NOVARTIS

Clinical Development

EMA401

CEMA401A2201 / NCT03094195

A double-blind, placebo-controlled, randomized dose ranging trial to determine the safety and efficacy of three dose levels of EMA401 in reducing 24-hour average pain intensity score in patients with post-herpetic neuralgia (EMPHENE)

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-Jun-2017	Prior to FPFV	Creation of final version	N/A – First version	NA
07-Jun-2019	Before DB lock	Creation of amendment 1	• Tables added as required for ClinicalTrials.gov and EudraCT • Clarification of the definition of newly occurring or worsening • Region names have changed. • modified FAS population has been added • [redacted] • vitals signs and Friderica's correction have been removed from demographic summary	2.8.1 Adverse events 2.8.3 Laboratoy data 2.8.4 Other safety data 1.1, Study design, [redacted] 2.2. Analysis sets [redacted] 2. 2.3 Patient disposition, demographics and other baseline characteristics
			• Analyses of prior and concomitant medicationshave partly been revised and described in more detail. Analyses regarding prohibited medications have been removed	2.4 Treatments (study treatment, rescue medication,concomitant therapies)
			• Supplementary analyses regarding the primary endpoint have been reduced. The second supplementary analysis has been kept • Tipping point analysis has been removed. A sensitivity analysis on the modified full analysis set has been added. • Supplementary analyses of responders have been reduced. BPI-SF, PGIC, worst NRS, ISI will be summarized descriptively. • Temporal items of NPSI will not be summarized descriptively. No summaries of the 5 dimensions of NPSI during the treatment withdrawal period will be provided	2.5 Analysis of primary objective 2.7 Analysis of secondary efficacy objective(s) 2.13 Other Exploratory analyses
			• Analyses of AEs have been reduced. No subgroup analyses and analyses of drug-related AEs will be provided • Dot plots and Kaplan Meier plots of AEs have been removed • Plot for liver function test have been removed	2.8.1 Adverse events (AEs) 2.8.1.2 Liver events 2.8.3 Laboratory data

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			• Section has been removed. • Summary statistics of laboratory parameters, vital signs and ECG intervals will not be presented • Shift tables of laboratory data have been removed • Bazett correction has been removed • [redacted]. • For derivation of exclusion windows PD date can not be used	2.8.4 Other safety data [redacted] 5.1.5 Prohibited medication for PDS

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List of abbreviations

ACR	Albumin-Creatinine Ratio
AE	Adverse Event
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
b.i.d.	twice a day
BL	Baseline
BPI-SF	Brief Pain Inventory-Short Form
[redacted]	[redacted]
CRO	Contract Research Organization
[redacted]	[redacted]
CSR	Clinical Study Report
DAR	Dose Administration Record
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED_{50}	The dose at which half of the maximum effect is reached
eGFR	Estimated Glomerular Filtration Rate
E_{max}	The maximum effect attributable to the drug
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	gamma-glutamyltransferase
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
[redacted]	[redacted]
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISI	Insomnia Severity Index
LFT	Liver function test
LoE	Lack of efficacy
MAR	Missing at random
mFAS	Modified Full Analysis Set
MCP-Mod	Multiple Comparison Procedure – Modelling
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numeric Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drugs
PCR	Protein-Creatinine Ratio

PHN	Post-Herpetic Neuralgia
PK	Pharmacokinetics
PGIC	Patient Global Impression of Change
PRO	Patient Reported Outcome
[redacted]	[redacted]
QTc	Corrected QT interval
QTcB	Bazett QT correction formula
QTcF	Fridericia QT correction formula
SAE	Serious Adverse Event
RDO	Retrieved drop-out
SAF	Safety population
[redacted]	[redacted]
SSRI	Selective Serotonin Reuptake Inhibitor
TBL	Total bilirubin
TD	Study Treatment Discontinuation
TEAE	Treatment-Emergent Adverse Events
ULN	Upper limit of Normal
USM	Urgent Safety Measures
VRS	Verbal Rating Scale
WHO	World Health Organization

Amendment 1

This amendment of the statistical analysis plan (SAP) is largely based on changes induced due to the early termination of the CEMA401A2201 study. 129 patients out of 360 planned patients have been randomized. As the number of patients included in the study isconsiderably reduced, an abbreviated Clinical Study Report (CSR) that still meets all requirements for reporting and disclosure of the demographics, primary endpoint, secondary endpoints and safety results to public registries will be created.

The primary analysis on the change from baseline to Week 12 in the weekly mean of the 24-hour average pain score will be performed as originally planned. Besides the primary estimand, which is of main clinical interest, the supplementary estimand, which provides insight into the magnitude of improvement in efficacy that might be achieved if all patients were able to take EMA401 as prescribed for 12 weeks, will be analysed. The other planned supplementary estimands will be dropped, as they are of minor interest in the situation with many study treatment discontinuations due to trial termination in the scope of the Urgent Safety Measures (USM).

To support the primary analysis and to get an idea about the effect that might be achieved if the trial had not been terminated and if all patients had the chance to complete the Week 12 assessment, a sensitivity analysis on a modified population will be performed. The modified full analysis set will include all patients who had a chance to complete the study before the termination date, i.e who had been randomized at least 12 weeks before study termination date.

Due to the considerably reduced number of patients who completed the study, only descriptive subgroup analyses will be provided. Moreover, most of the secondary [redacted] endpoints will also be summarized descriptively only. [redacted]

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CEMA401A2201, a Phase 2, double-blind, placebo-controlled, randomized dose ranging trial to determine the safety and efficacy of three dose levels of EMA401 in reducing 24-hour average pain intensity score in patients with post-herpetic neuralgia.

The content of this SAP is based on the final version of protocol CEMA401A2201 Amendment 1 (release date 14-May-2018). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data.

1.1 Study design

The study is interventional, randomized, parallel, placebo-controlled, dose ranging, double-blind treatment.

The study will consist of a Screening epoch (up to 5 weeks), a double-blind Treatment epoch (12 weeks), and a double-blind Treatment withdrawal epoch (1 week).

- In the initial cohort, patients will be randomized in a 1:1:1 ratio to treatment with placebo, EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d. (approximately 135 patients). Randomization of patients to the high dose arm (EMA401 300 mg b.i.d.) will only be initiated following an unblinded safety review by an independent Data Monitoring Committee (DMC) after exposure of 50 patients treated with EMA401 up to 100 mg b.i.d. for at least 8 weeks (i.e. 25 patients on 25 mg b.i.d. and 25 patients on 100 mg b.i.d.).
- Future patients will then be randomized in the second cohort in a 1:1:1:2 ratio to treatment with placebo, EMA401 25 mg b.i.d., EMA401 100 mg b.i.d., or EMA401 300 mg b.i.d. (approximately 225 patients).

Overall approximately 360 patients were estimated to be enrolled in the study (i.e. approximately 90 patients were planned to be enrolled in each treatment arm). Due to the early termination in the scope of USM the EMA401 300 mg b.i.d. treatment arm was not initiated as planned. The original 1:1:1 randomization ratio has been applied to treatment with placebo, EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d At Week 12 (Visit 199), all patients who completed the 12-week double-blind Treatment epoch will enter the 1-week double-blind Treatment withdrawal epoch. The IRT system will indicate the unique medication number for the package of study drug to be dispensed to the patient during the double-blind Treatment withdrawal epoch. This medication number will correspond to the blinded withdrawal regimen assigned at Baseline.

Randomization will be stratified by region (e.g. America, Europe and Australia, Asia) and use of concomitant pain medication for PHN (yes/no) in order to achieve balance of treatment allocation within the stratification factors.

Primary objective of this study is to characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12	**Endpoint(s) for primary objective(s)** • Dose-response in change in weekly mean of the 24-hour average pain score, using an 11-point Numeric Rating Scale (NRS), from Baseline to Week 12
Secondary Objective(s) • To compare the efficacy of EMA401 vs. placebo in 24-hour average pain intensity score at Week 12, using an 11 point Numeric Rating Scale (NRS) by testing the superiority of at least one active dose of EMA401 vs. placebo • To evaluate the efficacy of EMA401 compared to placebo, as measured by the Brief Pain Inventory-Short Form (BPI-SF) interference total score at Week 12 • To evaluate the efficacy of EMA401 compared to placebo, as measured by the weekly mean of the 24-hour worst pain intensity score, using an 11-point Numeric Rating Scale (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 effect of EMA401 compared to placebo on the Neuropathic Pain Symptom Inventory (NPSI) at Week 12 • To evaluate the safety and tolerability of EMA401 compared to placebo in PHN patients, as measured by treatment emergent adverse events (TEAEs), adverse events (AEs) leading to study	**Endpoint(s) for secondary objective(s)** • Change in weekly mean 24-hour average pain score (using the 11 point NRS) from Baseline to Week 12 • Change in BPI-SF interference total score from Baseline to Week 12 • Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS, from Baseline to Week 12 • PGIC at Week 12 • Proportion of patients meeting responder criteria from Baseline to Week 12 • Change in ISI from Baseline to Week 12 • Change in NPSI from Baseline to Week 12 • Number and severity of treatment emergent adverse events and the frequency of adverse events leading to discontinuation. Number of serious adverse events.

Objective(s)	Endpoint(s)
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	• Plasma pharmacokinetics of EMA401 will be characterized by population non-linear mixed effects modeling techniques
Exploratory Objective(s)	**Endpoint(s) for exploratory objective(s)**
• To evaluate the proportion of patients who need rescue medication and the time to first intake of rescue medication [redacted]	• Proportion of patients who need rescue medication and the time to first intake of rescue medication24-hour average NRS pain score by subgroup [redacted]

2 Statistical methods

2.1 Data analysis general information

The statistical analysis of the study will be performed by [redacted], a designated Contract Research Organization (CRO).

SAS version 9.4 will be used to perform all data analyses and to generate tables, figures and listings.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of frequency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics, i.e., n, mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum, and maximum.

No interim analysis will be performed for the efficacy evaluation. An external Data Monitoring Committee (DMC) will be established with the primary goal to perform an ongoing review of safety data.

2.1.1 General definitions

Investigational drug and study treatment

The investigational drug, EMA401, will be provided as capsules. The following oral dosage strengths will be used: 12.5 mg, 50 mg.

All dosage strengths of EMA401 and placebo will be identical in appearance.

For all treatment groups, each dose will be self-administered orally as two capsules with a full glass of non-carbonated water twice daily, consisting of a morning dose and an evening dose.

The following abbreviated treatment groups, independently of cohort number, will be used as the headers in the tables for the double-blind Treatment epoch:

- Placebo b.i.d.
- EMA401 25 mg b.i.d.
- EMA401 100 mg b.i.d.

The following abbreviated treatment groups will be used as the headers in the tables for the double-blind Treatment withdrawal epoch:

- Placebo b.i.d. -> Placebo b.i.d.
- EMA401 25 mg b.i.d. -> EMA401 25 mg b.i.d.
- EMA401 25 mg b.i.d. -> Placebo b.i.d.
- EMA401 100 mg b.i.d. -> EMA401 100 mg b.i.d.
- EMA401 100 mg b.i.d. -> Placebo b.i.d.

Date of first and last administration of study drug

The date/time of first administration of study drug is defined as the first date/time of administration as per Dosage Administration Record eCRF. The date/time of last administration of study drug is defined as the last date/time when a dose is administered as per Dosage Administration Record eCRF. This value has to be compared to the "End of study treatment" as recorded on the corresponding eCRF. In case of different dates, the latest will be used as treatment end.

For subjects with missing first dose date, the randomization date will be considered as reference start date.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date which is the date of first administration of study drug.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

Baseline

For safety and efficacy evaluations, the last available assessment (either scheduled or unscheduled) before the first administration of study drug and after the screening visit is defined as "baseline" assessment. If patients have no value prior to first administration of study drug the baseline result will be missing.

Post-baseline

For safety and efficacy evaluations all assessments after the first administration of study drug are defined as "post-baseline" assessment.

Change and percent change from baseline for continuous parameter.

Change from baseline and percent change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

percent change from baseline = 100 * change from baseline / baseline value.

For summary statistics the raw values (and not imputed values) will be used.

Study periods and date of last contact

The overall observation period will be divided into three mutually exclusive segments:

- A screening phase of up to 5 weeks
- A double-blind treatment phase starting with first dose of study drug at Visit 101 and covering 12 weeks of treatment.
- A double-blind treatment withdrawal phase for one week starting after 12 weeks of treatment with Visit 201.

Inferential analysis will be performed on either only treatment phase or on both treatment and treatment withdrawal phase separately. It is never the case that both phases will be pooled together.

Visit windows

Visit windows will be applied for all measurements except NRS scores. The definition of seamless windows can be found in the following [redacted] location [redacted] he most recent version of this document available before the database lock will be used to determine the visit windows for baseline and post baseline visits and treatment discontinuation visit mapping.

These visit windows need not to be exactly the same as the formal visit windows what the sites have to follow for their scheduling.

2.2 Analysis sets

The following analysis populations will be used for analysis.

- The Enrolled population will include all patients who were enrolled into the study.
- The Full Analysis Set (FAS) will include all patients randomized. Mis-randomized patients will be excluded from the FAS.
- The modified Full Analysis Set (mFAS) will include all patients who could have completed Week 12 by the study termination date. That means, all patients which were randomized at least 12 weeks prior to 25-Feb-2019 will be included.
- The Safety population (SAF) will include all patients who took at least one dose of study medication and who had at least one post-baseline safety assessment.

The primary efficacy analysis will be the FAS.

[redacted]

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, ethnicity, relevant medical history/current medical condition present before signing informed consent, height, weight, body mass index (BMI), prior concurrent medications, QTc using Fridericia's correction, NRS at screening, [redacted].

In addition, the following categorizations of continuous variables will be done:

- Age into 18-64 years, 65- 84 years, >= 85 years
- Duration of PHN into < 1 year, > 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 - 20 years, and > 20 years;

Demographic and background information will be summarized for the FAS population using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables). Relevant medical history/current medical conditions will be summarized by system organ class and preferred term of the MedDRA dictionary.

2.3.1 Patient disposition

For each study phase (i.e., screening, treatment epoch and treatment withdrawal epoch), the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation. The summary of the screening phase will be done for the Enrolled set, for the treatment and treatment withdrawal epoch the analyses will be based on the FAS population.

Patients who prematurely discontinue the study medication will be listed along with the reason for discontinuation.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration (days) of exposure to double-blind study medication will be summarized by treatment group and treatment phase (treatment epoch and treatment withdrawal epoch seperately). In addition, the number of subjects with exposure of at least certain time thresholds (any exposure, >= 1 week, >= 2 weeks, >= 4 weeks, >= 6 weeks, >= 8 weeks, >= 10 weeks, >= 12 weeks) will be displayed.

Compliance will be recorded as source documentation only and not analysed.

The analyses will be based on the SAF population.

2.4.2 Prior, concomitant and post therapies

The number and percentage of patients who used concomitant medications (coded by World Health Organization [WHO] Anatomic Therapeutic Chemical classification [ATC]) will be presented by treatment group and treatment phase (Treatment epoch and Treatment withdrawal epoch separately).

Separate tabulations will be provided for medications taken prior to start of study medication and while a patient is on study drug (i.e. concomitant, between the first day on study drug and the day of last visit).The PHN medications recorded on the Screening PHN Medication Log will be summarized using a frequency table for each medication. The primary reason for treatment failure will also be tabulated.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment. For the Treatment epoch concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the end of the treatment epoch, including those which were started pre-baseline and continued into the treatment period. For the Treatment withdrawal epoch concomitant medications are any medications given at least once between the day of first dose of study medication in the treatment withdrawal epoch, and the end of the epoch, including those which were started pre-baseline or in the treatment period epoch, and continued into the treatment withdrawal epoch.

Non-drug therapies will be listed.

2.4.2.1 Rescue medication

The number and percentage of patients who received rescue medication (Acetaminophen/ Paracetamol as reported on the diary page) will also be summarized by treatment and by visit during the double blind and treatment withdrawal period separately. Visit mapping will be done according to the visit window strategy document. The dose received will be listed.

Analysis of time to first use of rescue medication will be performed using Kaplan-Meier curves.

Number of patients with at least one intake will also be summarized.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary efficacy variable will be the change from baseline to Week 12 in the weekly mean of the 24-hour average pain score, using an 11-point Numeric Rating Scale (NRS).

The NRS is captured in the e-diary daily by the patient as the intensity of pain in the past 24 hours. To calculate the weekly mean pain intensity score for a given week, the daily pain intensity scores collected by the patient in the e-diary during the 7 days of that week will be averaged.

The primary population will be the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The aim is to estimate the treatment effect of the investigational drug (EMA401) compared to placebo, for the target population on the primary pain parameter. The definition and the justification of the corresponding primary estimand, as well as the definition of the supplementary and secondary estimands are detailed in the Estimand Charter.

The primary estimation method is based on an Analysis of Covariance (ANCOVA) model including region (America orEurope and Australia, Asia), treatment, sex, use of concomitant pain medication for PHN (yes/no) as factors and age and baseline (mean pain intensity) score as covariate. The analysis will account for different intercurrent events (i.e. events that occur post-randomization) as follows:

- **Changes in doses of concomitant medication for PHN:** Efficacy observations collected during the period of changes in doses of concomitant medication for PHN (compared to baseline) and the 2-days thereafter will be excluded, since they are considered affected by the concomitant medication dose change. The resulting missing data after this step will be multiply imputed using the Missing at random (MAR) assumption.
- **Intake of rescue medication:** Efficacy data collected during intake of rescue medication will be used for analysis.

- **Intake of prohibited medications with potential confounding effect prior to study treatment discontinuation**: The prohibited medications with a potential confounding effect are defined as those listed in Table 2-1 requiring study treatment discontinuation. A list of prohibited medications is available at the following [redacted] Efficacy observations collected during the intake period of such prohibited medications and the 7-days thereafter will be excluded, since they are considered affected by the prohibited medication intake. The resulting missing data after this step will be multiply imputed using the MAR assumption.

Table 2-1 Prohibited medication

Medication	Prohibition period	Action taken for study treatment
Prohibited prior to Randomization and throughout study		
High dose capsaicin patch (8%)	3 months prior to Randomization and after Randomization	Discontinue study treatment
Prohibited 2 week prior to Randomization and throughout the study		
Any skeletal muscle relaxant (e.g. baclofen, orphenadrine, methocarbamol)	2 weeks prior to Randomization and after Randomization	None
Mexiletine	2 weeks prior to Randomization and after Randomization	None
Dextromethorphan	2 weeks prior to Randomization and after Randomization	None
Memantine	2 weeks prior to Randomization and after Randomization	None
Alpha-lipoic acid	2 weeks prior to Randomization and after Randomization	None
Other anti-epileptic drugs (e.g. valproic acid, carbamazepine, phenytoin)	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Oral or injectable steroids	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Monoamine oxidase inhibitors or any other antidepressants (except stable dosage of SSRI)	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use

Medication	Prohibition period	Action taken for study treatment
Antipsychotic or neuroleptic medications	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Cannabinoids (e.g. marijuana)	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Prescribed opioids, including codeine	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Any prescription systemic pain medication, or *topical* treatment for PHN, including lidocaine plaster	2 weeks prior to Randomization and after Randomization	Discontinue study treatment upon 2nd episode of medication use
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or any other over-the-counter pain medications	2 weeks prior to Randomization and after Randomization	None
Any non-drug therapies that could modulate the perception of pain either directly or indirectly (i.e. transcutaneous electrical nerve simulation (TENS) or surgery)	2 weeks prior to Randomization and after Randomization	Discontinue study treatment
Other medications that may have potential drug-drug interactions (e.g. felodipine, eplerenone, nisoldipine, ticagrelor, tacrolimus, avasimibe, rifampin, cyclosporine, gemfibrozil, clarithromycin, St. John's Wort; oral, injected or implanted hormonal methods of contraception) , Antiviral medications (e.g. valacyclovir, acyclovir, amantadine, anti-HIV), Antifungals (e.g Azoles)	2 weeks prior to Randomization and after Randomization	None
Prohibited after Randomization and throughout study		
Any change to a different standard of care medication from baseline (e.g. switch from pregabalin to gabapentin) will be treated as prohibited medication	After randomization	Discontinue study treatment

Retrieved drop-out (RDO) patients are defined as patients who discontinue study treatment and decide to remain in the study by following an abbreviated schedule of assessments. These patients must continue to adhere to protocol requirements (see respective protocol Table 6-2). The design feature of retrieved drop-outs, considered in order to minimize the occurrence of missing data on primary pain parameter, is exploited for the statistical analysis as follows:

- **Permanent discontinuation of study treatment due to AE, lack of efficacy (LoE) and use of prohibited medication:** If retrieved drop-out data are available, these will be used for analysis. If no data was retrieved after study treatment discontinuation, missing data

will be multiply imputed based on placebo arm data, i.e. "jump to reference" (J2R) assumption for the EMA401 arms, missing at random assumption for placebo arm (Carpenter, Roger, and Kenward 2013). If no RDO data was collected after study treatment permanent discontinuation, missing data will be multiply imputed based on the J2R assumption for the EMA arms and under the MAR assumption for placebo arm. Of note, alternatively one could build the imputation model based on the RDO data, however, we expect sparse RDO data which will likely hinder us to build an imputation model. More details on the imputation model are specified in Section 5.

- **Permanent discontinuation of study treatment due to other reasons than AE, LoE and use of prohibited medication (including discontinuation due to USM):** If efficacy data collected after study treatment discontinuation are available (retrieved drop-out), then the retrieved drop-out data will be excluded and missing data after study treatment discontinuation will be multiply imputed using the MAR assumption.

The multiple imputations will be carried out on the weekly mean pain score. Details on multiple imputation can be found in Section 5 of this document.

If the 300 mg b.i.d dose would have been initiated: The primary objective would have been achieved if the null hypothesis of flat dose-response curve (where all dose means are equal to the placebo mean) at Week 12 is rejected using alpha=0.025 one-sided. The null hypothesis of a flat dose-response curve will be tested using Multiple Comparison Procedure – Modelling (MCP-Mod) with three E_{max} and two sigmoidal-E_{max} dose response models as the candidate shapes. The following ED_{50} (the dose at which half of the maximum effect is reached) values will be used for the E_{max} models: 17, 80, and 200. The parameters of the sigmoidal E_{max} models (ED_{50}, h) will be as follows: (77, 3) and (175, 1.5), where h is the Hill parameter that determines the steepness of the dose-response shape. The MCP-Mod dose response test will be performed at each post-baseline visit. No multiplicity adjustment by visit will be carried out.

Dose-response estimation will be performed based on the ANCOVA least square estimates using MCP-Mod as described in Pinheiro et al (2014). The same candidate models as above will be used in a model averaging approach to obtain an estimate of the dose-response curve. The final estimate of the dose-response curve is the median of the dose-response curves obtained.

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

Summary statistics for absolute values and change from baseline by treatment and visit will be provided for the original measurements (i.e. the raw data prior to multiple imputation) of the primary efficacy variable. If a measurement is collected under the period of use of prohibited medications or the 7 days thereafter, it will be excluded from the summaries. [redacted]

In the event the EMA401 300 mg b.i.d. dose cannot be initiated, the trend tests deduced from the set of candidate models will be performed but the dose response estimation will not be performed. In that case, the first secondary objective will be evaluated to compare the efficacy of the remaining doses of EMA401 over placebo in 24-hour average pain intensity score at Week 12, using an 11 point Numeric Rating Scale (NRS). This comparison will be done by

testing the null hypotheses of superiority of EMA401 25 mg b.i.d. over placebo and of EMA401 100 mg b.i.d. over placebo, while adjusting for multiplicity. The estimation of the treatment difference and missing data handling will be performed using the method of analysis mentioned for the primary analysis. Multiplicity adjustment for the pairwise comparisons will be performed using the Hochberg procedure. To facilitate the interpretation of the estimated treatment difference a standardized effect size will be provided and will be calculated based on the results of the ANCOVA analysis.

2.5.3 Handling of missing values/censoring/discontinuations

Handling of missing daily pain score values within a week (within-week imputation)

The 24-hour average pain score is measured daily for seven consecutive days prior to randomization and then every day through the end of the study. At each week, the weekly mean of the seven 24-hour average pain assessments will be calculated.

The weekly mean will be calculated based on the available assessments. If only one measurement is available, the mean will be based on that value. Assessments made under treatment will not be mixed up with RDO data. If there is at least one value among the seven values in one week which is on-treatment (i.e. collected prior to study treatment discontinuation), the mean will be calculated based on those on-treatment values. If all seven values in one week are off-treatment because collected after study treatment discontinuation (RDO), the resulting weekly average will be regarded as an RDO value for analysis.

Handling of missing weekly mean pain score values (weekly mean imputation)
The multiple imputation for the primary variable will be carried out on the weekly mean pain score.

The imputation procedure related to primary analysis is described in Section 2.5.2 while the imputation procedure for the supplementary analyses is included in Section 2.5.4. The details of these imputation rules are specified in the Estimand Charter and in Section 5.

For all analyses, imputation of intermittent missing observations before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms.

2.5.4 Supportive analyses

2.5.4.1 Supplementary analysis

The following supplementary analysis to the primary analysis will be performed on the FAS population

to quantify the treatment effect of the investigational drug compared to placebo, that would have been observed had all patients remained on their assigned treatment for 12 weeks. The handling of post randomization events will be same as for the primary analysis, except that missing data after discontinuation for any reason in both treatment arms will be imputed using the MAR assumption.

2.5.4.2 Sensitivity analysis

A sensitivity analysis will be performed on the mFAS population using the same ANCOVA model and the same rules for handling intercurrent events as for the primary analysis.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The following secondary efficacy variables will be evaluated for the FAS:

2.7.1 Testing of superiority with regard to NRS at Week 12

To compare the efficacy of EMA401 over placebo in 24-hour average pain intensity score at Week 12, using an 11 point Numeric Rating Scale (NRS). This comparison will be done by testing the null hypotheses of superiority of EMA401 25 mg or over placebo and of EMA401 100 mg over placebo while adjusting for multiplicity. Multiplicity adjustment for the pairwise comparisons will be performed using the Hochberg procedure. Based on the set of candidate models as specified in Section 2.5.2 trend tests will be performed to evaluate the existence of a dose-response effect using MCP-mod.

2.7.2 Responder Analysis

Responder analyses (based on at least a 30%, 50% improvement from baseline on NRS) will be performed in order to facilitate the interpretation of the results of the primary and supplementary analyses from a clinical relevance perspective. These analyses will be performed on the FAS population. One secondary estimand is considered, together with one supplementary estimand.

The secondary estimand and the supplementary estimand to the secondary estimand differ from the primary and supplementary estimands in two ways:

- First, the variable of interest is the responder status in NRS score, with response status corresponding to at least a 30% (50%) improvement in pain from baseline.
- Second, the measure of intervention effect is the odds ratio of the proportions of responders between investigational drug and placebo.

The other features characterizing these responder analyses are exactly the same as for the primary and the supplementary analysis, respectively.

From an analysis point of view, the responder status for each patient will be calculated on the continuous weekly score measurements after missing data are multiply imputed based on the approach specified corresponding to the primary analysis and the supplementary analyses. If the patient is a completer but week 12 measurement is affected by the changes in doses of concomitant medication for PHN or the use of prohibited medication then the responder criteria will be defined based on the multiply imputed values by MAR. The resulting responder variable will be analyzed using a logistic regression model including all randomized patients and adjusting for the same covariates as the ANCOVA model for the primary analysis.

From an analysis point of view, the resulting responder variables will be analyzed using a logistic regression model including all randomized patients (FAS population) and adjusting for the same covariates as the ANCOVA model for the primary analysis. Odds ratios will be estimated along with their 95% CIs.

The responder analyses will be performed for each visit, with the obvious modification in the definition for the week of interest.

2.7.3 Other secondary efficacy objectives

1. BPI-SF interference total score will be summarized descriptively by treatment and visit.
2. Weekly mean of the 24-hour **worst** NRS pain score, using an 11-point Numeric Rating Scale (NRS). This variable will be summarized descriptively by treatment and visit.
3. Number of patients in each level of PGIC at Week 12 will be presented by treatment. PGIC classification will also be combined into two categories: Either a "very much improved" or a "much improved" reported, and the five remaining categories.
4. Change from baseline to Week 4, Week 8 and Week 12 in NPSI. The total score NPSI (sum of 10 descriptor items) variable will be analyzed according to the same ANCOVA model as the one used for the primary variable. NPSI total score will also be summarized descriptively by treatment and visit. The same supplementary analysis as for the primary endpoint will be performed. Multiple imputation will be carried out in a similar fashion as for the primary analysis of the NRS pain score. The 5 dimensions of pain (burning pain, deep/pressing pain, paroxysmal pain, evoked pain, paraesthesia/dysesthesia) will be summarized descriptively by treatment and visit in the double-blind treatment epoch.

5. Insomnia Severity Index (ISI) will be summarized descriptively by treatment and visit.

2.8 Safety analyses

Safety analyses will be conducted using the safety (SAF) population. Patients will be analysed by the actual treatment they received. All the safety analyses including AEs, vital signs, Laboratory parameters, ECGs [redacted] will be reported for double blind treatment period as well as for the treatment withdrawal period separately.

2.8.1 Adverse events (AEs)

Treatment-emergent adverse events (TEAEs) are defined as any adverse events that develops after initiation of study treatment or any event already present that worsens following exposure to the study treatment.

If an adverse event starts at the date of week 12 visit it should be allocated to the treatment epoch and not to the treatment withdrawal epoch.

TEAEs will be summarized (number of cases as a percentage of number at risk) by treatment group separately for treatment epoch and treatment withdrawal epoch. Adverse events reported 21 days after end of study date in the scope of USM will not be included in the summary tables, but will be listed. Number and percentage of patients with TEAE will be summarized by primary system organ class and preferred term for each treatment group during the double blind Treatment epoch and during the double-blind Treatment withdrawal epochSeverity will be classified as “mild”, “moderate” and “severe”. Serious TEAEs, TEAEs by maximum severity and TEAEs leading to premature discontinuation from study drug will be presented in a similar format as adverse events. Additionally, a listing of patients with TEAE will be presented. Drug abuse-related adverse events (identified using a pre-specified search criterion) will be summarized during the double-blind Treatment epoch. To assess the potential for withdrawal

effect, drug abuse-related adverse events will be summarized for the double-blind Treatment withdrawal epoch.

The following additional analysis will be performed.

- Analysis of TEAES with onset date before 25-Feb-2019

For rash adverse events, following details will be listed:

- Laterality and location of rash
- Did the subject start any new topical non-pharmaceutical products within the last 14 days prior to the start of rash?
- Topical Non-pharmaceutical Products related to the event of rash including soap, detergent, perfume, cologne and lotion.
- Were there any additional contributing factors that may have led to the rash?
- Did the dermatologist agree with the event?
- Additional investigation performed to diagnose that event: yes, no

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted otherwise.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

Allergic dermatitis, elevation in hepatic enzymes and neutropenia are the potential risks related to EMA401. Dizziness, headache, nausea, pre syncope and upper respiratory tract infections are the expected events related to EMA401. In addition suicidality and drug abuse related events will be adverse events of special interest. The search criterion for each of these risks and events will be defined based on MedDRA and on the Program Compound Case Retrieval Sheet.

The most recent Compound Case Retrieval Strategy (eCRS) at the time of database lock will be used to determine the MedDRA search criteria to identify events of special interests.

2.8.2 Deaths

The primary reason for death will be summarized by system organ class and preferred term. All deaths will be listed. Deaths for screen failures will be listed separately.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests: Hematology, Chemistry and Urinalysis.

The number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria at any post-baseline visit will be summarized by laboratory parameter. For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value that is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value that is clinically notable and also have a worse post-baseline value. For patients with missing baseline value, any post-baseline notable value will be considered as newly occurring.

Incidence of newly occurring liver enzymes abnormalities and renal events will be summarized using the number and percentage of patients by treatment group. Notable laboratory values will be listed.

Laboratory assessements performed at the follow-up visits in the scope of the USM will not be included in the summaries but will be listed. That means, assessments reported 21 days after end of study date will not be included in the summary tables.

Liver function tests (LFT)

To evaluate potential drug-induced liver injury, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests at any time post-baseline will be summarized by treatment. The same approach as for notable laboratory values will be used to define newly occurring or worsening abnormalities in liver function tests.

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur at the same time (i.e., within the same sample). A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

Listings of patients with clinically notable LFT values will be provided.

The same analysis will be repeated for the Treatment withdrawal epoch.

2.8.4 Other safety data

2.8.4.1 ECG

The (uncorrected) QT interval will be corrected according to Fridericia's formulae. The incidence rates of newly occurring or worsening clinically notable ECG abnormalities will be summarized. The same approach as for notable laboratory values will be used to define a newly occurring notable QTc value and a worsening notable QTc value. Notable ECG values will be listed.

Notable criteria are:

- QTcF > 500 msec or
- increase from baseline > 60 msec

If the single ECG shows a QTcF > 500 ms (males or females), 2 additional ECG replicates should be recorded to confirm the safety findings and copies forwarded to the central ECG laboratory for assessment. The results from those triplicate ECGs will be averaged and analysed as one value for summary and notable tables.

2.8.4.2 Vital signs

The number and percentage of subjects with clinically notable vital signs will be presented. The same approach as for notable laboratory values will be used to define newly occurring notable vital sign values. Notable vital sign values will be listed.

Notable criteria are:

Variable	Criterion value		Change relative to baseline
Heart rate/pulse	120 bpm 50 bpm	and an and a	increase of ≥ 15 bpm decrease of ≥ 15 bpm
Systolic blood pressure	180 mm Hg 90 mm Hg	and an and a	increase of ≥ 20 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	105 mm Hg 50 mm Hg	and an and a	increase of ≥ 15 mm Hg decrease of ≥ 15 mm Hg
Weight	Baseline weight (kg)	and an and a	increase of ≥ 7% decrease of ≥ 7%

bpm= beats per minute

Data of subjects with newly occurring notable vital signs abnormalities will be listed in an additional listing.

2.8.4.3 Physical examination

Physical examination including examination of skin will be source documentation only.

[redacted]

[redacted]

2.9 Pharmacokinetic endpoints

Scatter plots of EMA401 plasma concentrations will be displayed in linear and semilogarithmic view in a CSR addendum.

2.10 PD and PK/PD analyses

Evaluation of effect of EMA401 exposure on efficacy variables (e.g. change from baseline of pain score), via the development of a continuous descriptive Pharmacokinetics/ Pharmacodynamics (PK/PD) was planned in the protocol. All population PK/PD analyses and simulations were to be carried out using a non-linear mixed-effects modelling approach. Due to early study termination the planned model based exposure-response analysis will not be performed and replaced with a graphical assessment of the exposure-response relationship.

This will be reported in a separate report.

2.11 Patient-reported outcomes

Please refer to efficacy analysis for details on all Patient Reported Outcomes (PRO).

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

The following exploratory analysis will be performed:

1. The proportion of patients who need rescue medication (at each visit and at least once during the study) will be evaluated. The corresponding binary variables will be derived and analyzed based on a logistic regression model with the same factors as the ANCOVA model for the primary analysis.
2. The Kaplan-Meier estimates of the proportion of patients with rescue medication intake, along with the associated 95% confidence intervals using the Greenwood's formula will be provided.
3. The proportion of EMA401 patients achieving a 30%, 50% reduction in the weekly mean of the 24-hour average NRS pain score compared to placebo at Week 4 and at Week 12 will be evaluated after multiple imputation is done on the primary variable. The corresponding responder variables will be derived and analyzed based on a logistic

regression model with the same factors as the ANCOVA model for the primary analysis. Cumulative responder plots will be displayed.

[redacted]

2.14 Interim analysis - Safety

The DMC is responsible for unblinded safety review to stagger patient exposure to the study drug. Randomization of patients to the high dose arm (EMA401 300 mg b.i.d.) will only be initiated following an unblinded safety review by an independent DMC after exposure of 50 patients treated with EMA401 up to 100 mg b.i.d. for at least 8 weeks (i.e. 25 patients on 25 mg b.i.d. and 25 patients on 100 mg b.i.d.). Furthermore, another unblinded safety review was planned after the completion of 12 weeks exposure of 30 patients in the EMA401 300 mg b.i.d. treatment arm to determine if 300 mg b.i.d. dosing can be continued as planned. Due to the early termination in the scope of USM the EMA401 300 mg b.i.d. treatment arm was not initiated as planned.

The DMC reviews cumulative safety data, including patient narratives for deaths, serious adverse events (SAEs), discontinuations due to adverse events and cases of interest (allergic dermatitis, and clinically significant abnormal hepatic and hematology values).

The details of the analysis required for DMC had been specified in a separate DMC analysis plan and not repeated here in detail.

3 Sample size calculation

With the planned sample size of N=(90, 90, 90, 90) for placebo, 25 mg b.i.d., 100 mg b.i.d. and 300 mg b.i.d., the power of the dose-response trend test [to reject the null hypothesis of a flat dose-response curve where all dose means of EMA401 (EMA401 25 mg b.i.d., EMA401 100 mg b.i.d., EMA401 300 mg b.i.d.) are equal to the placebo mean] for the primary variable is at least 77% under the candidate models using the MCP-Mod methodology using alpha=0.025 one-sided.

The power calculation is based on the following assumptions:

- The assumed true dose-response curves for power calculation are the 5 candidate shapes (see Section 2.5) with the model parameter chosen so that the maximum effect in the dose-range is 1.0 attained with the 300 mg b.i.d. dose.
- The standard deviation is 2.6 points (based on data from pregabalin historical trials – see FDA Approval Package Medical Review, 2004). In Study EMA401-003, a standard deviation of approximately 2.0 points was observed. A slightly higher value of 2.6 has been chosen to account for a possible higher variability due to a higher number of centers and due to multiple imputations (as opposed to single imputation) in the analysis.

The planned sample size allows to estimate the placebo-corrected response (the treatment difference between the active EMA401 doses and placebo) with a root mean squared error of 0.34 averaged over the three active doses and taking the maximum over the 5 candidate models.

4 Change to protocol specified analyses

An additional population, the mFAS population, has been defined.

The following analyses were specified in the protocol but will not be performed due the early termination of study:

- first and third supplementary analysis to the primary analysis
- tipping point analysis
- supplementary responder analyses
- ANCOVA analyses for BPI-SF, worst NRS pain score, ISI
- Proportional odds model for PGIC
- Apart from analyses of clinical abnormalities summaries of laboratory data, vital signs and ECG intervals have been removed.
- Shift tables of laboratory data
- No safety figures will be presented
- Bazett correction for QTc
- time to "sustained" pain reduction

The following analyses have been added:

- sensitivity analyses on modified full analysis population
- analyses of TEAEs with onset before study termination date

The analyses of patient disposition for the treatment and treatment withdrawal epoch will be based on the FAS population only.

Analyses of duration of exposure to study treatment will be based on the SAF population only.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of study treatment will not be imputed.

5.1.2 Diagnosis of PHN

Rules for imputing date of first diagnosis of PHN will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 AE date imputation

Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.4 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.5 Prohibited medication for PHN

Exclusion period of values in case of changed PHN medication or intake of prohibited medication will be derived as follows:

- Programming Dataset Specification (PDS) will describe how to identify dose changes of concomitant PHN medications and prohibited medications
- deterimine exclusion period: CM end date + x days where x=3 for changes in dose and x=7 for intake of prohibited medications with potential confounding effect
- if no medication end date available, then all values from medication start date onwards should be excluded

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Laboratory parameters derivations

Liver events defined by laboratory parameter abnormalities (additional non-lab criteria as provided in the protocol are covered under the adverse events analysis, safety topics of interest):

- ALT or AST > 5 × ULN
- ALP > 2 × ULN
- TBL > 2 × ULN
- ALT or AST > 3 × ULN and INR > 1.5
- ALT or AST > 3 × ULN and TBL > 2 × ULN AND ALP ≤ 2 × ULN (Potential Hy's Law cases)

- ALT or AST > 3 × ULN

Renal events defined by laboratory parameter abnormalities (additional non-lab criteria as provided in the protocol are ignored):

- Serum creatinine increase 25 – 49% compared to baseline
- Serum creatinine increase ≥ 50% compared to baseline
- New dipstick proteinuria ≥1+
- New dipstick glycosuria ≥1+ not due to diabetes
- New dipstick hematuria ≥1+ not due to trauma
- Albumin- or Protein-creatinine ratio increase ≥2-fold
- Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol
- Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol

Laboratory results will be reported in SI units.

5.4 Derivation of index values and scores

For details on handling of missing items and derivation of scores refer to the note to file at path [redacted]

5.4.1 11-point Numeric Rating Scale (NRS)

The Numeric Rating Scale (NRS) is an 11–point scale for patient self-reporting of pain. The averaged score will be computed for every week, regardless of visits.

24-hour Average Pain Score

The 24-hour average pain score will be assessed using the 11-point numeric rating scale (NRS) scale ranging from zero to ten.

24-hour Worst Pain Score

The 24-hour worst pain score will also be assessed using the 11-point NRS scale ranging from zero to ten.

5.4.2 Verbal Rating Scale (VRS) pain intensity

The Verbal Rating Scale (VRS) is a questionnaire administered by the clinician to capture the patient's level of pain. The response will be recorded as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The score is recorded at baseline only.

5.4.3 Brief Pain Inventory- Short Form (BPI-SF)

Patients will be asked to complete the 7-item pain interference scale which assesses the degree to which pain interferes with walking and other physical activity, work, mood, relations with others and sleep using a zero to ten numeric rating scale, with zero being "does not interfere" and ten being "completely interferes". The score is recorded at Visits 101, 104, 106, 199, TD visit.

The BPI interference total score will derived as the sum of the 7 responses for the questions 9A-9G. The total score ranges from 0 to 70.

5.4.4 Patient Global Impression of Change (PGIC)

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 score is recorded at Visit 199 and TD visit only.

5.4.5 Neuropathic Pain Symptom Inventory (NPSI)

The Neuropathic Pain Symptom Inventory (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 score is recorded at Visits 101, 104, 106, 199, 201 and TD visit.

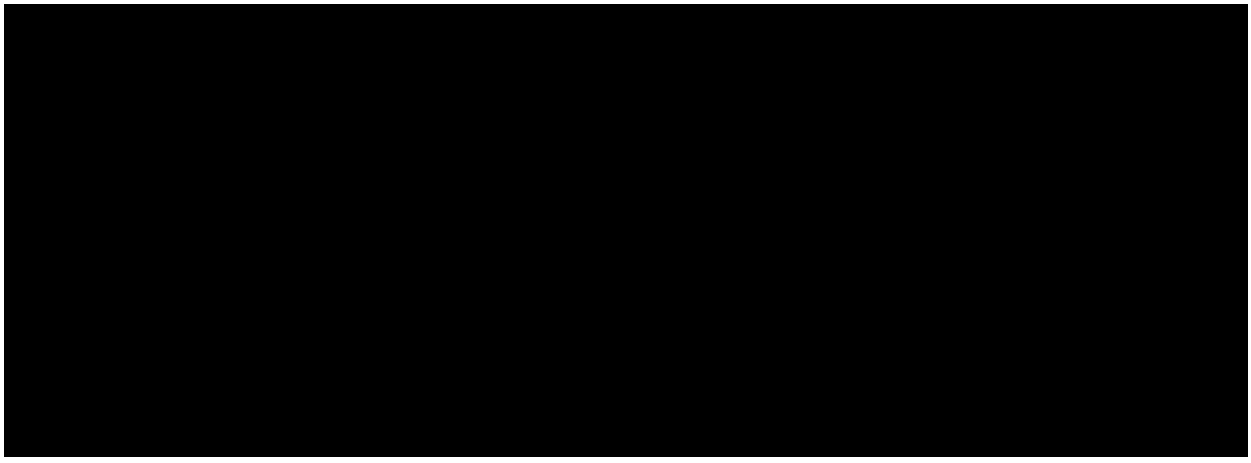
The sum of the responses to the 10 questions (all except qn. 4 and qn. 7) will be regarded as the total score and will be used for the analysis.
The dimensional score of each of the five dimensions are calculated as follows :

- Burning = Q1
- Pressing = (Q2 + Q3) /2
- Paroxysmal = (Q5 + Q6) /2
- Evoked = (Q8 + Q9 + Q10) /3
- Paraesthesia / dysesthesia = (Q11 + Q12)/2

5.4.6 Insomnia Severity Index (ISI)

Patients will be asked to complete the ISI using five-point Likert-style scale as a measure of perceived sleep difficulties. Scores can range from zero to 28, with a cut-off score of eight suggesting the presence of sub-threshold insomnia. The questionnaire assesses the severity of insomnia, satisfaction with current sleep pattern, sleep interference, "noticeability" of sleeping problem to others and concern about sleeping problems. The score is recorded at Visits 101, 199 and TD visit.

The sum of seven responses represents the total score. Each of the 7 items is scored using a range from 0 to 4, thus the total score values can range from zero to 28.



5.5 Statistical models

SAS codes for all statistical methodology described in this section will be included as programming note in TFL Shells.

5.5.1 Primary analysis

5.5.1.1 ANCOVA

The primary analysis (and all other analyses of continuous variables) will be done using analysis of covariance. The model is:

mean pain score = intercept + region + treatment + sex + age + PHNmed (yes/no) + baseline (mean pain intensity) + error.

The SAS procedure MIXED will be used for computing p-values and 95% confidence intervals for LS means.

5.5.1.2 Missing data imputation

For the purpose of missing data imputation, the following two scenarios will be considered:

- Jump to reference (J2R)
- Missing At Random (MAR)

The imputation will be based on all available data (i.e. from all scheduled time points) using all covariates as specified in the ANCOVA model. For J2R only placebo data will be used, for MAR data from the same treatment arm will be used for building the imputation model.

5.5.2 Secondary analysis

5.5.2.1 Logistic regression

The proportion of responders will be analyzed using a repeated measures logistic regression. The model is similar to the ANCOVA model:

Response = intercept + region + treatment + sex + age + PHNmed (yes/no) + baseline (mean pain intensity) + error.

The SAS procedure GENMOD will be used.

Odds ratios will be presented along with 95% confidence intervals and p-values for the treatment contrasts.

5.5.3 Exploratory analysis

5.6 Rule of exclusion criteria of analysis sets

Rule of exclusion criteria from analysis sets due to protocol deviations will be included prior to database lock.

6 References

Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.

CEMA401A2201 Handling of missing items in the derivation of total scores for efficacy measures (last version available before DB lock is used)

CEMA401A2201 Estimand charter (last version available before DB lock is used)

CEMA401A Visit Windows for Baseline and Post-baseline visits and Treatment Discontinuation (TD) visit mapping (last version available before DB lock is used)

Permutt T (2015) Sensitivity analysis for missing data in regulatory submissions. Stat Med; 35:2876-9

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Statist Med; 33:1646–61.

Markus et. al. (1976), On closed testing procedures with special reference to ordered analysis of variance, Biometrika (1976), 63, 3 pp 655-60