 65-84 years	3	3	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.5	37.0	37.3
standard deviation	± 14.43	± 12.89	± 14.48
Gender categorical Units: Subjects			
Female	45	47	44
Male	25	25	25

Reporting group values	Safety Population - Placebo		
Number of subjects	72		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	69		
From 65-84 years	3		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	37.0		
standard deviation	± 12.89		

Gender categorical			
Units: Subjects			
Female	47		
Male	25		

End points

End points reporting groups

Reporting group title	Double-Blind Phase - Nirogacestat
Reporting group description: Nirogacestat 150 mg twice daily	
Reporting group title	Double-Blind Phase - Placebo
Reporting group description: Placebo twice daily.	
Subject analysis set title	Intent-to-treat Population - Nirogacestat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat Population consisted of all participants who were enrolled and randomized to study treatment.	
Subject analysis set title	Intent-to-treat Population - Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat Population consisted of all participants who were enrolled and randomized to study treatment.	
Subject analysis set title	Safety Population - Nirogacestat
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population consisted of all randomized participants who took at least 1 dose of study treatment.	
Subject analysis set title	Safety Population - Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population consisted of all randomized participants who took at least 1 dose of study treatment.	

Primary: Efficacy: Progression Free Survival (PFS)

End point title	Efficacy: Progression Free Survival (PFS)
End point description: Progression will be determined radiographically using RECIST v1.1 (Eisenhauer, 2009) or clinically as assessed by the investigator. Clinical progression is defined as the onset or worsening of symptoms resulting in a global deterioration of health status causing the permanent discontinuation from study treatment and the initiation of emergent treatment (e.g., radiotherapy, surgery, or systemic therapy including chemotherapy or tyrosine kinase inhibitors) for DT/AF. Events of clinical progression will be adjudicated by an independent blinded central Endpoint Adjudication Committee (EAC) which will qualify events of clinical progression for inclusion in the PFS endpoint prior to study unblinding according to an EAC Review Charter.	
End point type	Primary
End point timeframe: On the first day of every 3 cycles (each cycle is 28 days) until disease progression is observed or death, whichever comes first, assessed up to approximately 2 years.	

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70 ^[1]	72 ^[2]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	15.1 (8.4 to 99999)		

Notes:

[1] - 99999 denotes not evaluated as < 50% of the participants had events in Nirogacestat treatment arm

[2] - 99999 denotes that upper 95% CI is not reached

Statistical analyses

Statistical analysis title	Statistical Analysis 1
----------------------------	------------------------

Statistical analysis description:

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

Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.55

Notes:

[3] - p-value was from a one-sided stratified log-rank test with placebo as reference.

Secondary: Efficacy: Objective Response Rate Using RECIST Version 1.1 Criteria

End point title	Efficacy: Objective Response Rate Using RECIST Version 1.1 Criteria
-----------------	---

End point description:

Objective response rate (ORR) is defined as the proportion of participants having a confirmed Best Overall Response (BOR) of CR or PR by central reader using RECIST v1.1 criteria. Responses obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any responses, which occurred after a new anticancer therapy was received, will not be included. ORR is presented by percentages of responders.

End point type	Secondary
----------------	-----------

End point timeframe:

On the first day of every 3 cycles (each cycle is 28 days) through study completion, an average of 2 years.

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Percentage of participants				
number (confidence interval 95%)	41 (29.8 to 53.8)	8 (3.1 to 17.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cochran-Mantel-Haenszel test for general association stratified by tumor location. Placebo was reference treatment.	
Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Two-sided p-value

Secondary: Efficacy: Change From Baseline at Cycle 10 in the Brief Pain Inventory (BPI) Average Pain Intensity (API) Score

End point title	Efficacy: Change From Baseline at Cycle 10 in the Brief Pain Inventory (BPI) Average Pain Intensity (API) Score
End point description:	
The Brief Pain Inventory consists of 9 questions and utilizes a 11-point Numerical pain Rating Scale from 0-10 measuring severity from "no pain" to "pain as bad as you can imagine," with a 24-hour recall period. Average Pain Intensity is calculated as the 7-day average (when results on at least 4 days for a VISIT are available) of Brief Pain Inventory Question #3 - Worst Pain in last 24 hours. The minimum and maximum of the actual score are (0, 8) for Nirogacestat and (0,9) for Placebo, respectively. A positive change from Baseline value indicates worsening of Average Pain Intensity and a negative change from Baseline value indicates improvement of Average Pain Intensity. The minimum and maximum of change from baseline score are (-7, 3) for Nirogacestat and (-5, 5) for Placebo, respectively.	
End point type	Secondary

End point timeframe:

Daily for the last 7 days of every cycle (each cycle is 28 days) through study completion, an average of 2 years

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval	-1.583 (-2.157	-0.241 (-0.822		

95%)	to -1.009)	to 0.340)
------	------------	-----------

Statistical analyses

Statistical analysis title	Superiority Mixed Models Analysis
Statistical analysis description:	
Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline Brief Pain Inventory Short Form score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 40 and 31 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively	
Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[5] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary: Efficacy: Change From Baseline at Cycle 10 in the GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Tumor Symptom Scale (DTSS) - Total Score

End point title	Efficacy: Change From Baseline at Cycle 10 in the GOunder/Desmoid Tumor Research Tumor Foundation (DTRF) DEsmoid Tumor Symptom Scale (DTSS) - Total Score
End point description:	
The DEsmoid Tumor Symptom Scale is an 11-point, numeric rating scale from 0 to 10 to measure severity from "none" to "as bad as you can imagine," with a 24-hour recall period. The Total Symptom Score is calculated as the mean of Pain items (Items 1-3) as a single score, then a mean of this with items 4-7). Weekly summary scores will be created by averaging the daily scores over the 7 days period prior to each visit. A weekly score will be derived only if 4 or more out of 7 days period have non-missing scores. The weekly summary score will be used in analyses. If no weekly summary score is calculable, the participant will have data considered as missing at that visit. Higher scores represent worse symptom severity. The minimum and maximum of the actual score are (0,7) for Nirogacestat and (0,10) for Placebo. A positive change from Baseline value indicated worsening of symptoms. The minimum and maximum of change from baseline are (-6,1) for Nirogacestat and (-4,5) for Placebo.	
End point type	Secondary

End point timeframe:

Daily for the last 7 days of every cycle (each cycle is 28 days) through study completion, an average of 2 years.

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.110 (-1.569 to -0.651)	0.457 (-0.009 to 0.923)		

Statistical analyses

Statistical analysis title	Superiority Mixed Models Analysis
----------------------------	-----------------------------------

Statistical analysis description:

Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline DEsmoid Tumor Symptom Scale score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 40 and 32 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively.

Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[6] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary: Efficacy: Change From Baseline in the GOunder/Desmoid Tumor Research Foundation (DTRF) DEsmoid Tumor Impact Scale (DTIS) - Physical Functioning Domain Score

End point title	Efficacy: Change From Baseline in the GOunder/Desmoid Tumor Research Foundation (DTRF) DEsmoid Tumor Impact Scale (DTIS) - Physical Functioning Domain Score
-----------------	--

End point description:

The items are evaluated on a 5-point Likert Scale ranging from "none of the time" to "all of the time" to measure frequency, with a 7-day recall period. The Physical Function Domain Score are calculated as the average Item 01 Moving, Item 02 Reaching (Freq), Item 06 Vigorous Activity, Item 7 Moderate Activity, and Item 08 Accomplished Less. Higher scores represent worst impact severity. The minimum and maximum of the actual score are (1, 5) for Nirogacestat and (1,5) for Placebo, respectively. A positive change from baseline value indicates worsening impact and a negative change from baseline value indicates improvement in impact. The minimum and maximum of change from baseline score are (-3, 0) for Nirogacestat and (-1, 2) for Placebo, respectively.

End point type	Secondary
----------------	-----------

End point timeframe:

On the last day of every cycle (each cycle is 28 days) through study completion, average of 2 years.

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-0.613 (-0.808 to -0.418)	0.094 (-0.113 to 0.300)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
----------------------------	------------------------

Statistical analysis description:

Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 39 and 28 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively.

Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[7] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary: Efficacy: Change From Baseline at Cycle10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) Scale

End point title	Efficacy: Change From Baseline at Cycle10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) Scale
-----------------	--

End point description:

The EORTC Quality of Life Questionnaire-Core 30 version 3.0 was used with a 7-day recall period. It consists of 30 questions with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The instrument yields the following scales: 5 functional scales, 3 symptom scales, and a global health status/quality of life scale. A high score for the global health status/QoL represents a high QoL. The minimum and maximum of the actual score are (33, 100) for Nirogacestat and (8,92) for Placebo, respectively. A positive change from baseline indicated improvement of global health status and a negative change from baseline value indicated worsening of global health status. The minimum and maximum of change from baseline score are (-58, 67) for Nirogacestat and (-67, 42) for Placebo, respectively.

End point type	Secondary
----------------	-----------

End point timeframe:

Last day of every cycle (each cycle is 28 days) through study completion, an average of 2 years

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval 95%)	2.935 (-3.115 to 8.985)	-8.466 (-15.065 to -1.867)		

Statistical analyses

Statistical analysis title	Superiority Mixed Models Analysis
Statistical analysis description:	
Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 38 and 27 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively.	
Comparison groups	Intent-to-treat Population - Placebo v Intent-to-treat Population - Nirogacestat
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.006
Method	Mixed models analysis

Notes:

[8] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary: Efficacy: Change From Baseline at Cycle 10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Physical Functioning

End point title	Efficacy: Change From Baseline at Cycle 10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Physical Functioning
-----------------	---

End point description:

The EORTC Quality of Life Questionnaire-Core 30 version 3.0 was used with a 7-day recall period. It consists of 30 questions with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The instrument yields the following scales: 5 functional scales, 3 symptom scales, and a global health status/quality of life scale. A high score for a Physical functional scale represents a high/healthy level of functioning. The minimum and maximum of the actual score are (27, 100) for Nirogacestat and (7, 100) for Placebo, respectively. A positive change from baseline indicated improvement of global health status and a negative change from baseline value indicated worsening of physical functioning scores. The minimum and maximum of change from baseline score are (-7, 40) for Nirogacestat and (-40, 27) for Placebo, respectively.

End point type	Secondary
End point timeframe:	
Last day of every cycle (each cycle is 28 days) through study completion, an average of 2 years	

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval 95%)	9.143 (5.619 to 12.668)	-5.225 (-9.060 to -1.390)		

Statistical analyses

Statistical analysis title	Superiority Mixed Models Analysis
----------------------------	-----------------------------------

Statistical analysis description:

Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 38 and 28 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively.

Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[9] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Secondary: Efficacy: Change From Baseline at Cycle 10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Role Functioning

End point title	Efficacy: Change From Baseline at Cycle 10 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Role Functioning
-----------------	---

End point description:

The EORTC Quality of Life Questionnaire-Core 30 version 3.0 was used with a 7-day recall period. It consists of 30 questions with all items scored 1 ("not at all") to 4 ("very much") except for the 2 items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The instrument yields the following scales: 5 functional scales, 3 symptom scales, and a global health status/quality of life scale. A positive change from baseline indicated improvement of global health status and a negative change from baseline value indicated worsening of global health status and functioning scores. The minimum and maximum of change from baseline score are (-17, 83) for Nirogacestat and (-100, 50) for Placebo, respectively. The minimum and maximum of the actual score are (33, 100) for Nirogacestat and (0,100) for Placebo, respectively.

End point type	Secondary
----------------	-----------

End point timeframe:

Last day of every cycle (each cycle is 28 days) through study completion, an average of 2 years

End point values	Intent-to-treat Population - Nirogacestat	Intent-to-treat Population - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (confidence interval 95%)	13.293 (7.080 to 19.506)	-5.590 (-12.320 to 1.139)		

Statistical analyses

Statistical analysis title	Superiority Mixed Models Analysis
Statistical analysis description:	
Mixed model with repeated measures (MMRM) with treatment and visit as factors, Baseline score and primary tumor location (intra-abdominal or extra-abdominal) as covariates, included baseline by visit and treatment by visit interactions. Only participants with a Baseline and at least one post-baseline score were included in the analysis. 38 and 28 participants contributed to this analysis at Cycle 10 from Nirogacestat and Placebo respectively.	
Comparison groups	Intent-to-treat Population - Nirogacestat v Intent-to-treat Population - Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.001
Method	Mixed models analysis

Notes:

[10] - An unstructured covariance structure was used and degrees of freedom were estimated using the Kenward-Roger approximation.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All SAEs and AEs were collected from the time of signing ICF until 30 days after the last dose of study treatment, an average of 1 years and 4 months and up to 2 years and 10 months.

Adverse event reporting additional description:

One patient randomized to Nirogacestat arm, discontinued prior to receiving any study drug.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	Safety Population - Nirogacestat
-----------------------	----------------------------------

Reporting group description:

One patient randomized to Nirogacestat arm, discontinued prior to receiving any study drug.

Reporting group title	Safety Population- Placebo
-----------------------	----------------------------

Reporting group description: -

Serious adverse events	Safety Population - Nirogacestat	Safety Population- Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 69 (20.29%)	8 / 72 (11.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Spindle cell sarcoma			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 69 (1.45%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 69 (1.45%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial Fibrillation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 69 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 69 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	0 / 69 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian failure			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Premature menopause subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 69 (4.35%) 3 / 3 0 / 0	0 / 72 (0.00%) 0 / 0 0 / 0	
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 1 / 1 0 / 0	0 / 72 (0.00%) 0 / 0 0 / 0	
Drug-induced liver injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 69 (0.00%) 0 / 0 0 / 0	1 / 72 (1.39%) 0 / 1 0 / 0	
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 69 (0.00%) 0 / 0 0 / 0	1 / 72 (1.39%) 0 / 1 0 / 0	
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 1 / 1 0 / 0	0 / 72 (0.00%) 0 / 0 0 / 0	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 69 (1.45%) 0 / 1 0 / 0	0 / 72 (0.00%) 0 / 0 0 / 0	
Infections and infestations Abdominal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Abdominal infection	1 / 69 (1.45%) 0 / 1 0 / 0	0 / 72 (0.00%) 0 / 0 0 / 0	

subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 69 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	1 / 69 (1.45%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 69 (0.00%)	3 / 72 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Population - Nirogacestat	Safety Population- Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 69 (100.00%)	69 / 72 (95.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	5 / 69 (7.25%)	12 / 72 (16.67%)	
occurrences (all)	5	16	
Vascular disorders			
Hot flush			
subjects affected / exposed	13 / 69 (18.84%)	4 / 72 (5.56%)	
occurrences (all)	14	4	
Hypertension			
subjects affected / exposed	10 / 69 (14.49%)	8 / 72 (11.11%)	
occurrences (all)	18	11	
Hypotension			
subjects affected / exposed	4 / 69 (5.80%)	1 / 72 (1.39%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 69 (5.80%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
Fatigue			
subjects affected / exposed	35 / 69 (50.72%)	26 / 72 (36.11%)	
occurrences (all)	56	31	
Influenza like illness			
subjects affected / exposed	7 / 69 (10.14%)	2 / 72 (2.78%)	
occurrences (all)	7	2	
Non-cardiac chest pain			
subjects affected / exposed	5 / 69 (7.25%)	5 / 72 (6.94%)	
occurrences (all)	5	5	
Oedema peripheral			
subjects affected / exposed	4 / 69 (5.80%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
Pyrexia			
subjects affected / exposed	5 / 69 (7.25%)	6 / 72 (8.33%)	
occurrences (all)	7	10	

Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	5 / 69 (7.25%)	0 / 72 (0.00%)	
occurrences (all)	5	0	
Menstruation irregular			
subjects affected / exposed	6 / 69 (8.70%)	4 / 72 (5.56%)	
occurrences (all)	6	4	
Ovarian failure			
subjects affected / exposed	12 / 69 (17.39%)	0 / 72 (0.00%)	
occurrences (all)	14	0	
Premature menopause			
subjects affected / exposed	8 / 69 (11.59%)	0 / 72 (0.00%)	
occurrences (all)	11	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 69 (15.94%)	3 / 72 (4.17%)	
occurrences (all)	18	3	
Dysphonia			
subjects affected / exposed	4 / 69 (5.80%)	0 / 72 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	11 / 69 (15.94%)	4 / 72 (5.56%)	
occurrences (all)	15	4	
Epistaxis			
subjects affected / exposed	10 / 69 (14.49%)	1 / 72 (1.39%)	
occurrences (all)	11	1	
Nasal congestion			
subjects affected / exposed	7 / 69 (10.14%)	2 / 72 (2.78%)	
occurrences (all)	11	2	
Oropharyngeal pain			
subjects affected / exposed	5 / 69 (7.25%)	3 / 72 (4.17%)	
occurrences (all)	5	3	
Productive cough			
subjects affected / exposed	4 / 69 (5.80%)	0 / 72 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 8	5 / 72 (6.94%) 6	
Insomnia subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 11	8 / 72 (11.11%) 8	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	12 / 69 (17.39%) 17	6 / 72 (8.33%) 11	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 16	8 / 72 (11.11%) 12	
Blood follicle stimulating hormone increased subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9	1 / 72 (1.39%) 1	
SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 8	10 / 72 (13.89%) 10	
Weight decreased subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 10	7 / 72 (9.72%) 8	
Weight increased subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 19	5 / 72 (6.94%) 12	
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 3	5 / 72 (6.94%) 8	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 10	4 / 72 (5.56%) 5	
Headache subjects affected / exposed occurrences (all)	20 / 69 (28.99%) 25	11 / 72 (15.28%) 15	
Memory impairment			

subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5	2 / 72 (2.78%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	4 / 72 (5.56%) 6	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 16	8 / 72 (11.11%) 18	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4	3 / 72 (4.17%) 4	
Abdominal pain subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 16	9 / 72 (12.50%) 18	
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6	1 / 72 (1.39%) 1	
Constipation subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9	7 / 72 (9.72%) 8	
Diarrhoea subjects affected / exposed occurrences (all)	58 / 69 (84.06%) 129	25 / 72 (34.72%) 32	
Dry mouth subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 9	3 / 72 (4.17%) 3	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	6 / 72 (8.33%) 6	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 6	3 / 72 (4.17%) 3	
Mouth ulceration			

subjects affected / exposed	4 / 69 (5.80%)	0 / 72 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	37 / 69 (53.62%)	28 / 72 (38.89%)	
occurrences (all)	53	32	
Stomatitis			
subjects affected / exposed	20 / 69 (28.99%)	3 / 72 (4.17%)	
occurrences (all)	43	3	
Vomiting			
subjects affected / exposed	14 / 69 (20.29%)	14 / 72 (19.44%)	
occurrences (all)	21	17	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 69 (18.84%)	1 / 72 (1.39%)	
occurrences (all)	13	1	
Dermatitis acneiform			
subjects affected / exposed	15 / 69 (21.74%)	0 / 72 (0.00%)	
occurrences (all)	22	0	
Dry skin			
subjects affected / exposed	11 / 69 (15.94%)	5 / 72 (6.94%)	
occurrences (all)	13	5	
Hidradenitis			
subjects affected / exposed	6 / 69 (8.70%)	0 / 72 (0.00%)	
occurrences (all)	12	0	
Pruritus			
subjects affected / exposed	9 / 69 (13.04%)	6 / 72 (8.33%)	
occurrences (all)	12	6	
Rash			
subjects affected / exposed	13 / 69 (18.84%)	5 / 72 (6.94%)	
occurrences (all)	15	6	
Rash maculo-papular			
subjects affected / exposed	22 / 69 (31.88%)	4 / 72 (5.56%)	
occurrences (all)	40	8	
Hyperhidrosis			
subjects affected / exposed	4 / 69 (5.80%)	2 / 72 (2.78%)	
occurrences (all)	5	2	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 69 (11.59%)	9 / 72 (12.50%)	
occurrences (all)	9	9	
Back pain			
subjects affected / exposed	9 / 69 (13.04%)	7 / 72 (9.72%)	
occurrences (all)	10	9	
Flank pain			
subjects affected / exposed	2 / 69 (2.90%)	4 / 72 (5.56%)	
occurrences (all)	2	5	
Muscular weakness			
subjects affected / exposed	5 / 69 (7.25%)	2 / 72 (2.78%)	
occurrences (all)	7	2	
Muscle spasms			
subjects affected / exposed	4 / 69 (5.80%)	4 / 72 (5.56%)	
occurrences (all)	6	5	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 69 (2.90%)	4 / 72 (5.56%)	
occurrences (all)	2	5	
Myalgia			
subjects affected / exposed	4 / 69 (5.80%)	0 / 72 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			
subjects affected / exposed	5 / 69 (7.25%)	6 / 72 (8.33%)	
occurrences (all)	6	6	
Infections and infestations			
COVID-19			
subjects affected / exposed	12 / 69 (17.39%)	11 / 72 (15.28%)	
occurrences (all)	12	13	
Folliculitis			
subjects affected / exposed	9 / 69 (13.04%)	0 / 72 (0.00%)	
occurrences (all)	25	0	
Sinusitis			
subjects affected / exposed	6 / 69 (8.70%)	0 / 72 (0.00%)	
occurrences (all)	9	0	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5	1 / 72 (1.39%) 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 69 (15.94%)	8 / 72 (11.11%)	
occurrences (all)	13	11	
Hypokalaemia			
subjects affected / exposed	8 / 69 (11.59%)	1 / 72 (1.39%)	
occurrences (all)	12	1	
Hypocalcaemia			
subjects affected / exposed	4 / 69 (5.80%)	0 / 72 (0.00%)	
occurrences (all)	6	0	
Hypophosphataemia			
subjects affected / exposed	29 / 69 (42.03%)	5 / 72 (6.94%)	
occurrences (all)	66	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2018	<p>Protocol Amendment 1</p> <ul style="list-style-type: none">• The MD Anderson Symptom Inventory PRO was replaced with the EORTC QLQ 30 because it more accurately captured concepts important to patients with desmoid tumors.• The PROMIS PF and the 3 additional questions were added to supplement the DTIS.• Stratification by target tumor location was changed from "favorable" versus "unfavorable" to "intra-abdominal" versus "extra-abdominal" to more accurately reflect the way these tumors are described in clinical practice.• Situations where breaking the blind would be acceptable were further detailed and broken out into 3 distinct categories: emergency situations, confirmed progressive disease, and all estimated number of PFS events have been observed.• The language regarding the calculation and analysis of the secondary endpoint of duration of response was revised for clarity.
14 October 2019	<p>Protocol Amendment 2</p> <ul style="list-style-type: none">• The sample size was increased for screened and randomized patients.• Updated inclusion/exclusion criteria.• Added potential risk of nirogacestat to interact with drugs that are substrates of cytochrome P450 3A4.• Added potential risk of gastric acid reducing agents to reduce absorption and lower exposure prior to dosing of nirogacestat.• Added new section for AESIs.• Changed serial PK draw and observation period from 2 hours to 3 hours.• Updated the methodology for selecting target lesions to specify that target lesions will be selected by the investigator. The location of the target tumor(s) selected by the investigators as the basis for inclusion in the study were documented on the Pre Randomization RECIST v1.1 Calculation Worksheet.
27 January 2020	<p>Protocol Amendment 3</p> <ul style="list-style-type: none">• Clarification to ensure menstrual irregularities/infertility were captured as part of the medical history.• Added blood sampling for hormone levels from males and females.• Added risks of Notch-related effects on reproductive function and fertility.• Reproductive system disorders including amenorrhea and premature menopause/primary ovarian insufficiency were added as AESIs to enable additional safety follow-up while gastrointestinal events including nausea, vomiting/dyspepsia, and diarrhea were removed as these were known and expected events related to nirogacestat.
09 February 2021	<p>Protocol Amendment 5</p> <p>No participants were initially consented under Protocol Amendment 5 as screening had previously closed.</p> <ul style="list-style-type: none">• Revised the definition of PFS to include events of clinical progression in the analysis of PFS for the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported