Clinical trial results:
A double-blind, placebo-controlled, randomized trial to determine the safety and efficacy of EMA401 100 mg b.i.d. in reducing 24-hour average pain intensity score in patients with painful diabetic neuropathy (EMPADINE)

Summary

EudraCT number	2016-000281-39
Trial protocol	NO GB HU ES DK BE SK FI DE AT PT BG
Global end of trial date	25 March 2019

Results information

Result version number	v1 (current)
This version publication date	06 April 2020
First version publication date	06 April 2020

Trial information

Trial identification

Sponsor protocol code	CEMA401A2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03297294
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	25 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

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	14 March 2018
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	Australia: 6
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	137
EEA total number of subjects	123

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)	67
From 65 to 84 years	69
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Three hundred six patients were screened and 137 randomized

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	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	EMA401 100mg BID DB

Arm description:

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

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

Dosage and administration details:

2 50 mg capsules b.i.d taken orally

Arm title	Placebo BID DB

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 b.i.d.

Number of subjects in period 1	EMA401 100mg BID DB	Placebo BID DB
Started	70	67
Completed	32	30
Not completed	38	37
Consent withdrawn by subject	4	4
Physician decision	1	1

Adverse event, non-fatal	3	1
Study Terminated by Sponsor	30	31

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 100mg BID -> EMA401 100mg BID TW

Arm description:

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

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

Dosage and administration details:

2 50 mg capsules b.i.d taken orally

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 DB 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 b.i.d.

Arm title	Placebo BID -> Placebo BID TW

Arm description:

Participants on placebo remained on placebo at end of DB 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 b.i.d.

Number of subjects in period 2[1]	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW
Started	14	12	27
Completed	14	11	27
Not completed	0	1	0
Study Terminated by Sponsor	-	1	-

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: All subjects who completed the double-blind treatment period did not enter the treatment withdrawal period

Baseline characteristics

Reporting groups	
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 100mg BID DB	Placebo BID DB	Total
Number of subjects	70	67	137
Age Categorical Units:			
18 - 64 years	34	33	67
65 - 84 years	36	33	69
≥ 85 years	0	1	1
Sex: Female, Male Units: participants			
Female	20	24	44
Male	50	43	93
Race/Ethnicity, Customized Units: Subjects			
Caucasian	70	63	133
Asian	0	1	1
Other	0	3	3
Body mass index Units: kg/m2			
median	30.8	30.2	
full range (min-max)	22.7 to 43.2	19.5 to 48.2	-

End points

End points reporting groups

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 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 DB 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 DB treatment period (week 12)	
Reporting group title	Placebo BID -> Placebo BID TW
Reporting group description:	
Participants on placebo remained on placebo at end of DB treatment period (week 12)	

Primary: 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
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	Primary
End point timeframe:	
Baseline up to Week 12	

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
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 analyses

Statistical analysis title	EMA401 vs placebo at week 12
Comparison groups	Placebo BID DB v EMA401 100mg BID DB
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.101
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.39

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 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
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 analyses

Statistical analysis title	EMA401 vs placebo at week 12
Comparison groups	EMA401 100mg BID DB v Placebo BID DB

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.168
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.38

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

End point description:

The BPI-SF is a validated, self-administered (at clinic) questionnaire that assesses pain severity and its mpact 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

End point timeframe:

Baseline up to Week 12

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: scores on a numeric rating scale				
arithmetic mean (standard deviation)	-12.03 (± 13.336)	-10.83 (± 14.602)		

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

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

End point timeframe:

Baseline up to Week 12

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: scores on numeric rating scale				
arithmetic mean (standard deviation)	-1.63 (± 1.837)	-1.28 (± 1.577)		

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

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

End point timeframe:

Baseline up to Week 12

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: participants				
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		

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

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% 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 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: % of participants - model adjusted rate				
number (not applicable)				
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 analyses

Statistical analysis title	EMA401 vs placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.255
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	3.9

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 Week 12 on NRS 11 point scale

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 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[1]	67[2]		
Units: % of participants - model adjusted rate				
number (not applicable)	31.4	14.1		

Notes:

[1] - Responders n=8

[2] - Responders n=4

Statistical analyses

Statistical analysis title	EMA401 vs placebo
Comparison groups	EMA401 100mg BID DB v Placebo BID DB
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	9.6

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 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: scores on a scale				
arithmetic mean (standard deviation)	-4.00 (± 4.854)	-1.03 (± 6.312)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12

End point title	Plasma Pharmacokinetics (PK) Concentrations at Week 8 and 12[3]

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 (Cmax, Tmax, AUC) were derived for this study. Only, summary statistics of the plasma concentrations were calculated

End point type	Secondary

End point timeframe:

Week 8, Week 12

Notes:

[3] - 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 analysis was performed

End point values	EMA401 100mg BID DB			
Subject group type	Reporting group			
Number of subjects analysed	32			
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)			

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

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

End point timeframe:

From 3 weeks after end of study up to 16 weeks after end of study

End point values	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	27	
Units: participants				
Peritoneal adhesions	1	0	0	
Cholelithiasis	1	0	0	
Liver abscess	1	0	0	
Blood creatinine increased	0	0	1	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Patients were allowed to take acetaminophen/paracetamol up to a maximum of 3 g daily (divided into 4 times/day) for unacceptable pain due to any reason during the study. This medication use was to be recorded in eDiary prior to use. Percentages of patients presented are those who required rescue meds within 7 days prior to visit.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	67		
Units: Percentage of participants				
number (not applicable)				
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		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who required rescue medication in treatment withdrawal period

End point title	Percentage of patients who required rescue medication in treatment withdrawal period

End point description:

Patients were allowed to take acetaminophen/paracetamol up to a maximum of 3 g daily (divided into 4 times/day) for unacceptable pain due
to any reason during the study. This medication use was to be recorded in eDiary prior to use. Percentages of patients presented are those
who required rescue meds within 7 days prior to visit.

End point type	Secondary

End point timeframe:

Week 12 to Week 13

End point values	EMA401 100mg BID -> EMA401 100mg BID TW	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	27	
Units: Percentage of patients				
number (not applicable)	14.3	8.3	7.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first rescue medication intake

End point title	Time to first rescue medication intake

End point description:

Patients were allowed to take acetaminophen/paracetamol up to a maximum of 3 g daily (divided into 4 times/day) for unacceptable pain due to any reason during the study. This medication use was to be recorded in eDiary prior to use. Patients who did not take any rescue medication were censored at the last date of double-blind treatment period.

End point type	Secondary

End point timeframe:

Baseline up to week 12

End point values	EMA401 100mg BID DB	Placebo BID DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[4]	67[5]		
Units: days				
median (full range (min-max))	44.0 (2 to 90)	56.5 (2 to 92)		

Notes:

[4] - 14 required rescue medication

[5] - 13 required rescue medication

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 21 days post treatment, up to maximum duration of 111 days	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the study treatment plus the 21 days post treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
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 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 DB 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 DB treatment period (week 12)	
Reporting group title	Placebo BID -> Placebo BID TW
Reporting group description:	
Participants on placebo remained on placebo at end of DB treatment period (week 12)	

Serious adverse events	EMA401 100mg BID DB	Placebo BID DB	EMA401 100mg BID -> EMA401 100mg BID TW
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 69 (7.25%)	3 / 66 (4.55%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Product intolerance			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 69 (2.90%)	0 / 66 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	0 / 14 (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
Localised infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 66 (0.00%)	0 / 14 (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

Serious adverse events	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 12 (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			
Product intolerance			
subjects affected / exposed	0 / 12 (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	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 12 (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	
Cholelithiasis			
subjects affected / exposed	0 / 12 (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	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 12 (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			
Erysipelas			
subjects affected / exposed	0 / 12 (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	
Localised infection			
subjects affected / exposed	0 / 12 (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 100mg BID DB	Placebo BID DB	EMA401 100mg BID -> EMA401 100mg BID TW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 69 (33.33%)	10 / 66 (15.15%)	1 / 14 (7.14%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 69 (5.80%)	1 / 66 (1.52%)	0 / 14 (0.00%)
occurrences (all)	4	1	0
Lipase increased			
subjects affected / exposed	6 / 69 (8.70%)	0 / 66 (0.00%)	1 / 14 (7.14%)
occurrences (all)	6	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 69 (1.45%)	2 / 66 (3.03%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 69 (0.00%)	1 / 66 (1.52%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 69 (5.80%)	4 / 66 (6.06%)	0 / 14 (0.00%)
occurrences (all)	4	5	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 69 (7.25%)	0 / 66 (0.00%)	0 / 14 (0.00%)
occurrences (all)	5	0	0
Nausea			
subjects affected / exposed	4 / 69 (5.80%)	1 / 66 (1.52%)	0 / 14 (0.00%)
occurrences (all)	4	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 69 (5.80%)	6 / 66 (9.09%)	0 / 14 (0.00%)
occurrences (all)	4	7	0

Non-serious adverse events	EMA401 100mg BID -> Placebo BID TW	Placebo BID -> Placebo BID TW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	0 / 26 (0.00%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Lipase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 12 (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? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported