NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Olodanrigan

Trial Indication(s)

Post-herpetic neuralgia

Protocol Number

CEMA401A2201

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: June 2017 (Actual)
Primary Completion Date: March 2019 (Actual)
Study Completion Date: March 2019 (Actual)

Reason for Termination (If applicable)

The study was terminated early due to pre-clinical toxicity data that became available after start of trial

Study Design/Methodology

This was an interventional, randomized, parallel, placebo-controlled, dose ranging, double blind treatment study consisting of 3 epochs i.e. Screening, Treatment, and Treatment withdrawal. The study was planned in two cohorts. The initial cohort had three treatment arms i.e. Placebo b.i.d., EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d. Following an unblinded safety review by an independent data monitoring committee the second cohort was to be initiated that had an additional treatment arm i.e. EMA401 300 mg b.i.d. Due to the premature study termination, the second cohort was not initiated. A total of 360 patients were planned to be enrolled in the study. Owing to early study termination, the planned sample size was not attained. Thus, total number of patients screened and randomized at study termination were 230 and 129, respectively.

Upon study termination, Novartis implemented an Urgent Safety Measure (USM) which instructed sites to discontinue study treatment immediately and to have all patients return for additional laboratory assessments (full hematology including. coagulation and clinical chemistry panel). Safety data from the USM was presented in a separate secondary outcome measure and not included in the Adverse Event reporting.

Centers

45 centers in 16 countries: Germany(7), United Kingdom(2), Denmark(1), Norway(1), Austria(2), Slovakia (Slovak Republic)(3), Belgium(1), France(2), Hungary(3), Portugal(2), Czech Republic(4), Spain(2), Japan(10), Canada(3), Italy(1), Poland(1)

Objectives:

Primary objective:

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

Secondary objectives:

- To compare the efficacy of EMA401 vs. placebo in 24-hour average pain intensity score at Week 12, using an 11-point Numeric Rating Scale (NRS) by testing the superiority of at least one active dose of EMA401 vs. placebo.
- To evaluate the efficacy of EMA401 compared to placebo, as measured by the Brief Pain Inventory-Short Form (BPI-SF) interference total score at Week 12.
- To evaluate the efficacy of EMA401 compared to placebo, as measured by the weekly mean of the 24-hour worst pain intensity score, using an 11-point numeric rating scale at Week 12.
- To evaluate the efficacy of EMA401 compared to placebo, on the Patient Global Impression of Change (PGIC) at Week 12.
- To evaluate the proportion of EMA401 patients achieving a ≥ 30% and a ≥ 50% reduction in weekly mean 24-hour average pain intensity score using the numeric rating scale compared to placebo (i.e., responder rates) at Week 12.
- To evaluate the effect of EMA401 compared to placebo on the Insomnia Severity Index (ISI) at Week 12.
- To evaluate the effect of EMA401 compared to placebo on the Neuropathic Pain Symptom Inventory (NPSI) at Week 12.
- To evaluate the safety and tolerability of EMA401 compared to placebo in post-herpetic neuralgia (PHN) patients, as measured by treatment emergent adverse events (TEAEs), adverse events (AEs) leading to study drug discontinuation and serious adverse events (SAEs) throughout the study.
- To evaluate the pharmacokinetics (PK) of EMA401 and exposure-response (decrease in pain intensity) relationship for EMA401 throughout the study.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral capsules of EMA401 25 mg b.i.d., EMA 100 mg b.i.d., Placebo

Statistical Methods

Efficacy:

The primary analysis population was the full analysis set that comprised of all randomized patients. Mis-randomized patients were excluded from the full analysis set.

The primary estimation method was based on an Analysis of Covariance (ANCOVA) model including region (e.g. America or Europe and Australia, Asia), treatment, sex, use of concomitant pain medication for post-herpetic neuralgia (yes/no) as factors and age and baseline (mean pain intensity) score as covariates.

Since the EMA 300 mg b.i.d. dose was not initiated, the dose-response characterization was not carried out. Specifically, the trend tests deduced from the set of candidate models were performed; however, the dose response estimation was not conducted. In this case, the first secondary objective was to be evaluated to compare the efficacy of the remaining doses of EMA401 over placebo in 24-hour average pain intensity score at Week 12, using an 11-point numeric rating scale. This comparison was done by testing the null hypothesis of superiority of at least one active dose of EMA401 over placebo, while adjusting for multiplicity. The estimation of the treatment effect of primary clinical interest (primary estimand) was performed taking into account the intercurrent events of changes in dose of concomitant medication for PHN, intake of rescue medication, intake of prohibited medications with potential confounding effect prior to study treatment discontinuation, discontinuation of study treatment due to a) AEs, b) lack of efficacy, c) use of prohibited medication and d) other reasons. The handling of the affected observations and missing data was done via multiple imputation using different imputation mechanisms based on reason of study treatment discontinuation. Multiplicity adjustment for the pairwise comparisons was performed using the Hochberg procedure.

The same ANCOVA model was applied at the visits prior to Week 12.

Safety:

Safety analyses were conducted using the safety set that comprised of all patients who took at least one dose of study medication and who had at least one post-baseline safety assessment. Patients were analyzed by the actual treatment received. All the safety analyses including AEs, vital signs, laboratory assessments, ECGs and Columbia-Suicide Severity Rating Scale (C-SSRS) were reported for double blind treatment epoch as well as for the treatment withdrawal epoch separately.

Laboratory assessments performed at the additional unscheduled follow-up visits due to the early termination and USM were presented in a separate secondary outcome measure table.

Study Population: Key Inclusion/Exclusion Criteria

- Inclusion Criteria:
  - At the time of Screening, must have had documented diagnosis of PHN (ICD-10 code B02.29), defined as pain in the region of the rash persisting for more than 6 months after onset of herpes zoster rash.
  - Assessed as suffering from moderate to severe neuropathic pain across the Screening epoch (NRS ≥ 4).

- Patients must have had documented past and/or ongoing inadequate treatment response (having insufficient pain relief with treatment or inability to tolerate) to at least 2 different prescribed therapies commonly used to treat and considered effective by the Investigator for the treatment of PHN.
- Patient must have been willing to complete daily eDiary

Exclusion Criteria:
- History or had current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study
- Had a major depressive episode within 6 months prior to Screening and/or a history of diagnosed recurrent major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.
- Had evidence of significant renal insufficiency or pre-existing liver condition
- Had platelets ≤ 100 x 10^9/L, or neutrophil count < 1.2 x 10^9/L (or equivalent), hemoglobin ≤ 100 g/L for women or hemoglobin ≤ 110 g/L for men.
- Patients who had a known diagnosis of diabetes and are stable on medication with a hemoglobin A1c > 8%. Those who did not have a known diagnosis of diabetes with a hemoglobin A1c > 7%.

Participant Flow Table

Double-Blind Treatment Period (DB)

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

			treatment period	treatment period (week 12)	treatment period (week 12)	treatment period (week 12)	treatment period (week 12)		
Started	43	43	43	0	0	0	0	0	129
Completed	28	30	29	0	0	0	0	0	87
Not Completed	15	13	14	0	0	0	0	0	42
Study terminated by sponsor	12	10	11	0	0	0	0	0	33
Adverse Event	3	2	1	0	0	0	0	0	6
Physician Decision	0	0	1	0	0	0	0	0	1
Withdrawal by Subject	0	1	1	0	0	0	0	0	2

Treatment withdrawal period (TW)

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

Started	0	0	0	13	13	15	13	26	80
Completed	0	0	0	13	13	15	13	26	80
Not Completed	0	0	0	0	0	0	0	0	0

Baseline Characteristics

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB	Total
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period	
Number of Participants [units: participants]	43	43	43	129
Age, Customized (units: participants)				
18 - 64 years	4	8	7	19
65 - 84 years	36	34	36	106
≥ 85 years	3	1	0	4
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	20	15	30	65

Male	23	28	13	64
Race/Ethnicity, Customized (units: participants)				
Caucasian	33	32	32	97
Asian	9	10	10	29
Other	1	1	1	3
Body mass index (units: kg/m2) Median (Full Range)				
	25.9 (18.4 to 36.4)	25.2 (17.4 to 33.0)	24.9 (17.9 to 39.4)	25.4 (17.4 to 39.4)

Summary of Efficacy

Primary Outcome Result(s)

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period

Number of Participants Analyzed [units: participants]	0	0	0
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 (units:) ()			

Secondary Outcome Result(s)

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43

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

Groups	EMA401 25mg BID DB, Placebo BID DB	
P Value	0.689	
Method	ANCOVA	Multiplicity adjustment for the pairwise comparisons has been performed using the Hochberg procedure. Adjusted p-value 0.689
Other least squares mean	-0.2	
Standard Error of the mean	0.56	
95 % Confidence Interval 2-Sided	-1.3 to 0.9	

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB	
P Value	0.350	
Method	ANCOVA	Multiplicity adjustment for the pairwise comparisons has been performed using

		the Hochberg procedure. Adjusted p-value 0.689
Other LS Mean	-0.5	
Standard Error of the mean	0.54	
95 % Confidence Interval 2-Sided	-1.6 to 0.6	

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	**EMA401 100mg BID DB**	**Placebo BID DB**
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Change in Brief Pain Inventory-Short Form interference (BPI-SF) mean total score from Baseline to Week 12 (units: scores on a numeric rating scale) Mean ± Standard Deviation			

	-8.24 ± 12.994	-15.03 ± 13.280	-14.07 ± 12.535

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS, from Baseline to Week 12 (units: scores on numeric rating scale) Mean ± Standard Deviation			
n=24,24,24	-1.04 ± 1.851	-1.96 ± 2,365	-1.49 ± 2.215

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Number of participants per Patient Global Impression of Change category at Week 12 (units: participants) Count of Participants (Not Applicable)			
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

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Percentage of patients achieving at least 30% pain reduction at Week 12 on NRS 11 point scale (units: % of participants - model adjusted rate)			
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 Analysis

Groups	EMA401 25mg BID DB, Placebo BID DB
P Value	0.908
Method	Regression, Logistic
Odds Ratio (OR)	0.9

95 % Confidence Interval 2-Sided	0.3 to 3.2

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB
P Value	0.609
Method	Regression, Logistic
Odds Ratio (OR)	1.4
95 % Confidence Interval 2-Sided	0.4 to 4.5

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	**EMA401 100mg BID DB**	**Placebo BID DB**
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Percentage of patients achieving at least 50% pain reduction at Week			

12 on NRS 11 point scale (units: % of participants - model adjusted rate)			
Week 12 - at least 50% pain reduction	12.0	13.4	10.3

Statistical Analysis

Groups	EMA401 25mg BID DB, Placebo BID DB
P Value	0.800
Method	Regression, Logistic
Odds Ratio (OR)	0.9
95 % Confidence Interval 2-Sided	0.3 to 3.2

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB
P Value	0.653
Method	Regression, Logistic
Odds Ratio (OR)	1.4
95 % Confidence Interval 2-Sided	0.4 to 4.5

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period	Matching placebo capsules administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Mean change in Insomnia Severity Index (ISI) from Baseline to Week 12 (units: scores on a scale) Mean ± Standard Deviation			
	-1.29 ± 4.529	-4.14 ± 5.146	-3.44 ± 4.228

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

(Time Frame: Baseline up to Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB)	Ema401 100 mg was administered orally twice a day during double blind (DB)	Matching placebo capsules administered orally twice a day during double blind

	treatment period	treatment period	(DB) treatment period
Number of Participants Analyzed [units: participants]	43	43	43
Change in Neuropathic Pain Symptom Inventory (NPSI) from Baseline to Week 12 (units: scores on a scale) Least Squares Mean ± Standard Error			
	-0.4 ± 0.35	-1.0 ± 0.37	-1.0 ± 0.38

Statistical Analysis

Groups	EMA401 25mg BID DB, Placebo BID DB
P Value	0.225
Method	ANCOVA
Other LS mean difference	0.6
Standard Error of the mean	0.49
95 % Confidence Interval 2-Sided	-0.4 to 1.6

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB
P Value	0.914

Method	ANCOVA
Other LS mean difference	0.1
Standard Error of the mean	0.53
95 % Confidence Interval 2-Sided	-1.0 to 1.1

Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12

(Time Frame: Week 8, Week 12)

	EMA401 25mg BID DB	EMA401 100mg BID DB
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	28	31
Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
Week 8 Prior dose n=26,31	4.8 (86.3%)	15.9 (134.0%)
Week 8 1-3 hours n=26,31	75.9 (159.9%)	226.9 (138.5%)
Week 8 4-6 hours n= n=28,31	12.6 (86.6%)	48.9 (79.1%)

Week 12 Prior dose n=25,28	4.9 (69.3%)	13.6 (67.7%)
Week 12 1-3 hours n=25,27	69.3 (163.7%)	184.00 (178.4%)
Week 12 4-6 hours n=25,28	13.7 (112.2%)	63.6 (98.1%)

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)
(Time Frame: Baseline, Week 8, Week 12)

	EMA401 25mg BID DB	**EMA401 100mg BID DB**
Arm/Group Description	Ema401 25 mg was administered orally twice a day during double blind (DB) treatment period	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	0	0
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) (units: scores on a scale)		

Mean ± Standard Deviation

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

(Time Frame: Approximately from 3 weeks after end of study up to 16 weeks)

	EMA401 25mg BID -> EMA401 25mg BID	EMA401 25mg BID -> Placebo BID	EMA401 100mg BID -> EMA401 100mg BID	EMA401 100mg BID -> Placebo BID	Placebo BID -> Placebo BID
Arm/Group Description	Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)	Participants on EMA401 25mg were randomized 1:1 to EMA401 25mg or placebo at end of treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of treatment period (week 12)	Participants on placebo remained on placebo at end of treatment period (week 12)
Number of Participants Analyzed [units: participants]	22	21	22	21	43
Treatment Emergent Adverse Events during Urgent Safety Measure (USM) Follow-Up (units: participants) Count of Participants (Not Applicable)					
Blood creatinine increased	0	1	0	0	0
Blood potassium increased	0	1	0	0	0
Glomerular filtration rate decreased	0	1	0	1	0
Alanine aminotransferase increased	0	0	0	1	0

Blood creatine phosphokinase increased	0	0	0	1	0
Blood glucose increased	0	0	1	0	0

Summary of Safety

Safety Results

All-Cause Mortality

	EMA401 25 mg b.i.d. N = 43	EMA401 100 mg b.i.d. N = 43	Placebo b.i.d. N = 43	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. N = 13	EMA401 25 mg b.i.d. - Placebo b.i.d. N = 13	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d. N = 15	EMA401 100 mg b.i.d. - Placebo b.i.d. N = 13	Placebo b.i.d. - Placebo b.i.d. N = 26
Arm/Group Description	EMA401 25 mg b.i.d.	EMA401 100 mg b.i.d.	Placebo b.i.d.	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d.	EMA401 25 mg b.i.d. - Placebo b.i.d.	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.	EMA401 100 mg b.i.d. - Placebo b.i.d.	Placebo b.i.d. - Placebo b.i.d.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	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
Additional Description	Any sign or symptom that occurs during the study treatment plus the 28 days post treatment
Source Vocabulary for Table Default	MedDRA (22.0)

Assessment Type for Table Default Systematic Assessment

	EMA401 25 mg b.i.d. N = 43	EMA401 100 mg b.i.d. N = 43	Placebo b.i.d. N = 43	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. N = 13	EMA401 25 mg b.i.d. - Placebo b.i.d. N = 13	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d. N = 15	EMA401 100 mg b.i.d. - Placebo b.i.d. N = 13	Placebo b.i.d. - Placebo b.i.d. N = 26
Arm/Group Description	EMA401 25 mg b.i.d.	EMA401 100 mg b.i.d.	Placebo b.i.d.	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d.	EMA401 25 mg b.i.d. - Placebo b.i.d.	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.	EMA401 100 mg b.i.d. - Placebo b.i.d.	Placebo b.i.d. - Placebo b.i.d.
Total participants affected	0 (0.00%)	3 (6.98%)	3 (6.98%)	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders								
Angina pectoris	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions								
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations								
Lower respiratory tract infection	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications								
Traumatic haematoma	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations								
Electrocardiogram ST segment elevation	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Musculoskeletal and connective tissue disorders								
Back pain	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoarthritis	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Central nervous system lymphoma	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders								
Lumbar radiculopathy	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	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
Additional Description	Any sign or symptom that occurs during the study treatment plus the 28 days post treatment
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	EMA401 25 mg b.i.d. N = 43	**EMA401 100 mg b.i.d. N = 43**	**Placebo b.i.d. N = 43**	**EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d. N = 13**	**EMA401 25 mg b.i.d. - Placebo b.i.d. N = 13**	**EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d. N = 15**	**EMA401 100 mg b.i.d. - Placebo b.i.d. N = 13**	**Placebo b.i.d. - Placebo b.i.d. N = 26**

Arm/Group Description	EMA401 25 mg b.i.d.	EMA401 100 mg b.i.d.	Placebo b.i.d.	EMA401 25 mg b.i.d. - EMA401 25 mg b.i.d.	EMA401 25 mg b.i.d. - Placebo b.i.d.	EMA401 100 mg b.i.d. - EMA401 100 mg b.i.d.	EMA401 100 mg b.i.d. - Placebo b.i.d.	Placebo b.i.d. - Placebo b.i.d.
Total participants affected	8 (18.60%)	12 (27.91%)	14 (32.56%)	0 (0.00%)	1 (7.69%)	2 (13.33%)	1 (7.69%)	1 (3.85%)
Gastrointestinal disorders								
Diarrhoea	3 (6.98%)	2 (4.65%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspepsia	0 (0.00%)	3 (6.98%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations								
Nasopharyngitis	3 (6.98%)	2 (4.65%)	4 (9.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	2 (4.65%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications								
Tongue injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Investigations								
Amylase increased	1 (2.33%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Blood creatinine increased	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Lipase increased	1 (2.33%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Nervous system disorders								
Dizziness	1 (2.33%)	1 (2.33%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	2 (4.65%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post herpetic neuralgia	1 (2.33%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	1 (7.69%)	0 (0.00%)	0 (0.00%)	1 (3.85%)

Other Relevant Findings

N/A

Conclusion:

- The purpose of this study was to characterize the dose-response relationship of three different doses of EMA401 and evaluate the safety and efficacy of the EMA401 at these doses as compared to placebo in patients with PHN.
- The study was terminated early due to pre-clinical toxicity data that became available after start of trial.
- EMA401 was generally safe and well tolerated in PHN patients at the tested doses of 25 mg b.i.d. and 100 mg b.i.d. in this study. No liver events as defined in the protocol were reported in any of the treated patients during the study.
- Additionally, reduction in pain from baseline was observed in all the treatment arms including placebo over the 12 weeks of treatment. The pattern of pain reduction was slightly different for EMA401 25 mg b.i.d. and EMA401 100 mg b.i.d. arms with no clear separation after Week 4. However, the efficacy of EMA401 in the treatment of PHN patients could not be confirmed in this study due to premature study termination.

Date of Clinical Trial Report

23-Jan-2020