Clinical trial results:
A randomized, placebo-controlled, double-blind, parallel-group, multicenter combined Phase 2a/2b study to assess the efficacy and safety of BAY 1817080 in patients with diabetic neuropathic pain

Summary

EudraCT number	2020-002066-14
Trial protocol	DE NO CZ FI SE HU SK DK PL
Global end of trial date	17 December 2021

Results information

Result version number	v1 (current)
This version publication date	24 December 2022
First version publication date	24 December 2022

Trial information

Trial identification

Sponsor protocol code	BAY1817080/20887

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04641273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	17 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This Phase 2 study had a dual objective: Part A (Phase 2a) aimed to reach proof of concept, i.e. show good efficacy and safety of Eliapixant in diabetic neuropathic pain (DNP) patients. Part B (Phase 2b) was planned to explore the dose response relationship and, thus, serve as a dose finding study. This study was terminated due to lack of efficacy after completion of Part A in line with the decision criteria pre-specified in the protocol.

Part A: to evaluate the efficacy of BAY1817080 on the treatment of pain associated with DNP as compared with placebo

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 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	Norway: 6
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Czechia: 43
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Hungary: 4
Worldwide total number of subjects	154
EEA total number of subjects	154

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)	80
From 65 to 84 years	72
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 42 centers in 10 countries with first subject first visit on 22-Jan-2021 and last subject last visit on 18-Oct-2021 for Part A. This study was terminated due to lack of efficacy after completion of Part A in line with the decision criteria pre-specified in the protocol.

Pre-assignment

Screening details:

Overall, 224 subjects were enrolled and 70 subjects failed screening. A total of 154 subjects were randomly assigned to treatment (77 in each treatment arm) and received at least 1 dose of study intervention.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Eliapixant 150 mg BID

Arm description:

Subjects were randomized to receive 150 mg oral doses of Eliapixant, administered twice daily over the course of 8 weeks

Arm type	Experimental
Investigational medicinal product name	Eliapixant
Investigational medicinal product code	BAY1817080
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg twice daily (BID), administered orally for 8 weeks. The tablets were administered approximately at the same time each day 12 hours apart.

Arm title	Placebo

Arm description:

Subjects were randomized to receive matching placebo, administered twice daily over the course of 8 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:

Matching placebo tablets administered BID orally for 8 weeks. The tablets were administered approximately at the same time each day 12 hours apart.

Number of subjects in period 1	Eliapixant 150 mg BID	Placebo
Started	77	77
Completed	67	68
Not completed	10	9
COVID-19 pandemic	2	-
Physician decision	2	-
Adverse event, non-fatal	4	2
Subject decision	1	5
Other	-	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Eliapixant 150 mg BID
Reporting group description:	
Subjects were randomized to receive 150 mg oral doses of Eliapixant, administered twice daily over the course of 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomized to receive matching placebo, administered twice daily over the course of 8 weeks	

Reporting group values	Eliapixant 150 mg BID	Placebo	Total
Number of subjects	77	77	154
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 65.2 ± 9.2	 62.7 ± 9.3	 -
Gender categorical Units: Subjects			
Female	28	26	54
Male	49	51	100
Baseline weekly mean 24-hour average pain intensity score using the 11-point numeric rating scale			
NRS is an one-item assessment of average neuropathic pain intensity which is presented as an 11-point Likert scale with 0 as "no pain" and 10 as "worst imaginable pain" Used per protocol set (PPS): Eliapixant 150 mg BID (N=71), Placebo (N=73)			
Units: Scores on a scale arithmetic mean standard deviation	 5.87 ± 1.21	 5.77 ± 1.05	 -
Baseline Neuropathic Pain Symptom Inventory (NPSI) score			
The NPSI was developed to evaluate different symptoms of neuropathic pain. It contained 12 items, of which five summary pain scores were calculated. The total score was summed over 100 by adding each of the five categories together. The 10 descriptive items used to derive the domain summary scores were each rated on an 11-point numeric rating scale. The remaining two items reported how consistently pain had been present and the number of pain episodes Used per protocol set (PPS): Eliapixant 150 mg BID (N=71), Placebo (N=73)			
Units: Scores on a scale arithmetic mean standard deviation	 35.61 ± 14.39	 36.78 ± 15.99	 -

End points

End points reporting groups

Reporting group title	Eliapixant 150 mg BID
Reporting group description:	
Subjects were randomized to receive 150 mg oral doses of Eliapixant, administered twice daily over the course of 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomized to receive matching placebo, administered twice daily over the course of 8 weeks	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who were randomized to a treatment group and had at least one non-missing post-baseline measurement	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who were randomized to a treatment group and had taken at least one unit of the study medication	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Included subjects had no validity findings affecting efficacy endpoints	

Primary: Change in weekly mean 24-hour average pain intensity score using the 11-point numeric rating scale (NRS) from baseline to the end of intervention (EOI)

End point title	Change in weekly mean 24-hour average pain intensity score using the 11-point numeric rating scale (NRS) from baseline to the end of intervention (EOI)
End point description:	
NRS was an one-item assessment of average neuropathic pain intensity which was presented as an 11-point Likert scale with 0 as “no pain” and 10 as “worst imaginable pain”	
End point type	Primary
End point timeframe:	
At baseline (week 0) and at EOI (week 8)	

End point values	Eliapixant 150 mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[1]	73[2]		
Units: Scores of the scale				
arithmetic mean (standard deviation)	-1.50 (± 1.94)	-2.18 (± 1.85)		

Notes:

[1] - PPS

[2] - PPS

Statistical analyses

Statistical analysis title	Bayesian Repeated measures ANCOVA

Statistical analysis description:

Posterior mean, 90% credible interval and posterior probabilities were calculated based on a Bayesian repeated measures ANCOVA adjusting for the treatment (Eliapixant 150mg BID or placebo), timepoint (weeks 4, 6 and 8) and treatment-timepoint interaction as factors having fixed effects and baseline score as a continuous covariate, with an unstructured covariance matrix

Comparison groups	Eliapixant 150 mg BID v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.063
upper limit	1.141

Notes:

[3] - Proof-of-Concept decision based on Bayesian criteria (based on posterior probability)

Secondary: Change in Neuropathic Pain Symptom Inventory (NPSI) score from baseline to the EOI

End point title	Change in Neuropathic Pain Symptom Inventory (NPSI) score from baseline to the EOI

End point description:

The Neuropathic Pain Symptom Inventory (NPSI) was a Patient-reported outcome (PRO) developed to evaluate different symptoms of neuropathic pain. The NPSI contained 12 items, of which five summary pain scores were calculated. The total score was summed over 100 by adding each of the five categories together. The 10 descriptive items used to derive the domain summary scores were each rated on an 11-point numeric rating scale (0= "no (symptom)" and 10= "worst (symptom) imaginable"); each item had a recall period of the past 24 hours. The remaining two items reported how consistently pain had been present and the number of pain episodes

End point type	Secondary

End point timeframe:

At baseline (week 0), weeks 2, 4 and at EOI (week 8)

End point values	Eliapixant 150 mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[4]	73[5]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-9.38 (± 18.90)	-11.87 (± 18.05)		

Notes:

[4] - PPS

[5] - PPS

Statistical analyses

Statistical analysis title	Repeated measures ANCOVA

Statistical analysis description:

Mean, 90% confidence interval and p-values are calculated based on a repeated measures ANCOVA

adjusting for the treatment
(Eliapixant 150mg BID or placebo), timepoint (weeks 2, 4, 8) and treatment-timepoint interaction as factors having fixed effects and baseline score as a continuous covariate, with an unstructured covariance matrix.

Comparison groups	Eliapixant 150 mg BID v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4648
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.498
upper limit	6.463
Variability estimate	Standard error of the mean
Dispersion value	2.7

Secondary: Patient Global Impression of Change (PGI-C) at the EOI

End point title	Patient Global Impression of Change (PGI-C) at the EOI

End point description:

The PGI-C was an one-item, self-reported instrument used to assess patients' impression of disease severity and change, with a 7-point scale response-option. Scores range from 1 ("very much better") to 7 ("very much worse")

PGI-C responder was defined as very much better or much better on the PGI-C scale at EOI

End point type	Secondary

End point timeframe:

At EOI (week 8)

End point values	Eliapixant 150 mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[6]	67[7]		
Units: Number of subjects				
VERY MUCH BETTER	4	8		
MUCH BETTER	11	17		
A LITTLE BETTER	21	21		
NO CHANGE	19	15		
A LITTLE WORSE	5	3		
MUCH WORSE	4	3		
VERY MUCH WORSE	1	0		

Notes:

[6] - PPS

[7] - PPS

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Odds ratio, 90% CI and p-value follow from a logistic regression adjusting for treatment as a fixed effects factor, based on multiple imputation (MI)-based approach for imputing missing PGIC responses at week 8 (MI performed using MCMC under MAR assumption).

Comparison groups	Eliapixant 150 mg BID v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.27
upper limit	0.96

Secondary: The proportion of subjects achieving a ≥30% and a ≥50% reduction in weekly mean 24-hour average pain intensity score using NRS

End point title	The proportion of subjects achieving a ≥30% and a ≥50% reduction in weekly mean 24-hour average pain intensity score using NRS

End point description:

Percentage number was based on number of subjects in the analysis set with non-missing weekly mean pain NRS at the timepoint.

End point type	Secondary

End point timeframe:

From baseline (Week 0) to EOI (Week 8)

End point values	Eliapixant 150 mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[8]	73[9]		
Units: Percentage of subjects				
number (not applicable)				
>=30% improvement in pain (n=50;58)	40.0	58.6		
>=50% improvement in pain (n=50;58)	28.0	36.2		

Notes:

[8] - PPS

[9] - PPS

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Odds ratio, 90% CI and p-value follow from a logistic regression adjusting for treatment as a fixed

effects factor, based on multiple imputation (MI)-based approach for imputing missing NRS responses at week 8 (MI performed using MCMC under MAR assumption).

Comparison groups	Eliapixant 150 mg BID v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.29
upper limit	0.95

Statistical analysis title	Logistic regression

Statistical analysis description:

Odds ratio, 90% CI and p-value follow from a logistic regression adjusting for treatment as a fixed effects factor, based on multiple imputation (MI)-based approach for imputing missing NRS responses at week 8 (MI performed using MCMC under MAR assumption).

Comparison groups	Eliapixant 150 mg BID v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.37
upper limit	1.3

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical study subject, that occurred after providing written informed consent, whether or not considered related to the study intervention

Treatment-emergent adverse event (TEAE) was defined as any adverse event arising or worsening after the start of study intervention administration until 14 days after the last intake of study intervention

End point type	Secondary

End point timeframe:

Start of intervention to 14 days after stop of treatment

End point values	Eliapixant 150 mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77[10]	77[11]		
Units: Subjects				
Any TEAE	39	37		
Any study drug-related TEAE	20	11		
Any serious TEAE	3	1		
Any TEAE with permanent stop of study drug	6	3		

Notes:

[10] - SAF

[11] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study intervention administration until 14 days after the last study medication intake. Adverse event reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Eliapixant 150 mg BID

Reporting group description:

Subjects were randomized to receive 150 mg oral doses of Eliapixant, administered twice daily over the course of 8 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive matching placebo, administered twice daily over the course of 8 weeks.

Serious adverse events	Eliapixant 150 mg BID	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
IIIrd nerve disorder			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (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			
Appendicitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Eliapixant 150 mg BID	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 77 (49.35%)	37 / 77 (48.05%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	
occurrences (all)	1	2	
Malaise			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	
Hiccups			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Investigations			

Amylase increased			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	
Blood bilirubin increased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Blood fibrinogen increased			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	
occurrences (all)	4	1	
Blood glucose increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Heart rate increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Blood glucose fluctuation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Cystatin C increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Muscle rupture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 77 (2.60%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Thermal burn			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Inflammation of wound			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	
occurrences (all)	4	2	
Anosmia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Diabetic neuropathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Dizziness			

subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	8 / 77 (10.39%)	0 / 77 (0.00%)	
occurrences (all)	8	0	
Headache			
subjects affected / exposed	5 / 77 (6.49%)	8 / 77 (10.39%)	
occurrences (all)	11	8	
Hypoaesthesia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Hypogeusia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Parosmia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Hyperfibrinogenaemia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	
occurrences (all)	4	1	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Eye irritation			

subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	2	
Vision blurred			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	1 / 77 (1.30%)	3 / 77 (3.90%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
occurrences (all)	4	1	
Dry mouth			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 77 (2.60%)	1 / 77 (1.30%)	
occurrences (all)	2	1	

Oesophageal pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Rash macular			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	
occurrences (all)	3	6	
Back pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			

subjects affected / exposed	2 / 77 (2.60%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Muscular weakness			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Limb discomfort			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Sacroiliac joint dysfunction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	
occurrences (all)	1	1	
Fungal skin infection			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Osteomyelitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	

Periodontitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Skin bacterial infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Diabetic foot infection			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
Oral fungal infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Herpes dermatitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	3 / 77 (3.90%)	1 / 77 (1.30%)	
occurrences (all)	3	1	
Weight fluctuation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	0 / 77 (0.00%)	2 / 77 (2.60%)	
occurrences (all)	0	2	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2021	Protocol amendment 1 (global), dated 22 JUN 2021: • Visit schedule was adapted to allow for testing of liver parameters every 2 weeks during the treatment period as precautionary measure • Adaptation of exclusion criterion 6 with addition of an example for extremely low body weight to support the investigator decisions on subject selection
22 October 2021	Protocol amendment 2 (global), dated 22 OCT 2021, key modifications for Part A: • Coronavirus disease 2019 (COVID-19) tests to be performed at every onsite visit • Update of visit numbering to facilitate programming by the use of an integer number for all visits • The potential risk of phototoxicity was removed and a liver safety monitoring board was implemented according to newly available data • The endpoint definitions were updated as EOI visit • Inclusion criteria were separated for Part A and Part B • Exclusion criteria were adapted to clarify that the normal ranges provided by the central laboratory should be followed • Clarification was added that no special lifestyle considerations have to be taken based on newly available data • The use of rescue medication including the allowed daily dose was updated • General statement was included to further clarify the trial termination • Additional hematology and blood chemistry parameters were added • The definition of the serious adverse events (SAE) reporting timelines was revised to provide a clear guidance for the investigator for the SAE reporting in order to meet a general requirement provided by the German health authority to other protocols

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported