



Clinical trial results:

A double-blind, placebo-controlled, randomized dose ranging trial to determine the safety and efficacy of three dose levels of EMA401 in reducing 24-hour average pain intensity score in patients with post-herpetic neuralgia (EMPHENE)

Summary

EudraCT number	2016-000280-16
Trial protocol	DE GB SK AT NO DK ES CZ HU FR BE PT PL
Global end of trial date	07 March 2019

Results information

Result version number	v1 (current)
This version publication date	22 March 2020
First version publication date	22 March 2020

Trial information

Trial identification

Sponsor protocol code	CEMA401A2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03094195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	129
EEA total number of subjects	96

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)	19
From 65 to 84 years	106
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Two hundred thirty patients were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	EMA401 25mg BID DB
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Arm description:

Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period

Arm type	Experimental
Investigational medicinal product name	EMA401
Investigational medicinal product code	EMA401
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 12.5 mg capsules taken twice a day for a total daily dose of 50 mg per day

Arm title	EMA401 100mg BID DB
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Arm description:

Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period

Arm type	Experimental
Investigational medicinal product name	EMA401
Investigational medicinal product code	EMA401
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 50 mg capsules taken twice a day for a total daily dose of 200 mg per day

Arm title	Placebo BID DB
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Arm description:

Matching placebo capsules administered orally twice a day during double blind (DB) treatment period

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

Dosage and administration details:

2 matching placebo capsules taken twice a day

Number of subjects in period 1	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Started	43	43	43
Completed	28	30	29
Not completed	15	13	14
Consent withdrawn by subject	-	1	1
Physician decision	-	-	1
Adverse event, non-fatal	3	2	1
Study terminated by sponsor	12	10	11

Period 2

Period 2 title	Treatment withdrawal period (TW)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	EMA401 25mg BID -> EMA401 25mg BID TW

Arm description:

Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)

Arm type	Experimental
Investigational medicinal product name	EMA401
Investigational medicinal product code	EMA401
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 12.5 mg capsules taken twice a day for a total daily dose of 50 mg per day

Arm title	EMA401 25mg BID -> Placebo BID TW
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Arm description:

Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)

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

Dosage and administration details:

2 matching placebo capsules taken twice a day

Arm title	EMA401 100mg BID -> EMA401 100mg BID TW
Arm description: Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	
Arm type	Experimental
Investigational medicinal product name	EMA401
Investigational medicinal product code	EMA401
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2 50 mg capsules taken twice a day for a total daily dose of 200 mg per day	
Arm title	EMA401 100mg BID -> Placebo BID TW
Arm description: Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	
Arm type	Placebo
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2 matching placebo capsules taken twice a day	
Arm title	Placebo BID -> Placebo BID TW
Arm description: Participants on placebo remained on placebo at end of treatment period (week 12)	
Arm type	Placebo
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2 matching placebo capsules taken twice a day	

Number of subjects in period 2^[1]	EMA401 25mg BID -> EMA401 25mg BID TW	EMA401 25mg BID -> Placebo BID TW	EMA401 100mg BID -> EMA401 100mg BID TW
Started	13	13	15
Completed	13	13	15

Number of subjects in period 2^[1]	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW
Started	13	26
Completed	13	26

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all patients entered second period

Baseline characteristics

Reporting groups

Reporting group title	EMA401 25mg BID DB
Reporting group description:	
Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	
Reporting group title	EMA401 100mg BID DB
Reporting group description:	
Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	
Reporting group title	Placebo BID DB
Reporting group description:	
Matching placebo capsules administered orally twice a day during double blind (DB) treatment period	

Reporting group values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Number of subjects	43	43	43
Age Categorical			
Units: participants			
18 - 64 years	4	8	7
65 - 84 years	36	34	36
≥ 85 years	3	1	0
Sex: Female, Male			
Units: participants			
Female	20	15	30
Male	23	28	13
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	33	32	32
Asian	9	10	10
Other	1	1	1
Body mass index			
Units: kg/m ²			
median	25.9	25.2	24.9
full range (min-max)	18.4 to 36.4	17.4 to 33.0	17.9 to 39.4

Reporting group values	Total		
Number of subjects	129		
Age Categorical			
Units: participants			
18 - 64 years	19		
65 - 84 years	106		
≥ 85 years	4		
Sex: Female, Male			
Units: participants			
Female	65		
Male	64		
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	97		

Asian	29		
Other	3		

Body mass index			
Units: kg/m2			
median			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	EMA401 25mg BID DB
Reporting group description: Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	
Reporting group title	EMA401 100mg BID DB
Reporting group description: Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	
Reporting group title	Placebo BID DB
Reporting group description: Matching placebo capsules administered orally twice a day during double blind (DB) treatment period	
Reporting group title	EMA401 25mg BID -> EMA401 25mg BID TW
Reporting group description: Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)	
Reporting group title	EMA401 25mg BID -> Placebo BID TW
Reporting group description: Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)	
Reporting group title	EMA401 100mg BID -> EMA401 100mg BID TW
Reporting group description: Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	
Reporting group title	EMA401 100mg BID -> Placebo BID TW
Reporting group description: Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	
Reporting group title	Placebo BID -> Placebo BID TW
Reporting group description: Participants on placebo remained on placebo at end of treatment period (week 12)	

Primary: Dose-response in change in weekly mean of the 24-hour average pain score, using an 11-point Numeric Rating Scale (NRS), from Baseline to Week 12

End point title	Dose-response in change in weekly mean of the 24-hour average pain score, using an 11-point Numeric Rating Scale (NRS), from Baseline to Week 12 ^[1]
End point description: Since the 300 mg b.i.d. dose of EMA401 could not be initiated in the study due to premature study termination, the dose-response characterization was not performed. Specifically, only the trend test deduced from the set of candidate models was performed but the dose response estimation was not conducted.	
End point type	Primary
End point timeframe: Baseline up to Week 12	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was done because the high dose was never implemented due to study termination	

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: scores on a scale				
number (not applicable)				

Notes:

[2] - Study was terminated and 300 mg dose was not initiated

[3] - Study was terminated and 300 mg dose was not initiated

[4] - Study was terminated and 300 mg dose was not initiated

Statistical analyses

No statistical analyses for this end point

Secondary: Change in weekly mean 24-hour average pain score using the 11 point Numerical Rating Scale (NRS) from Baseline to Week 12

End point title	Change in weekly mean 24-hour average pain score using the 11 point Numerical Rating Scale (NRS) from Baseline to Week 12
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End point description:

The NRS is an 11-point scale ranging from zero ("no pain") to ten ("pain as bad as you can imagine") for self-reporting of pain by patients. The following parameters were evaluated using the 11-point NRS: 24-hour Average Pain Score and 24-hour Worst Pain Score. Patients evaluated their "average pain" and "worst pain" during the past 24 hours in the evening prior to sleep by touching the appropriate corresponding number between zero and ten on a eDiary device.

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: scores on a scale				
least squares mean (standard error)				
Week 4	-0.4 (± 0.23)	-0.9 (± 0.25)	-0.5 (± 0.23)	
Week 8	-1.0 (± 0.29)	-1.0 (± 0.29)	-0.7 (± 0.30)	
Week 12	-0.9 (± 0.40)	-1.2 (± 0.38)	-0.7 (± 0.40)	

Statistical analyses

Statistical analysis title	EMA401 25mg BID vs Placebo
Comparison groups	EMA401 25mg BID DB v Placebo BID DB

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.689
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	EMA401 100mg BID vs Placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.35
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.54

Secondary: Change in Brief Pain Inventory-Short Form interference (BPI-SF) mean total score from Baseline to Week 12

End point title	Change in Brief Pain Inventory-Short Form interference (BPI-SF) mean total score from Baseline to Week 12
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End point description:

The BPI-SF is a validated, self-administered (at clinic) questionnaire that assesses pain severity and its impact on daily functions. Patients were asked to complete the 7-item pain interference scale that assessed the degree to which pain interfered with walking and other physical activity, work, mood, relations with others and sleep using a zero to ten numeric rating scale (NRS) with zero being "does not interfere" and ten being "completely interferes". A reduction in mean indicates improvement

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: scores on a numeric rating scale				
arithmetic mean (standard deviation)	-8.24 (± 12.994)	-15.03 (± 13.280)	-14.07 (± 12.535)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS, from Baseline to Week 12

End point title	Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS, from Baseline to Week 12
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End point description:

The NRS is an 11-point scale ranging from zero ("no pain") to ten ("pain as bad as you can imagine") for self-reporting of pain by patients. The following parameters were evaluated using the 11-point NRS: 24-hour Average Pain Score and 24-hour Worst Pain Score. Patients evaluated their "average pain" and "worst pain" during the past 24 hours in the evening prior to sleep by touching the appropriate corresponding number between zero and ten on a eDiary device.

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: scores on numeric rating scale				
arithmetic mean (standard deviation)	-1.04 (± 1.851)	-1.96 (± 2.365)	-1.49 (± 2.215)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants per Patient Global Impression of Change category at Week 12

End point title	Number of participants per Patient Global Impression of Change category at Week 12
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End point description:

The Patient Global Impression of Change (PGIC) is a patient-reported instrument that measures change in overall status on a scale ranging from one ("very much improved") to seven ("very much worse"). The PGIC is based on the validated Clinical Global Impression of Change scale.

The PGIC was to be completed by patients using the electronic tablet at the site

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: participants				
Very much improved	1	0	2	
Much improved	2	5	7	
Minimally improved	9	12	9	
No change	20	18	12	
Minimally worse	3	2	1	
Much worse	1	0	3	
Very much worse	0	0	0	
Missing	7	6	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving at least 30% pain reduction at Week 12 on NRS 11 point scale

End point title	Percentage of patients achieving at least 30% pain reduction at Week 12 on NRS 11 point scale
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End point description:

The NRS is an 11-point scale ranging from zero ("no pain") to ten ("pain as bad as you can imagine") for self-reporting of pain by patients. The number of patients with observed response, i.e. a decrease of 30% /50% units in weekly mean of the 24-hour average pain score NRS. Logistic regression model with region, treatment, sex, use of PHN medications (yes/no) as factors and age and baseline NRS as covariates. An odds ratio >1 = higher chance of a clinically important improvement.

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: % of participants - model adjusted rate				
number (not applicable)				
Week 4 - at least 30% pain reduction	7.5	15.6	12.6	
Week 12 - at least 30% pain reduction	22.3	29.6	23.6	

Statistical analyses

Statistical analysis title	EMA401 25mg BID vs Placebo
Comparison groups	EMA401 25mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.908
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.2

Statistical analysis title	EMA401 100mg BID vs Placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.609
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	4.5

Secondary: Percentage of patients achieving at least 50% pain reduction at Week 12 on NRS 11 point scale

End point title	Percentage of patients achieving at least 50% pain reduction at
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End point description:

The NRS is an 11-point scale ranging from zero ("no pain") to ten ("pain as bad as you can imagine") for self-reporting of pain by patients. The number of patients with observed response, i.e. a decrease of 50% units in weekly mean of the 24-hour average pain score NRS. Logistic regression model with region, treatment, sex, use of PHN medications (yes/no) as factors and age and baseline NRS as covariates. An odds ratio >1 = higher chance of a clinically important improvement.

End point type

Secondary

End point timeframe:

Baseline up to Week 12

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: % of participants - model adjusted rate				
number (not applicable)	12.0	13.4	10.3	

Statistical analyses

Statistical analysis title	EMA401 25mg BID vs Placebo
Comparison groups	EMA401 25mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.2

Statistical analysis title	EMA401 100mg BID vs Placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.653
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	4.5

Secondary: Mean change in Insomnia Severity Index (ISI) from Baseline to Week 12

End point title	Mean change in Insomnia Severity Index (ISI) from Baseline to Week 12
End point description: Patients were asked to complete the ISI using five-point Likert-style scale as a measure of perceived sleep difficulties. Scores ranged from zero to 28, with a cut-off score of eight suggesting the presence of sub-threshold insomnia. The questionnaire assessed the severity of insomnia, satisfaction with current sleep pattern, sleep interference, "noticeability" of sleeping problem to others and concern about sleeping problems.	
End point type	Secondary
End point timeframe: Baseline up to Week 12	

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: scores on a scale				
arithmetic mean (standard deviation)	-1.29 (± 4.529)	-4.14 (± 5.146)	-3.44 (± 4.228)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Neuropathic Pain Symptom Inventory (NPSI) from Baseline to Week 12

End point title	Change in Neuropathic Pain Symptom Inventory (NPSI) from Baseline to Week 12
End point description: The NPSI is a 12-item patient reported outcome measure that contains 10 descriptors representing 5 dimensions of pain (burning pain, deep/pressing pain, paroxysmal pain, evoked pain and paraesthesia/dysesthesia) and 2 temporal items designed to assess pain duration and the number of pain paroxysms. The NPSI was to be completed by patients using the electronic tablet at the site	
End point type	Secondary
End point timeframe: Baseline up to Week 12	

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: scores on a scale				
least squares mean (standard error)	-0.4 (± 0.35)	-1.0 (± 0.37)	-1.0 (± 0.38)	

Statistical analyses

Statistical analysis title	EMA401 25mg BID vs Placebo
Comparison groups	EMA401 25mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.225
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.49

Statistical analysis title	EMA401 100mg BID vs Placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.914
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.53

Secondary: Plasma Pharmacokinetic (PK) Concentrations at Weeks 8 and 12

End point title	Plasma Pharmacokinetic (PK) Concentrations at Weeks 8 and 12 ^[5]
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End point description:

Due to the premature termination of the study, the number of patients and observations providing PK data was much smaller than planned, and no PK model was developed. As a consequence, no PK parameters (C_{max}, T_{max}, AUC) were derived for this study. Only, summary statistics of the plasma concentrations were calculated

End point type	Secondary
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End point timeframe:

Week 8, Week 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics only done on EMA401 arms

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 8 Prior dose n=26,31	6.4 (± 6.13)	27.2 (± 37.88)		
Week 8 1-3 hours n=26,31	120.7 (± 110.47)	356.3 (± 336.49)		
Week 8 4-6 hours n= n=28,31	16.6 (± 13.21)	62.5 (± 50.53)		
Week 12 Prior dose n=25,28	5.4 (± 3.94)	16.4 (± 10.93)		
Week 12 1-3 hours n=25,27	108.9 (± 88.57)	289.6 (± 241.92)		
Week 12 4-6 hours n=25,28	22.8 (± 37.63)	89.9 (± 88.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure-response (decrease in pain intensity) via Evaluation of effect of EMA401 exposure on efficacy variables (e.g. change from baseline of pain score), via descriptive Pharmacokinetics/ Pharmacodynamics (PK/PD)

End point title	Exposure-response (decrease in pain intensity) via Evaluation of effect of EMA401 exposure on efficacy variables (e.g. change from baseline of pain score), via descriptive Pharmacokinetics/ Pharmacodynamics (PK/PD) ^[6]
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End point description:

Due to the premature termination of the study, the number of patients providing data for PKPD analysis data was much smaller than planned and no model to correlate drug exposure (PK) with the change in the pain score (PD) was developed

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 12

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was done

End point values	EMA401 25mg BID DB	EMA401 100mg BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: scores on a scale				
arithmetic mean (standard deviation)	10 (± 1)	10 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Emergent Adverse Events during Urgent Safety Measure (USM) Follow-Up

End point title	Treatment Emergent Adverse Events during Urgent Safety Measure (USM) Follow-Up
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End point description:

Participants were instructed to stop taking drug immediately upon termination of study and asked to come in for two unscheduled visits for follow up safety assessments

End point type	Secondary
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End point timeframe:

Approximately from 3 weeks after end of study up to 16 weeks

End point values	EMA401 25mg BID -> EMA401 25mg BID TW	EMA401 25mg BID -> Placebo BID TW	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	15	13
Units: participants				
Blood creatinine increased	0	1	0	0
Blood potassium increased	0	1	0	0
Glomerular filtration rate decreased	0	1	0	1
Alanine aminotransferase increased	0	0	0	1
Blood creatine phosphokinase increased	0	0	0	1
Blood glucose increased	0	0	1	0

End point values	Placebo BID -> Placebo BID TW			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: participants				

Blood creatinine increased	0			
Blood potassium increased	0			
Glomerular filtration rate decreased	0			
Alanine aminotransferase increased	0			
Blood creatine phosphokinase increased	0			
Blood glucose increased	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of 123 days

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus the 28 days post treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	EMA401 25 mg b.i.d. DB
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Reporting group description:

Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period

Reporting group title	EMA401 100 mg b.i.d. DB
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Reporting group description:

Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period

Reporting group title	Placebo b.i.d. DB
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Reporting group description:

Matching placebo capsules administered orally twice a day during double blind (DB) treatment period

Reporting group title	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. TW
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Reporting group description:

Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)

Reporting group title	EMA401 25 mg b.i.d. - Placebo b.i.d. TW
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Reporting group description:

Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)

Reporting group title	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.
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Reporting group description:

Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)

Reporting group title	EMA401 100 mg b.i.d. - Placebo b.i.d. TW
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Reporting group description:

Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)

Reporting group title	Placebo b.i.d. - Placebo b.i.d. TW
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Reporting group description:

Participants on placebo remained on placebo at end of treatment period (week 12)

Serious adverse events	EMA401 25 mg b.i.d. DB	EMA401 100 mg b.i.d. DB	Placebo b.i.d. DB
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	3 / 43 (6.98%)	3 / 43 (6.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. TW	EMA401 25 mg b.i.d. - Placebo b.i.d. TW	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Traumatic haematoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EMA401 100 mg b.i.d. - Placebo b.i.d. TW	Placebo b.i.d. - Placebo b.i.d. TW	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	EMA401 25 mg b.i.d. DB	EMA401 100 mg b.i.d. DB	Placebo b.i.d. DB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 43 (18.60%)	12 / 43 (27.91%)	14 / 43 (32.56%)
Investigations			
Amylase increased			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Blood creatinine increased			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	1 / 43 (2.33%)	3 / 43 (6.98%)	0 / 43 (0.00%)
occurrences (all)	1	3	0
Injury, poisoning and procedural complications			

Tongue injury subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 43 (0.00%) 0	0 / 43 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 43 (2.33%) 1	3 / 43 (6.98%) 3
Headache subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	2 / 43 (4.65%) 2	3 / 43 (6.98%) 4
Post herpetic neuralgia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 43 (0.00%) 0	1 / 43 (2.33%) 1
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	2 / 43 (4.65%) 2	3 / 43 (6.98%) 3
Dyspepsia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	3 / 43 (6.98%) 3	1 / 43 (2.33%) 1
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	2 / 43 (4.65%) 2	4 / 43 (9.30%) 4
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	2 / 43 (4.65%) 2	3 / 43 (6.98%) 3

Non-serious adverse events	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. TW	EMA401 25 mg b.i.d. - Placebo b.i.d. TW	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	2 / 15 (13.33%)
Investigations			
Amylase increased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Blood creatinine increased			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	1 / 15 (6.67%) 1
Lipase increased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Injury, poisoning and procedural complications Tongue injury subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	1 / 15 (6.67%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Post herpetic neuralgia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1	0 / 15 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 13 (0.00%) 0	0 / 15 (0.00%) 0

Non-serious adverse events	EMA401 100 mg b.i.d. - Placebo b.i.d. TW	Placebo b.i.d. - Placebo b.i.d. TW	
Total subjects affected by non-serious adverse events			

subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Lipase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Tongue injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			

subjects affected / exposed	0 / 13 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2018	- Update of Inclusion criteria #5 to modify the wording related to inadequate treatment response to at least two different therapies of PHN for more clarity: two previous therapies with inadequate treatment response also include analgesics prescribed for the treatment of PHN by general practitioners and other treating physicians. - Update of Inclusion criteria #6 to include the patient's willingness to complete eDiary. - Update of Exclusion criteria #3 to clarify the comorbid ECG abnormalities. - Update of Exclusion criteria #6 considering the total study duration of only 13 weeks, the medical history of malignancy of any organ system in the past 2 years before screening was considered to be sufficient for the study. - Update of Exclusion criteria #10 on Women of Child Bearing Potential (WOCBP) was based on the latest toxicity data. - Deletion of Exclusion criteria #11 based on the data from genotoxic studies, as well as from the recently completed reproductive toxicity studies. - Update of Exclusion criteria #14 to include positive urine drug screen at Screening. - Update of Exclusion criteria #15 to clarify that patients with only active gallbladder or bile duct disease were not considered for the study. - Deletion of Exclusion criteria #21 to consider for enrolment patients who had previously taken herpes zoster vaccine (HZV). - The patients who needed to come off the prohibited concomitant medication after Screening visit had to take last dose of prohibited concomitant medication at least 2 weeks (14 days) prior to V101 (i.e. Baseline visit)

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.

Study was terminated early due to preclinical toxicity data. Novartis discontinued study treatment immediately and patients were instructed to return for additional laboratory due to Urgent Safety Measure. Related AE data was reported in separate End

Notes: