Clinical trial results:
A double-blind, placebo-controlled, randomised trial to prove the therapeutic concept and to determine the safety, tolerability and pharmacokinetic profile of EMA401 (angiotensin II type 2 receptor antagonist) administered orally in patients with postherpetic neuralgia

Summary

EudraCT number	2011-000977-29
Trial protocol	CZ BG
Global end of trial date	11 July 2012

Results information

Result version number	v1 (current)
This version publication date	12 June 2016
First version publication date	12 June 2016

Trial information

Trial identification

Sponsor protocol code	EMA401-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	11 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of EMA401 when administered orally, twice daily (100 mg b.i.d.), in patients with postherpetic neuralgia, as assessed by difference in mean pain intensity score compared to 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	10 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Georgia: 14
Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	Ukraine: 68
Country: Number of subjects enrolled	South Africa: 44
Worldwide total number of subjects	183
EEA total number of subjects	50

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)	81
From 65 to 84 years	97
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligibility for the study was determined by Screening tests and fulfilment of eligibility criteria including assessment of pain. Seven consecutive days of pain assessment was required during the 14 day Screening Period.

Period 1

Period 1 title	Treatment plus Follow-up Period (overall period)
Is this the baseline period?	Yes
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 100 mg BID

Arm description:

Two EMA401 50 mg capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of 100 mg on the morning of Day 29. Followed by a follow-up period until day 42.

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

Dosage and administration details:

Two EMA401 50 mg capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of 100 mg on the morning of Day 29.

Arm title	Placebo BID

Arm description:

Two placebo capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of placebo on the morning of Day 29. Followed by a follow-up period until day 42.

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

Dosage and administration details:

Two placebo capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of placebo on the morning of Day 29.

Number of subjects in period 1	EMA401 100 mg BID	Placebo BID
Started	92	91
Completed	86	83
Not completed	6	8
Consent withdrawn during follow-up	1	1
Adverse event, non-fatal	1	3
Consent withdrawn during treatment period	4	4

Baseline characteristics

Reporting groups	
Reporting group title	EMA401 100 mg BID
Reporting group description:	
Two EMA401 50 mg capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of 100 mg on the morning of Day 29. Followed by a follow-up period until day 42.	
Reporting group title	Placebo BID
Reporting group description:	
Two placebo capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of placebo on the morning of Day 29. Followed by a follow-up period until day 42.	

Reporting group values	EMA401 100 mg BID	Placebo BID	Total
Number of subjects	92	91	183
Age categorical			
Units: Subjects			
Adults (18-64 years)	40	41	81
From 65-84 years	50	47	97
85 years and over	2	3	5
Age continuous			
Units: years			
arithmetic mean	62.5	63.4	
standard deviation	± 14.9	± 14.4	-
Gender categorical			
Units: Subjects			
Female	49	51	100
Male	43	40	83

End points

End points reporting groups

Reporting group title	EMA401 100 mg BID

Reporting group description:

Two EMA401 50 mg capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of 100 mg on the morning of Day 29. Followed by a follow-up period until day 42.

Reporting group title	Placebo BID

Reporting group description:

Two placebo capsules twice daily (morning and evening), at least 1 hour before a meal, for 28 days, and a single dose of placebo on the morning of Day 29. Followed by a follow-up period until day 42.

Primary: Change from Baseline in Mean Pain Intensity Score at Week 4

End point title	Change from Baseline in Mean Pain Intensity Score at Week 4

End point description:

The daily pain intensity score was assessed using the 11-Point Numerical Rating Scale/Likert Scale (NRS). Every evening, patients evaluated their average pain during the past 24 hours by circling the appropriate corresponding number between 0 (“no pain”) and 10 (“pain as bad as you can imagine”). LOCF= last observation carried forward

End point type	Primary

End point timeframe:

Baseline and Week 4

End point values	EMA401 100 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[1]	91[2]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline	6.306 (± 1.024)	6.325 (± 1.086)		
Week 4	4.017 (± 2.054)	4.724 (± 1.896)		
Change from Baseline at Week 4	-2.289 (± 1.753)	-1.601 (± 1.661)		

Notes:

[1] - Change from Baseline at Week 4 N's are based on LOCF imputation method for missing data.

[2] - Change from Baseline at Week 4 N's are based on LOCF imputation method for missing data.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	EMA401 100 mg BID v Placebo BID

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0066 [3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.6922
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1888
upper limit	-0.1957
Variability estimate	Standard error of the mean
Dispersion value	0.2516

Notes:

[3] - p-value for treatment group comparison was based on ANCOVA with baseline mean of pain intensity score, treatment, age and gender as covariates.

Secondary: Change from Baseline in Mean Pain Intesity Score at Weeks 1, 2 and 3

End point title	Change from Baseline in Mean Pain Intesity Score at Weeks 1, 2 and 3

End point description:

The daily pain intensity score was assessed using the 11-Point Numerical Rating Scale/Likert Scale (NRS). Every evening, patients evaluated their average pain during the past 24 hours by circling the appropriate corresponding number between 0 ("no pain") and 10 ("pain as bad as you can imagine").

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2 and 3

End point values	EMA401 100 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[4]	91[5]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Change from Baseline at Week 1	-0.675 (± 0.927)	-0.546 (± 1.096)		
Change from Baseline at Week 2	-1.272 (± 1.165)	-1.037 (± 1.398)		
Change from Baseline at Week 3	-1.786 (± 1.461)	-1.254 (± 1.553)		

Notes:

[4] - Based on LOCF imputation method for missing data.

[5] - Based on LOCF imputation method for missing data.

Statistical analyses

Statistical analysis title	Statistical Analysis - Week 1
Comparison groups	EMA401 100 mg BID v Placebo BID

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4153 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.1228
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4197
upper limit	0.174
Variability estimate	Standard error of the mean
Dispersion value	0.1504

Notes:

[6] - p-value for treatment group comparison was based on ANCOVA with baseline mean of pain intensity score, treatment, age and gender as covariates.

Statistical analysis title	Statistical Analysis - Week 2
Comparison groups	EMA401 100 mg BID v Placebo BID
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2217 [7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.234
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6105
upper limit	0.1425
Variability estimate	Standard error of the mean
Dispersion value	0.1908

Notes:

[7] - p-value for treatment group comparison was based on ANCOVA with baseline mean of pain intensity score, treatment, age and gender as covariates.

Statistical analysis title	Statistical Analysis - Week 3
Comparison groups	EMA401 100 mg BID v Placebo BID
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0188 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.5264
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9645
upper limit	-0.0883

Variability estimate	Standard error of the mean
Dispersion value	0.222

Notes:

[8] - p-value for treatment group comparison was based on ANCOVA with baseline mean of pain intensity score, treatment, age and gender as covariates.

Secondary: Percentage of Participants Achieving a ≥ 30% Decrease in Mean Pain Intensity Score from Baseline to Week 4

End point title	Percentage of Participants Achieving a ≥ 30% Decrease in Mean Pain Intensity Score from Baseline to Week 4

End point description:

The daily pain intensity score was assessed using the 11-Point Numerical Rating Scale/Likert Scale (NRS). Every evening, patients evaluated their average pain during the past 24 hours by circling the appropriate corresponding number between 0 ("no pain") and 10 ("pain as bad as you can imagine"). Participants with available Week 4 data were classified as responders when the mean pain intensity score was at least 30% lower than it was at Baseline.

End point type	Secondary

End point timeframe:

Week 4

End point values	EMA401 100 mg BID	Placebo BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	91		
Units: percentage of participants				
number (not applicable)	56.5	34.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	EMA401 100 mg BID v Placebo BID
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0024 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.392
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.719

Notes:

[9] - p-value for treatment group comparison was based on logistic regression model including baseline mean pain intensity score, treatment, age and gender as covariates.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Treatment Emergent Serious Adverse Events (SAEs) for the Safety Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	EMA401 100 mg BID
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	EMA401 100 mg BID	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 92 (1.09%)	2 / 91 (2.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	EMA401 100 mg BID	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 92 (17.39%)	9 / 91 (9.89%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 92 (6.52%)	2 / 91 (2.20%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 92 (1.09%)	3 / 91 (3.30%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	3 / 92 (3.26%)	3 / 91 (3.30%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	3 / 92 (3.26%)	1 / 91 (1.10%)	
occurrences (all)	3	1	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	3 / 92 (3.26%)	0 / 91 (0.00%)	
occurrences (all)	3	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