Clinical trial results:
A Dose Escalation, Proof of Concept, Phase IIA Study to Investigate the Safety and Tolerability, the Pharmacokinetic and the Pharmacodynamic of BN82451B, Administered Twice Daily Over 4 Weeks, in Male Patients with Huntington's Disease

Summary

EudraCT number	2013-002899-41
Trial protocol	DE
Global end of trial date	31 March 2016

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017

Trial information

Trial identification

Sponsor protocol code	8-55-52966-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02231580
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 Quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Vice President Early Development & Clinical Pharmacology, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Vice President Early Development & Clinical Pharmacology, Ipsen Pharma, clinical.trials@ipsen.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	31 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2016
Global end of trial reached?	Yes
Global end of trial date	31 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of BN82451B versus placebo after oral administration twice daily (b.i.d) for 28 days in subjects with Huntington's Disease (HD).

Protection of trial subjects:

The clinical study was conducted in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, under the ethical principles laid down in the Declaration of Helsinki. In addition, this clinical study adhered to all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2014
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	Germany: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was a double blind, placebo controlled, randomised, sequential dose ranging repeated dose trial where patients were recruited to a single study centre in Germany. It was planned to enrol 30 patients (10 in each of 3 cohorts). Patients were enrolled to the study from 1 September 2014 until early termination of the study on 31 March 2016.

Pre-assignment

Screening details:

Male patients 20-70 years with a documented diagnosis of HD with at least 36 cytosine adenine guanine repeats in the Huntington gene were screened. Eligibile patients needed to meet defined criteria during quantitative motor function assessments. 25 patients were screened, 17 were enrolled and randomised to treatment.

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

Blinding implementation details:

The study medications were supplied in a common high density polyethylene bottle, and the placebo capsules matched the BN52451B capsules with respect to size, colour, smell, taste and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	BN82451B

Arm description:

Patients were randomised to receive oral study medication, BN82451B, b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of BN82451B was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 milligrams (mg) b.i.d.
For cohort 1, 40 mg BN82451B b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg BN82451B b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg BN82451B b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Arm type	Experimental
Investigational medicinal product name	BN82451B
Investigational medicinal product code	BN82451B
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg BN82451B capsules were administered orally in planned doses of 40, 60 or 80 mg b.i.d. with a maximum of 2 glasses of water in fed conditions except on days of PK evaluations (Days 1, 7, 14, 21 and 28) where the study medication was administered with a maximum of 2 glasses of water 1 hour before breakfast or the evening meal and no additional liquid intake was allowed within 1 hour before and after study medication administration.

Arm title	Placebo

Arm description:

Patients were randomised to receive oral placebo b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of placebo was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 mg b.i.d.
For cohort 1, 40 mg placebo b.i.d. was administered during the first 14 days. If this dose was well

tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28. For cohort 2, 60 mg placebo b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28. For cohort 3 it was planned to administer 80 mg placebo b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules were administered orally b.i.d. with a maximum of 2 glasses of water in fed conditions except on days of PK evaluations (Days 1, 7, 14, 21 and 28) where the study medication was administered with a maximum of 2 glasses of water 1 hour before breakfast or the evening meal and no additional liquid intake was allowed within 1 hour before and after study medication administration.

Number of subjects in period 1	BN82451B	Placebo
Started	14	3
Cohort 1	8 [1]	2 [2]
Cohort 2	6 [3]	1 [4]
Completed	9	3
Not completed	5	0
Adverse event, non-fatal	5	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The first milestone represents the number of patients who were randomised to receive BN82451B in the first cohort. The numbers of patients in the overall period includes the number of patients in milestone 1 and 2.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The second milestone represents the number of patients who were randomised to receive placebo in the second cohort. The numbers of patients in the overall period includes the number of patients in milestone 1 and 2.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The second milestone represents the number of patients who were randomised to receive BN82451B in the second cohort. The numbers of patients in the overall period includes the number of patients in milestone 1 and 2.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The first milestone represents the number of patients who were randomised to receive placebo in the first cohort. The numbers of patients in the overall period includes the number of patients in milestone 1 and 2.

Baseline characteristics

Reporting groups	
Reporting group title	BN82451B

Reporting group description:

Patients were randomised to receive oral study medication, BN82451B, b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of BN82451B was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 milligrams (mg) b.i.d.
For cohort 1, 40 mg BN82451B b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg BN82451B b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg BN82451B b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive oral placebo b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of placebo was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 mg b.i.d.
For cohort 1, 40 mg placebo b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg placebo b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg placebo b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Reporting group values	BN82451B	Placebo	Total
Number of subjects	14	3	17
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	46.6	50	
standard deviation	± 14.4	± 8.7	-
Gender Categorical Units: Subjects			
Female	0	0	0
Male	14	3	17

End points

End points reporting groups

Reporting group title	BN82451B

Reporting group description:

Patients were randomised to receive oral study medication, BN82451B, b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of BN82451B was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 milligrams (mg) b.i.d.
For cohort 1, 40 mg BN82451B b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg BN82451B b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg BN82451B b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive oral placebo b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of placebo was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 mg b.i.d.
For cohort 1, 40 mg placebo b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg placebo b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg placebo b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Subject analysis set title	BN82451B Cohort 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients randomised to receive BN82451B in cohort 1 received doses ranging from 40 to 60 mg BN82451B orally b.i.d. for up to 28 days.

Subject analysis set title	BN82451B Cohort 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients randomised to receive BN82451B in cohort 2 received doses ranging from 60 to 80 mg BN82451B orally b.i.d. for up to 28 days.

Primary: Numbers of patients experiencing treatment emergent adverse events (TEAEs).

End point title	Numbers of patients experiencing treatment emergent adverse events (TEAEs).[1]

End point description:

The safety and tolerability of BN82451B versus placebo was determined after oral administration b.i.d. for 28 days in patients with HD. Numbers of patients experiencing TEAEs, including information on seriousness, intensity, drug relationship and those leading to withdrawal are presented for all doses of BN82451B and placebo.

End point type	Primary

End point timeframe:

From Day 1 to end of study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned and performed for the primary end point, as this was a safety measure in a small study population.

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	3		
Units: Participants				
Patients with any TEAEs	11	2		
Patients with any serious TEAE	0	0		
Patients with at least 1 severe TEAE	0	0		
Patients with at least 1 moderate TEAE	8	1		
Patients with at least 1 mild TEAE	11	1		
Patients with TEAEs related to study medication	9	0		
Patients with TEAEs leading to withdrawal	5	0		
Patients with any TEAEs leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration time curve (AUC)

End point title	Area under the plasma concentration time curve (AUC)

End point description:

The AUC was determined for BN82451B and its metabolites BN2468 and BN7167 within a dosage interval (0-12 hours) on Days 1, and 14 and 28. Day 1 data represent the AUC after the first dose (AUC[0-12]). The data for Days 14 and 28 (AUC[τ,ss]) represent the AUC at steady state at the initial cohort dose and following dose escalation, respectively. Data is presented for cohorts 1 and 2, as the study terminated prior to dosing of cohort 3.

End point type	Secondary

End point timeframe:

0-12 hours on Days 1, 14 and 28

End point values	BN82451B Cohort 1	BN82451B Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	6[2]		
Units: hours*nanograms per millilitre (h*ng/mL)				
arithmetic mean (standard deviation)				
Day 1 BN82451B AUC(0-12)	512.93 (± 112.53)	783.78 (± 144.45)		
Day 1 BN2468 AUC(0-12)	90.66 (± 40.68)	0 (± 0)		
Day 1 BN7167 AUC(0-12)	16.82 (± 9.01)	31.67 (± 24.63)		
Day 14 BN82451B AUCτ,ss	1521.11 (± 593.22)	2594.05 (± 1077.08)		
Day 14 BN2468 AUC(τ,ss)	735.51 (± 203.91)	1531 (± 412.43)		
Day 14 BN7167 AUC(τ,ss)	33.39 (± 20.08)	46.73 (± 36.76)		

Day 28 BN82451B AUC(τ,ss)	2357.95 (± 977.74)	3313.45 (± 1517.6)		
Day 28 BN2468 AUC(τ,ss)	1509.67 (± 105.94)	1936.35 (± 569.97)		
Day 28 BN7167 AUC(τ,ss)	34.64 (± 16.05)	63.81 (± 57.7)		

Notes:

[2] - For BN82451B Cohort 2, BN2468 AUC(0-12) was not computed as Cmax (tmax) occurred at 12 hours.

Statistical analyses

No statistical analyses for this end point

Secondary: Peak plasma concentration (Cmax)

End point title	Peak plasma concentration (Cmax)

End point description:

Cmax was determined for BN82451B and its metabolites BN2468 and BN7167 on Days 1, 14 and 28. Day 1 data represent the PK after the first dose (Cmax). The data for Days 14 and 28 represent the Cmax at steady state (Cmax,ss) at the initial cohort dose and following dose escalation, respectively. Data is presented for cohorts 1 and 2, as the study terminated prior to dosing of cohort 3.

End point type	Secondary

End point timeframe:

Days 1, 14 and 28

End point values	BN82451B Cohort 1	BN82451B Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	6		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 BN82451B Cmax	71.61 (± 14.81)	101.45 (± 16.25)		
Day 1 BN2468 Cmax	9.03 (± 4.14)	18.87 (± 13)		
Day 1 BN7167 Cmax	3.62 (± 1.62)	5.61 (± 3.62)		
Day 14 BN82451B Cmax,ss	162.88 (± 56.31)	271.64 (± 99.9)		
Day 14 BN2468 Cmax,ss	75.34 (± 15.16)	125.34 (± 38.13)		
Day 14 BN7167 Cmax,ss	4.9 (± 2.35)	6.28 (± 3.55)		
Day 28 BN82451B Cmax,ss	251.77 (± 105.64)	340.41 (± 156.61)		
Day 28 BN2468 Cmax,ss	135.19 (± 5.06)	171.64 (± 47.64)		
Day 28 BN 7167 Cmax,ss	5.51 (± 1.82)	9.54 (± 6.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to peak plasma concentration (Tmax)

End point title	Time to peak plasma concentration (Tmax)

End point description:

Tmax is the empirical time of Cmax and was determined for BN82451B and its metabolites BN2468 and BN7167 on Days 1, 14 and 28. Day 1 data represent the PK after the first dose (Tmax). The data for Days 14 and 28 represent the Tmax at steady state (Tmax,ss) at the initial cohort dose and following dose escalation, respectively. Data is presented for cohorts 1 and 2, as the study terminated prior to dosing of cohort 3.

End point type	Secondary

End point timeframe:

Days 1, 14 and 28

End point values	BN82451B Cohort 1	BN82451B Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	6		
Units: hours				
median (full range (min-max))				
Day 1 BN82451B Tmax	3 (2 to 3)	2.51 (2 to 3)		
Day 1 BN2468 Tmax	9.98 (1 to 12.02)	11.92 (11.92 to 11.92)		
Day 1 BN7167 Tmax	1 (1 to 2)	1 (1 to 2)		
Day 14 BN82451B Tmax,ss	3 (2 to 4)	3 (2 to 3.5)		
Day 14 BN2468 Tmax,ss	4 (1.05 to 8)	2.51 (1 to 8)		
Day 14 BN7167 Tmax,ss	1 (1 to 2.13)	1 (1 to 2)		
Day 28 BN82451B Tmax,ss	3 (2.02 to 4)	2.56 (2 to 3.02)		
Day 28 BN2468 Tmax,ss	4.06 (2 to 6)	2.06 (1 to 12)		
Day 28 BN7167 Tmax,ss	1 (0.55 to 2)	1.52 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 28 in the position-index as determined by Choreomotography

End point title	Change from Baseline to Day 28 in the position-index as determined by Choreomotography

End point description:

Choreatic (involuntary) movements were assessed using Choreomotography by calculating a position-index and orientation-index. Patients were asked to grasp and lift a device equipped with an electromagnetic sensor, and were asked to hold the device as stable as possible. Three dimensional (3D) changes in position (x, y and z) and orientation (roll, pitch and yaw) were recorded and used to calculate a position-index and an orientation-index. This method provided an objective measure of the involuntary movements. 5 trials of 20 seconds duration were performed with each hand, and the start and end of each trial was signalled by a cueing tone. The mean changes from Baseline to Day 28 in the position-index of the right and left hands are presented as raw data. The statistical analyses present geometric least squares (GLS) mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: metres per second (m/s)				
arithmetic mean (standard deviation)				
Left hand position-index	0.021 (± 0.024)	0.009 (± 0.007)		
Right hand position-index	0.018 (± 0.014)	0.009 (± 0.006)		

Statistical analyses

Statistical analysis title	Left hand position-index

Statistical analysis description:

The Mixed Effect Model Repeat Measurement (MMRM) analysis was performed on log-transformed data using the restricted maximum likelihood (REML) model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5743
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.104
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.823
upper limit	1.482

Statistical analysis title	Right hand position-index

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4349
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.141

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.862
upper limit	1.51

Secondary: Change from Baseline to Day 28 in the orientation-index as determined by Choreomotography

End point title	Change from Baseline to Day 28 in the orientation-index as determined by Choreomotography

End point description:

Choreatic (involuntary) movements were assessed using Choreomotography by calculating a position-index and orientation-index. Patients were asked to grasp and lift a device equipped with an electromagnetic sensor, and were asked to hold the device as stable as possible. 3D changes in position (x, y and z) and orientation (roll, pitch and yaw) were recorded and used to calculate a position-index and an orientation-index. This method provided an objective measure of the involuntary movements. 5 trials of 20 seconds duration were performed with each hand, and the start and end of each trial was signalled by a cueing tone. The mean changes from Baseline to Day 28 in the orientation-index of the right and left hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: radians per second (radians/s)				
arithmetic mean (standard deviation)				
Left hand orientation-index	0.131 (± 0.125)	0.082 (± 0.1)		
Right hand orientation-index	0.098 (± 0.087)	0.054 (± 0.045)		

Statistical analyses

Statistical analysis title	Left hand orientation-index

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8937
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.035
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.675
upper limit	1.587

Statistical analysis title	Right hand orientation-index

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.093
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	1.493

Secondary: Change from Baseline to Day 28 in the mean grip force variability as determined by Manumotography

End point title	Change from Baseline to Day 28 in the mean grip force variability as determined by Manumotography

End point description:

The coordination of isometric grip forces in the precision grip between the thumb and index finger were assessed by Manumotography. Grip forces were assessed during grip initiation, object transport and in a static holding phase. Subjects were instructed to grasp and lift a device equipped with a force transducer and 3D position sensor in the precision grip between thumb and index finger and hold it stable adjacent to a marker 10 centimetres high. Grip forces and 3D position and orientation of the object were recorded. Mean isometric grip forces and grip force variability in the static phase (expressed as coefficient of variation = standard deviation/mean x 100 [GFV-C]) were calculated during a 15 second period. 5 trials of 20 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the grip force variability of each hand are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: percentage of variation				
arithmetic mean (standard deviation)				
Left hand grip force variability	5.74 (± 4.38)	2.61 (± 4.57)		
Right hand grip force variability	5.82 (± 7.94)	2.35 (± 1.17)		

Statistical analyses

Statistical analysis title	Left hand grip force variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2865
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.247
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.886
upper limit	1.756

Statistical analysis title	Right hand grip force variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5338
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.16

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.781
upper limit	1.724

Secondary: Change from Baseline to Day 28 in the mean isometric grip forces as determined by Manumotography

End point title	Change from Baseline to Day 28 in the mean isometric grip forces as determined by Manumotography

End point description:

The coordination of isometric grip forces in the precision grip between the thumb and index finger were assessed by Manumotography. Grip forces were assessed during grip initiation, object transport and in a static holding phase. Subjects were instructed to grasp and lift a device equipped with a force transducer and 3D position sensor in the precision grip between thumb and index finger and hold it stable adjacent to a marker 10 centimetres high. Grip forces and 3D position and orientation of the object were recorded. Mean isometric grip forces and grip force variability in the static phase (expressed as coefficient of variation = standard deviation/mean x 100 [GFV-C]) were calculated during a 15 second period. 5 trials of 20 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the mean isometric grip forces of each hand are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: Newton				
arithmetic mean (standard deviation)				
Left hand isometric grip forces	-0.75 (± 2.86)	1.55 (± 1.99)		
Right hand isometric grip forces	-2.06 (± 6)	0.91 (± 1.67)		

Statistical analyses

Statistical analysis title	Left hand isometric grip forces

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0864
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.693
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.487
upper limit	0.985

Statistical analysis title	Right hand isometric grip forces

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0399
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.686
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.508
upper limit	0.925

Secondary: Change from Baseline to Day 28 in the mean duration and variability of inter onset intervals (IOI) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of inter onset intervals (IOI) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of tap IOI in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of IOI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left finger IOI variability	0.039 (± 0.048)	-0.009 (± 0.002)		
Right finger IOI variability	0.057 (± 0.062)	0.038 (± 0.049)		
Left finger IOI duration	0.088 (± 0.075)	-0.015 (± 0.041)		
Right finger IOI duration	0.069 (± 0.059)	0.032 (± 0.031)		

Statistical analyses

Statistical analysis title	Left finger IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0574
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.509
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	2.15

Statistical analysis title	Right finger IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8277
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.953
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.662
upper limit	1.372

Statistical analysis title	Left finger IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0162
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.238
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.074
upper limit	1.426

Statistical analysis title	Right finger IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.038

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.912
upper limit	1.182

Secondary: Change from Baseline to Day 28 in the mean duration and variability of tap durations (TD) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of tap durations (TD) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of TD in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of TD for the left and right hands are presented a raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left finger Variability of TD	0.007 (± 0.024)	-0.007 (± 0.015)		
Right finger Variability of TD	0.017 (± 0.016)	0.012 (± 0.017)		
Left finger Duration of TD	0.01 (± 0.021)	-0.011 (± 0.039)		
Right finger Duration of TD	0.012 (± 0.021)	0.001 (± 0.025)		

Statistical analyses

Statistical analysis title	Left finger Variability of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3005
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.308
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.85
upper limit	2.014

Statistical analysis title	Right finger Variability of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4793
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.177
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.804
upper limit	1.722

Statistical analysis title	Left finger Duration of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2653
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.15

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.934
upper limit	1.416

Statistical analysis title	Right finger Duration of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6777
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.045
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.875
upper limit	1.248

Secondary: Change from Baseline to Day 28 in the mean duration and variability of inter peak intervals (IPI) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of inter peak intervals (IPI) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of tap IPI in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of IPI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left finger IPI variability	0.04 (± 0.049)	-0.009 (± 0.007)		
Right finger IPI variability	0.057 (± 0.067)	0.038 (± 0.044)		
Left finger IPI duration	0.088 (± 0.076)	-0.017 (± 0.042)		
Right finger IPI duration	0.069 (± 0.059)	0.031 (± 0.03)		

Statistical analyses

Statistical analysis title	Left finger IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0326
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.618
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.124
upper limit	2.331

Statistical analysis title	Right finger IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6016
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.886

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.605
upper limit	1.299

Statistical analysis title	Left finger IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0152
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.242
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.077
upper limit	1.433

Statistical analysis title	Right finger IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6033
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.042
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.915
upper limit	1.186

Secondary: Change from Baseline to Day 28 in the mean duration and variability of

inter tap intervals (ITI) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of inter tap intervals (ITI) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of ITI in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of ITI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left finger ITI Variability	0.041 (± 0.05)	-0.007 (± 0.01)		
Right finger ITI Variability	0.053 (± 0.068)	0.03 (± 0.034)		
Left finger ITI Duration	0.078 (± 0.076)	-0.005 (± 0.006)		
Right finger ITI Duration	0.056 (± 0.048)	0.03 (± 0.046)		

Statistical analyses

Statistical analysis title	Left finger ITI Variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.657

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.086
upper limit	2.529

Statistical analysis title	Right finger ITI Variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6978
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.916
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	1.333

Statistical analysis title	Left finger ITI Duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0522
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.298
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.043
upper limit	1.614

Statistical analysis title	Right finger ITI Duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9012
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.014
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.837
upper limit	1.229

Secondary: Change from Baseline to Day 28 in the mean duration and variability of IOI as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of IOI as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of IOI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left hand IOI variability	0.032 (± 0.135)	0.036 (± 0.023)		
Right hand IOI variability	0.031 (± 0.094)	0.163 (± 0.276)		
Left hand IOI duration	0.054 (± 0.114)	0.028 (± 0.043)		
Right hand IOI duration	0.074 (± 0.101)	0.074 (± 0.132)		

Statistical analyses

Statistical analysis title	Left hand IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6176
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.168
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.697
upper limit	1.955

Statistical analysis title	Right hand IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4541
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.759
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.411
upper limit	1.399

Statistical analysis title	Left hand IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2018
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.119
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.967
upper limit	1.294

Statistical analysis title	Right hand IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6527
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.046
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.886
upper limit	1.234

Secondary: Change from Baseline to Day 28 in the mean duration and variability of TD as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of TD as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of TD for the left and right hands

are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left hand variability of TD	0.001 (± 0.138)	0.023 (± 0.026)		
Right hand variability of TD	-0.012 (± 0.073)	0.078 (± 0.128)		
Left hand duration of TD	-0.006 (± 0.088)	0.017 (± 0.027)		
Right hand duration of TD	-0.019 (± 0.089)	0.022 (± 0.069)		

Statistical analyses

Statistical analysis title	Left hand variability of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8279
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.929
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.529
upper limit	1.63

Statistical analysis title	Right hand variability of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2738
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.612
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.292
upper limit	1.283

Statistical analysis title	Left hand duration of TD

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9218
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.018
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.752
upper limit	1.378

Statistical analysis title	Right hand TD duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5032
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.847

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.561
upper limit	1.277

Secondary: Change from Baseline to Day 28 in the mean duration and variability of IPI as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of IPI as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of IPI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left hand IPI variability	0.045 (± 0.124)	0.049 (± 0.046)		
Right hand IPI variability	0.027 (± 0.07)	0.131 (± 0.219)		
Left hand IPI duration	0.057 (± 0.109)	0.029 (± 0.04)		
Right hand IPI duration	0.079 (± 0.105)	0.066 (± 0.118)		

Statistical analyses

Statistical analysis title	Left hand IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6759
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.677
upper limit	1.917

Statistical analysis title	Right hand IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5764
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.815
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.444
upper limit	1.496

Statistical analysis title	Left hand IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2127
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.115

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.965
upper limit	1.289

Statistical analysis title	Right hand IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5661
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.059
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.897
upper limit	1.25

Secondary: Change from Baseline to Day 28 in the mean duration and variability of ITI as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of ITI as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the duration and variability of ITI for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left hand ITI variability	0.036 (± 0.061)	0.015 (± 0.017)		
Right hand ITI variability	0.053 (± 0.082)	0.017 (± 0.018)		
Left hand ITI duration	0.064 (± 0.07)	0.006 (± 0.029)		
Right hand ITI duration	0.094 (± 0.097)	0.022 (± 0.014)		

Statistical analyses

Statistical analysis title	Left hand ITI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0874
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.571
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.018
upper limit	2.424

Statistical analysis title	Right hand ITI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6431
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.18

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.644
upper limit	2.162

Statistical analysis title	Left hand ITI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0389
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.193
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.038
upper limit	1.371

Statistical analysis title	Right hand ITI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1641
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.138
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.976
upper limit	1.327

Secondary: Change from Baseline to Day 28 in the mean duration and variability of

IOI as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of IOI as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The mean changes from Baseline to Day 28 in the duration and variability of IOI for the left and right feet are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left foot IOI variability	0.146 (± 0.353)	-0.1 (± 0.122)		
Right foot IOI variability	0.12 (± 0.177)	0.09 (± 0.15)		
Left foot IOI duration	0.109 (± 0.354)	-0.123 (± 0.199)		
Right foot IOI duration	0.267 (± 0.461)	0.075 (± 0.164)		

Statistical analyses

Statistical analysis title	Left foot IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	2.163
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.295
upper limit	3.614

Statistical analysis title	Right foot IOI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5136
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.274
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.688
upper limit	2.361

Statistical analysis title	Left foot IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0218
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.56
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.139
upper limit	2.137

Statistical analysis title	Right foot IOI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.251
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.825
upper limit	1.899

Secondary: Change from Baseline to Day 28 in the mean duration and variability of TD as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of TD as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The mean changes from Baseline to Day 28 in the duration and variability of TD for the left and right feet are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left foot TD variability	0.225 (± 0.332)	-0.056 (± 0.058)		
Right foot TD variability	0.306 (± 0.566)	0.105 (± 0.14)		
Left foot TD duration	0.179 (± 0.28)	-0.04 (± 0.106)		
Right foot TD duration	0.358 (± 0.609)	0.083 (± 0.133)		

Statistical analyses

Statistical analysis title	Left foot TD variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.915
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.911
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.017
upper limit	3.592

Statistical analysis title	Right foot TD variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2745
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.687
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.762
upper limit	3.737

Statistical analysis title	Left foot TD duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1148
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.598
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	2.608

Statistical analysis title	Right foot TD duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.454
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.789
upper limit	2.679

Secondary: Change from Baseline to Day 28 in the mean duration and variability of IPI as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of IPI as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The mean changes from Baseline to Day 28 in the duration and variability of IPI for the left and right feet are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left foot IPI variability	0.115 (± 0.248)	-0.108 (± 0.131)		
Right foot IPI variability	0.117 (± 0.15)	0.098 (± 0.164)		
Left foot IPI duration	0.117 (± 0.383)	-0.123 (± 0.206)		
Right foot IPI duration	0.295 (± 0.469)	0.073 (± 0.158)		

Statistical analyses

Statistical analysis title	Left foot IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	2.272
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.381
upper limit	3.737

Statistical analysis title	Right foot IPI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0204
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.686
upper limit	2.133

Statistical analysis title	Left foot IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0204
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.564
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.144
upper limit	2.138

Statistical analysis title	Right foot IPI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3144
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.269

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.856
upper limit	1.884

Secondary: Change from Baseline to Day 28 in the mean duration and variability of ITI as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean duration and variability of ITI as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The mean changes from Baseline to Day 28 in the duration and variability of ITI for the left and right feet are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: seconds				
arithmetic mean (standard deviation)				
Left foot ITI variability	0.003 (± 0.203)	-0.047 (± 0.108)		
Right foot ITI variability	0.023 (± 0.118)	-0.016 (± 0.089)		
Left foot ITI duration	-0.049 (± 0.232)	-0.076 (± 0.092)		
Right foot ITI duration	-0.016 (± 0.121)	-0.012 (± 0.056)		

Statistical analyses

Statistical analysis title	Left foot ITI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0324
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.914
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.167
upper limit	3.141

Statistical analysis title	Right foot ITI variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.462
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.85
upper limit	2.515

Statistical analysis title	Left foot ITI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1057
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.387

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.994
upper limit	1.935

Statistical analysis title	Right foot ITI duration

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7342
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.074
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.758
upper limit	1.523

Secondary: Change from Baseline to Day 28 in the mean variability of peak tapping forces (TF) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean variability of peak tapping forces (TF) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of TD in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the variability of TF for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: percentage of variation				
arithmetic mean (standard deviation)				
Left finger TF	0.65 (± 6.97)	-6.43 (± 6.26)		
Right finger TF	3.75 (± 12.86)	-0.11 (± 8.26)		

Statistical analyses

Statistical analysis title	Left finger TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1779
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.198
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.494

Statistical analysis title	Right finger TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8036
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.966
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.765
upper limit	1.22

Secondary: Change from Baseline to Day 28 in the mean tapping frequency (freq) as assessed by Digitomotography

End point title	Change from Baseline to Day 28 in the mean tapping frequency (freq) as assessed by Digitomotography

End point description:

Digitomotography was used to assess the duration and the variability of TD in an index finger speeded tapping task. The patient placed their hand on a hand rest with their index finger positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The tapping frequency was calculated as the number of taps between the onsets of the first and the last tap divided by the time in between. The mean changes from Baseline to Day 28 in the tapping frequency for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: Hertz				
arithmetic mean (standard deviation)				
Left finger freq	-0.492 (± 0.382)	-0.001 (± 0.315)		
Right finger freq	-0.466 (± 0.389)	-0.365 (± 0.231)		

Statistical analyses

Statistical analysis title	Left finger freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0177
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.812

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.706
upper limit	0.935

Statistical analysis title	Right finger freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6491
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.967
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.856
upper limit	1.093

Secondary: Change from Baseline to Day 28 in the mean variability of peak TF as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean variability of peak TF as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The mean changes from Baseline to Day 28 in the variability of TF for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day-1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: percentage of variation				
arithmetic mean (standard deviation)				
Left hand TF variability	3.5 (± 7.44)	9.98 (± 2.22)		
Right hand TF variability	2.5 (± 10.87)	3.61 (± 2.42)		

Statistical analyses

Statistical analysis title	Left hand TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5668
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.755
upper limit	1.147

Statistical analysis title	Right hand TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8686
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.978
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.778
upper limit	1.229

Secondary: Change from Baseline to Day 28 in the mean tapping frequency as assessed by Dysdiadochomotography

End point title	Change from Baseline to Day 28 in the mean tapping frequency as assessed by Dysdiadochomotography

End point description:

Dysdiadochomotography was used to assess the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps were recorded, with their hand positioned on a force transducer, and recordings were started after practice runs. The patient was then instructed to hand tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each hand. The tapping frequency was calculated as the number of taps between the onsets of the first and the last tap divided by the time in between. The mean changes from Baseline to Day 28 in the tapping frequency for the left and right hands are presented as raw data. GLS mean ratios are in original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	3		
Units: Hertz				
arithmetic mean (standard deviation)				
Left hand freq	-0.185 (± 0.402)	-0.073 (± 0.088)		
Right hand freq	-0.236 (± 0.349)	-0.121 (± 0.189)		

Statistical analyses

Statistical analysis title	Left hand freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1244
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.879

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.765
upper limit	1.009

Statistical analysis title	Right hand freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3535
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.919
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.789
upper limit	1.069

Secondary: Change from Baseline to Day 28 in the mean variability of peak TF as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean variability of peak TF as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The mean changes from Baseline to Day 28 in the variability of TF for the left and right feet are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: percentage of variation				
arithmetic mean (standard deviation)				
Left foot TF variability	11.63 (± 16.38)	-20.19 (± 34.3)		
Right foot TF variability	-2.52 (± 22.35)	-18.31 (± 6.52)		

Statistical analyses

Statistical analysis title	Left foot TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1027
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.392
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.997
upper limit	1.943

Statistical analysis title	Right foot TF variability

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4494
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	1.158

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.84
upper limit	1.595

Secondary: Change from Baseline to Day 28 in the mean tapping frequency as assessed by Pedomotography

End point title	Change from Baseline to Day 28 in the mean tapping frequency as assessed by Pedomotography

End point description:

Pedomotography was used to assess the tap duration and variability in a foot speeded tapping task. The patient placed their foot on the foot device such that the ball of the foot was positioned above a force transducer, and recordings were started after practice runs. The patient was then instructed to foot tap as fast as possible between 2 auditory cues. The beginning of a tap was defined as a rise of the force by 0.05 N above maximal baseline level. The tap ended when it dropped to 0.05 N before the maximal baseline level was reached again. 5 trials of 10 seconds duration were performed with each foot. The tapping frequency was calculated as the number of taps between the onsets of the first and the last tap divided by the time in between. The mean changes from Baseline to Day 28 in the tapping frequency for the left and right hands are presented as raw data. The statistical analyses present GLS mean ratios in the original units.

End point type	Secondary

End point timeframe:

Baseline (Day -1) to Day 28

End point values	BN82451B	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Hertz				
arithmetic mean (standard deviation)				
Left foot freq	-0.259 (± 0.513)	0.556 (± 0.678)		
Right foot freq	-0.383 (± 0.481)	-0.18 (± 0.55)		

Statistical analyses

Statistical analysis title	Left foot freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.699
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.53
upper limit	0.922

Statistical analysis title	Right foot freq

Statistical analysis description:

The MMRM analysis was performed on log-transformed data using the REML model including fixed categorical effects of treatment/cohort group, visit and treatment/cohort by visit interaction as well as the continuous fixed covariate of baseline value. Cohort was fitted as random effect.

Comparison groups	BN82451B v Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3556
Method	MMRM
Parameter estimate	GLS mean ratio
Point estimate	0.853
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.136

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to the end of study visit (a period of up to 7 weeks, consisting of up to 28 days of treatment and up to 3 weeks follow up).

Adverse event reporting additional description:

AE data is reported as TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive oral placebo b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of placebo was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 mg b.i.d.
For cohort 1, 40 mg placebo b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg placebo b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg placebo b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Reporting group title	BN82451B

Reporting group description:

Patients were randomised to receive oral study medication, BN82451B, b.i.d. from Day 1 to Day 27, under double-blinded conditions. On Day 28 only one morning dose of BN82451B was administered. It was planned for patients to be assigned to 3 cohorts to receive 3 dose levels ranging between 40 and 80 milligrams (mg) b.i.d.
For cohort 1, 40 mg BN82451B b.i.d. was administered during the first 14 days. If this dose was well tolerated then it was increased to 60 mg b.i.d. for 13 days and one morning dose of 60 mg on Day 28.
For cohort 2, 60 mg BN82451B b.i.d. was administered during the first 14 days. If 60 mg b.i.d was well tolerated then it was increased to 80 mg b.i.d. for 13 days and one morning dose of 80 mg on Day 28.
For cohort 3 it was planned to administer 80 mg BN82451B b.i.d for 27 days with one morning dose of 80 mg on Day 28. The study was terminated early before completion of cohort 2.

Serious adverse events	Placebo	BN82451B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	BN82451B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	11 / 14 (78.57%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Excoriation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	4	
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Dyskinesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	3	
Face oedema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	5 / 14 (35.71%)	
occurrences (all)	0	5	
Acne			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rash generalised			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hyperhidrosis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Impetigo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 14 (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 December 2014	Change in exclusion criteria to exclude subjects with alanine aminotransferase or aspartate aminotransferase values ≥2x upper limit of normal (ULN) or both Gamma Glutamyl Transferase (GGT) and alkaline phosphatase values >3xULN. Removal of early study termination/subject withdrawal criteria of GGT >3xULN for 2 repeated observations. Change in criteria related to dose escalation related to clinically significant laboratory abnormalities to remove criterion of GGT >2xULN and include criterion of bilirubin >2xULN.
12 November 2015	Change in inclusion criteria to include subjects aged ≥20 to ≤70 years. Extension of study duration to approximately 2 years. Administrative changes (Sponsor's medically responsible person and pharmacovigilance/emergency contact updates).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated prematurely due to subject recruitment problems before the completion of cohort 2.

Notes: