



Clinical trial results:

A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Anamorelin HCl for the Treatment of Malignancy Associated Weight Loss and Anorexia in adult patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2018-002927-40
Trial protocol	DE BE PL HR RO
Global end of trial date	27 December 2022

Results information

Result version number	v1 (current)
This version publication date	12 April 2024
First version publication date	12 April 2024

Trial information

Trial identification

Sponsor protocol code	ANAM-17-21
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03743064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via Pian Scairolo 9, 6912 Pazzallo-Lugano, Switzerland,
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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	Final
Date of interim/final analysis	16 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2022
Global end of trial reached?	Yes
Global end of trial date	27 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of anamorelin HCl vs placebo on the gain in body weight and improvement in anorexia symptoms.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in the Ninth revision, 64th meeting, Fortaleza) [World Medical Association, 2013], and the International Council for Harmonisation (ICH) guidelines. Before undertaking any study-related procedures with patients, the purpose and nature of the study, as well as possible adverse effects, were explained to them in understandable terms, and written informed consent was obtained from each individual. Each ICF was to be appropriately signed and dated by the patient and the person obtaining the consent. Each patient was to receive a copy of the signed ICF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Romania: 117
Country: Number of subjects enrolled	Croatia: 10
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Ukraine: 72
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Australia: 4
Worldwide total number of subjects	318
EEA total number of subjects	170

Notes:

Subjects enrolled per age group

In utero	0
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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)	166
From 65 to 84 years	145
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at a total of 49 study sites in Australia (2 sites), Belgium (2 sites), Croatia (3 sites), Germany (3 sites), Poland (5 sites), Romania (7 sites), Russia (10 sites), Ukraine (8 sites), and USA (9 sites). First Patient Enrollment (date of randomization) was on 06MAY2019.

Pre-assignment

Screening details:

This study included adults ≥ 18 years of age with advanced NSCLC, a body mass index (BMI) $< 20 \text{ kg/m}^2$, involuntary weight loss of $> 2\%$ within 6 months prior to Screening, and anorexia. A total of 373 patients were screened; 55 patients were screen failures; 318 patients were randomized to anamorelin (154 patients) and placebo (164 patients).

Period 1

Period 1 title	Overall trial (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

Blinding implementation details:

This was a double-blind study. The blinding of the study drugs was guaranteed by the use of anamorelin HCl film-coated tablets and matching placebo tablets. Patients were randomized using the Interactive Web Response System (IWRS). Any unblinding of the study treatment was performed using the IWRS.

Arms

Are arms mutually exclusive?	Yes
Arm title	100 mg Anamorelin HCl

Arm description:

Anamorelin HCl 100 mg film-coated tablets taken orally once daily while fasting for a total of 24 weeks.

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

Dosage and administration details:

Anamorelin HCl 100 mg film-coated tablets were to be taken orally once daily while fasting at least 1 hour before the first meal of the day for a total of 24 weeks.

Arm title	Placebo
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Arm description:

Placebo matching film-coated tablets taken orally once daily while fasting for a total of 24 weeks.

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 matching film-coated tablets were to be taken orally once daily while fasting at least 1 hour before the first meal of the day for a total of 24 weeks.

Number of subjects in period 1	100 mg Anamorelin HCl	Placebo
Started	154	164
Completed	83	90
Not completed	71	74
Adverse event, serious fatal	25	28
Consent withdrawn by subject	28	25
Physician decision	2	4
Disease/Clinical progression	5	2
Adverse event, non-fatal	7	9
War	1	-
Lost to follow-up	3	6

Baseline characteristics

Reporting groups

Reporting group title	100 mg Anamorelin HCl
Reporting group description:	
Anamorelin HCl 100 mg film-coated tablets taken orally once daily while fasting for a total of 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo matching film-coated tablets taken orally once daily while fasting for a total of 24 weeks.	

Reporting group values	100 mg Anamorelin HCl	Placebo	Total
Number of subjects	154	164	318
Age categorical			
Units: Subjects			
Adults (18-64 years)	78	88	166
From 65-84 years	74	71	145
85 years and over	2	5	7
Age continuous			
Units: years			
arithmetic mean	64.0	63.6	
standard deviation	± 8.49	± 9.73	-
Gender categorical			
Units: Subjects			
Female	42	50	92
Male	112	114	226
Race			
Units: Subjects			
Asian	4	4	8
Black or African American	0	2	2
White	148	157	305
Other	0	1	1
Multiple	2	0	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	8	7	15
Missing	146	156	302
Chemotherapy line			
Units: Subjects			
First Line	104	104	208
Second Line	36	39	75
Third Line	14	21	35
Anti-cancer treatment			
Units: Subjects			
Immunotherapy	39	46	85
Non-immunotherapy	115	118	233
5-IASS score			
Units: Subjects			

≤10	102	107	209
>10	52	57	109
NSCLC stage at study entry Units: Subjects			
IIIA	2	1	3
IIIB	30	19	49
IV	122	143	265
Missing	0	1	1
Height Units: cm			
arithmetic mean	171.03	169.96	
standard deviation	± 8.690	± 9.164	-
Weight Units: kg			
arithmetic mean	54.09	52.84	
standard deviation	± 7.029	± 7.925	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	18.38	18.16	
standard deviation	± 1.328	± 1.579	-
Body weight loss within 6 months prior to screening Units: percent			
arithmetic mean	10.03	10.86	
standard deviation	± 6.177	± 6.612	-

Subject analysis sets

Subject analysis set title	Intent-to-Treat (ITT) Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Set included all randomized patients and was analyzed as per planned treatment.

Reporting group values	Intent-to-Treat (ITT) Set		
Number of subjects	318		
Age categorical Units: Subjects			
Adults (18-64 years)	166		
From 65-84 years	145		
85 years and over	7		
Age continuous Units: years			
arithmetic mean	63.8		
standard deviation	± 9.14		
Gender categorical Units: Subjects			
Female	92		
Male	226		
Race Units: Subjects			
Asian	8		

Black or African American	2		
White	305		
Other	1		
Multiple	2		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	15		
Missing	302		
Chemotherapy line Units: Subjects			
First Line	208		
Second Line	75		
Third Line	35		
Anti-cancer treatment Units: Subjects			
Immunotherapy	85		
Non-immunotherapy	233		
5-IASS score Units: Subjects			
≤10	209		
>10	109		
NSCLC stage at study entry Units: Subjects			
IIIA	3		
IIIB	49		
IV	265		
Missing	1		
Height Units: cm			
arithmetic mean	170.48		
standard deviation	± 8.940		
Weight Units: kg			
arithmetic mean	53.44		
standard deviation	± 7.519		
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	18.27		
standard deviation	± 1.465		
Body weight loss within 6 months prior to screening Units: percent			
arithmetic mean	10.46		
standard deviation	± 6.408		

End points

End points reporting groups

Reporting group title	100 mg Anamorelin HCl
Reporting group description: Anamorelin HCl 100 mg film-coated tablets taken orally once daily while fasting for a total of 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo matching film-coated tablets taken orally once daily while fasting for a total of 24 weeks.	
Subject analysis set title	Intent-to-Treat (ITT) Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Set included all randomized patients and was analyzed as per planned treatment.	

Primary: Mean change from baseline in body weight over 12 weeks

End point title	Mean change from baseline in body weight over 12 weeks
End point description: The co-primary efficacy endpoint was mean change from baseline in body weight (kg) over 12 weeks in the anamorelin HCl group versus placebo group. Mean change was computed as sum of the changes from baseline over 12 weeks by the time of the last assessment (either week 12 or before in case of death), and then divided by the number of assessments (observed or imputed) from baseline up to the time of the last assessment.	
End point type	Primary
End point timeframe: Mean change from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: kg				
least squares mean (standard error)	1.822 (\pm 0.263)	0.538 (\pm 0.250)		

Statistical analyses

Statistical analysis title	Co-primary analysis: body weight
Statistical analysis description: The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.	
Comparison groups	100 mg Anamorelin HCl v Placebo

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.718
upper limit	1.851
Variability estimate	Standard error of the mean
Dispersion value	0.289

Primary: Mean change from baseline in 5-IASS over 12 weeks

End point title	Mean change from baseline in 5-IASS over 12 weeks
End point description:	
<p>The co-primary efficacy endpoint was mean change from baseline in 5-item Anorexia Symptom Subscale (5-IASS) (points) over 12 weeks in the anamorelin HCl group versus placebo group. Mean change was computed as sum of the changes from baseline over 12 weeks by the time of the last assessment (either week 12 or before in case of death), and then divided by the number of assessments (observed or imputed) from baseline up to the time of the last assessment.</p> <p>FAACT-A/CS (Functional Assessment Anorexia Cachexia Therapy) is a 12-item measure of patients' perceptions of anorexia/cachexia symptoms and concerns. From this questionnaire, the 5-item section referring to anorexia symptoms (i.e., "good appetite," "interest in food drops," "food tastes unpleasant," "get full quickly," and "difficulty eating rich/heavy foods") was used to assess 5-IASS. The range of possible scores is 0-20. Higher scores indicate lower levels of symptom burden.</p>	
End point type	Primary
End point timeframe:	
Mean change from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: Points				
least squares mean (standard error)	3.432 (± 0.360)	3.291 (± 0.342)		

Statistical analyses

Statistical analysis title	Co-primary analysis: 5-IASS
Statistical analysis description:	
<p>The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin</p>	

rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.

Comparison groups	100 mg Anamorelin HCl v Placebo
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7241
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.641
upper limit	0.923
Variability estimate	Standard error of the mean
Dispersion value	0.399

Secondary: Duration of treatment benefit (weeks) from baseline over 12 weeks in body weight (≥ 0 kg)

End point title	Duration of treatment benefit (weeks) from baseline over 12 weeks in body weight (≥ 0 kg)
End point description:	
The duration of treatment benefit (weeks) over 12 weeks was measured as the period, or the sum of the periods, over 12 weeks (or less in case of death), in which the patient observed a change from baseline in body weight of ≥ 0 kg.	
End point type	Secondary
End point timeframe:	
Duration of treatment benefit from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: Weeks				
least squares mean (standard error)	8.859 (\pm 0.525)	6.778 (\pm 0.496)		

Statistical analyses

Statistical analysis title	Duration of treatment benefit: body weight ≥ 0 kg
Statistical analysis description:	
The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.	

Comparison groups	100 mg Anamorelin HCl v Placebo
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.946
upper limit	3.216
Variability estimate	Standard error of the mean
Dispersion value	0.579

Secondary: Duration of treatment benefit (weeks) from baseline over 12 weeks in body weight (≥ 1.5 kg)

End point title	Duration of treatment benefit (weeks) from baseline over 12 weeks in body weight (≥ 1.5 kg)
End point description:	
The duration of treatment benefit (weeks) over 12 weeks was measured as the period, or the sum of the periods, over 12 weeks (or less in case of death), in which the patient observed a change from baseline in body weight of ≥ 1.5 kg.	
End point type	Secondary
End point timeframe:	
Duration of treatment benefit from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: Weeks				
least squares mean (standard error)	5.490 (\pm 0.431)	3.087 (\pm 0.409)		

Statistical analyses

Statistical analysis title	Duration of treatment benefit: body weight ≥ 1.5 kg
Statistical analysis description:	
The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.	
Comparison groups	100 mg Anamorelin HCl v Placebo

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.471
upper limit	3.337
Variability estimate	Standard error of the mean
Dispersion value	0.476

Secondary: Duration of treatment benefit (weeks) from baseline over 12 weeks in 5-IASS (≥0 points)

End point title	Duration of treatment benefit (weeks) from baseline over 12 weeks in 5-IASS (≥0 points)
End point description:	
The duration of treatment benefit (weeks) over 12 weeks was measured as the period, or the sum of the periods, over 12 weeks (or less in case of death), in which the patient observed a change from baseline in 5-IASS of ≥0 points.	
End point type	Secondary
End point timeframe:	
Duration of treatment benefit from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: Weeks				
least squares mean (standard error)	9.470 (± 0.392)	8.842 (± 0.370)		

Statistical analyses

Statistical analysis title	Duration of treatment benefit: 5-IASS ≥0 points
Statistical analysis description:	
The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.	
Comparison groups	Placebo v 100 mg Anamorelin HCl

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1443
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.629
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.215
upper limit	1.472
Variability estimate	Standard error of the mean
Dispersion value	0.431

Secondary: Duration of treatment benefit (weeks) from baseline over 12 weeks in 5-IASS (≥3 points)

End point title	Duration of treatment benefit (weeks) from baseline over 12 weeks in 5-IASS (≥3 points)
End point description:	
The duration of treatment benefit (weeks) over 12 weeks was measured as the period, or the sum of the periods, over 12 weeks (or less in case of death), in which the patient observed a change from baseline in 5-IASS of ≥3 points.	
End point type	Secondary
End point timeframe:	
Duration of treatment benefit from baseline over 12 weeks.	

End point values	100 mg Anamorelin HCl	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	164		
Units: Weeks				
least squares mean (standard error)	5.143 (± 0.410)	4.992 (± 0.387)		

Statistical analyses

Statistical analysis title	Duration of treatment benefit: 5-IASS ≥3 points
Statistical analysis description:	
The Multiple Imputation process (N=100) was performed leading to least squares mean (LSM) and standard error (SE) estimates using the ANOVA model (including treatment group and the 3 stratification factors at randomization as categorical covariates). The estimates were pooled using Rubin rule, with corresponding p-value for difference between treatment groups. The 95% confidence interval (CI) was calculated for each treatment group and for the pooled difference between the groups.	
Comparison groups	100 mg Anamorelin HCl v Placebo

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7376
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.734
upper limit	1.036
Variability estimate	Standard error of the mean
Dispersion value	0.452

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious adverse events (SAEs) were collected from the time of Informed Consent signature through Day 183 (+3) days post study drug administration on Day 1.

Adverse event reporting additional description:

SAE section reports treatment-emergent SAEs.

Non-serious AEs were not summarized. Non-serious AE section reports all treatment-emergent AEs (non-serious TEAEs and treatment-emergent SAEs).

AEs were analyzed using the Safety Set, which included all patients who received any study drug and was analyzed as per actual treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	100 mg Anamorelin HCl
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Reporting group description:

Anamorelin HCl 100 mg film-coated tablets taken orally once daily while fasting for a total of 24 weeks.

Reporting group title	Placebo
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Reporting group description:

Placebo matching film-coated tablets taken orally once daily while fasting for a total of 24 weeks.

Serious adverse events	100 mg Anamorelin HCl	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 154 (28.57%)	46 / 164 (28.05%)	
number of deaths (all causes)	20	25	
number of deaths resulting from adverse events	20	25	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	18 / 154 (11.69%)	19 / 164 (11.59%)	
occurrences causally related to treatment / all	0 / 18	0 / 19	
deaths causally related to treatment / all	0 / 13	0 / 18	
Malignant neoplasm progression			
subjects affected / exposed	2 / 154 (1.30%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cancer pain			

subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Social circumstances			
Disability			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 154 (0.65%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 154 (0.65%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary infarction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 154 (0.65%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	2 / 154 (1.30%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 154 (0.65%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 154 (2.60%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 154 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Toxic epidermal necrolysis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	3 / 154 (1.95%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia			
subjects affected / exposed	3 / 154 (1.95%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			

subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
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 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 154 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	100 mg Anamorelin HCl	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 154 (78.57%)	136 / 164 (82.93%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	27 / 154 (17.53%)	37 / 164 (22.56%)	
occurrences (all)	28	39	
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 154 (3.25%)	4 / 164 (2.44%)	
occurrences (all)	6	4	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 154 (4.55%)	13 / 164 (7.93%)	
occurrences (all)	7	15	
Atrial fibrillation			
subjects affected / exposed	6 / 154 (3.90%)	6 / 164 (3.66%)	
occurrences (all)	7	7	
Sinus bradycardia			
subjects affected / exposed	3 / 154 (1.95%)	4 / 164 (2.44%)	
occurrences (all)	3	4	
Ventricular extrasystoles			
subjects affected / exposed	3 / 154 (1.95%)	4 / 164 (2.44%)	
occurrences (all)	3	5	
Atrioventricular block			
subjects affected / exposed	2 / 154 (1.30%)	4 / 164 (2.44%)	
occurrences (all)	2	5	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	12 / 154 (7.79%) 12	5 / 164 (3.05%) 5	
Headache subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 9	5 / 164 (3.05%) 6	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	19 / 154 (12.34%) 24	22 / 164 (13.41%) 26	
Chest pain subjects affected / exposed occurrences (all)	13 / 154 (8.44%) 14	10 / 164 (6.10%) 12	
Fatigue subjects affected / exposed occurrences (all)	7 / 154 (4.55%) 7	2 / 164 (1.22%) 2	
Oedema peripheral subjects affected / exposed occurrences (all)	7 / 154 (4.55%) 9	5 / 164 (3.05%) 8	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	30 / 154 (19.48%) 39	39 / 164 (23.78%) 56	
Neutropenia subjects affected / exposed occurrences (all)	10 / 154 (6.49%) 10	7 / 164 (4.27%) 14	
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 154 (5.19%) 11	4 / 164 (2.44%) 7	
Leukopenia subjects affected / exposed occurrences (all)	6 / 154 (3.90%) 6	4 / 164 (2.44%) 6	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	18 / 154 (11.69%) 28	12 / 164 (7.32%) 16	

Diarrhoea subjects affected / exposed occurrences (all)	10 / 154 (6.49%) 10	6 / 164 (3.66%) 7	
Vomiting subjects affected / exposed occurrences (all)	6 / 154 (3.90%) 8	6 / 164 (3.66%) 9	
Abdominal pain subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 6	4 / 164 (2.44%) 4	
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 5	2 / 164 (1.22%) 2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	14 / 154 (9.09%) 16	10 / 164 (6.10%) 12	
Cough subjects affected / exposed occurrences (all)	6 / 154 (3.90%) 7	8 / 164 (4.88%) 8	
Haemoptysis subjects affected / exposed occurrences (all)	2 / 154 (1.30%) 3	6 / 164 (3.66%) 6	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 154 (0.00%) 0	5 / 164 (3.05%) 5	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 10	2 / 164 (1.22%) 2	
Rash subjects affected / exposed occurrences (all)	4 / 154 (2.60%) 4	4 / 164 (2.44%) 5	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 154 (2.60%) 6	1 / 164 (0.61%) 1	

Back pain subjects affected / exposed occurrences (all)	4 / 154 (2.60%) 4	1 / 164 (0.61%) 1	
Infections and infestations			
Corona virus infection subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 5	5 / 164 (3.05%) 6	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 6	1 / 164 (0.61%) 1	
Pneumonia subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 5	4 / 164 (2.44%) 7	
Metabolism and nutrition disorders			
Hyponatraemia subjects affected / exposed occurrences (all)	6 / 154 (3.90%) 8	4 / 164 (2.44%) 5	
Decreased appetite subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 7	6 / 164 (3.66%) 6	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 5	1 / 164 (0.61%) 1	
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 154 (2.60%) 4	0 / 164 (0.00%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 154 (0.65%) 1	7 / 164 (4.27%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2018	Protocol v2.0 (Amendment 1): <ul style="list-style-type: none">• To provide details on the sensitivity and supportive analyses of the primary efficacy endpoint.• To clarify the computation of some QoL scores.• The endpoint "Change in FAACT total score from baseline to Week 9" was changed from an exploratory endpoint to a secondary endpoint.
04 February 2019	Protocol v3.0 (Amendment 2): <ul style="list-style-type: none">• Methylphenidate was removed because this drug may induce reduction of appetite; therefore, it was not consistent with Exclusion Criterion #5.• The term "medical" was removed because the Sponsor did not want to differentiate between medical and recreational marijuana. Marijuana had to be avoided independently of the intended use, i.e., medical or recreational.• Blinding procedure was clarified according to a specific request by the German Ministry of Health about Clinical Study Protocol ANAM-17-21.• Duration of contraception period was specified for completeness of information.• Vital signs measurements were reported consistently throughout the entire protocol where applicable.• Pregnancy reporting and related follow-up was extended to the female partner of male patients in the study for clarification and accurate follow-up.
22 March 2021	Protocol v4.0 (Amendment 3): <ul style="list-style-type: none">• Section 1.5 of the study protocol provides a rationale for the amendment: "Further to FDA advice obtained on the primary endpoints analysis, the Sponsor re-defined the primary efficacy endpoints to duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS). Based on this new approach a re-definition of the secondary and exploratory endpoints was also included. In order to measure duration of treatment benefit, a definition of a threshold of the relevant changes in body weight and anorexia (5-IASS) was needed. To determine clinically meaningful thresholds for body weight, similarly to what was currently planned for anorexia, the Sponsor was to use an anchor-based method using PGIS and PGIC as anchors."• Assessment of primary and secondary endpoints was shifted from Week 9 to Week 12.• An estimand approach based on ICH E9(R1) was introduced to handle data in case of study drug discontinuation and death. The section on statistics was entirely rewritten to account for the changed primary, secondary, and exploratory endpoints. This included expanded considerations on sample size, missing data, and multiplicity, formulation of new hypotheses for primary, supportive, and secondary efficacy analyses, specification of analysis models for exploratory efficacy endpoints, specification of process order, i.e., first threshold determination then unblinding, and determination of the clinically meaningful responder threshold in weight change in a new section.• Specified the visit considered as end of study regarding overall survival.• Specified use of corticosteroids and prohibited medication as beta-blockers, and olanzapine and mirtazapine during study.• Added a more detailed description of assessment instruments PGIS and PGIC considering added questionnaires on weight perception.• Clarified role of Investigator for CT procedures.

03 September 2021	<p>Protocol v4.A (Amendment 4.A):</p> <ul style="list-style-type: none"> • Further to FDA advice obtained on the primary endpoints analysis, the Sponsor re-defined the primary efficacy endpoints to duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS). Based on this new approach, a re-definition of the secondary and exploratory endpoints was also included. • Methods were added to determine clinically meaningful thresholds for body weight increase and anorexia symptoms improvement through patient interviews conducted within 14 days after Week 12 (Visit 6). Up to 50 interviews were planned to be conducted with patients only in selected countries. • The SF-12 questionnaire was added, which was to be used to collect QoL assessments. This was administered to patients at Week 1 (Visit 2), Week 6 (Visit 4), and Week 12 (Visit 6). The questionnaire was to be administered to patients only in selected countries, and was to be evaluated outside the study following a dedicated analysis plan.
13 July 2022	<p>Protocol v5.0 (Amendment 4) and v5.A (Amendment 5.A):</p> <ul style="list-style-type: none"> • During the course of the study, an error was discovered in the algorithm used to determine the statistical power for the evaluation of the duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS) co-primary endpoints. Corrected calculations revealed that each trial, with the current planned sample size of 316 patients, would be underpowered for the 5-IASS endpoint. Based on corrected simulations and calculations, obtaining an acceptable power would require at least doubling the sample size. At the current stage of the studies, such a huge change in sample size would be of great impact for cachectic cancer patients who are currently looking at anamorelin as the only promising investigational agent in development for treating the 2 important unmet needs of malignancy associated weight loss and anorexia and hoping in its prompt approval. The Sponsor endorses the importance of having 2 adequate and well controlled trials, each achieving statistical significance. To achieve proper power for the analysis of the 5-IASS co-primary endpoint, the Sponsor decided to perform the analysis by adopting the same methodological approach and same variables, i.e., 2 co-primary endpoints, still keeping body weight and 5-IASS as efficacy variables; however, measuring the mean change from baseline in replacement of the duration of treatment benefit, as defined based on scientific and clinical experts' feedback and confirmed as a feasible endpoint by sample size calculations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported