NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Olodanrigan

Trial Indication(s)

Painful diabetic neuropathy

Protocol Number

CEMA401A2202

Protocol Title

A double-blind, placebo-controlled, randomized trial to determine the safety and efficacy of EMA401 in reducing 24-hour average pain intensity score in patients with painful diabetic neuropathy (EMPADINE)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: March 2018 (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. Novartis implemented an Urgent Safety Measure (USM) and instructed sites to discontinue study 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 separately in an outcome measure separate from the Adverse Event reporting.

Study Design/Methodology

This was an interventional, randomized, parallel, placebo-controlled, double-blind study consisting of 3 periods i.e. Screening, double-blind Treatment (12 weeks planned duration), and double-blind Treatment withdrawal (1 week planned duration). Patients were randomized in a 1:1 ratio to Placebo b.i.d. or EMA401 100 mg b.i.d treatment arms. At the end of the double-blind treatment period patients receiving active treatment were randomized in a 1:1 ratio to either stop treatment abruptly (i.e. receive placebo) or to continue the active treatment assigned during the double-blind treatment epoch for an additional week.

A total of 400 patients were planned to be enrolled in the study but due to early study termination, the planned sample size was not attained. Thus, total number of patients randomized at study termination was 137.

Centers

49 centers in 16 countries: Norway(1), Slovakia (Slovak Republic)(3), United Kingdom(4), Australia(3), Hungary(6), Belgium(3), Denmark(3), Spain(2), Austria(2), Germany(7), Canada(4), Finland(1), Portugal(3), Poland(3), Bulgaria(3), France(1)

Objectives:

Primary objective:

- 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 EMA401 100 mg b.i.d. vs. placebo.

Key secondary objective:

- To compare the efficacy of EMA401 vs. placebo in Neuropathic Pain Symptom Inventory (NPSI) by testing the superiority of EMA401 100 mg b.i.d. vs. placebo.

Secondary objectives:

- 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 the24-hour worst pain intensity score, using an 11-point NRS 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 NRS 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 safety and tolerability of EMA401 compared to placebo in painful diabetic neuropathy (PDN) 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.
- To evaluate the proportion of patients who need rescue medication separately for the double-blind treatment epoch and treatment withdrawal epoch and the time first intake of rescue medication during the double-blind treatment epoch.

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

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

Statistical Methods

Efficacy:

The primary analysis population was the FAS that comprised of all randomized patients.

The primary efficacy variable was change from baseline to Week 12 in the weekly mean of the 24-hour average pain score, using an 11-point NRS. The key secondary efficacy endpoint was change from baseline to Week 12 in the NPSI total score calculated as the sum of 10 descriptors outcome measure out of the 12 items measured in the NPSI.

Premature study termination had an impact on the power for the final efficacy analysis of EMA401 in PDN since not all planned patients (N=400) were enrolled in the study (N=137 in the FAS). For this reason, the p-values reported for the primary endpoint and key secondary endpoint for the comparison of 100 mg b.i.d. dose vs. placebo are intended only as descriptive measures and should be interpreted with caution.

Safety:
Safety analyses were conducted using the Safety Analysis Set that comprised of all patients who took at least one dose of study medication. Patients were analyzed by the actual treatment received. All the safety analyses were reported for double blind treatment period as well as for the treatment withdrawal period separately.

Laboratory assessments performed at the additional unscheduled follow-up visits (which resulted in a reportable adverse events) and other adverse events collected more than 21 days after the end of study, for each patient, were not included in the adverse event summary tables. These adverse events were only listed in the outcome measure table Treatment Emergent Adverse Events during Urgent Safety Measure period.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- At the time of Screening, must have had documented diagnosis of Type I OR Type II diabetes mellitus (DM) with painful distal symmetrical sensorimotor neuropathy (ICD-10 code G63.2) of more than 6 months duration with any one or more of the following:
--Neuropathic symptoms (e.g. numbness, non-painful paresthesias or tingling, non-painful sensory distortions or misinterpretations, etc.)
--Decreased distal sensation (e.g. decreased vibration, pinprick sensation, light touch, etc.)

-Been assessed as suffering from moderate to severe neuropathic pain across the Screening epoch (NRS ≥ 4).
-A score of ≥4 on the Douleur Neuropathique en 4 Questions (DN4) questionnaire at Screening.

Exclusion Criteria:
-Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for 3 days after stopping of study medication. Highly effective contraception methods included:
--Total abstinence (when this was is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception.
--Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow up hormone level assessment.
--Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should have been the sole partner for that subject.
--Placement of an intrauterine device (IUD) or intrauterine system (IUS).

- History or current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study.
- 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.
- 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.
- Participants whose glycemic control had been unstable within 3 months immediately prior to screening (e.g., ketoacidosis requiring hospitalization, any recent episode of hypoglycemia requiring assistance through medical intervention, uncontrolled hyperglycemia)
- Patients who had any differential diagnosis of PDN including but not limited to other neuropathies (e.g. Vitamin B12 deficiency, Chronic Inflammatory Demyelinating Polyneuropathy), polyradiculopathies, central disorders (e.g. demyelinating disease), or rheumatological disease (e.g., foot arthritis, plantar fasciitis).
- Patient was unwilling or unable to complete daily eDiary.

Participant Flow Table

Double-Blind Treatment Period (DB)

	EMA401 100mg BID DB	Placebo BID DB	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW	Total
Arm/Group Description	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 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on placebo remained on placebo at end of DB treatment period (week 12)	
Started	70	67	0	0	0	137
Completed	32	30	0	0	0	62
Not Completed	38	37	0	0	0	75
Study terminated by sponsor	30	31	0	0	0	61
Withdrawal by Subject	4	4	0	0	0	8
Adverse Event	3	1	0	0	0	4
Physician Decision	1	1	0	0	0	2

Treatment withdrawal period (TW)

	EMA401 100mg BID DB	Placebo BID DB	EMA401 100mg BID -> EMA401	EMA401 100mg BID ->	Placebo BID -> Placebo BID TW	Total

			100mg BID TW	Placebo BID TW		
Arm/Group Description	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 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on placebo remained on placebo at end of DB treatment period (week 12)	
Started	0	0	14	12	27	53
Completed	0	0	14	11	27	52
Not Completed	0	0	0	1	0	1
Study terminated by sponsor	0	0	0	1	0	1

Baseline Characteristics

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

	treatment period	treatment period	
Number of Participants [units: participants]	70	67	137
Age, Customized (units:) Count of Participants (Not Applicable)			
18 - 64 years	34	33	67
65 - 84 years	36	33	69
≥ 85 years	0	1	1
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	20	24	44
Male	50	43	93
Race/Ethnicity, Customized (units:) Count of Participants (Not Applicable)			
Caucasian	70	63	133
Asian	0	1	1
Other	0	3	3
Body mass index (units: kg/m2) Median (Full Range)			
	30.8 (22.7 to 43.2)	30.2 (19.5 to 48.2)	30.6 (19.5 to 48.2)

Summary of Efficacy

Primary 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 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
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	-1.0 ± 0.21	-0.8 ± 0.18
Week 8	-1.7 ± 0.29	-1.1 ± 0.26
Week 12	-1.9 ± 0.31	-1.3 ± 0.27

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB	
Non-Inferiority/Equivalence Test	Superiority	at week 12
P Value	0.101	

Method	ANCOVA
Other least squares mean	-0.6
Standard Error of the mean	0.39
95 % Confidence Interval 2-Sided	-1.4 to 0.1

Secondary Outcome Result(s)

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

(Time Frame: Baseline up to Week 12)

	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
Change in Neuropathic Pain Symptom Inventory (NPSI) from Baseline to Week 12 (units: scores on a scale) Least Squares Mean ± Standard Error		
Week 4	-1.2 ± 0.19	-1.0 ± 0.18

Week 8	-1.3 ± 0.25	-0.9 ± 0.22
Week 12	-1.6 ± 0.32	-1.1 ± 0.26

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB	At week 12
P Value	0.168	
Method	ANCOVA	
Other LS mean difference	-0.5	
Standard Error of the mean	0.38	
95 % Confidence Interval 2-Sided	-1.3 to 0.2	

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 100mg BID DB	**Placebo BID DB**
Arm/Group Description	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]	70	67
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		
	-12.03 ± 13.336	-10.83 ± 14.602

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 100mg BID DB	**Placebo BID DB**
Arm/Group Description	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]	70	67
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=29,29	-1.63 ± 1.837	-1.28 ± 1.577

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

(Time Frame: Baseline up to Week 12)

	EMA401 100mg BID DB	**Placebo BID DB**
Arm/Group Description	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]	70	67
Number of participants per Patient Global Impression of Change category at Week 12 (units: participants) Count of Participants (Not Applicable)		
Very much improved	4	2
Much improved	7	11
Minimally improved	17	18
No change	18	14
Minimally worse	3	2

Much worse	0	0
Very much worse	0	0
Missing	21	20

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 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
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 n=18,14	34.0	24.7
Week 12 - at least 30% pain reduction n=14,12	52.7	40.4

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB

P Value	0.255
Method	Regression, Logistic
Odds Ratio (OR)	1.6
95 % Confidence Interval 2-Sided	0.7 to 3.9

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 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
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 n=8,4	31.4	14.1

Statistical Analysis

Groups	EMA401 100mg BID DB, Placebo BID DB
P Value	0.100
Method	Regression, Logistic
Odds Ratio (OR)	2.8
95 % Confidence Interval 2-Sided	0.8 to 9.6

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

(Time Frame: Baseline up to Week 12)

	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
Mean change in Insomnia Severity Index (ISI) from Baseline to Week 12 (units: scores on a scale)		

Mean ± Standard Deviation		
n=33,33	-4.00 ± 4.854	-1.03 ± 6.312

Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12

(Time Frame: Week 8, Week 12)

	EMA401 100mg BID DB
Arm/Group Description	Ema401 100 mg was administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	32
Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)	
Week 8 Prior dose n=32	30.5 (126.6%)
Week 8 1-3 hours n=32	205.1 (212.8%)
Week 8 4-6 hours n=32	72.8 (115.2%)
Week 12 Prior dose n=25	29.5 (209.3%)
Week 12 1-3 hours n=26	118.4 (278.3%)
Week 12 4-6 hours n=26	89.8 (117.0%)

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 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW
Arm/Group Description	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on placebo remained on placebo at end of DB treatment period (week 12)
Number of Participants Analyzed [units: participants]	34	35	66
Treatment Emergent Adverse Events during Urgent Safety Measure (USM) Follow-Up (units: participants) Count of Participants (Not Applicable)			
Peritoneal adhesions	1	0	0
Cholelithiasis	1	0	0
Liver abscess	1	0	0
Blood creatinine increased	0	0	1

Percentage of patients who required rescue medication in double-blind treatment period

(Time Frame: Baseline up Week 12)

	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	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]	70	67
Percentage of patients who required rescue medication in double-blind treatment period (units: Percentage of participants)		
Week 1	13.0	10.6
Week 2	7.7	9.5
Week 4	8.6	7.0
Week 6	7.8	7.5
Week 8	9.3	9.5
Week 10	5.3	13.2
Week 12	2.9	8.6
At least once during double-blind period	20.0	19.4

Percentage of patients who required rescue medication in treatment withdrawal period

(Time Frame: Week 12 to Week 13)

	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW
Arm/Group Description	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on placebo remained on placebo at end of DB treatment period (week 12)
Number of Participants Analyzed [units: participants]	35	35	67
Percentage of patients who required rescue medication in treatment withdrawal period (units: Percentage of participants)			
Week 13	14.3	8.3	7.4

Time to first rescue medication intake

(Time Frame: Baseline up to week 12)

	EMA401 100mg BID DB	Placebo BID DB
Arm/Group Description	Ema401 100 mg was administered	Matching placebo capsules

	orally twice a day during double blind (DB) treatment period	administered orally twice a day during double blind (DB) treatment period
Number of Participants Analyzed [units: participants]	70	67
Time to first rescue medication intake (units: days) Median (Full Range)		
Time to 1st med n=14,13 (took rescue med)	44.0 (2 to 90)	56.5 (2 to 92)

Summary of Safety

Safety Results

All-Cause Mortality

	EMA401 100mg BID DB N = 69	Placebo BID DB N = 66	EMA401 100mg BID -> EMA401 100mg BID TW N = 14	EMA401 100mg BID -> Placebo BID TW N = 12	Placebo BID -> Placebo BID TW N = 26
Arm/Group Description	Ema401 100 mg was administered orally twice a	Matching placebo capsules administered	Participants on EMA401 100mg were randomized	Participants on EMA401 100mg were randomized	Participants on placebo remained on placebo at

	day during double blind (DB) treatment period	orally twice a day during double blind (DB) treatment period	1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	end of DB treatment period (week 12)
Total participants affected	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 21 days post treatment, up to maximum duration of 111 days
Additional Description	Any sign or symptom that occurs during the study treatment plus the 21 days post treatment
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment

	EMA401 100mg BID DB N = 69	**Placebo BID DB N = 66**	**EMA401 100mg BID -> EMA401 100mg BID TW N = 14**	**EMA401 100mg BID -> Placebo BID TW N = 12**	**Placebo BID -> Placebo BID TW N = 26**
Arm/Group Description	Ema401 100 mg was administered orally twice a day during double blind (DB)	Matching placebo capsules administered orally twice a day during double blind (DB)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at	Participants on placebo remained on placebo at end of DB treatment

	treatment period	treatment period	end of DB treatment period (week 12)	end of DB treatment period (week 12)	period (week 12)
Total participants affected	5 (7.25%)	3 (4.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders					
Acute coronary syndrome	0 (0.00%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions					
Product intolerance	1 (1.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders					
Cholecystitis acute	2 (2.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholelithiasis	1 (1.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations					
Erysipelas	0 (0.00%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Localised infection	1 (1.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Chronic obstructive pulmonary disease	0 (0.00%)	1 (1.52%)	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 21 days post treatment, up to maximum duration of 111 days
Additional Description	Any sign or symptom that occurs during the study treatment plus the 21 days post treatment
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	EMA401 100mg BID DB N = 69	**Placebo BID DB N = 66**	**EMA401 100mg BID -> EMA401 100mg BID TW N = 14**	**EMA401 100mg BID -> Placebo BID TW N = 12**	**Placebo BID -> Placebo BID TW N = 26**
Arm/Group Description	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 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on EMA401 100mg were randomized 1:1 to EMA401 100mg or placebo at end of DB treatment period (week 12)	Participants on placebo remained on placebo at end of DB treatment period (week 12)
Total participants affected	23 (33.33%)	10 (15.15%)	1 (7.14%)	2 (16.67%)	0 (0.00%)
Cardiac disorders					
Palpitations	0 (0.00%)	1 (1.52%)	0 (0.00%)	1 (8.33%)	0 (0.00%)
Gastrointestinal disorders					
Abdominal pain upper	5 (7.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Nausea	4 (5.80%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations					
Nasopharyngitis	4 (5.80%)	6 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations					
Gamma-glutamyltransferase increased	4 (5.80%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lipase increased	6 (8.70%)	0 (0.00%)	1 (7.14%)	0 (0.00%)	0 (0.00%)
Nervous system disorders					
Headache	4 (5.80%)	4 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders					
Hypertension	1 (1.45%)	2 (3.03%)	0 (0.00%)	1 (8.33%)	0 (0.00%)

Other Relevant Findings

N/A

Conclusion:

- 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 PDN patients at the dose of 100 mg b.i.d. in this study. No liver events as defined in the protocol were reported in any of the treated patients in the EMA401 arm during the study.
- Additionally, reduction in pain from baseline was observed in both the treatment arms over the 12 weeks of treatment however; the reduction was numerically in favor of EMA401. The efficacy of EMA401 in the treatment of PDN patients could not be confirmed in this study due to premature study termination.

Date of Clinical Trial Report

04-Feb-2020