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	2018-002926-22
Trial protocol	HU BG IT RO
Global end of trial date	11 February 2023

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-17-20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03743051
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via Pian Scairolo 9, 6912 Pazzallo-Lugano, Switzerland,
Public contact	Florin Muraru, Helsinn Healthcare SA, +41 91985 21 21, Florin.Muraru@helsinn.com
Scientific contact	Florin Muraru, Helsinn Healthcare SA, +41 91985 21 21, Florin.Muraru@helsinn.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	Final
Date of interim/final analysis	15 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2023
Global end of trial reached?	Yes
Global end of trial date	11 February 2023
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:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 March 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	Romania: 34
Country: Number of subjects enrolled	Bulgaria: 93
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	Serbia: 51
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	318
EEA total number of subjects	188

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)	156
From 65 to 84 years	159
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at a total of 46 study sites in Bulgaria (4 sites), Hungary (5 sites), Italy (5 sites), Romania (6 sites), Russia (10 sites), Serbia (5 sites), and USA (11 sites). First Patient Enrollment (date of randomization) was on 05MAR2019.

Pre-assignment

Screening details:

This study included adults ≥18 years of age with advanced NSCLC, a body mass index (BMI) <20kg/m^2, involuntary weight loss of >2% within 6 months prior to Screening, and anorexia. A total of 374 patients were screened; 56 patients were screen failures; 318 patients were randomized to anamorelin and placebo (159 patients in each group).

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

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	159	159
Completed	78	76
Not completed	81	83
Adverse event, serious fatal	27	26
Consent withdrawn by subject	32	19
Physician decision	10	15
Disease/Clinical progression	3	6
Adverse event, non-fatal	5	9
Lost to follow-up	4	8

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	159	159	318
Age categorical Units: Subjects			
Adults (18-64 years)	74	82	156
From 65-84 years	84	75	159
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	64.5	62.2	
standard deviation	± 9.20	± 10.55	-
Gender categorical Units: Subjects			
Female	43	47	90
Male	116	112	228
Race Units: Subjects			
Asian	1	3	4
Black or African American	3	3	6
White	154	152	306
Other	1	1	2
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	10	11	21
Missing	147	148	295
Chemotherapy line Units: Subjects			
First Line	112	113	225
Second Line	29	31	60
Third Line	18	15	33
Anti-cancer treatment Units: Subjects			
Immunotherapy	47	48	95
Non-immunotherapy	112	111	223
5-IASS score Units: Subjects			
≤10	108	109	217

>10	51	50	101
NSCLC stage at study entry Units: Subjects			
Stage IIIA	1	3	4
Stage IIIB	25	30	55
Stage IV	128	121	249
Missing	5	5	10
Height Units: cm			
arithmetic mean	170.47	172.09	
standard deviation	± 10.438	± 9.910	-
Weight Units: kg			
arithmetic mean	53.71	54.49	
standard deviation	± 8.049	± 8.627	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	18.35	18.24	
standard deviation	± 1.386	± 1.578	-
Body weight loss within 6 months prior to screening Units: percent			
arithmetic mean	12.04	11.05	
standard deviation	± 7.160	± 6.489	-

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)	156		
From 65-84 years	159		
85 years and over	3		
Age continuous Units: years			
arithmetic mean	63.4		
standard deviation	± 9.95		
Gender categorical Units: Subjects			
Female	90		
Male	228		
Race Units: Subjects			
Asian	4		
Black or African American	6		

White	306		
Other	2		
Ethnicity Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	21		
Missing	295		
Chemotherapy line Units: Subjects			
First Line	225		
Second Line	60		
Third Line	33		
Anti-cancer treatment Units: Subjects			
Immunotherapy	95		
Non-immunotherapy	223		
5-IASS score Units: Subjects			
≤10	217		
>10	101		
NSCLC stage at study entry Units: Subjects			
Stage IIIA	4		
Stage IIIB	55		
Stage IV	249		
Missing	10		
Height Units: cm			
arithmetic mean	171.28		
standard deviation	± 10.194		
Weight Units: kg			
arithmetic mean	54.10		
standard deviation	± 8.339		
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	18.30		
standard deviation	± 1.484		
Body weight loss within 6 months prior to screening Units: percent			
arithmetic mean	11.54		
standard deviation	± 6.840		

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	159	159		
Units: kg				
least squares mean (standard error)	1.938 (± 0.285)	0.594 (± 0.285)		

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	1.345
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.718
upper limit	1.971
Variability estimate	Standard error of the mean
Dispersion value	0.32

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:

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.

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.

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	159	159		
Units: Points				
least squares mean (standard error)	3.816 (± 0.383)	3.194 (± 0.385)		

Statistical analyses

Statistical analysis title	Co-primary analysis: 5-IASS

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	= 0.1514
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.622
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.228
upper limit	1.472
Variability estimate	Standard error of the mean
Dispersion value	0.434

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	159	159		
Units: Weeks				
least squares mean (standard error)	9.871 (± 0.476)	7.462 (± 0.475)		

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	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.367
upper limit	3.453
Variability estimate	Standard error of the mean
Dispersion value	0.532

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	159	159		
Units: Weeks				
least squares mean (standard error)	4.967 (± 0.434)	3.631 (± 0.429)		

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	= 0.0057
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.336
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.388
upper limit	2.284
Variability estimate	Standard error of the mean
Dispersion value	0.484

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	159	159		
Units: Weeks				
least squares mean (standard error)	10.523 (± 0.362)	9.496 (± 0.359)		

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	100 mg Anamorelin HCl v Placebo

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0108
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.238
upper limit	1.816
Variability estimate	Standard error of the mean
Dispersion value	0.403

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	159	159		
Units: Weeks				
least squares mean (standard error)	6.185 (± 0.423)	5.650 (± 0.426)		

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	= 0.2605
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.535
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.397
upper limit	1.466
Variability estimate	Standard error of the mean
Dispersion value	0.475

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

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.

Serious adverse events	100 mg Anamorelin HCl	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 159 (27.04%)	39 / 159 (24.53%)	
number of deaths (all causes)	23	20	
number of deaths resulting from adverse events	23	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	15 / 159 (9.43%)	16 / 159 (10.06%)	
occurrences causally related to treatment / all	0 / 15	0 / 16	
deaths causally related to treatment / all	0 / 15	0 / 15	
Metastases to central nervous system			
subjects affected / exposed	3 / 159 (1.89%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to liver			

subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 159 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 159 (1.26%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 159 (1.26%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 159 (1.26%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 159 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 159 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 159 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical peritonitis			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 159 (1.26%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 159 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 159 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 159 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
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			
Leukopenia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Autoimmune colitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal ulcer perforation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 159 (1.26%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 159 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Sepsis			
subjects affected / exposed	1 / 159 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Empyema			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
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	102 / 159 (64.15%)	101 / 159 (63.52%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	16 / 159 (10.06%)	17 / 159 (10.69%)	
occurrences (all)	17	18	

Investigations			
Platelet count decreased			
subjects affected / exposed	4 / 159 (2.52%)	4 / 159 (2.52%)	
occurrences (all)	4	4	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 159 (1.26%)	4 / 159 (2.52%)	
occurrences (all)	2	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 159 (1.89%)	4 / 159 (2.52%)	
occurrences (all)	3	4	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 159 (2.52%)	3 / 159 (1.89%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 159 (5.03%)	5 / 159 (3.14%)	
occurrences (all)	9	6	
Fatigue			
subjects affected / exposed	6 / 159 (3.77%)	11 / 159 (6.92%)	
occurrences (all)	6	13	
Oedema peripheral			
subjects affected / exposed	6 / 159 (3.77%)	7 / 159 (4.40%)	
occurrences (all)	9	12	
Chest pain			
subjects affected / exposed	2 / 159 (1.26%)	7 / 159 (4.40%)	
occurrences (all)	2	7	
Pyrexia			
subjects affected / exposed	2 / 159 (1.26%)	4 / 159 (2.52%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 159 (8.81%)	19 / 159 (11.95%)	
occurrences (all)	17	25	
Leukopenia			

subjects affected / exposed	5 / 159 (3.14%)	1 / 159 (0.63%)	
occurrences (all)	5	1	
Neutropenia			
subjects affected / exposed	2 / 159 (1.26%)	4 / 159 (2.52%)	
occurrences (all)	5	5	
Thrombocytopenia			
subjects affected / exposed	2 / 159 (1.26%)	5 / 159 (3.14%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 159 (5.66%)	7 / 159 (4.40%)	
occurrences (all)	9	7	
Diarrhoea			
subjects affected / exposed	4 / 159 (2.52%)	5 / 159 (3.14%)	
occurrences (all)	5	5	
Vomiting			
subjects affected / exposed	4 / 159 (2.52%)	7 / 159 (4.40%)	
occurrences (all)	5	10	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 159 (3.77%)	10 / 159 (6.29%)	
occurrences (all)	6	11	
Cough			
subjects affected / exposed	0 / 159 (0.00%)	4 / 159 (2.52%)	
occurrences (all)	0	4	
Pleural effusion			
subjects affected / exposed	0 / 159 (0.00%)	4 / 159 (2.52%)	
occurrences (all)	0	4	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 159 (0.00%)	4 / 159 (2.52%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	6 / 159 (3.77%)	2 / 159 (1.26%)	
occurrences (all)	7	2	

Decreased appetite subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 6	4 / 159 (2.52%) 4	
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 5	1 / 159 (0.63%) 1	

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): ● 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): ● 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 identical 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): ● 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	Protocol v4.A (Amendment 4.A): ● 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	Protocol v5.0 (Amendment 4) and v5.A (Amendment 5.A): ● 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