Clinical trial results:
A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)

Summary

EudraCT number	2021-003154-23
Trial protocol	SE FI PL HR
Global end of trial date	20 November 2023

Results information

Result version number	v1 (current)
This version publication date	01 December 2024
First version publication date	01 December 2024

Trial information

Trial identification

Sponsor protocol code	1402-0030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05103657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	16 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2023
Global end of trial reached?	Yes
Global end of trial date	20 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to provide proof of concept (PoC) of orally administered BI 1358894 125 mg after eight weeks treatment in patients with PTSD compared to placebo.

Protection of trial subjects:

A log of all patients enrolled into the trial (i.e. who have signed informed consent) was maintained in the Investigator Site File (ISF) irrespective of whether they had been treated with investigational drug or not.

If retrospectively it was found that a patient has been randomized in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate was to be contacted immediately. Based on an individual benefit-risk assessment a decision was to be made whether continued trial participation is possible or not.

After premature trial drug discontinuation, patients were asked to further attend scheduled trial visits unless they withdrew consent to participate in the trial. The importance of continuing trial participation and the value of collecting data for all randomized patients was explained to the patients.

Measures to control the withdrawal rate included careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the options for early discontinuation and explanation of the consequences in case of withdrawals.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason had to be documented in the patient files and case report form (CRF). If applicable, the requirements for adverse event (AE) collection reporting had to be consider.

If new efficacy/safety information became available, Boehringer Ingelheim (BI) was to review the benefit-riskassessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to ensure the safety of the trial patients.

Even if the trial treatment was discontinued, the patients remained in the trial and, given their agreement, were to undergo the procedures for early treatment discontinuation and follow-up as outlined in the flow charts.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 31
Country: Number of subjects enrolled	Finland: 8

Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	United States: 516
Worldwide total number of subjects	673
EEA total number of subjects	122

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)	668
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase II, 8-week-treatment, multicentre, randomised, double blind, placebocontrolled, parallel-group trial in patients with Post-Traumatic Stress Disorder (PTSD).

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

Period 1 title	Randomised period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	BI 1358894 125 mg

Arm description:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Placebo	BI 1358894 125 mg
Started	160	158
Completed	159	157
Not completed	1	1
Not Treated	1	1

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Arm type	Placebo
Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Arm title	BI 1358894 125 mg

Arm description:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Arm type	Experimental
Investigational medicinal product name	BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 contains the randomised subjects. Baseline characteristics are reported for the subjects who started the treatment period i.e. treated subjects and not the randomised subjects.

Number of subjects in period 2[2]	Placebo	BI 1358894 125 mg
Started	159	157
Completed	133	127
Not completed	26	30
Other reasons than listed	9	8
Adverse event, non-fatal	6	14

Perceived lack of efficacy	1	1
Protocol deviation	2	2
No reason available	5	4
Burden of study procedures	3	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 673 screened subjects only 318 were randomised.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.	
Reporting group title	BI 1358894 125 mg
Reporting group description:	
Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.	

Reporting group values	Placebo	BI 1358894 125 mg	Total
Number of subjects	159	157	316
Age categorical			
Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	159	157	316
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.			
Units: years			
arithmetic mean	44.0	42.8	
standard deviation	± 12.9	± 12.4	-
Sex: Female, Male			
Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.			
Units: Participants			
Female	101	111	212
Male	58	46	104
Race (NIH/OMB)			
Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.			
Units: Subjects			
American Indian or Alaska Native	6	10	16
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	46	26	72

White	102	119	221
More than one race	3	1	4
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.			
Units: Subjects			
Hispanic or Latino	29	35	64
Not Hispanic or Latino	130	122	252
Unknown or Not Reported	0	0	0
CAPS−5 total severity score at baseline			
Clinician-administered Post Traumatic Stress Disorder (PTSD) Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (CAPS-5) is a 30-item clinician-administered structured interview that can be used to, make current (past month) diagnosis of PTSD and assess PTSD symptoms over the past week. The CAPS-5 as used in this trial has 20 items, each scored 0-4, to yield a score with a possible range of 0-80. Higher scores mean worse outcome. Study characteristic reported for the treated set (TS).			
Units: score on a scale			
arithmetic mean	41.3	42.0	
standard deviation	± 9.9	± 9.6	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Reporting group title	BI 1358894 125 mg

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Reporting group title	Placebo

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Reporting group title	BI 1358894 125 mg

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Primary: Change from baseline in Clinician-Administered Post Traumatic Stress Disorder (PTSD) Scale for DSM-5 (CAPS-5) total severity score at Week 8

End point title	Change from baseline in Clinician-Administered Post Traumatic Stress Disorder (PTSD) Scale for DSM-5 (CAPS-5) total severity score at Week 8

End point description:

CAPS-5 is a 30-item clinician-administered structured interview that can be used to, make current (past month) diagnosis of PTSD and assess PTSD symptoms over the past week. Each of the 20 symptom items in the CAPS-5 is rated from 0 (absent) to 4 (extreme/incapacitating) with a single severity score combining information about frequency/amount and intensity which is yield by summing each item scores and ranges from 0 to 80 with higher scores indicating higher symptom severity. Least Squares (LS) means and confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed model repeated measures (MMRM) including the fixed categorical covariates of treatment, and the stratification indicator of presence of significant childhood trauma (yes vs. no), the continuous fixed covariate of baseline CAPS−5 total severity score, time since index event (in years) and the treatment−by−visit interaction. Patient is considered as random. Unstructured covariance matrix was used.

End point type	Primary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated CAPS-5 measurements from baseline, Week 4, and Week 8. The data represents the Least Squares Mean at Week 8.

End point values	Placebo	BI 1358894 125 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[1]	151[2]		
Units: units on a scale				
least squares mean (confidence interval 95%)	-17.19 (-19.56 to -14.81)	-17.13 (-19.52 to -14.74)		

Notes:

[1] - Endpoint is reported for the full analysis set.

[2] - Endpoint is reported for the full analysis set.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Least Squares (LS) means differences and confidence intervals were estimated by REML−based MMRM including the fixed categorical covariates of treatment, and the stratification indicator of presence of significant childhood trauma (yes vs. no), the continuous fixed covariate of baseline CAPS−5 total severity score, time since index event (in years) and the treatment−by−visit interaction. Patient is considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125 mg
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.9726
Method	Mixed Models for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	3.43

Notes:

[3] - Least Squares mean of "BI 1358894 125 mg" - Least Square mean of "Placebo".

Secondary: CAPS-5 response, defined as ≥30% CAPS-5 reduction from baseline at Week 8

End point title	CAPS-5 response, defined as ≥30% CAPS-5 reduction from baseline at Week 8

End point description:

Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (CAPS-5) is a 30-item clinician-administered structured interview that can be used to, make current (past month) diagnosis of PTSD and assess PTSD symptoms over the past week. Each of the 20 symptom items in the CAPS-5 is rated from 0 (absent) to 4 (extreme/incapacitating) with a single severity score combining information about frequency/amount and intensity which is yield by summing each item scores and ranges from 0 to 80 with higher scores indicating higher symptom severity.
Number of participants with ≥30% CAPS-5 reduction from baseline at Week 8 is reported.
This endpoint is reported for the full analysis set which consisted of all patients in the treated set (TS) that had a baseline and at least one evaluable post-baseline measurement for the primary endpoint.

End point type	Secondary

End point timeframe:

At baseline and at 8 weeks after start of treatment.

End point values	Placebo	BI 1358894 125 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: Participants	77	77		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Logistic regression was adjusted for fixed factors of treatment and presence of significant childhood trauma (yes vs. no).	
Comparison groups	Placebo v BI 1358894 125 mg
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.9945
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.65

Notes:

[4] - BI 1358894 125 mg vs. Placebo

Secondary: CAPS-5 response, defined as ≥50% CAPS-5 reduction from baseline at Week 8

End point title	CAPS-5 response, defined as ≥50% CAPS-5 reduction from baseline at Week 8

End point description:

Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (CAPS-5) is a 30-item clinician-administered structured interview that can be used to, make current (past month) diagnosis of PTSD and assess PTSD symptoms over the past week. Each of the 20 symptom items in the CAPS-5 is rated from 0 (absent) to 4 (extreme/incapacitating) with a single severity score combining information about frequency/amount and intensity which is yield by summing each item scores and ranges from 0 to 80 with higher scores indicating higher symptom severity.
Number of participants with ≥50% CAPS-5 reduction from baseline at Week 8 is reported.
This endpoint is reported for the full analysis set which consisted of all patients in the treated set (TS) that had a baseline and at least one evaluable post-baseline measurement for the primary endpoint.

End point type	Secondary

End point timeframe:

At baseline and at 8 weeks after start of treatment.

End point values	Placebo	BI 1358894 125 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: Participants	53	50		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Logistic regression was adjusted for fixed factors of treatment and presence of significant childhood trauma (yes vs. no).	
Comparison groups	Placebo v BI 1358894 125 mg
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.7167
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.912
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.552
upper limit	1.504

Notes:

[5] - BI 1358894 125 mg vs. Placebo

Secondary: Change from baseline on the PTSD Checklist for DSM-5 (PCL-5) total score at Week 8

End point title	Change from baseline on the PTSD Checklist for DSM-5 (PCL-5) total score at Week 8

End point description:

The PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (PCL-5) is a 20-item patient-reported assessment designed to measure the presence and severity of PTSD symptoms in the past month. Items on the PCL-5 correspond with DSM-5 criteria for PTSD. Each item is rated on a five point Likert scale, from 0 (not at all) to 4 (extremely) yielding a total score from 0-80 with higher scores indicating higher severity of the symptoms.
Least Square (LS) means and confidence intervals were estimated by restricted maximum likelihood (REML)−based mixed model repeated measures (MMRM) including the fixed categorical covariates of treatment, and the stratification indicator of presence of significant childhood trauma (yes vs. no), the continuous fixed covariate of baseline CAPS−5 total severity score, time since index event (in years) and the treatment−by−visit interaction. Patient is considered as random. Unstructured covariance matrix was used.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated PCL-5 measurements from baseline, Week 4, and Week 8. The data represents the Least Squares Mean at Week 8.

End point values	Placebo	BI 1358894 125 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[6]	151[7]		
Units: units on a scale				
least squares mean (confidence interval 95%)	-19.21 (-21.80 to -16.61)	-18.55 (-21.12 to -15.98)		

Notes:

[6] - Endpoint is reported for the full analysis set.

[7] - Endpoint is reported for the full analysis set.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Least Square (LS) means differences and confidence intervals were estimated by REML−based MMRM including the fixed categorical covariates of treatment, and the stratification indicator of presence of significant childhood trauma (yes vs. no), the continuous fixed covariate of baseline CAPS−5 total severity score, time since index event (in years) and the treatment−by−visit interaction. Patient is considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125 mg
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.723
Method	Mixed Models for Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

"All-Cause Mortality" "Serious Adverse Events" and "Other Adverse Events": From first administration of BI 1358894 or placebo to last administration of BI 1358894 or placebo + 4 weeks of residual effect period, up to 13 weeks.

Adverse event reporting additional description:

Treated Set (TS): consisted of all patients that were randomised and had received at least one administration of trial drug. Patients were analysed according to the actual received treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	BI 135889 125mg

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks 125 milligrams (mg) of BI 1358894. The dosage of 125 milligrams consisted of two film-coated tablets of 50 mg and 1 film-coated tablet of 25 mg. BI 135889 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Reporting group title	Placebo

Reporting group description:

Patients received orally, once daily for 8 consecutive weeks film-coated tablets of placebo matching BI 1358894. Placebo matching BI 1358894 was administered with water and in a consistent way, i.e. either with or without food every morning at approximately the same time.

Serious adverse events	BI 135889 125mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 157 (7.64%)	10 / 159 (6.29%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 157 (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	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 157 (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	
Hypertension			
subjects affected / exposed	0 / 157 (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	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 157 (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	
Encephalopathy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	4 / 157 (2.55%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	4 / 8	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 157 (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	
Wound infection			
subjects affected / exposed	0 / 157 (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	
Appendicitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (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: 5 %

Non-serious adverse events	BI 135889 125mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 157 (67.52%)	88 / 159 (55.35%)	
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Hot flush			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Haematoma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 157 (6.37%)	2 / 159 (1.26%)	
occurrences (all)	11	2	
Chills			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Feeling jittery			

subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Inflammation			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	4 / 157 (2.55%)	0 / 159 (0.00%)	
occurrences (all)	6	0	
Pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Pre-existing condition improved			
subjects affected / exposed	3 / 157 (1.91%)	3 / 159 (1.89%)	
occurrences (all)	6	3	
Pyrexia			
subjects affected / exposed	2 / 157 (1.27%)	3 / 159 (1.89%)	
occurrences (all)	2	3	
Thirst			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Social circumstances			

Physical assault			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Caregiver			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Impaired driving ability			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Sexual dysfunction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Polymenorrhoea			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	3	
Intermenstrual bleeding			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Heavy menstrual bleeding			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Erectile dysfunction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	1 / 157 (0.64%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Breast tenderness			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Rhinitis allergic			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract congestion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anhedonia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Abnormal dreams			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Affect lability			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Agitation			

subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Initial insomnia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	4 / 157 (2.55%)	1 / 159 (0.63%)	
occurrences (all)	6	1	
Intentional self-injury			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Irritability			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Libido decreased			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Listless			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	3	0	
Middle insomnia			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Mood swings			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	2 / 157 (1.27%)	3 / 159 (1.89%)	
occurrences (all)	3	4	
Panic attack			
subjects affected / exposed	4 / 157 (2.55%)	1 / 159 (0.63%)	
occurrences (all)	4	1	
Post-traumatic stress disorder			

subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)		
occurrences (all)	1	0		
Anxiety				
subjects affected / exposed	2 / 157 (1.27%)	4 / 159 (2.52%)		
occurrences (all)	2	6		
Apathy				
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)		
occurrences (all)	1	1		
Confusional state				
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)		
occurrences (all)	1	0		
Depersonalisation/derealisation disorder				
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)		
occurrences (all)	1	0		
Depressed mood				
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)		
occurrences (all)	0	1		
Depression				
subjects affected / exposed	4 / 157 (2.55%)	1 / 159 (0.63%)		
occurrences (all)	6	1		
Depressive symptom				
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)		
occurrences (all)	1	0		
Euphoric mood				
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)		
occurrences (all)	1	1		
Illusion				
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)		
occurrences (all)	2	0		
Restlessness				
subjects affected / exposed	4 / 157 (2.55%)	1 / 159 (0.63%)		
occurrences (all)	6	1		
Sleep disorder				
subjects affected / exposed	2 / 157 (1.27%)	3 / 159 (1.89%)		
occurrences (all)	3	3		

Sleep talking			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Somnambulism			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Investigations			
Weight increased			
subjects affected / exposed	11 / 157 (7.01%)	3 / 159 (1.89%)	
occurrences (all)	11	3	
Hepatic enzyme increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Amylase increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	3	1	
Blood creatinine increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 157 (1.27%)	2 / 159 (1.26%)	
occurrences (all)	3	2	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
C-reactive protein increased			
subjects affected / exposed	1 / 157 (0.64%)	6 / 159 (3.77%)	
occurrences (all)	1	8	
Crystal urine present			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Heart rate increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
White blood cell count decreased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Arthropod bite			

subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Intentional product misuse			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	2	
Muscle strain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Sedation complication			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Stress fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Sunburn			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Traumatic haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			

subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Congenital, familial and genetic disorders			
Hyperexplexia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 157 (7.64%)	8 / 159 (5.03%)	
occurrences (all)	12	13	
Headache			
subjects affected / exposed	34 / 157 (21.66%)	20 / 159 (12.58%)	
occurrences (all)	66	34	
Amnesia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Brain fog			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Circadian rhythm sleep disorder			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Clumsiness			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Cold-stimulus headache			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Coordination abnormal			

subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	3 / 157 (1.91%)	3 / 159 (1.89%)	
occurrences (all)	4	3	
Drug withdrawal headache			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Hypoaesthesia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Lethargy			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	5 / 157 (3.18%)	2 / 159 (1.26%)	
occurrences (all)	6	3	
Psychogenic seizure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Sedation			
subjects affected / exposed	1 / 157 (0.64%)	2 / 159 (1.26%)	
occurrences (all)	1	2	
Somnolence			
subjects affected / exposed	6 / 157 (3.82%)	3 / 159 (1.89%)	
occurrences (all)	7	3	
Syncope			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Taste disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Tension headache			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Tremor			

subjects affected / exposed	2 / 157 (1.27%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	
Neutrophilia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	3 / 157 (1.91%)	0 / 159 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Vision blurred			

subjects affected / exposed	2 / 157 (1.27%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Visual impairment			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 157 (4.46%)	15 / 159 (9.43%)	
occurrences (all)	8	15	
Toothache			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	3	0	
Abdominal discomfort			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	3 / 157 (1.91%)	2 / 159 (1.26%)	
occurrences (all)	6	2	
Acid peptic disease			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	5 / 157 (3.18%)	3 / 159 (1.89%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	5 / 157 (3.18%)	6 / 159 (3.77%)	
occurrences (all)	6	7	
Dry mouth			
subjects affected / exposed	3 / 157 (1.91%)	1 / 159 (0.63%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	

Flatulence			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 157 (0.64%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Rosacea			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 157 (0.64%)	3 / 159 (1.89%)	
occurrences (all)	1	3	
Pruritus			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	
Night sweats			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Neurodermatitis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Mechanical urticaria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Dermatitis allergic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Dermal cyst			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Pollakiuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 157 (3.82%)	3 / 159 (1.89%)	
occurrences (all)	8	4	
Back pain			
subjects affected / exposed	1 / 157 (0.64%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Exostosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	5 / 157 (3.18%)	1 / 159 (0.63%)	
occurrences (all)	5	1	
Neck pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 157 (0.00%)	3 / 159 (1.89%)	
occurrences (all)	0	3	
Spinal pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 157 (1.27%)	2 / 159 (1.26%)	
occurrences (all)	2	3	

Acarodermatitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	1 / 157 (0.64%)	4 / 159 (2.52%)	
occurrences (all)	1	4	
Cellulitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Dacryocystitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Infected bite			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	0 / 157 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	2	

Mycoplasma infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	7 / 157 (4.46%)	5 / 159 (3.14%)	
occurrences (all)	11	8	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	3 / 157 (1.91%)	4 / 159 (2.52%)	
occurrences (all)	3	4	
Streptococcal infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	2 / 157 (1.27%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	5 / 157 (3.18%)	5 / 159 (3.14%)	
occurrences (all)	5	5	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	

Viral infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Groin abscess			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	8 / 157 (5.10%)	2 / 159 (1.26%)	
occurrences (all)	8	2	
Decreased appetite			
subjects affected / exposed	1 / 157 (0.64%)	5 / 159 (3.14%)	
occurrences (all)	1	5	
Diabetes mellitus			
subjects affected / exposed	0 / 157 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Fluid retention			
subjects affected / exposed	3 / 157 (1.91%)	1 / 159 (0.63%)	
occurrences (all)	3	1	
Food craving			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Glucose tolerance impaired			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	5 / 157 (3.18%)	1 / 159 (0.63%)	
occurrences (all)	5	1	
Obesity			
subjects affected / exposed	1 / 157 (0.64%)	0 / 159 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2022	Global amendment 1 included the following changes toin the protocol: Addition of pregnancy test at End of Study (EOS) Inclusion of pregnancy test at V1A; Addition of counseling about the need of contraception and of information about the risk of medication-induced birth deficits; Sexual abstinence as contraceptive method no longer allowed; Added required reiteration that woman of childbearing potential (WOCBP) had to use appropriate methods of contraception; Description of a pivotal embryo-fetal development study in Goettingen minipigs added which had identified embryofetal development toxicity at relevant human exposure levels; Added how the risk for teratogenicity was to be mitigated; The permitted use of nonbenzodiazepine-. non-Z-drug hypnotics during the trial was changed from a dose equivalent to ≤1.0 mg lorazepam per day to the lowest dose of the compound as noted in the Summary of Product Characteristic (or SmPC).
26 September 2022	Global amendment 2 included the following changes to the protocol: Added that the fulfillment of the inclusion criterion no. 7 the use of required regarding contraception by WOCBP had to be confirmed by the investigator; Added that the investigator had to obtain the confirmation of the required use of contraception from WOCBP at all visits; Added that the investigator had to ensure that the patient understood the contraception requirements for the trial and could reliably comply with contraception use during the trial; Guidance in the event the requirements for contraception were not met; Added that due to results from a Drug-Drug Interaction (DDI) trial restrictions to sensitive substrates of CYP2B6 were no longer needed; Restriction for sensitive substrates of CYP2B6 removed; The order of assessments was made more flexible.
18 January 2023	Global amendment 3 included the following changes to the protocol: Added description of assessment and categorization of index traumatic events.
09 June 2023	Global amendment 4 included the following changes to the protocol: The exception of "in situ carcinoma" in exclusion criterion no. 18 was more precisely defined as "in situ carcinoma of uterine cervix"; Added local erythrocyte sedimentation rate (ESR) (ESR) assessment and that the ESR testing results were not intended to be used as safety parameter or for medical management decisions; For medical management decisions of safety relevant inflammation parameter, the C-Reactive Protein (CRP) test was to be used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported