Clinical trial results:
A multicenter, open-label post authorization safety study to evaluate the effect of LysaKare infusion on serum potassium levels in GEP-NET subjects eligible for Lutathera treatment

Summary

EudraCT number	2019-004073-76
Trial protocol	NL IT PL
Global end of trial date	18 November 2023

Results information

Result version number	v1
This version publication date	25 November 2024
First version publication date	25 November 2024

Trial information

Trial identification

Sponsor protocol code	CAAA001A12401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04524442
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH 4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.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	18 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of LysaKare administration on serum potassium concentrations in GEP-NET subjects eligible for Lutathera treatment

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2021
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	United Kingdom: 9
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 21
Worldwide total number of subjects	42
EEA total number of subjects	33

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)	29
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 42 participants were enrolled in 7 centers in 4 countries.

Pre-assignment

Screening details:

The study schedule for each participant consisted of a screening period followed by an infusion day with an optional overnight in-clinic stay, and a follow-up call.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GEP-NET

Arm description:

One dose of arginine/lysine solution administered intravenously over a 4-hour period

Arm type	Experimental
Investigational medicinal product name	LysaKare
Investigational medicinal product code	
Other name	2.5% Lys-Arg solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study treatment was a 1000 mL solution of LysaKare (2.5% Lys-Arg solution for infusion), administered intravenously over a 4-hour period (infusion rate: 250 mL/h). Only 1 infusion was administered in the treatment phase of the study.

Number of subjects in period 1	GEP-NET
Started	42
Treated	41
Not treated	1 [1]
Post-trtment f/u ph-48 hrs post-infusion	40 [2]
Completed	41
Not completed	1
Subject Decision	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 subject was not treated and so was not included in the number of patients who completed the study
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 subject was not treated and so was not included in the number of patients who completed the study

Baseline characteristics

Reporting groups	
Reporting group title	GEP-NET
Reporting group description:	
One dose of arginine/lysine solution administered intravenously over a 4-hour period	

Reporting group values	GEP-NET	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Adults (18-64 years)	29	29	
From 65-84 years	13	13	
Age Continuous			
Mean age reported is from 41 subjects who received study treatment, and not from 42 subjects who were enrolled in the study.			
Units: years			
arithmetic mean	57.7		
standard deviation	± 9.46	-	
Sex: Female, Male Units: Participants			
Female	20	20	
Male	22	22	
Race/Ethnicity, Customized Units: Subjects			
White	39	39	
Black or African American	3	3	

End points

End points reporting groups

Reporting group title	GEP-NET

Reporting group description:

One dose of arginine/lysine solution administered intravenously over a 4-hour period

Primary: Mean change from baseline in serum potassium levels over 24 hours

End point title	Mean change from baseline in serum potassium levels over 24 hours[1]

End point description:

Serum potassium levels at each collection time point will be measured at local laboratories of study sites using validated methods. The potassium concentration results will be summarized descriptively and will include mean change, maximum change, time to the maximum change, and the overall dynamics of the potassium concentration curve during and after the arginine/lysine infusion.

End point type	Primary

End point timeframe:

Day 0/Infusion Day (Hour 0, Hour 2, Hour 4, Hour 6, Hour 8, Hour 12, Hour 24)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	25[2]			
Units: mmol/L				
arithmetic mean (standard deviation)				
Pre-dose (hour 0)	4.3 (± 0.397)			
Change from Baseline (BL) to Hour 2	0.25 (± 0.452)			
Change from Baseline (BL) to Hour 4	0.60 (± 0.666)			
Change from Baseline (BL) to Hour 6	0.49 (± 0.602)			
Change from Baseline (BL) to Hour 8	0.38 (± 0.487)			
Change from Baseline (BL) to Hour 12	0.24 (± 0.557)			
Change from Baseline (BL) to Hour 24	0.07 (± 0.396)			

Notes:

[2] - Evaluable Set had 25 subjects who had pre-dose & at least1 post-dose serum potassium measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with treatment Adverse Events (AEs) & Serious Adverse Events (SAEs)

End point title	Percentage of Participants with treatment Adverse Events (AEs) & Serious Adverse Events (SAEs)

End point description:

Safety measured by the percentage of participants with treatment emergent adverse events (starting from the signing of the ICF until the end of the follow-up call (48 hours after infusion).

End point type	Secondary

End point timeframe:

Day 0/Infusion Day up to 48 hours post infusion

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[3]			
Units: Participants				
Adverse Event (AEs)	11			
Treatment-related AEs	6			
Serious Adverse Events (SAEs)	0			
Fatal SAEs	0			
AEs leading to discontinuation	0			
AEs leading to Interrruption	0			
AEs requiring additional therapy	5			
Treatment related AEs req. additional therapy	3			

Notes:

[3] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Notable Changes in vital signs

End point title	Number of Participants with Notable Changes in vital signs

End point description:

Safety measured by the notable post-baseline changes in vital signs: (systolic blood pressure, diastolic blood pressure, pulse rate & weight) compared to baseline.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 2, 4, 6, 8, 12 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[4]			
Units: Participants				
SBP(mmHg): ≥180 with increase from baseline of ≥20	0			
SBP(mmHg): ≤ 90 with decrease from baseline of ≥20	0			
DBP(mmHg): ≥105 with increase from baseline of ≥15	0			
DBP(mmHg): ≤ 50 with decrease from baseline of ≥15	0			
Pulse rate (bpm): ≥100 & >25% increase from BL	0			

Pulse rate (bpm): ≤ 50 & > 25% decrease from BL	0			
Weight (kg): increase ≥10% from Baseline	0			
Weight (kg): decrease > 10% from Baseline	0			

Notes:

[4] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Notable Changes in electrocardiogram (ECG)

End point title	Number of Participants with Notable Changes in electrocardiogram (ECG)

End point description:

Safety measured by the notable post-baseline changes in ECG values compared to baseline PR, QRS, QT, QTcF, and RR intervals were obtained from 12-lead ECGs for each subject during the study

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 4, 8 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[5]			
Units: Participants				
QTcF (ms): Increase >30 to ≤ 60 ms	7			
QTcF (ms): Increase >60 ms	0			
QTcF (ms): New >450 to ≤ 480 ms (n = 39)	7			
QTcF (ms): New >480 to ≤ 500 ms	0			
QTcF (ms); New >500 ms	0			
QT (ms): Increase >30 to ≤ 60 ms	9			
QT (ms): Increase >60 ms	2			
QT (ms): New >450 to ≤ 480 ms (n = 39)	6			
QT (ms): New >480 to ≤ 500 ms	1			
QT (ms): New >500 ms	0			
PR (ms): Increase >25% and PR >200 ms (n = 29)	1			
PR (ms): New PR >200 ms (n = 29)	6			
QRS (ms): Increase >25% and QRS >120 ms	2			
QRS (ms): New QRS >120 ms	2			
HR (bpm): Increase >25% and HR >100 bpm	0			
HR (bpm): Decrease >25% and HR <50 bpm	0			

Notes:

[5] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Notable Changes in Hematology parameters

End point title	Number of Participants with Notable Changes in Hematology parameters

End point description:

Safety measured by the notable post-baseline changes in Hematology parameters compared to baseline as represented by Shift tables based on common toxicity criteria (CTC) grades. Each participant was counted only for the worst grade observed post-baseline. Notable change is the shift to higher grades from baseline.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[6]			
Units: Participants	0			

Notes:

[6] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Notable Changes in Chemistry parameters

End point title	Number of Participants with Notable Changes in Chemistry parameters

End point description:

Safety measured by the notable post-baseline changes in Chemistry parameters compared to baseline. Each participant was counted only for the worst grade observed post-baseline. Notable change is the shift to higher grades from baseline.
Key shifts were in the following parameters: creatinine and lactate dehydrogenase and creatinine clearance.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[7]			
Units: Participants				
For creatinine (increase)	4			
Lactate dehydrogenase (increase)	3			
For creatinine clearance (decrease)	4			

Notes:

[7] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Notable Changes in Electrolyte parameters

End point title	Number of Participants with Notable Changes in Electrolyte parameters

End point description:

Safety measured by the notable post-baseline changes in Electrolyte parameters compared to baseline. Each participant was counted only for the worst grade observed post-baseline. Notable change is the shift to higher grades from baseline.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 2, 4, 6, 8, 12 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[8]			
Units: Participants				
For Potassium (increase)	7			
For sodium (decrease)	12			

Notes:

[8] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in blood gas parameter, pH, over 24 hours

End point title	Mean change from baseline in blood gas parameter, pH, over 24 hours

End point description:

Safety measured by the mean changes in blood gas compared to baseline. Blood gas parameter: pH.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 2, 4, 6, 8, 12 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[9]			
Units: unitless				
arithmetic mean (standard deviation)				
Day 0/Infusion Day (Pre-dose) (hour 0) (n = 36)	7.35 (± 0.046)			
Change from Baseline (BL) to Hour 2 (n = 36)	-0.03 (± 0.046)			
Change from Baseline (BL) to Hour 4 (n = 36)	-0.06 (± 0.055)			
Change from Baseline (BL) to Hour 6 (n = 36)	-0.05 (± 0.051)			
Change from Baseline (BL) to Hour 8 (n = 35)	-0.05 (± 0.056)			
Change from Baseline (BL) to Hour 12 (n = 33)	-0.03 (± 0.054)			
Change from Baseline (BL) to Hour 24 (n = 35)	-0.04 (± 0.051)			

Notes:

[9] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in blood gas parameter, Lactic Acid, over 24 hours

End point title	Mean change from baseline in blood gas parameter, Lactic Acid, over 24 hours

End point description:

Safety measured by the mean changes in blood gas compared to baseline. Blood gas parameter: Lactic Acid

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 2, 4, 6, 8, 12 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[10]			
Units: mmol/L				
arithmetic mean (standard deviation)				
Day 0/Infusion Day (Pre-dose) (hour 0) (n = 35)	1.40 (± 0.604)			
Change from Baseline (BL) to Hour 2 (n = 35)	-0.07 (± 0.671)			
Change from Baseline (BL) to Hour 4 (n = 35)	-0.23 (± 0.523)			

Change from Baseline (BL) to Hour 6 (n = 35)	-0.26 (± 0.546)			
Change from Baseline (BL) to Hour 8 (n = 33)	-0.19 (± 0.465)			
Change from Baseline (BL) to Hour 12 (n = 33)	-0.21 (± 0.657)			
Change from Baseline (BL) to Hour 24 (n = 34)	-0.16 (± 0.650)			

Notes:

[10] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in blood gas parameter, Partial Pressure Carbon Dioxide, over 24 hours

End point title	Mean change from baseline in blood gas parameter, Partial Pressure Carbon Dioxide, over 24 hours

End point description:

Safety measured by the mean changes in blood gas compared to baseline. Blood gas parameter: Partial Pressure Carbon Dioxide.

End point type	Secondary

End point timeframe:

Day 0/Infusion Day (0, 2, 4, 6, 8, 12 and 24 hours)

End point values	GEP-NET			
Subject group type	Reporting group			
Number of subjects analysed	41[11]			
Units: mmHg				
arithmetic mean (standard deviation)				
Day 0/Infusion Day (Pre-done) (hour 0) (n = 36)	50.53 (± 8.712)			
Change from Baseline (BL) to Hour 2 (n = 36)	-1.08 (± 6.670)			
Change from Baseline (BL) to Hour 4 (n = 36)	-2.44 (± 8.717)			
Change from Baseline (BL) to Hour 6 (n =36)	-4.90 (± 8.507)			
Change from Baseline (BL) to Hour 8 (n = 35)	-4.87 (± 8.399)			
Change from Baseline (BL) to Hour 12 (n = 33)	-5.71 (± 8.002)			
Change from Baseline (BL) to Hour 24 (n =35)	-2.54 (± 8.242)			

Notes:

[11] - One subject was not treated.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) were collected from the first dose of study treatment up to 48 hours after last dose of study medication.	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the conduct of the trial and safety follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	All Subjects
Reporting group description:	
All subjects enrolled in the study who received one dose of arginine/lysine solution administered intravenously over a 4-hour period	

Serious adverse events	All Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 41 (26.83%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Headache			

subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 1 / 41 (2.44%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Proctalgia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 41 (2.44%) 1 2 / 41 (4.88%) 2 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1		
Respiratory, thoracic and mediastinal disorders Respiratory acidosis subjects affected / exposed occurrences (all)	 1 / 41 (2.44%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2021	Exclusion criteria #1: For Poland only, added required hyperkalemia level > 5.5mmol/L per local protocol amendment
01 December 2022	Clarification on the sampling requirements for laboratory assessments as the Sponsor identified discrepancies in sampling used for electrolytes which were not performed as per protocol requested procedures; The target enrollment number was revised from "40" to "approximately 45" to ensure at least 25 subjects have valid data to fulfill the study primary objective

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported