Clinical trial results:
A randomized, placebo-controlled, double-blind, parallel-group, multi-center, proof-of-concept study to assess the efficacy and safety of BAY 1817080 in patients with overactive bladder (OAB) over a 12-week treatment period

Summary

EudraCT number	2019-002575-34
Trial protocol	CZ SE PL PT GB DE AT
Global end of trial date	21 January 2022

Results information

Result version number	v1 (current)
This version publication date	05 January 2023
First version publication date	05 January 2023

Trial information

Trial identification

Sponsor protocol code	BAY1817080/19733

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04545580
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 30300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30300139003, 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	18 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of eliapixant 125 mg twice a day (BID) in comparison to placebo in the treatment of OAB with urgency urinary incontinence (UUI) over a 12-week treatment period

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	16 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czechia: 31
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	99
EEA total number of subjects	92

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)	60
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 28 centers in 9 countries with first subject first visit on 16-Sep-2020 and last subject last visit on 21-Jan-2022

Pre-assignment

Screening details:

Overall, 202 subjects were screened and 43 subjects failed screening. 159 subjects were assigned to run-in period, 59 of whom failed run-in. A total of 100 subjects were randomly assigned to 2 treatment arms (51 to eliapixant 125 mg BID and 49 to placebo). One subject in the placebo arm did not receive any study drug.

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

Blinding implementation details:

During the run-in period, subjects were blinded for run-in treatment. Investigator and sponsor knew that subjects received run-in placebo treatment. After randomization, subject, investigator and sponsor were blinded to the identity of the randomized study intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	Eliapixant 125mg BID

Arm description:

Subjects received 125 mg oral doses of eliapixant, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks

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

Dosage and administration details:

125 mg twice daily (BID), administered orally for 12 weeks

Arm title	Placebo

Arm description:

Subjects received oral doses of placebo, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 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 twice daily (BID), administered orally for 12 weeks

Number of subjects in period 1	Eliapixant 125mg BID	Placebo
Started	51	48
Completed	40	41
Not completed	11	7
Consent withdrawn by subject	-	3
Adverse event, non-fatal	5	-
Pregnancy	1	-
COVID-19 pandemic related	-	1
Lack of efficacy	4	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Eliapixant 125mg BID
Reporting group description:	
Subjects received 125 mg oral doses of eliapixant, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects received oral doses of placebo, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks	

Reporting group values	Eliapixant 125mg BID	Placebo	Total
Number of subjects	51	48	99
Age categorical			
Units: Subjects			
Adults (18-64 years)	33	27	60
From 65-84 years	18	21	39
Age continuous			
Units: years			
arithmetic mean	58.37	59.29	
standard deviation	± 10.74	± 14.32	-
Gender categorical			
Units: Subjects			
Female	41	40	81
Male	10	8	18
Baseline mean number of UUI episodes per 24 hours			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: number of UUI episodes per 24 hours			
arithmetic mean	2.64	2.84	
standard deviation	± 2.11	± 1.98	-
Baseline mean number of urinary incontinence (UI) episodes per 24 hours			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: number of UI episodes per 24 hours			
arithmetic mean	3.05	3.06	
standard deviation	± 2.29	± 2.11	-
Baseline mean number of micturition episodes per24 hours			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: number of micturition episodes per 24 h			
arithmetic mean	11.98	10.83	
standard deviation	± 2.78	± 2.22	-
Baseline mean number of urgency episodes (Grade 3 or 4) per 24 hours			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: number of urgency episodes per 24 hours			

arithmetic mean	5.94	5.63	
standard deviation	± 3.46	± 3.37	-
Baseline mean number of nocturia episodes per 24 hours			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: number of nocturia episodes per 24 hours			
arithmetic mean	1.40	1.73	
standard deviation	± 0.96	± 0.94	-
Baseline mean volume voided per micturition			
Used per protocol set (PPS): Eliapixant 125 mg BID (N=43), Placebo (N=42)			
Units: mL			
arithmetic mean	167.19	176.94	
standard deviation	± 71.61	± 68.31	-

End points

End points reporting groups

Reporting group title	Eliapixant 125mg BID
Reporting group description:	
Subjects received 125 mg oral doses of eliapixant, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects received oral doses of placebo, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomly assigned to the double-blind treatment and who took at least 1 dose of the double-blind study intervention were included in the SAF	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects randomly assigned to the double-blind treatment, who took at least 1 dose of the double-blind study intervention and for whom no validity finding was recorded were included in the PPS.	

Primary: Average change from baseline over Week 4, 8 and 12 (EoT) in mean number of UUI episodes per 24 hours based on electronic bladder diary

End point title	Average change from baseline over Week 4, 8 and 12 (EoT) in mean number of UUI episodes per 24 hours based on electronic bladder diary
End point description:	
Week 4: Eliapixant 125 mg BID (n=43), Placebo (n=41) Week 8: Eliapixant 125 mg BID (n=40), Placebo (n=42) Week 12: Eliapixant 125 mg BID (n=37), Placebo (n=34) An urgency urinary incontinence episode was defined as any urinary incontinence (UI) episode accompanied by urgency classified by the subject as a grade 3 or 4 on the Patient Perception of Intensity of Urgency Scale (PPIUS).	
End point type	Primary
End point timeframe:	
From baseline up to 12 weeks	

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[1]	42[2]		
Units: number of UUI episodes per 24 hours				
arithmetic mean (standard deviation)				
Week 4	-1.20 (± 1.25)	-1.31 (± 1.25)		
Week 8	-1.43 (± 1.51)	-1.68 (± 1.49)		
Week 12	-1.59 (± 1.35)	-1.60 (± 1.57)		

Notes:
[1] - PPS
[2] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible intervals were calculated.
The posterior probability of eliapixant treatment resulting in a larger reduction of UUI episodes compared to placebo treatment over Week 4, 8 and 12 was 40.3%. According to the prespecified decision criterion, the targeted posterior probability of 90% could not be reached and no treatment effect could be obtained.

Comparison groups	Eliapixant 125mg BID v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.046
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.377

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of UUI episodes per 24 hours

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of UUI episodes per 24 hours

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[3]	34[4]		
Units: number of UUI episodes per 24 hours				
arithmetic mean (standard deviation)	-1.59 (± 1.35)	-1.60 (± 1.57)		

Notes:
[3] - PPS
[4] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger reduction of UUI episodes compared to placebo at Week 12 was 45.5%.

Comparison groups	Eliapixant 125mg BID v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.469

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of urinary incontinence (UI) episodes per 24 hours

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of urinary incontinence (UI) episodes per 24 hours

End point description:

A urinary incontinence episode was defined as the complaint of any involuntary leakage of urine.
A urinary incontinence episode was also counted if a subject experienced an episode type of both micturition and incontinence.

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[5]	34[6]		
Units: number of UI episodes per 24 hours				
arithmetic mean (standard deviation)	-1.85 (± 1.61)	-1.75 (± 1.56)		

Notes:

[5] - PPS

[6] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger reduction of UI episodes compared to placebo at Week 12 was 49.8%.

Comparison groups	Eliapixant 125mg BID v Placebo

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.001
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.473

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of micturition episodes per 24 hours

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of micturition episodes per 24 hours

End point description:

A micturition episode was defined as any voluntary urination episode, excluding urinary incontinence only episodes.
A micturition was also counted if a subject experienced an episode type of both micturition and incontinence.

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[7]	34[8]		
Units: number of micturition episodes / 24 h				
arithmetic mean (standard deviation)	-1.72 (± 2.14)	-1.20 (± 2.54)		

Notes:

[7] - PPS

[8] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger reduction of micturition episodes compared to placebo at Week 12 was 84.3%.

Comparison groups	Eliapixant 125mg BID v Placebo

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.509
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.334

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of urgency episodes (Grade 3 or 4) per 24 hours

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of urgency episodes (Grade 3 or 4) per 24 hours

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[9]	34[10]		
Units: number of urgency episodes per 24 hours				
arithmetic mean (standard deviation)	-1.71 (± 2.94)	-2.03 (± 2.45)		

Notes:

[9] - PPS

[10] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger reduction of urgency episodes (Grade 3 or 4) compared to placebo at Week 12 was 40.3%.

Comparison groups	Eliapixant 125mg BID v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.134

Confidence interval	
level	95 %
sides	1-sided
upper limit	1.049

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of nocturia episodes per 24 hours

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean number of nocturia episodes per 24 hours

End point description:

Nocturia was the complaint that the subject woke up at night to void. In this study, it was defined as a micturition episode associated with sleep disturbance, between the time the subject went to bed with the intention to sleep until the time the subject woke up in the morning with the intention to stay awake.

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[11]	34[12]		
Units: number of nocturia episodes per 24 hours				
arithmetic mean (standard deviation)	-0.12 (± 0.84)	-0.18 (± 0.91)		

Notes:

[11] - PPS

[12] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger reduction of nocturia episodes compared to placebo at Week 12 was 51.6%.

Comparison groups	Eliapixant 125mg BID v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.007
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.271

Secondary: Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean volume voided per micturition

End point title	Change from baseline to Week 12 (EoT) based on electronic bladder diary in mean volume voided per micturition

End point description:

Volume voided per micturition was the urine volume measured for each reported micturition episode.

End point type	Secondary

End point timeframe:

From baseline up to 12 weeks

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[13]	34[14]		
Units: mL				
arithmetic mean (standard deviation)	14.40 (± 43.63)	4.75 (± 43.36)		

Notes:

[13] - PPS

[14] - PPS

Statistical analyses

Statistical analysis title	Bayesian mixed model

Statistical analysis description:

95% one sided upper credible interval was calculated.
The posterior probability of eliapixant leading to a larger increase of volume voided per micturition compared to placebo at Week 12 was 75.9%.

Comparison groups	Eliapixant 125mg BID v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	6.29
Confidence interval	
level	95 %
sides	1-sided
lower limit	-8.324

Secondary: Number of subjects with adverse events (AE)

End point title	Number of subjects with adverse events (AE)

End point description:

AE was defined as any untoward medical occurrence in a study subject, whether or not considered related to the study intervention, occurring from the start of study until the follow-up visit.
A treatment-emergent adverse event (TEAE) was defined as any event arising or worsening after the

start of randomized study intervention administration until 14 days after the last study intervention intake.

End point type	Secondary

End point timeframe:

From the start of study intervention (at start of run-in) until the follow-up visit (up to 18 weeks)

End point values	Eliapixant 125mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[15]	48[16]		
Units: subject				
Any AE	34	29		
Maximum intensity for any AE: Mild	18	19		
Maximum intensity for any AE: Moderate	14	10		
Maximum intensity for any AE: Severe	2	0		
Any SAE	1	0		
Any AE resulting in discontinuation of drug	6	1		
Any TEAE	32	27		
Any study drug-related TEAE	23	9		
Any serious TEAE	1	0		
Any TEAE resulting in discontinuation of drug	5	1		

Notes:

[15] - SAF

[16] - 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 (at start of run-in) until the follow-up visit (up to 18 weeks)
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	24.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received oral doses of placebo, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks.

Reporting group title	Eliapixant 125 mg BID

Reporting group description:

Subjects received 125 mg oral doses of eliapixant, administered twice daily at approximately the same time each day 12 hours apart over the course of 12 weeks.

Serious adverse events	Placebo	Eliapixant 125 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
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: 0 %

Non-serious adverse events	Placebo	Eliapixant 125 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 48 (60.42%)	34 / 51 (66.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Anogenital warts			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Hot flush			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 48 (4.17%)	4 / 51 (7.84%)	
occurrences (all)	3	5	
Oedema peripheral			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Thirst			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
General physical health deterioration			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Therapeutic product effect decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Prostatomegaly			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	

Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	3	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Amylase increased			
subjects affected / exposed	1 / 48 (2.08%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Blood fibrinogen increased			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	
occurrences (all)	1	3	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
International normalised ratio increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Prothrombin time prolonged			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Lipase increased			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	
occurrences (all)	1	3	
Weight increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nitrite urine present			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Lipase abnormal			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Muscle strain			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Anosmia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Dizziness postural			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	2 / 48 (4.17%)	5 / 51 (9.80%)	
occurrences (all)	2	5	
Headache			
subjects affected / exposed	2 / 48 (4.17%)	1 / 51 (1.96%)	
occurrences (all)	3	3	
Hypogeusia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Presyncope			

subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Taste disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Vertigo positional			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	2 / 48 (4.17%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			

subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Dry mouth			
subjects affected / exposed	5 / 48 (10.42%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Gastritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 48 (4.17%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Noninfective sialoadenitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Scab			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Skin irritation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Urinary tract inflammation			

subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Exostosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Osteoarthritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	2 / 48 (4.17%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Obesity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Dyslipidaemia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2020	• Exclusion criterion #15 was modified to exclude subjects with systolic/diastolic blood pressure levels ≥160/100 mmHg. • Positive hepatitis B and C were added in exclusion criterion #19. • Section on potential phototoxicity and instructions to avoid excessive exposure to sunlight were removed. • Text for the organic-anion-transporting polypeptide 1B1/1B3 (OATP1B1/1B3), breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) substrates in Table 6-1 was revised. • Statistical considerations adjusted for coronavirus disease 2019 (COVID-19) related issues. • Additional information will also be recorded for smell-related AEs if reported spontaneously by the subject. • Anti-hepatitis D and E virus antibodies were added in the list of laboratory assessments for liver safety in case close observation is to be initiated. • Wording for non-specific symptoms which might be associated with liver dysfunction in Section 2.3.3.4 was revised and the pre-existing text in Section 10.6.2 was moved to Section 10.6.1. • Wording of repeated follow-up samplings was revised. • Stopping criteria for close liver observation was added. • Instructions were added that for study subjects who take biotin-containing supplements, the last dose of the supplement should be at least 72 hours prior to FSH hormone or ferritin testing. • Wording randomly assigned to "study intervention" was changed to randomly assigned to "double-blind treatment". • Row for "mRNA (anti-HCV and HCV mRNA)" was deleted. • Anti-native double-stranded deoxyribonucleic acid (DNA) Antibodies was changed to "Anti-nuclear antibodies (ANA)" • "Anti-Smith antibodies" was changed to "anti-smooth muscle antibodies". • Text for the increase of concentrations of total serum bilirubin in studies with healthy volunteers was removed. • Wordings of the primary, secondary and exploratory endpoints were updated. • Psychometric analyses of bladder diary were planned to be conducted alongside the statistic
22 June 2021	• Protocol version number was included in the Title page and removed from the header. Date is added in the header. • 2 new visits added for taking blood samples for liver monitoring. • Text updated regarding one case of moderate liver injury. • Text on blood samples for liver monitoring added. • Addition of extremely low body weight as an example to criterion #21.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported