Clinical trial results:
A Phase 2 open label biomarker study of angiotensin II type 2 receptor antagonist EMA401 for the treatment of pain in patients with chemotherapy-induced peripheral neuropathy.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2011-004033-13
Trial protocol	GB
Global end of trial date	09 May 2014

Results information

Result version number	v1 (current)
This version publication date	05 July 2018
First version publication date	05 July 2018

Trial information

Trial identification

Sponsor protocol code	EMA401-005

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	Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, 41 613241111 ,
Scientific contact	Novartis Pharma AG, 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	09 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of EMA401 100 mg orally twice daily for 28 days in reducing spontaneous neuropathic pain from baseline to Week 4 in patients with chemotherapy-induced peripheral neuropathy (CIPN).

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	20 September 2012
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	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	17

From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential patients were contacted to describe general inclusion criteria, including diagnosis, medical history and current medications.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	EMA401 100 mg BID

Arm description: -

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:

EMA401 Sodium Salt was presented as 50 mg capsules.
Patients were asked to self-administer 2 capsules, each containing 50 mg EMA401, twice a day (morning and evening) for 28 days (i.e. a dose of 100 mg twice daily for a total daily dose of 200 mg). Capsules were to be taken on an empty stomach at least 1 hour before a meal, with at least 200 mL non-carbonated water.

Number of subjects in period 1	EMA401 100 mg BID
Started	31
Completing the Treatment Period	28
Completing the Follow-Up Period	29
Completed	28
Not completed	3
Physician decision	1
Consent withdrawn by subject	1
Inability or failure to comply with protocol	1

Baseline characteristics

Reporting groups	
Reporting group title	EMA401 100 mg BID

Reporting group description: -

Reporting group values	EMA401 100 mg BID	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	14	14	
Age continuous Units: years			
arithmetic mean	60.3		
standard deviation	± 12.46	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	14	14	

End points

End points reporting groups

Reporting group title	EMA401 100 mg BID
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all patients who received EMA401 and for whom at least one post-dosing efficacy assessment was available.

Primary: Change in Spontaneous Mean Pain Intensity Score from Baseline

End point title	Change in Spontaneous Mean Pain Intensity Score from Baseline[1]

End point description:

Patients evaluated their average pain since their last self-assessment by circling the appropriate corresponding number between 0 ("no pain") and 10 ("pain as bad as you can imagine").

End point type	Primary

End point timeframe:

Baseline and Week 4

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses have not been specified for this primary end point as only one arm is reported.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30[2]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline	6.5 (± 1.58)			
Week 1	6.1 (± 1.87)			
Change from Baseline at Week 1	-0.4 (± 0.81)			
Week 2	6 (± 2.05)			
Change from Baseline at Week 2	-0.7 (± 0.94)			
Week 3	5.5 (± 1.98)			
Change from Baseline at Week 3	-1 (± 1.04)			
Week 4	5.3 (± 2.15)			
Change from Baseline at Week 4	-1.3 (± 1.25)			
Follow-up	5.7 (± 2.36)			
Change from Baseline at Follow-up	-1 (± 1.7)			

Notes:

[2] - Baseline n=30, Week 1 n=30, Week 2 n=27, Week 3 n=27, Week 4 n= 27, Follow-up n= 28

Statistical analyses

No statistical analyses for this end point

Secondary: Decrease of at Least 30% in Spontaneous Mean Pain Intensity Score over Time

End point title	Decrease of at Least 30% in Spontaneous Mean Pain Intensity Score over Time

End point description:

Patients evaluated their average pain since their last self-assessment 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, can be classified as responders when the mean pain intensity score was at least 30% lower at Week 4 compared to Baseline.

End point type	Secondary

End point timeframe:

Week 4

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: Percentage of participants				
number (confidence interval 95%)				
Baseline	0 (0 to 0)			
Week 1 n=30	6.7 (0.8 to 22.1)			
Week 2 n=27	7.4 (0.9 to 24.3)			
Week 3 n=27	7.4 (0.9 to 24.3)			
Week 4 n=27	29.6 (13.8 to 50.2)			
Follow-Up n=28	25 (10.7 to 44.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Evoked (Light Touch) Mean Pain Intensity Score from Baseline over Time

End point title	Change in Evoked (Light Touch) Mean Pain Intensity Score from Baseline over Time

End point description:

Patients evaluated their average pain since their last self-assessment 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 to Week 4

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30[3]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline	3.8 (± 3.07)			
Week 1	3.5 (± 2.92)			
Change from Baseline at Week 1	-0.3 (± 1.8)			
Week 2	3.3 (± 3.03)			
Change from Baseline at Week 2	-0.6 (± 1.52)			
Week 3	3.2 (± 3.01)			
Change from Baseline at Week 3	-0.6 (± 1.73)			
Week 4	3 (± 3.02)			
Change from Baseline at Week 4	-0.8 (± 1.62)			
Follow-up	3.3 (± 3.24)			
Change from Baseline at Follow-up	-0.4 (± 1.55)			

Notes:

[3] - Baseline n=30, Week 1 n=30, Week 2 n=27, Week 3 n=27, Week 4 n= 27, Follow-up n= 28

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Evoked (Cold Touch) Mean Pain Intensity Score over Time

End point title	Change in Evoked (Cold Touch) Mean Pain Intensity Score over Time

End point description:

Patients evaluated their average pain since their last self-assessment 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 to Week 4

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30[4]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline	3.8 (± 3.42)			
Week 1	3.5 (± 3.44)			
Change from Baseline at Week 1	-0.4 (± 1.36)			
Week 2	3.3 (± 3.29)			
Change from Baseline at Week 2	-0.5 (± 1.68)			
Week 3	2.9 (± 3.33)			
Change from Baseline at Week 3	-0.8 (± 1.72)			
Week 4	2.8 (± 3.27)			
Change from Baseline at Week 4	-1 (± 1.67)			
Follow-up	3.1 (± 3.27)			

Change from Baseline at Follow-up	-0.6 (± 2.21)			

Notes:

[4] - Baseline n=30, Week 1 n=30, Week 2 n=27, Week 3 n=27, Week 4 n= 27, Follow-up n= 28

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Short Form McGill Pain Questionnaire-2 Scores from Baseline

End point title	Change in Short Form McGill Pain Questionnaire-2 Scores from Baseline

End point description:

The SF-MPQ-2 is a 22-item self-administered patient questionnaire that is used to measure the different qualities of pain and related symptoms. The questionnaire provides patients with a list of words that describe some of the different qualities of pain and related symptoms and patients rated the intensity of each type of pain they felt during the past week on a scale from 0 to 10.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and Follow-Up visits

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30[5]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Total Pain - Baseline	72.1 (± 43.79)			
Total Pain - Week 4	48.7 (± 44.71)			
Total Pain - Early Withdrawal	122 (± 57.98)			
Total Pain - Follow-Up	57.9 (± 45.39)			
Continuous Pain - Baseline	18.9 (± 12.42)			
Continuous Pain - Week 4	13.3 (± 13.89)			
Continuous Pain - Early Withdrawal	29 (± 16.97)			
Continuous Pain - Follow-Up	16.1 (± 12.97)			
Intermittent Pain - Baseline	16 (± 15.02)			
Intermittent Pain - Week 4	9.8 (± 11.16)			
Intermittent Pain - Early Withdrawal	28.5 (± 26.16)			
Intermittent Pain - Follow-Up	13 (± 14.77)			
Neuropathic Pain - Baseline	25.8 (± 12.87)			
Neuropathic Pain - Week 4	18.4 (± 14.95)			
Neuropathic Pain - Early Withdrawal	31 (± 18.38)			
Neuropathic Pain - Follow-Up	21.1 (± 14.18)			
Affective Descriptors - Baseline	11.3 (± 10.67)			
Affective Descriptors - Week 4	7.3 (± 9.92)			
Affective Descriptors - Early Withdrawal	33.5 (± 3.54)			
Affective Descriptors - Follow-up	7.7 (± 9.82)			
Total Pain - Week 4 Change from Baseline	-22.8 (± 26.38)			

Total Pain - Early Withdrawal Change from Baseline	10 (± 26.87)			
Total Pain - Follow-Up Change from Baseline	-14.3 (± 35.62)			
Continuous Pain - Week 4 Change from Baseline	-5.9 (± 8.36)			
Continuous Pain - E W Change from Baseline	-1 (± 12.73)			
Continuous Pain - Follow-Up Change from Baseline	-2.8 (± 10.64)			
Intermittent Pain - Week 4 Change from Baseline	-6.1 (± 9.79)			
Intermittent Pain - E W Change from Baseline	3.5 (± 3.54)			
Intermittent Pain - Follow-Up Change from Baseline	-3.1 (± 14.67)			
Neuropathic Pain - Week 4 Change from Baseline	-7.8 (± 9.41)			
Neuropathic Pain - E W Change from Baseline	0.5 (± 0.71)			
Neuropathic Pain - Follow-Up Change from Baseline	-5.2 (± 9.18)			
Affective Descriptors - Week 4 Change from BL	-3 (± 7.51)			
Affective Descriptors - E W Change from Baseline	7 (± 9.9)			
Affective Descriptors - F/U Change from Baseline	-3.3 (± 10.12)			

Notes:

[5] - Actual vs Change: Baseline n=29/na Week 4 n=28/27, Early Withdrawal n=2/2, Follow-Up n=29/28

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC)

End point title	Patient Global Impression of Change (PGIC)

End point description:

The PGIC is a patient-reported instrument that measures change in overall status on a scale ranging from 1 ("very much improved") to 7 ("very much worse").

End point type	Secondary

End point timeframe:

Week 4 and Follow-Up Visits

End point values	EMA401 100 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (not applicable)				
Week 4 - Very much improved	7.1			
Week 4 - Much improved	28.6			
Week 4 - Minimally improved	39.3			
Week 4 - No change	25			

Week 4 - Minimally worse	0			
Week 4 - Much worse	0			
Week 4 - Very much worse	0			
Follow-up - Very much improved	10.3			
Follow-up - Much improved	24.1			
Follow-up - Minimally improved	27.6			
Follow-up - No change	20.7			
Follow-up - Minimally worse	10.3			
Follow-up - Much worse	6.9			
Follow-up - Very much worse	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Skin Biopsy Parameters

End point title	Change from Baseline in Skin Biopsy Parameters

End point description:

Two 3mm skin punch biopsies were to be taken from the lateral distal calf for quantitative analyses using immunostaining for nerve fibres, as well as antibodies to other key factors in nerve degeneration/regeneration and pain, including:
o sensory ion channels and receptors;
o neuropeptide markers of sub-sets of sensory and autonomic fibres: substance P, Calcitonin gene-related peptide, Neuropeptide Y;
o neurotrophic factors and GAP-43;
o Further antibodies as appropriate.

End point type	Secondary

End point timeframe:

Change from Baseline at Week 4 and Early Withdrawal visits

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	30[6]			
Units: mm				
arithmetic mean (standard deviation)				
PGP9.5 (IEF) IENF/mm-Week 4	-0.1 (± 1.32)			
PGP9.5 (IEF) IENF/mm-Early Withdrawal	1.9 (± 0.999)			
TRPV1 (IEF) IENF/mm-Week 4	0.3 (± 0.93)			
TRPV1 (IEF) IENF/mm-Early Withdrawal	-4.1 (± 0.999)			
SNSR (IEF) IENF/mm-Week 4	0.1 (± 1.01)			
SNSR (IEF) IENF/mm-Early Withdrawal	0.6 (± 0.999)			
GAP43 (IEF) IENF/mm-Week 4	0.3 (± 0.85)			
GAP43 (IEF) IENF/mm-Early Withdrawal	-0.5 (± 0.999)			

Notes:

[6] - Week 4 n=12; Early Withdrawal n=1
Note: value 0.999 indicates no value reported

Statistical analyses

No statistical analyses for this end point

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	EMA401 100 mg BID

Reporting group description: -

Serious adverse events	EMA401 100 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	EMA401 100 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			

Pain in extremity subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: