NOVARTIS

Global Clinical Development - General Medicine

EMA401/ Olodanrigan

Clinical Trial Protocol 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)

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**Clinical Trial Protocol Template Version 3.2 (July 2016)**

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## List of abbreviations

| | |
|---|---|
| ACR | Albumin-Creatinine Ratio |
| AE | Adverse Event |
| AIDS | Acquired immunodeficiency syndrome |
| ALP | Alkaline Phosphate |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of covariance |
| aPTT | activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| $AT_2$ | Angiotensin II type 2 receptor |
| ATC | Anatomic Therapeutic Chemical classification |
| AUC | Area under the Curve |
| AV Block | Atrioventricular block |
| b.i.d. | twice a day |
| BL | Baseline |
| BPI-SF | Brief Pain Inventory-Short Form |
| CBC | Complete Blood Cell count |
| [redacted] | [redacted] |
| CFR | US Code of Federal Regulations |
| CINP | Chemotherapy Induced Neuropathic Pain |
| CK | Creatine kinase |
| CL/F | Apparent total clearance of the drug from plasma after oral administration |
| $C_{max}$ | Maximum concentration |
| CNS | Central Nervous System |
| CPO | Country Pharma Organization |
| CRA | Clinical Research Associate |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| [redacted] | [redacted] |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP2C9 | Cytochrome P450 2C9 |
| CYP3A4 | Cytochrome P450 3A4 |
| DAR | Dose Administration Record |
| DDI | Drug-Drug Interactions |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic Acid |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders, 5th Edition |
| EC | Ethics Committee |
| [redacted] | [redacted] |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| $ED_{50}$ | The dose at which half of the maximum effect is reached |

[redacted]

| | |
|---|---|
| EDC | Electronic Data Capture |
| eDiary | Electronic diary |
| EFD | Embryo-Fetal Development |
| eGFR | Estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| $E_{max}$ | The maximum effect attributable to the drug |
| EoT | End of Trial |
| ePRO | Electronic Patient Reported Outcome |
| [redacted] | [redacted] |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| γ-GT | gamma-glutamyltransferase |
| [redacted] | [redacted] |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C vírus |
| HIV | Human Immunodeficiency Virus |
| [redacted] | [redacted] |
| HR | Heart Rate |
| [redacted] | [redacted] |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICF | Informed Consent Form |
| IEC | Independent Ethics Committee |
| IN | Investigator Notification |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISI | Insomnia Severity Index |
| LFT | Liver function test |
| LoE | Lack of efficacy |
| LPLV | Last patient last visit |
| MAD | Multiple Ascending Dose |
| MAR | Missing at random |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCP-Mod | Multiple Comparison Procedure – Modelling |
| [redacted] | [redacted] |
| MCV | Mean Corpuscular Volume |
| MDE | Major Depressive Episode |
| MDRD | Modification of Diet in Renal Disease |

[redacted]

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|---|---|
| MedDRA | Medical dictionary for regulatory activities |
| [redacted] | [redacted] |
| MTD | Maximum Tolerated Dose |
| NeuPSIG | Neuropathic Pain Special Interest Group |
| NPSI | Neuropathic Pain Symptom Inventory |
| NRS | Numeric Rating Scale |
| NSAID | Nonsteroidal Anti-inflammatory Drugs |
| OATP1B1 | Organic Anion Transporter Protein 1B1 |
| OATP1B3 | Organic Anion Transporter Protein 1B3 |
| OC/RDC | Oracle Clinical/Remote Data Capture |
| OCT2 | Organic Cation Transporter 2 |
| PCR | Protein-Creatinine Ratio |
| PDN | Painful diabetic neuropathy |
| PHN | Post-Herpetic Neuralgia |
| PK | Pharmacokinetics |
| PGIC | Patient Global Impression of Change |
| PRO | Patient Reported Outcome |
| PRN | pro re nata (as needed) |
| PT | Prothrombin Time |
| QM | Quality Management |
| [redacted] | [redacted] |
| QTc | Corrected QT interval |
| QTcF | Fridericia QT correction formula |
| RoW | Rest of World |
| SAD | Single Ascending Dose |
| SAE | Serious Adverse Event |
| SAF | Safety population |
| [redacted] | [redacted] |
| SOP | Standard Operating Procedure |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TBL | Total bilirubin |
| TD | Study Treatment Discontinuation |
| TENS | Transcutaneous Electrical Nerve Stimulation |
| TEAE | Treatment-Emergent Adverse Events |
| UGT | Uridine Diphosphate Glycosyltransferase |
| ULN | Upper limit of Normal |
| VRS | Verbal Rating Scale |
| WHO | World Health Organization |
| WoC | Withdrawal of Consent |

[redacted]

## Glossary of terms

| | |
|---|---|
| Cohort/arm | A specific group of patients/subjects fulfilling certain criteria |
| Control drug | Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Dosage | Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces.<br>EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care. |
| Enrollment | Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol) |
| Epoch | A portion of the study which serves a specific purpose. Epochs in this study are: screening, treatment, and treatment withdrawal |
| Investigational drug | The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.” |
| Patient/subject ID | A unique number assigned to each patient upon signing the informed consent |
| Personal data | Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource. |
| Study drug/treatment | Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy |
| Study Treatment Discontinuation (TD) | When the patient permanently stops taking study treatment prior to the defined study treatment completion date |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |
| Withdrawal of study consent (WoC) | Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data. |

[redacted]

## Amendment 1

**Amendment rationale**

This is the first global protocol amendment after protocol v00. The protocol is amended to:

- **Update Inclusion criteria list**
  - **Criterion No. 4:** The words electronic Patient Reported Outcome (ePRO) website of this criterion are replaced with electronic tablet. The patient eligibility is to be confirmed on electronic tablet and not ePRO website. This is now #4a.
  - **Criterion No 5**: The wording of this criterion related to inadequate treatment response to at least two different therapies of post herpetic neuralgia (PHN) has been modified, for more clarity. PHN patients are often treated by general practitioners or other physicians and are referred to tertiary care at later stage. Two previous therapies with inadequate treatment response also include analgesics prescribed for the treatment of PHN by general practitioners and other treating physicians. This is now #5a.
  - **Criterion No 6**: Study patients willingness to complete electronic Diary (eDiary) is now included as an inclusion criterion. This change is to better explain this criterion which was previously covered as an exclusion criterion.
- **Update Exclusion criteria list**
  - **Criterion No. 3** Editorial changes and text clarification has been done to this criterion on comorbid Electrocardiogram (ECG) abnormalities. This is now #3a.
  - **Criterion No 6**: As per Novartis standard text embedded in clinical trial protocols, the patients considered for interventional clinical trials have to be cleared of any medical history of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years regardless of whether there is evidence of local recurrences or metastases. This standard text is included to reduce probability of recurrence of the prior cancer in long term studies but does not consider studies with shorter duration. The total study duration is only 13 weeks in this protocol and therefore medical history of malignancy of any organ system in the past 2 years before screening are to be considered sufficient for the CEMA401A2201 study. This is now #6a.
  - **Criterion No. 10**: Criterion on Women of Child Bearing Potential (WOCBP) has been updated based on the latest toxicity data available since protocol V00 release. This is now #10a.
  - **Criteria No**. **11**: Criterion on sexually active males who must use a condom during intercourse (the same applying to vasectomized men) has been deleted based on data from genotoxic studies, as well as from the recently completed reproductive toxicity studies detailed in Investigator Brochure edition #11

[redacted]

Sections 4.3.5/4.3.7. Text has been added to clarify that this criterion has been removed in this amendment.

- **Criterion No.14**: Criterion about positive urine drug screen at Screening has been updated to refer to Section 6.5.4.5. This is now #14a.
- **Criterion No. 15**: Criterion has been updated to make it clearer that patients with only active gallbladder or bile duct disease are not considered for the study. This is now #15a.
- **Criterion No. 18:** Editorial changes and text clarification has been done to criteria regarding other pain conditions. This is now #18a with sub-bullets.
- **Criterion No. 20**: Text from this criterion "ongoing Social Security Disability, Workman's Compensation claim and/or" has been updated for better understanding. This is now #20a.
- **Criterion No 21**: This criterion has been removed to consider for enrolment patients who have previously taken herpes zoster vaccine (HZV). The previous history of vaccination is not considered to have an impact on the response to study drug. Hence the exclusion criterion with regards to the previous use of herpes zoster vaccine (HZV) is now removed which will allow patients that suffer from moderate to severe PHN pain even after vaccination in the study to potentially participate to the study. Text has been added to clarify that this criterion has been removed in this amendment.
- **Criterion No 22**: The criterion related to exclude patients unwilling to complete eDiary has been removed and replaced by addition of inclusion criteria no.6 for better understanding of the protocol language. Text has been added to clarify that this criterion has been removed in this amendment.

[redacted]

- **Update on study Design**:
  - The study screening period editorial update to clarify the 5 week screening period. In the previous version it was 5 weeks (35 days) however at certain places in the study design figure and text it was mentioned as "up to 4weeks (35 days)".
  - Patients will now be allowed to stop prohibited concomitant medication during the screening period after V1.
  - The patients who need to come off the prohibited concomitant medication after screening visit will need to take last dose of prohibited concomitant medication at least 2 weeks (14 days) prior to V101 (i.e. baseline visit)
  - Text has been modified to explain that patients will need to complete baseline 24-hour pain intensity scores daily from day of screening till the day they will return to the study site at Visit 101 (i.e. Baseline).

[redacted]

- **Update on concomitant medication:**
    - Text added to explain allowed concomitant medication can be initiated for patients during the screening period.
- **Update on prohibited medication:**
    - The prohibited medication criteria modified to consider the tapering of certain medications after screening and prior to randomization. Addition of antifungal medications (e.g Azoles) made to prohibited medication list with potential DDIs (Drug Drug Interactions) and a footnote added to allow the Investigators to refer to Section 5.1.5.2 of the Investigators Brochure Edition 11 for details of DDIs (Drug Drug Interactions)
    - It is also clarified in the table that any change in allowed concomitant medication post randomization will be considered as prohibited medication.
- **Addition of a third supplementary analysis:** this analysis is not of primary interest in this study, but it may help comparing the results of this trial with future trials that may target the treatment-policy estimand.
- **Update on Study Treatment**:
    - Capsule appearance description updated.
    - The criteria of patient re-screening updated to allow patients that fail due to "screening algorithm".
- **Update on rescue medication:**
    - The requirement of eDiary update for rescue medication taken for pain due to PHN clarified. It has been further explained that rescue medication taken for any other type of pain to be recorded in electronic Case Report Form (eCRF) as "other rescue medication".
- **Update Visit Assessment Schedule :**
    - Visit window proposed for encouraging adherence to protocol visit schedule. Explained the need to strictly follow the V199 and V201 dates as planned to avoid a patient's over-exposure to EMA401 beyond 13weeks.
    - Serum pregnancy has been added to V101 and deleted from V1 visit.
    - Urine pregnancy added at V1, V104, 106 and V201 visits in the assessment schedule.
    - Clarification text added for ease of understanding of the baseline visit and management of background concomitant medication of the patient.
- **Updated Discontinuation of Study Treatment:**
    - The independent consultation by dermatologist may not needed if the investigator is a dermatologist or for minor rash e.g. insect bite etc. This has been already updated in the Japan local protocol amendment. These changes are helpful for patient visit management.

[redacted]

- **Withdrawal of informed consent:**
  - The criteria of withdrawal of consent updated.
  - Text clarifying the use of data by Novartis as per applicable laws in the geographies added.

[redacted]

**Changes to the protocol**

- **Section 1.1 Background:** Updated information that safety data is based now on 8 phase 1 studies.

[redacted]

- **Section 3.1 and Figure 3-1 Study design:** clarification about the duration of the screening epoch, allowance of tapering of prohibited medication to allow stoppage during screening period, clarifications with principles of the blinded screening algorithm.
- **Section 3.3.3: Non-Clinical safety:** Minor text update to reflect latest information.
- **Section 3.3.4: Clinical Safety:** Updated an overview of the total numbers of subjects/patients enrolled in the EMA401 clinical program as well as numbers of subjects/patients having received EMA401 or placebo till a certain cut-off date.
- **Section 4.2: Inclusion criteria:**
  - Criterion No. 4, text modified. This is now #4a.
  - Criterion No. 5, text modified. This is now #5a.
  - Criterion No 6 added: Patients must be willing to complete daily eDiary.
- **Section 4.1: Exclusion criteria:**
  - Criterion No 3, No.18 and No 20 editorial changes and text clarification. These are now #3a, #18a (with sub-bullet points) and #20a.
  - Criterion No 6: The malignancy case history timeline criteria has been modified from 5 years to 2 years. This is now #6a.
  - Criterion No. 10: WOCBP criteria text has been updated. This is now #10a.
  - Criterion No. 14: Urine drug screen at Screening been updated to refer to Section 6.5.4.5. This is now #14a.
  - Criterion No. 15: Bullet point about known gallbladder or bile duct disease updated. This is now #15a.
  - Criterion No. 11, 21 and 22 deleted.

[redacted]

- **Section 5.1.1: Investigational and control drugs:** Description of capsule appearance updated.
- **Section 5.5.1: Patient numbering:** Updated patient identification and numbering detailed text; Patient re-screening allowed once.
- **Sections 5.5.6: Rescue medications:** Rescue medication recording explained.
- **Section 5.5.7: Concomitant medication:** Text updated to explain start of concomitant medication during screening period.
- **Section 5.5.8 and Table 5.2: Prohibited medications:** Text updated to consider the tapering of certain prohibited medications after screening and prior to randomization; Table of prohibited medications updated considering the different metabolic pathways of EMA401
- **Section 5.6.2: Discontinuation of study treatment**
- **Section 5.6.3: Withdrawal of informed consent:** Text added to clarify the withdrawal criteria's and the use of data for patients that withdraw from the study based on applicable laws.
- **Table 6-1: Visit schedule and assessments/Assessment Schedule**: The assessment schedule updated to add/modify the assessments. (e.g Urine pregnancy testing added)
- **Section 6.5.4.2: Clinical chemistry**: Serum pregnancy testing schedule updated.
- **Section 6.5.4.3: Urinalysis**: Albumin testing removed.
- [redacted]
- **Section 6.5.4.5: Urine drug screen**: Clarification that prescribed medications could be consumed abusively resulting in positive test. The testing could be repeated once during the screening period.
- **Section 6.5.6: Pregnancy and assessments of fertility**: Clarification that pre-menopausal women will have pregnancy testing as per the visit assessment schedule.
- [redacted]
- **Section 9: Data analysis:** Added a third planned supplementary analysis, align with the rest of the protocol amendment items.
- [redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

**Upon finalization of this protocol** the recruitment in the study is ongoing. Thirty eight (38) patients have been randomized by Czech Republic, Denmark, France, Germany, Hungary, Japan, Norway, Slovakia, Portugal, Austria, Belgium and United Kingdom.

[redacted]

**IRBs/IECs**

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

## Summary of previous amendments

### Local amendment (For Japan ONLY)

### Amendment rationale

The purpose of this amendment was to take into consideration the clinical practice about the management of patients suffering from Post-Herpetic Neuralgia (PHN) in Japan. Numerous dermatology clinics only have one qualified clinician specialized in dermatology. These qualified dermatologists are able to examine and treat patients on their own and would be the treating physician of the eligible patients in the EMA401A2201 study in Japan.

In case an event like a skin rash or other dermatologic event would occur while being on study treatment, the investigators who are dermatologists by education and practice medicine in dermatology clinics would be able to take their own decisions about the potential interruption/discontinuation of study treatment in the context of a suspicion of allergic dermatitis and ultimately be the ones to judge whether or not the study treatment could be re-started and thus making the consultation by an independent dermatologist as non-essential.

### Changes to the protocol

**Section 5.6.2**

Text corrected to remove the reference to the consultation with an independent dermatologist as the investigators/study doctors will be qualified to examine and treat patients in case of a skin rash or a dermatologic event that would occur while patients being on study treatment.

[redacted]

## Protocol summary

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| **Protocol number** | CEMA401A2201 |
| **Full Title** | 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) |
| **Brief title** | Dose response study of EMA401 in patients with post-herpetic neuralgia (PHN) |
| **Sponsor and Clinical Phase** | Novartis<br>Phase 2 |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | The purpose of this study is to characterize dose response, and evaluate safety and efficacy of three different doses of EMA401 compared to placebo in patients with post-herpetic neuralgia (PHN). Data from this study will be used to inform the selection of EMA401 doses for future Phase 3 clinical trials. |
| **Primary Objective(s)** | To characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12 |
| **Secondary Objectives** | • Objective 1: 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<br>• Objective 2: 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<br>• Objective 3: 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<br>• Objective 4: To evaluate the efficacy of EMA401 compared to placebo, on the Patient Global Impression of Change (PGIC) at Week 12<br>• Objective 5: 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<br>• Objective 6: To evaluate the effect of EMA401 compared to placebo on the Insomnia Severity Index (ISI) at Week 12<br>• Objective 7: To evaluate the effect of EMA401 compared to placebo on the Neuropathic Pain Symptom Inventory (NPSI) at Week 12<br>• Objective 8: 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 drug discontinuation and serious adverse events (SAEs) throughout the study<br>• Objective 9: To evaluate the pharmacokinetics (PK) of EMA401 and exposure-response (decrease in pain intensity) relationship for EMA401 throughout the study |

[redacted]

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| **Study design** | The study is interventional, randomized, parallel, placebo-controlled, dose ranging, double-blind treatment. |
| **Population** | The study population will consist of approximately 360 randomized male and female patients (≥ 18 years old) with PHN |
| **Key Inclusion criteria** | • At the time of Screening, have documented diagnosis of PHN (ICD-10 code B02.29), defined as pain in the region of the rash persisting for more than 6 months after onset of herpes zoster rash.<br>• Be assessed as suffering from moderate to severe neuropathic pain across the Screening epoch (NRS ≥ 4).<br>• Patients must have documented past and/or ongoing inadequate treatment response (having insufficient pain relief with treatment or inability to tolerate) to at least 2 different prescribed therapies/analgesics commonly used to treat and considered effective for the treatment of PHN.<br>• Patients must be willing to complete daily electronic Diary (eDiary) |
| **Key Exclusion criteria** | • Electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study.<br>• Major depressive episode within 6 months prior to Screening and/or a history of diagnosed recurrent major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria.<br>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using highly effective methods of contraception during dosing and for 3 days after stopping study medication. Highly effective contraceptive methods include:<br>  • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.<br>  • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.<br>  • Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.<br>  • Placement of an intrauterine device (IUD) or intrauterine system (IUS).<br>In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form (ICF)<br>• Have evidence of significant renal insufficiency or pre-existing liver condition.<br>• Have platelets ≤ 100 x $10^9$/L, or neutrophil count < 1.2 x $10^9$/L (or equivalent), hemoglobin ≤ 100 g/L for women or hemoglobin ≤ 110 g/L for men. |

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| | • Patients who have a known diagnosis of diabetes and are stable on medication with a hemoglobin A1C > 8%. Those who do not have a known diagnosis of diabetes with a hemoglobin A1c > 7%. |
| **Study treatment** | EMA401 and placebo |
| **Efficacy assessments** | • 11-point Numeric Rating Scale (NRS)<br>• Brief Pain Inventory-Short Form (BPI-SF)<br>• Patient Global Impression of Change (PGIC)<br>• Insomnia Severity Index (ISI)<br>• Neuropathic Pain Symptom Inventory (NPSI) |
| **Key safety assessments** | • Adverse event monitoring<br>• Physical examinations and vital signs<br>• Monitoring of laboratory markers in blood and urine<br>• ECGs<br>[redacted] |
| **Other assessments** | • Pharmacokinetics (PK)<br>[redacted]<br>• Intake of rescue medication<br>[redacted] |
| **Data analysis** | The primary objective will be to characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12.<br>The primary estimation method is based on an Analysis of covariance (ANCOVA) model including region (e.g. US, EU), treatment, sex, use of concomitant pain medication for PHN (yes/no) as factors and baseline (mean pain intensity) score and age as covariates. The analysis will account for different post-randomization events, such as changes in doses of concomitant medication for PHN, intake of rescue medication, intake of prohibited medications that have a potential confounding effect on efficacy of the investigational drug, and discontinuations of study treatment due to different reasons.<br>Dose-response estimation will be performed based on the ANCOVA least square estimates using Multiple Comparison Procedure – Modelling (MCP-Mod). |
| **Key words** | Post-herpetic neuralgia, neuropathic pain, angiotensin II type 2 receptor antagonist, dose ranging |

[redacted]

# 1 Introduction

## 1.1 Background

Neuropathic pain is recognized as having one of the most significant unmet needs of all the various forms of chronic pain. Painful diabetic neuropathy (PDN) is the most prevalent type of neuropathic pain, affecting up to 50% of diabetic patients (Mixcoatl-Zecuatl and Calcutt 2013). It is estimated that there will be over 8 million prevalent cases of PDN in US and Europe by the end of 2016, with 2.5% annual growth rate to reach 10 million cases by 2024 (Kravit and Kuranz 2015). The next most prevalent forms of neuropathic pain are HIV/AIDS-related neuropathy, neuropathic cancer pain and post-herpetic neuralgia (PHN). The latter two affect over 0.5 million patients each and the proportion of patients is expecting to grow at 1.4% annual growth rate till 2024. About 20% of patients with herpes zoster report some pain at 3 months after the onset of symptoms, and 15% report pain at 2 years (Johnson and Rice 2014). Neuropathic cancer pain is experienced by 29% of people living with inoperable cancer (Kravit and Kuranz 2015).

Post-herpetic neuralgia (PHN) is clinically defined as a persistent neuropathic pain following the appearance of the skin rash and is thought to be caused by scarring of the dorsal root ganglion and atrophy of the dorsal horn in areas affected by the zoster outbreak (Cunningham and Dworkin 2000). PHN manifests as an assortment of symptoms, including spontaneous aching or burning pain, continuous or the sudden onset of shooting pains, allodynia and hyperalgesia (Cunningham and Dworkin 2000).

Recent recommendations of Neuropathic Pain Special Interest Group (NeuPSIG) for the pharmacotherapy of neuropathic pain include use of tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin as first line agents (Finnerup et al 2015). Recommended second line therapy includes lidocaine patches, capsaicin high-concentration patches, and tramadol. These treatments however work in a subset of the patient population; significant proportion of patients get $\leq$ 50% pain reduction and are accompanied by side effects that limit their utility (Hempenstall et al 2005). High-dose monotherapy or combination of existing therapies is often used in patients with inadequate pain control in clinical practice. However, the benefit of the combination of currently available first or second line agents is limited due to additional tolerability issues, and disadvantages of combinations often outweigh the benefits. The majority of combinations evaluated to date involve drugs which share some element of central nervous system (CNS) depression (e.g. sedation, cognitive dysfunction). This aspect of side effect overlap between combinations results in high dropout rates and thus may substantially limit the utility of such combinations (Chaparro et al 2012). Given the prevalence and severity of PHN, a clear need exists for better treatments to reduce the condition's burden on patients and society.

EMA401 is an angiotensin II type 2 ($AT_2$) receptor antagonist that has been shown to be active in established animal and clinical neuropathic pain models (Rice et al 2014, Smith and Muralidharan 2015). Initial safety data for EMA401 has been generated in eight Phase 1 studies and one open label Phase 2 study in Chemotherapy Induced Neuropathic Pain (CINP). Additionally, a randomized, placebo-controlled, multi-centric, proof of concept Phase 2 efficacy study in PHN patients was completed, in which patients on EMA401 (100 mg b.i.d.) reported significant improvement in pain intensity compared to placebo following four weeks

of treatment (Rice et al 2014). EMA401 was well-tolerated and demonstrates a positive benefit risk profile based on all evidence generated to date.

## 1.2 Purpose

The purpose of this study is to characterize dose response, and evaluate safety and efficacy of three different doses of EMA401 (25 mg b.i.d. (i.e. 50 mg/day), 100 mg b.i.d. (i.e. 200 mg/day), 300 mg b.i.d. (i.e. 600 mg/day)) compared to placebo in patients with post-herpetic neuralgia (PHN). Data from this study will be used to inform the selection of EMA401 doses for future Phase 3 clinical trials.

# 2 Study objectives and endpoints

## 2.1 Objectives and related endpoints

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary Objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To characterize dose-response for change in the weekly mean of 24-hour average pain intensity scores at Week 12 | • 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)** | **Endpoint(s) for 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 | • Change in weekly mean 24-hour average pain score (using the 11 point NRS) from Baseline to Week 12 |
| • 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 | • Change in BPI-SF interference total score from Baseline to 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 | • Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS, from Baseline to Week 12 |
| • To evaluate the efficacy of EMA401 compared to placebo, on the Patient Global Impression of Change (PGIC) at Week 12 | • PGIC at Week 12 |

[redacted]

| Objective(s) | Endpoint(s) |
|---|---|
| • 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 | • Proportion of patients meeting responder criteria from Baseline to Week 12 |
| • To evaluate the effect of EMA401 compared to placebo on the Insomnia Severity Index (ISI) at Week 12 | • Change in ISI from Baseline to Week 12 |
| • To evaluate the effect of EMA401 compared to placebo on the Neuropathic Pain Symptom Inventory (NPSI) at Week 12 | • Change in NPSI from Baseline to 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 drug discontinuation and serious adverse events (SAEs) throughout the study | • Number and severity of treatment emergent adverse events and the frequency of adverse events leading to discontinuation. Number of serious adverse events. |
| • 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)** |
| [redacted] | |
| • To evaluate the proportion of patients who need rescue medication and the time to first intake of rescue medication | • Proportion of patients who need rescue medication and the time to first intake of rescue medication |
| [redacted] | |

[redacted]

| Objective(s) | Endpoint(s) |
|---|---|
| [redacted] | |

# 3 Investigational plan

## 3.1 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).

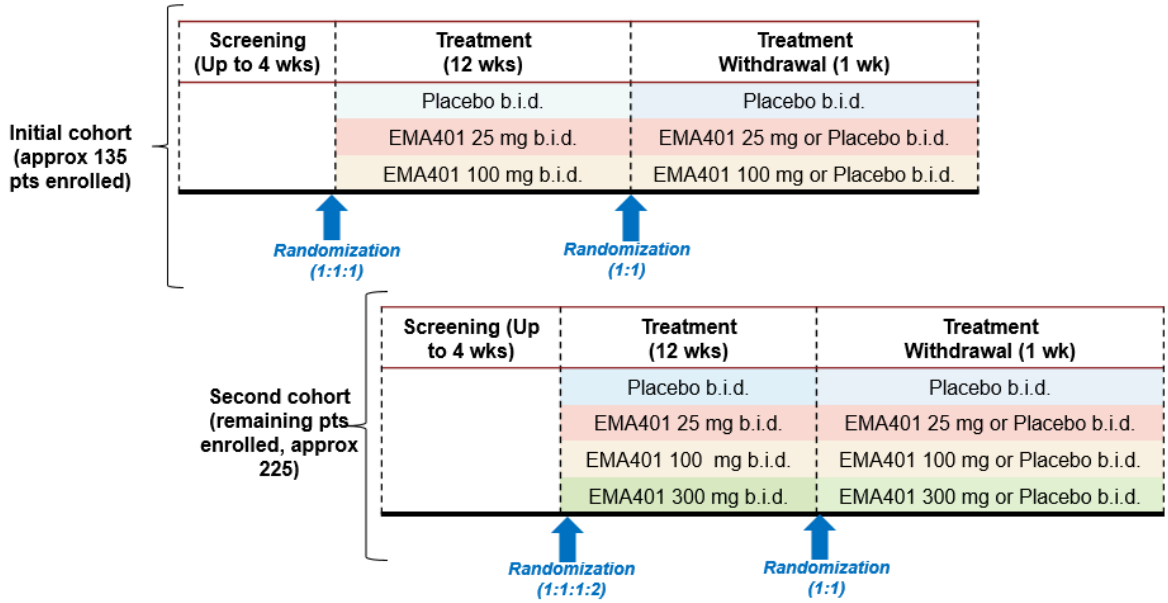
- In the initial cohort, patients will be randomized in a 1:1:1 ratio to treatment with placebo, EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d. (approximately 135 patients). Randomization of patients to the high dose arm (EMA401 300 mg b.i.d.) in study CEMA401A2201 will only be initiated following an unblinded 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 will be enrolled in the study (i.e. approximately 90 patients will be enrolled in each treatment arm). In the event that the EMA401 300 mg b.i.d. treatment arm is not initiated, the original 1:1:1 randomization ratio will remain and overall approximately 270 patients will be enrolled in the study (i.e. approximately 90 patients will be enrolled in each of the treatment arms of placebo, EMA401 25 mg b.i.d., and EMA401 100 mg b.i.d.). End of Trial (EoT) will occur when the last patient completes last visit (LPLV).

Figure 3-1 presents an overview of the study design.

[redacted]

**Figure 3-1 Study design**




***Screening epoch (Up to 5 weeks)***

Potential participants will be required to provide written informed consent prior to any study-specific screening procedures being performed. Once informed consent is obtained, patients will be evaluated for eligibility based on the inclusion and exclusion criteria (see Section 4), which will require review of medical history and concomitant medications, vital signs, physical examination, assessment of patients' current pain scores using the NRS, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations.

Patients who pass preliminary Screening assessments will receive their electronic patient reported outcome (ePRO) electronic diary (eDiary) device.

Washout of any prohibited concomitant medications (see Table 5-2) should be initiated from day of screening. The last dose of the prohibited medication should be taken minimum 2 weeks (14 days) prior to baseline visit.

Patients are required to complete their baseline 24-hour pain intensity scores daily from the day of screening till the day they return to the study site at Visit 101 (i.e. Baseline).

The patient's final eligibility will be based on an assessment of their 24-hour average pain intensity scores recorded in the eDiary device using a proprietary screening algorithm (Appendix 4) prior to randomization.

General principles of the algorithm will include:

Exclusion of patients with scores below the minimum mean baseline pain intensity of "4" using the NRS scale; and patients who:

- Were not compliant in completing the required data

OR

- Did not record accurate pain scores

OR

- Who had unacceptable variability in their baseline intensity.

Designated investigator site staff will need to check the electronic tablet to see if the patient meets these criteria to continue in the study and document the outcome in the patient's source document.

***Treatment epoch (12 weeks)***

Patients completing all Screening assessments will then be randomized into a 12-week double-blind Treatment epoch. Patients will visit the study site for assessments that are outlined in the visit assessment schedule (Table 6-1). At each scheduled visit the designated investigator site staff will perform various assessments outlined in the visit assessment schedule and will review the patient's weekly pain eDiary scores from the prior week(s) for compliance and entry errors, and retrain the patient's on eDiary entry as needed. Patients will be required to bring their eDiary device to every site visit. Patients will be instructed to continue recording their 24-hour average and worst pain intensity scores each day for the remainder of the study. Patients will be required to bring their previously dispensed supply of study medication to each scheduled visit in order that the designated investigator site staff can assess patient's compliance with the dosing regimen. Patients should bring their pregabalin /gabapentin medication (if applicable) with them to the study visits where PK is collected so it may be administered after the PK assessment, as required.

***Treatment withdrawal epoch (1 week)***

At the end of the 12-week double-blind Treatment epoch there will be a 1-week, double-blind Treatment withdrawal epoch. Patients receiving placebo treatment during the 12-week double-blind Treatment epoch will remain on placebo during the double-blind Treatment withdrawal epoch. Patients receiving active treatment will be randomized in a 1:1 ratio to either stop treatment abruptly (i.e. receive placebo) or to continue the active treatment assigned during the double-blind Treatment epoch.

## 3.2 Rationale for study design

The study is intended to provide information on the minimum effective dose and the optimal dose range for therapeutic doses of EMA401. It will evaluate the safety and efficacy of three dose levels of EMA401 in the treatment of PHN.

For each dose, 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 treatment

effect of interest accounts for post-randomization events in a way that reflects their possible relationship to the investigational treatment. In particular, the treatment effect of interest:

- shall not be confounded by events which are deemed non informative on the effect of the study medication, even if they may have the potential to confound it (e.g. some changes in concomitant medications), and
- shall account for events reflecting the unfavorable outcome when patients are unable to continue taking the study medication or unable to benefit from it (such as study treatment discontinuations for specific reasons).

Further details are provided in Section 9.4.2.

The standard methodology for the purpose of establishing evidence of a dose response based on the above treatment effect is to conduct a double-blind, placebo-controlled, randomized, parallel group study. Twelve weeks of exposure is required for assessment of treatment response and registration in chronic pain conditions. The staggered approach to randomizing patients to the EMA401 300 mg b.i.d. arm following DMC unblinded review of safety data, together with clinical assessments every two weeks will ensure patient safety.

The study will evaluate the potential for a rebound effect of EMA401 in both safety and efficacy after study drug discontinuation during a treatment withdrawal period designed to minimize bias.

## 3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose range planned to be studied includes: 25 mg b.i.d., 100 mg b.i.d., and 300 mg b.i.d. Guidelines on the clinical development of medicinal products intended for the treatment of pain state that dose response studies should evaluate ceiling effects for efficacy (EMA Guideline 2015, FDA Guideline 2014).

It is recommended that dose ranging studies should be designed for estimating dose response characteristics across a > 10 fold range (e.g. 0.1 – 1.0 of the maximum tolerated dose-MTD) and adapting to the reality of the specific drug and disease (EMA Report from Dose Finding Workshop, 2015).

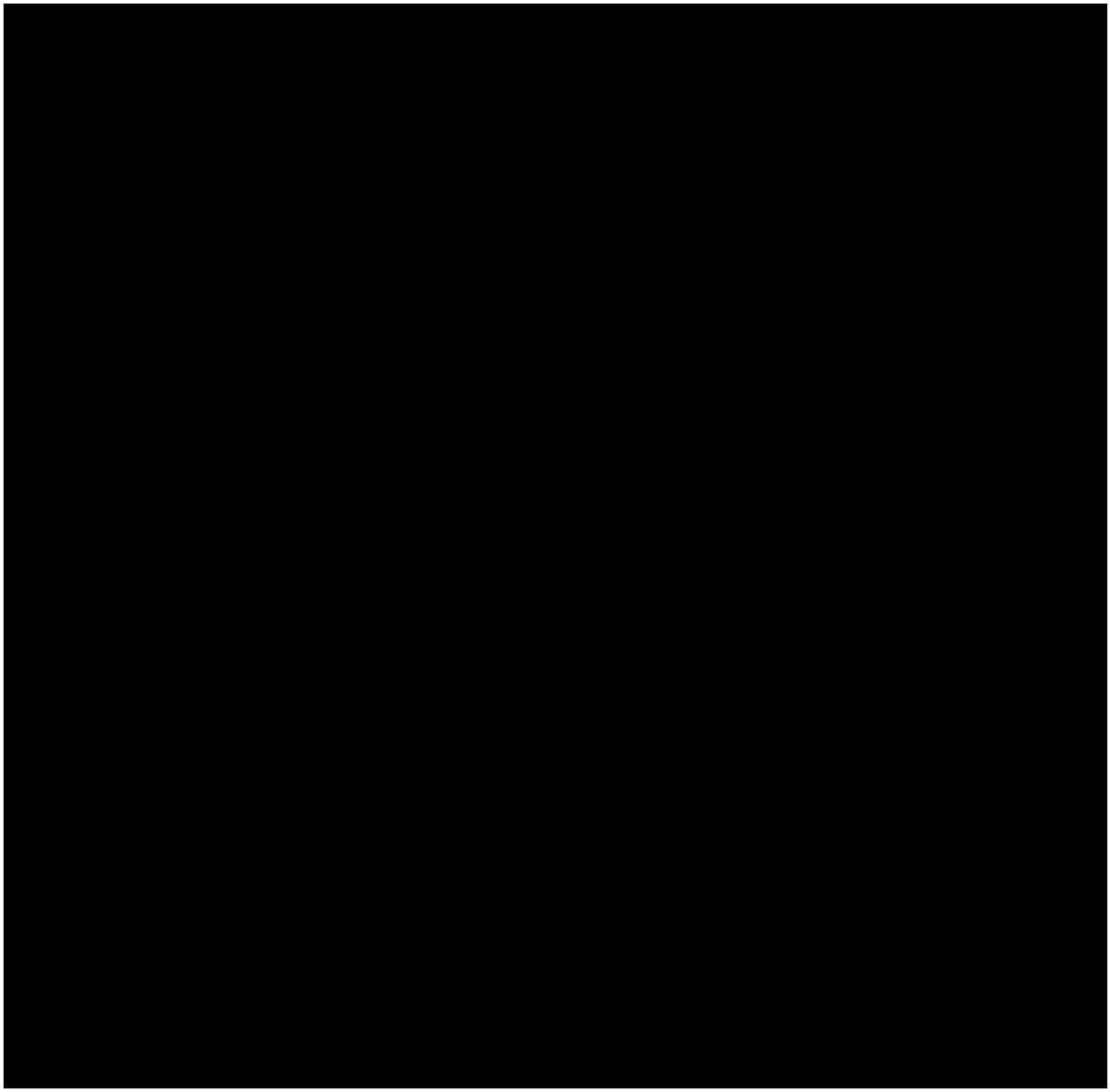
In healthy volunteers, maximum tolerated dose (MTD) levels of EMA401 for single and multiple (for 7 days) dosing have been established at 2000 mg and 800 mg b.i.d. (1600 mg/day) respectively (Study EMA401-008).

Doses selected will allow clear differentiation and characterization of pharmacodynamic dose response over 12 fold dose dynamic range.

### 3.3.1 Efficacy

In randomized, double-blind Study EMA401-003 (n=183), PHN patients on EMA401 at 100 mg b.i.d. reported significant reduction in pain compared to placebo (mean reductions in pain scores −2.29 vs. −1.60) following four weeks of treatment (p=0.0066).

[redacted]



### 3.3.3 Non-Clinical Safety

Non-clinical safety pharmacology and toxicology studies with EMA401 have been conducted in dogs (up to 4-week duration), rats and monkeys (up to 13-week duration) to support clinical trials of up to 13-week in duration and embryo-fetal development (EFD) toxicity studies in rats (definitive) and rabbits (preliminary) have been conducted. In the 13-week toxicity study in rats, mortality and excessive toxicity were noted at doses ≥ 1000/500 mg/kg/day. Oral administration of EMA401 resulted in various pathological changes in the gastrointestinal tract (especially the nonglandular stomach) and nasal turbinate at doses ≥ 150 mg/kg/day. In the 13-week toxicity study in monkeys, oral administration of EMA401 caused abnormal feces and vomitus/emesis at doses ≥ 100 mg/kg/day. Those effects were not adverse because they were transient, did not decrease body weight/body weight gain and thus did not affect the overall health of the animals. The non-clinical studies completed to date support the use of EMA401 up to dose of 300 mg

b.i.d. for up to 13 weeks including in Women of child bearing potential. A summary of completed non-clinical studies and their results can be found in the Investigator's Brochure.

### 3.3.4 Clinical Safety

Eight studies in healthy subjects and two in patients have been completed for EMA401. Three hundred seventy three unique subjects (250 healthy subjects, 92 patients with PHN, and 31 patients with Chemotherapy Induced Neuropathic Pain (CINP)) have received EMA401, and 183 subjects (92 healthy subjects and 91 patients with PHN) have received placebo in the clinical program till date. Maximum doses tested were up to 2000 mg in single ascending dose (SAD), 800 mg b.i.d. (1600 mg/d) for 7 days in multiple ascending dose (MAD), and 100 mg b.i.d. (200 mg/d) in Phase 2 for 28 days.

No deaths or SAEs have been attributed to EMA401.

Study EMA401-008 determined maximum tolerated doses (MTDs) for EMA401 in healthy volunteers. Gastrointestinal AEs (particularly nausea and diarrhea) were the most significant dose-related AEs in subjects who received EMA401. All reported TEAEs were mild to moderate in severity in both single and multiple ascending cohorts. There was an apparent dose-related trend in gastrointestinal events in both the SAD and MAD components with highest incidence in single dose of 2000 mg or 800 mg b.i.d. multiple dose cohorts. As a result, these two dose levels have been determined to be the single and short-term repeat maximum tolerated doses (MTDs) for EMA401, respectively.

In PHN patients (Study EMA401-003), EMA401 demonstrated an acceptable safety profile and was well-tolerated. Overall, 32 patients reported 56 treatment emergent adverse events (TEAEs) in the EMA401 group compared to 29 patients reporting 45 TEAEs in the placebo group. TEAEs of headache, allergic dermatitis and pharyngitis were observed more frequently with EMA401 treatment compared to placebo. All reported TEAEs events were mild to moderate in severity. Patients were allowed to use concomitant medications for PHN, including pregabalin and gabapentin, and other comorbid conditions (e.g. insomnia, depression). No safety concerns were identified with use of EMA401 and concomitant medications over 4 weeks.

## 3.4 Rationale for choice of comparator

In accordance with the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines, a placebo-control design was considered essential for this study as placebo-associated improvements are prominent in studies in chronic pain (Dworkin et al 2010).

## 3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

## 3.6 Risks and benefits

The available safety information, combined with the potential of EMA401 to effectively treat neuropathic pain symptoms in patients, suggests a favorable risk-benefit ratio for exposure up to 13 weeks (see Section 3.3). Appropriate exclusion criteria are defined to ensure patient safety and allow estimation of treatment response with minimal factors that confound assessment of neuropathic pain. The risk to patients in this trial will be minimized by compliance with the

[redacted]

eligibility criteria and study procedures, close clinical monitoring, monitoring for treatment emergent adverse events, and discontinuation of study treatment due to adverse events or based on judgment of the investigator (Section 5.6.2). In addition, the DMC will conduct quarterly full unblinded safety reviews. The DMC will review cumulative safety data, as well as 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). Novartis will also report the following events to the DMC on a "real time" basis: SUSARs, Death/outcome leading to death, and cases of interest as noted above.

Study population includes patients suffering from moderate to severe pain, which is often associated with comorbid conditions (e.g. anxiety, depression and sleep disturbances). Concomitant use of medications for pain (pregabalin or gabapentin) and other comorbid diseases at stable doses is therefore allowed, no safety concerns are foreseen.

# 4 Population

The study population will consist of male and female patients (≥ 18 years old) with post-herpetic neuralgia (PHN). The goal is to randomize a total of approximately 360 patients in approximately 100-120 centers worldwide. Since a 40% screening failure rate is expected, approximately 600 patients will be screened.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Males and females, 18 years and older.
3. At the time of Screening, have documented diagnosis of PHN (ICD-10 code B02.29), defined as pain in the region of the rash persisting for more than 6 months after onset of herpes zoster rash.

4a. Be assessed as suffering from moderate to severe neuropathic pain across the Screening epoch (NRS ≥ 4). The assessment of moderate and severe pain will be made using a proprietary screening algorithm (as described in Section 3.1). The designated investigator site staff will be informed immediately as to whether the patient is eligible or ineligible on the electronic tablet based on the patient entering all relevant pain scores in the eDiary device.

5a. Patients must have documented past and/or ongoing inadequate treatment response (having insufficient pain relief with treatment or inability to tolerate) to at least 2 different prescribed therapies / analgesics commonly used to treat and considered effective for the treatment of PHN.

6. Patient must be willing to complete daily eDiary

[redacted]

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.

3a. Electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study such as:

- Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree Atrioventricular block (AV block) without a pacemaker.
- History of familial long QT syndrome or known family history of Torsades de Pointes.

4. Patients taking medications prohibited by the protocol (see Section 5.5.8, Table 5-2).
5. Skin conditions in the affected dermatome that in the Investigator's opinion could alter sensation or active herpes zoster upon physical examination at Screening.

6a. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 2 years, regardless of whether there is evidence of local recurrence or metastases.

7. Major depressive episode within 6 months prior to Screening and/or a history of diagnosed recurrent major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria (see Appendix 6).

[redacted]

9. Pregnant or nursing (lactating) women.

10a. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using highly effective methods of contraception during dosing and for 3 days after stopping of study medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

[redacted]

- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form (ICF)

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

11. This criterion has been removed in this amendment.
12. Have evidence of significant renal insufficiency, indicated by an estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation of $< 40$ mL/min/1.73 $m^2$ at Screening (as calculated by the central laboratory).
13. Alcohol Use Disorder or other Substance-use disorders (other than nicotine or caffeine) in accordance with DSM-V criteria within 12 months of screening (see Appendix 7).

14a. Positive urine drug screen at Screening. (See section 6.5.4.5).

15a. Evidence of pre-existing liver condition as defined as any of the following:

- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 1.5$ X ULN (upper limit of normal), or total bilirubin or alkaline phosphatase >ULN for the central laboratory at Screening.
- Known history of or active hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
- Hepatitis A or B vaccination within 3 months of Screening.
- Active gallbladder or bile duct disease.
- Acute or chronic pancreatitis.

16. Have platelets $\leq 100 \times 10^9$/L, or neutrophil count $< 1.2 \times 10^9$/L (or equivalent), or hemoglobin $\leq 100$ g/L for women or hemoglobin $\leq 110$ g/L for men.
17. Patients who have a known diagnosis of diabetes and are stable on medication with a hemoglobin A1c > 8%. Those who do not have a known diagnosis of diabetes with a hemoglobin A1c > 7%.

18a. Other conditions :

- Have an active, uncontrolled medical condition (e.g., neurological, gastrointestinal, renal, hepatic, cardiovascular, pulmonary, metabolic, endocrine, hematological, genitourinary or other major disorder), psychotic disorder or any other uncontrolled psychiatric illness (patients who are not stable on medication for at least two months prior are excluded), or any other significant clinical disorder or laboratory finding.
- Had a clinically significant illness or operative procedure within four weeks of Screening (e.g., influenza, myocardial infarction).

[redacted]

- Have, any other pain in the region of the herpes zoster rash or any other moderate to severe pain that can be confused with the patient's PHN, or other chronic pain conditions including osteoarthritis, that may confound evaluation of treatment response.

19. Have undergone neurolytic or neurosurgical therapy or use a neuro stimulating device for PHN within 3 months of Screening or are using/ plan to use Transcutaneous Electrical Nerve Stimulation (TENS).

20a. Subjects with an ongoing litigation related to their pain disorder.

21. This criterion has been removed in this amendment

22. This criterion has been removed in this amendment.

# 5 Treatment

## 5.1 Study treatment

### 5.1.1 Investigational and control drugs

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

- 12.5 mg
- 50 mg
- 150 mg

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

No additional treatment beyond investigational drug and control drug are included in this trial.

## 5.2 Treatment arms

In the initial cohort, patients will be assigned at Baseline (Visit 101) to one of the following 3 treatment arms in the ratio of 1:1:1.

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

After unblinded safety review by an independent DMC, future patients will then be assigned in the second cohort at Baseline (Visit 101) to one of the following 4 treatment arms in the ratio of 1:1:1:2.

- Placebo b.i.d.
- EMA401 25 mg b.i.d.
- EMA401 100 mg b.i.d.
- EMA401 300 mg b.i.d.

In the event that the EMA401 300 mg b.i.d. treatment arm is not initiated, patients will continue to be randomized according to the original 1:1:1 ratio to placebo, EMA401 25 mg b.i.d., or

EMA401 100 mg b.i.d. until the planned enrollment in each dose arm is completed (i.e. 90 patients).

## 5.3 Treatment assignment and randomization

At Baseline (Visit 101), all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms in the double-blind Treatment epoch and to one of the treatment arms in the double-blind Treatment withdrawal epoch. Logistically, the randomization into all epochs will be pre-specified according to the following randomization scheme.

**Table 5-1 Randomization scheme**

| Treatment epoch (treatment arms) | Treatment withdrawal epoch (treatment arms) | Randomization ratio (initial cohort) | Randomization ratio (second cohort) |
|---|---|---|---|
| Placebo | Placebo | 2 | 2 |
| EMA401 25 mg | EMA401 25 mg | 1 | 1 |
| EMA401 25 mg | Placebo | 1 | 1 |
| EMA401 100 mg | EMA401 100 mg | 1 | 1 |
| EMA401 100 mg | Placebo | 1 | 1 |
| EMA401 300 mg | EMA401 300 mg | 0 | 2 |
| EMA401 300 mg | Placebo | 0 | 2 |

The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

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.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

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

[redacted]

For the primary analysis at Week 12, the overall study randomization ratio will be 1:1:1:1 for the treatment arms placebo, EMA401 25 mg b.i.d., EMA401 100 mg b.i.d., or EMA401 300 mg b.i.d. (refer to Section 9.8). In the event that the EMA401 300 mg b.i.d. treatment arm is not initiated, patients will continue to be randomized according to the original 1:1:1 ratio to placebo, EMA401 25 mg b.i.d., or EMA401 100 mg b.i.d. until the planned enrollment in each dose arm is completed (i.e. 90 patients).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

## 5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: Drug Supply Management, PK analyst and the IRT staff. (2) The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, and appearance.

The randomization codes associated with patients from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study. The external DMC and independent Contract Research Organization (CRO) will have access to unblinded data, as further described in Section 8.4.

## 5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

### 5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed of the site number and a sequential number. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the Case Report Form (CRF) book with a matching Subject Number from the Electronic Data Capture (EDC) system to enter data.

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Disposition CRF.

A patient may fail the Screening epoch one time; Investigators may re-screen a patient if there is reasonable certainty that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Some examples of re-screening reasons are listed below. If needed, questions regarding re-screen eligibility may be discussed with Novartis. Should this occur, the site should

[redacted]

re-consent the patient and assign a new subject identification number. Once randomized, the subject identification number must remain constant throughout the entire clinical study.

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation. (Note: Before screen failing and then re-screening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening phase.)
- The patient has a medical condition that can be stabilized or resolved prior to the repeat screening attempt.

Re-screening for patients will only be allowed once.

### 5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a specific dose. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

### 5.5.3 Handling of study and additional treatment

#### 5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

#### 5.5.3.2 Handling of additional treatment

Not applicable.

### 5.5.4 Instructions for prescribing and taking study treatment

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 study medication should be taken on an empty stomach at least one hour before a meal or at least two hours after a meal. **At the scheduled study visits where PK is collected (refer to Table 6-1), patients should be instructed not to take their morning dose of study medication (and pregabalin/gabapentin if applicable) prior to arriving at the site and completing the necessary assessments. Patients should bring their pregabalin/gabapentin (if applicable) with them to the study visits where PK is collected so it may be administered after the PK as required.**

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

### 5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational or other treatment dose adjustments and/or interruptions are not permitted.

### 5.5.6 Rescue medication

Patients will be allowed to take acetaminophen/paracetamol up to a maximum of 3 g daily (divided into 3 or 4 times/day) for unacceptable pain due to any reason during the study. Acetaminophen/paracetamol will not be provided by Novartis.

The patients will be instructed to complete the pain scores in eDiary before intake of acetaminophen/paracetamol when taken due to unacceptable pain due to PHN.

The intake of acetaminophen/paracetamol in eDiary is to be recorded by the patient only when taken for unacceptable pain due to PHN.

The intake of acetaminophen/paracetamol if taken, for unacceptable pain due to any other reason, should be recorded in the eCRF as "other rescue medication" by the designated investigator staff.

### 5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

[redacted]

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Allowed concomitant medications can be initiated for patients if deemed necessary by the investigator, however they should be on stable dose at least 2 weeks (14 days) prior to V101 (i.e. Baseline visit).

1. Patients will be allowed to take **only one** of the following prescribed medications for managing their PHN, provided the dose level has been stable for at least 2 weeks prior to the Randomization Visit (Visit 101 i.e Baseline visit) and must remain at stable doses throughout the study (PRN (as needed) use is not allowed):
   - Pregabalin
   - Gabapentin
2. In addition to other medications for non-pain related co-morbid conditions, patients will be allowed to take throughout the study the following medications for other concomitant medical conditions. The dose level must be stable at Baseline and must continue at stable doses throughout the study (PRN (as needed) use is not allowed):
   - A benzodiazepine, zolpidem, diphenhydramine or related drugs for insomnia.
   - A selective serotonin reuptake inhibitor (SSRI) for depression.
   - Oral aspirin (≤ 325 mg/day) for cardio-protection.

### 5.5.8 Prohibited medication

Medications that the patient may be taking for the treatment of neuropathic pain (i.e. pregabalin or gabapentin) must be stable for at least 2 weeks prior to Randomization, and must remain stable throughout the study.

In addition, use of the treatments displayed in Table 5-2 is prohibited.

**Table 5-2 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 weeks 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 |

[redacted]

| Medication | Prohibition period | Action taken for study treatment |
|---|---|---|
| Mexiletine | 2 weeks prior to Randomization and after Randomization | None |
| Dextromethorphan | 2 weeks prior to Randomization d 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 |
| 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 |

[redacted]

| Medication | Prohibition period | Action taken for study treatment |
|---|---|---|
| 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 |

(*Prohibited due to potential Drug-Drug Interactions (DDIs), please refer to Investigator Brochure Ed 11, Section 5.1.5.2 for details)

### 5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. If the IRT system is not available for technical reasons, the IRT help desk can facilitate emergency code break requests. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

[redacted]

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and the Study Team after an emergency treatment code break to assess whether or not investigational treatment should be discontinued for a given patient and, if applicable, whether the patient can continue into the next trial epoch.

## 5.6 Study completion and discontinuation

### 5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. The study will be considered complete (End of Trial) when the last patient completes last visit (i.e., LPLV) in the study.

Provision of study treatment after completion of this study is not planned as pre-clinical toxicological studies currently permit a maximum of 13 weeks of treatment administration in human subjects.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up.

### 5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 7.6)
- Use of prohibited treatment as described in Section 5.5.8
- Positive urine drug screen
- Any situation in which study participation might result in a safety risk to the patient
- Unsatisfactory therapeutic effect
- Patient's condition no longer requiring study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

In addition, study treatment must be interrupted/ discontinued under the following circumstances:

- Emergence of the following adverse events:

[redacted]

- Skin rash – Interrupt study treatment until consultation by a dermatologist (and documented in patient's source). Identified common dermatologic conditions symptoms, including rash that are clearly attributable to non-study drug related causes (i.e. insect bites, poison ivy etc.) can be evaluated and treated per standard of care by investigator. In cases of suspected allergic dermatitis, body temperature and blood chemistry (including Liver Function Tests (LFTs) and Complete Blood Cell Count (CBC)) will be obtained. Study treatment can be started again following recommendation of the dermatologist and investigator. Study treatment must be permanently discontinued thereafter if rash appears again after re-initiation of study treatment. All decisions should be documented in the patient's medical chart.
- Hepatic enzyme elevation – Refer to Appendix 2 for requirements for temporary and permanent discontinuation of study medication.
- Abnormal hematology evaluation, defined as any of the following, requires temporary discontinuation of study medication and repeat within 48 hours (via central or local laboratory) and follow up until recovery to ≤ grade 1 Common Terminology Criteria for Adverse Events (CTCAE). Study treatment must be permanently discontinued thereafter if hematology values are abnormal again (as defined below) after re-initiation of study treatment.
  - Platelets $<50 \times 10^9$/L
  - Absolute neutrophil count $<1.0 \times 10^9$/L
  - Hemoglobin <80 g/L

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit as detailed in Table 6-1. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information in the eCRF.

Patients who discontinue study drug should be treated according to the best standard of care and be encouraged to stay in the study and continue to be followed with an abbreviated schedule of assessments as indicated in Table 6-2.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

### 5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

[redacted]

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of world (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

### 5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

### 5.6.5 Early study termination by the sponsor

Novartis may terminate the trial for reasons related to the benefit risk assessment of treatment for participants in the study, or for regulatory or medical reasons (including slow enrollment). In the event that the study is terminated early, the Institutional Review Boards (IRBs)/Ethics Committees (ECs) will be informed and will be asked to approve the process to prematurely withdraw the participants. In general, the participant should be seen as soon as possible and assessed as a prematurely withdrawn participant from the study. The withdrawal process may include additional procedures to be followed, in order to ensure that adequate consideration is given to the protection of the participant's interests.

# 6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" or "S" when the visits are performed.

[redacted]

Patients must be seen for all visits on the designated date or as close to it as possible. (Suggested window is +/- 3 days with the exception of V199 and V201 which must be performed no later than 13-week after the Baseline visit.)

For V199 and V201, the scheduled dates should be strictly adhered to avoid treatment exposure of more than 13 weeks after baseline visit.

The scheduled visit date should be calculated based on V101 (BL) for all visits from V101 (week 0) till V201 (week 13).

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study treatment for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Treatment Discontinuation visit (TD) will be performed. At this visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF. If patients then agree to continue in the study (for further safety and efficacy data collection), subsequent visits will then be according to the Abbreviated schedule of assessments for patients with study treatment discontinuation as outlined in Table 6-2. Patients following the Abbreviated schedule of assessments must continue to adhere to the protocol requirements for changes to concomitant medications for neuropathic pain, rescue medication and prohibited medications.

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

[redacted]

**Table 6-1 Assessment schedule**

| Epoch | Screening | Treatment | | | | | | | | | Treatment withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **101** | **102** | **103** | **104** | **105** | **106** | **107** | **199** | | **201** |
| **Week** | **-5 to -1** | **0 (BL)** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **TD visit** | **13** |
| **Day** | **-35 to -7** | **1** | **8** | **15** | **29** | **43** | **57** | **71** | **85** | | **92** |
| Informed consent | X | | | | | | | | | | |
| Inclusion/Exclusion criteria | X | | | | | | | | | | |
| Demography | X | | | | | | | | | | |
| Disease & Medical History | X | | | | | | | | | | |
| Smoking, Alcohol, Liver History | X | | | | | | | | | | |
| Surgical and medical procedures/Concomitant Medications/Rescue Medications | X | X | X | X | X | X | X | X | X | X | X |
| Complete Physical exam | S | S | | | | | | | S | S | S |
| Brief Physical exam | | | S | S | S | S | S | S | | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | |
| Weight | X | X | | | | | | | X | X | |
| Urine drug screen | X | | | | X | | | | | | |
| Serum pregnancy test [1, 2] | | X | | | | | | | X | X | |
| Urine pregnancy test | X | | | | X | | X | | | | X |
| Hematology/Blood chemistry | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[3] | X | X | | | X | | X | | X | X | X |
| [redacted] | | | | | | | | | | | |
| 12-lead ECG[5, 6] | X | X | | | X | | X | | X | X | X |
| Contact IRT | X | X | X | X | X | X | X | X | X | X | X |
| Dispense study medication | | S | S | S | S | S | S | S | S[7] | | |

[redacted]

| Epoch | Screening | Treatment | | | | | | | | | Treatment withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **101** | **102** | **103** | **104** | **105** | **106** | **107** | **199** | | **201** |
| **Week** | **-5 to -1** | **0 (BL)** | **1** | **2** | **4** | **6** | **8** | **10** | **12** | **TD visit** | **13** |
| **Day** | **-35 to -7** | **1** | **8** | **15** | **29** | **43** | **57** | **71** | **85** | | **92** |
| Dosage Administration Record | | X | X | X | X | X | X | X | X | | X |
| Treatment Compliance | | | S | S | S | S | S | S | S | | S |
| Adverse Events/SAEs | X | X | X | X | X | X | X | X | X | X | X |
| Dispense ePRO eDiary device | S | | | | | | | | | | |
| Complete pain diary daily (NRS) | X | X | X | X | X | X | X | X | X | X | X |
| Record VRS pain intensity | | X | | | | | | | | | |
| Check electronic tablet for eligibility | | S | | | | | | | | | |
| BPI-SF | | X | | | X | | X | | X | X | |
| PGIC | | | | | | | | | X | X | |
| NPSI | | X | | | X | | X | | X | X | X |
| ISI[redacted] | | X | | | | | | | X | X | |
| [redacted] | | | | | | | | | | | |
| Pharmacokinetics | | X[10] | | | | | X[9,10] | | X[9,10] | | |
| [redacted] | | | | | | | | | | | |
| Screening disposition | X | | | | | | | | | | |
| Treatment epoch disposition | | | | | | | | | X | X | |
| Treatment withdrawal epoch disposition | | | | | | | | | | | X |

TD = Study Treatment Discontinuation visit
X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documentation only
[1]Collected as part of the blood chemistry.
[2]Required for all pre-menopausal women who are not surgically sterile.
[3]Urine dipstick to be performed at the site. If abnormalities are present, urine sample should be sent to the central laboratory for microscopy analysis.

[redacted]

| Epoch | Screening | Treatment | | | | | | | | | Treatment withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 199 | | 201 |
| Week | -5 to -1 | 0 (BL) | 1 | 2 | 4 | 6 | 8 | 10 | 12 | TD visit | 13 |
| Day | -35 to -7 | 1 | 8 | 15 | 29 | 43 | 57 | 71 | 85 | | 92 |

[redacted]

[5]Triplicate ECG and PK sample should also be collected if abnormal ECG result (QTcF>500 ms).

[6]Should blood sampling procedures, ECG and vital signs assessments be required at the same visit, the blood sampling procedures should be started after completion of the ECG collection and hemodynamic assessments as shown in the following sequence: 10 min resting period & pre-dose single ECG →Vital signs → Pre-dose PK & lab samples → Study drug administration.

[7]Drug dispensation only for patients continuing into Treatment withdrawal epoch. Patients will take their last dose of "Treatment" study medication from their old bottle at the site visit in the morning, and will take their first dose of "Treatment withdrawal" study medication from their new bottle that evening.

[redacted]

[9]PK samples for all patients should be collected according to the schedule detailed in Table 17-1. Patients should be instructed not to take their morning dose of study medication prior to arriving at the site and completing the necessary assessments. PK sample should also be collected if abnormal ECG result (QTcF>500 ms).

[10]Additional PK sample collected for patients taking pregabalin or gabapentin according to the schedule detailed in Table 17-2. Patients should be instructed not to take their morning dose of pregabalin/gabapentin prior to arriving at the site and completing the necessary assessments. Patients should bring their pregabalin/gabapentin (if applicable) with them to the study visits where PK is collected so it may be administered after the PK assessment, as required.

[redacted]

[redacted]

**Table 6-2 Abbreviated schedule of assessments for patients with data collected after study treatment discontinuation**

| Epoch | Treatment | | | | | | |
|---|---|---|---|---|---|---|---|
| **Visit[1,2]** | **102** | **103** | **104** | **105** | **106** | **107** | **199** |
| **Week** | **1** | **2** | **4** | **6** | **8** | **10** | **12** |
| **Day** | **8** | **15** | **29** | **43** | **57** | **71** | **85** |
| Complete Physical exam | | | | | | | S |
| Brief Physical exam | S | S | S | S | S | S | |
| Surgical and medical procedures/Concomitant Medications | X | X | X | X | X | X | X |
| Adverse Events/SAEs | X | X | X | X | X | X | X |
| Complete pain diary daily (NRS) | X | X | X | X | X | X | X |
| BPI-SF, NPSI | | | X | | X | | X |
| PGIC | | | | | | | X |
| [redacted] | | | | | | | |
| Treatment epoch disposition | | | | | | | X |

X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documentation only

[1]The abbreviated schedule should be adopted from the visit following the study treatment discontinuation. For example, if a patient discontinues study drug at Week 4, the patient should be scheduled for the TD visit (Table 6-1) as soon as possible and then follow the abbreviated schedule for Week 6 and subsequent visits (Table 6-2). At premature withdrawal from the study, or at completion of the study, the End of Study visit assessments (V199) should be performed instead of the next scheduled visit.

[2]Patients following the Abbreviated schedule of assessments must continue to adhere to the protocol requirements for changes to concomitant medications for neuropathic pain, rescue medication and prohibited medications.

[redacted]

## 6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the double-blind Treatment epoch will have the Screening phase disposition, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

## 6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses, and not symptoms, will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## 6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Investigator should also check the electronic patient diaries and remind the patient of the importance of daily completion.

Protocol Deviations should be recorded for patients with an overall compliance of less than 80% or patients with more than 3 full consecutive days of missed doses (more than 6 consecutive doses).

## 6.4 Efficacy

Assessments are to be collected as specified in Table 6-1. At study visits, all questionnaires should be completed first before any other study assessments are done.

A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

All questionnaires will be completed in the language most familiar to the respondent, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

[redacted]

All patients will complete the Patient Reported Outcome (PRO) questions via a handheld electronic device or an electronic tablet. Detailed training on use of the device should be provided and recorded in the patient's source document. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this should be documented in study source records.

Designated Investigator site staff will review eDiary compliance with the patient at each visit. Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs), and the review should be documented in the patient's source document accordingly. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

### 6.4.1 11-point Numeric Rating Scale (NRS)

The Numeric Rating Scale (NRS) is an 11–point scale for patient self-reporting of pain.

**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. Patients will evaluate their average pain during the past 24 hours in the evening prior to sleep by touching the appropriate corresponding number between zero ("no pain") and ten ("pain as bad as you can imagine") on the eDiary device.

The 24-hour average pain score should be completed daily for seven consecutive days prior to randomization and then every day through the end of the study. Patients will be allowed to record their pain scores up to 1 day in the past. Any entries >1 day old will not be allowed and will be considered missing data.

Please note that patients will be required to bring their eDiary device in to the clinic for every study visit, and should return the eDiary device at the end of study.

**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. Patients will rate their worst pain during the past 24 hours in the evening prior to sleep by touching the appropriate corresponding number between 0 ("no pain") and ten ("pain as bad as you can imagine") on the eDiary device.

The 24-hour worst pain score should be completed daily for seven consecutive days prior to randomization and then every day through the end of the study. Patients will be allowed to record their pain scores up to 1 day in the past. Any entries >1 day old will not be allowed and will be considered missing data.

Please note that patients will be required to bring their eDiary device in to the clinic for every study visit, and should return the eDiary device at the end of study.

### 6.4.2 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.

[redacted]

At Baseline, the designated investigator site staff will capture pain intensity information from each patient using the 4-point categorical VRS. The patient will be asked “What is your pain level at this time?” and the response will be recorded as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. This will be recorded in the electronic tablet at the site.

### 6.4.3 Brief Pain Inventory- Short Form (BPI-SF)

The Brief Pain Inventory-Short Form (BPI-SF) is a validated, self-administered questionnaire that assesses pain severity and its impact on daily functions.

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 7-item pain interference scale of the BPI-SF will be completed by patients using the electronic tablet at the site at the specified visits.

### 6.4.4 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 PGIC is based on the validated Clinical Global Impression of Change scale.

The PGIC will be completed by patients using the electronic tablet at the site at the specified visit.

### 6.4.5 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 NPSI will be completed by patients using the electronic tablet at the site at the specified visits.

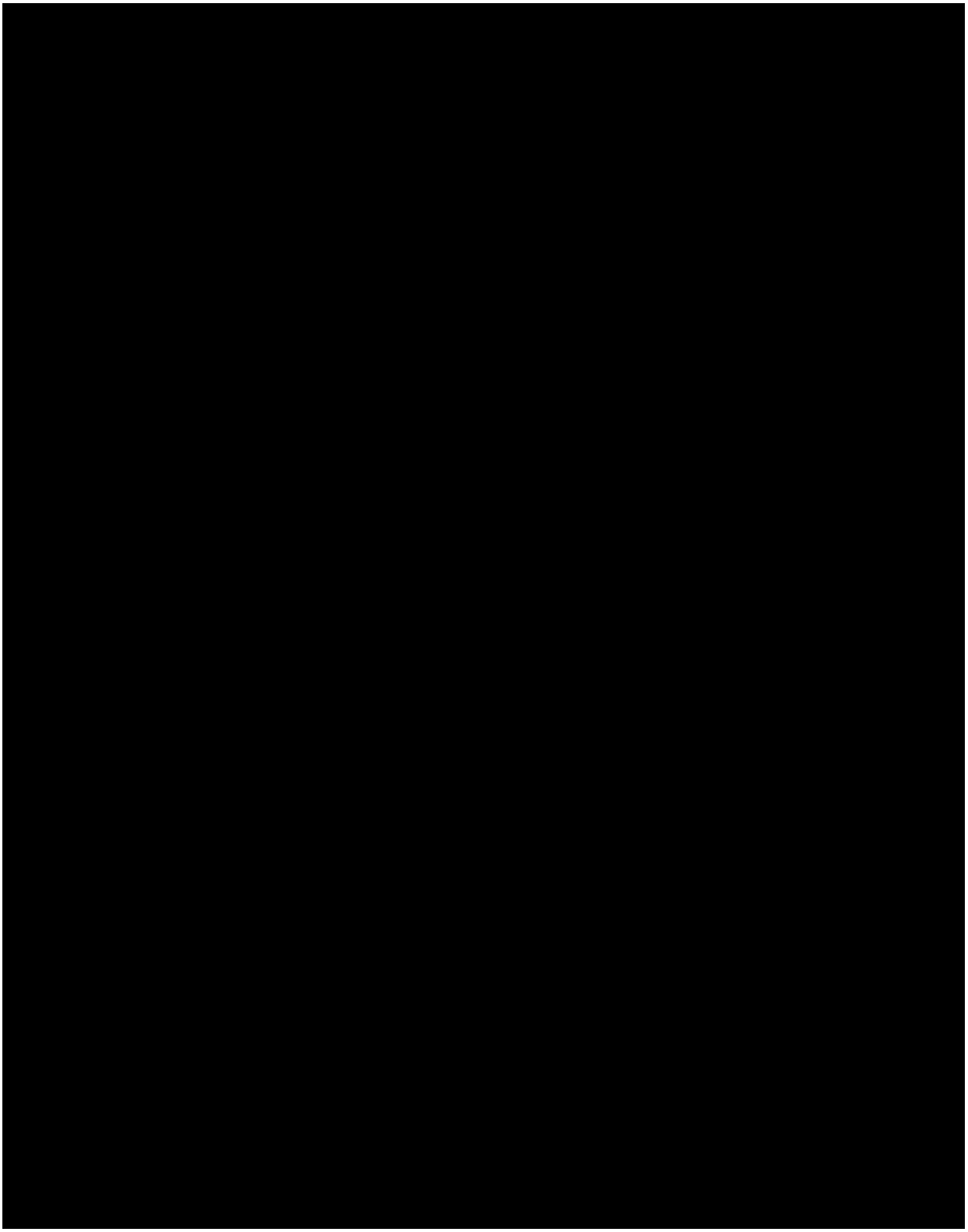
### 6.4.6 Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) is a validated seven-item patient questionnaire used to quantify perceived insomnia severity.

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 ISI will be completed by patients using the electronic tablet at the site at the specified visits.

[redacted]



### 6.4.10 Appropriateness of efficacy assessments

Efficacy assessments used for evaluation of pain relief (NRS) are standard recommended primary outcome measures for neuropathic pain clinical trials, also supported by Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. As chronic pain interferes with daily activities, quality of life, additional patient reported outcome measures (PROs) of physical functioning, [redacted] tools are recommended for assessing the patient's perception of the impact of disease and treatment on daily life physical, psychological and social functioning and well-being. Therefore BPI-SF, [redacted] are included.

Co-morbid anxiety and depression are common in chronic pain patients. Mood changes, anxiety and sleep disturbance may change pain perception and might affect efficacy assessments. Furthermore pharmacodynamic effects of EMA401 may influence these comorbidities. [redacted] ISI will be used to access impact on the comorbid conditions. Global Impression of Change reported by the patient is a useful supportive indicator of the overall perceived benefit of treatment in chronic pain trials.

NPSI is a multidimensional tool to evaluate treatment response on sensory and affective qualities of pain.

## 6.5 Safety

### 6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A brief physical exam, as per local practice, will include the examination of general appearance and will be at all visits, except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

### 6.5.2 Vital signs

Vital signs include blood pressure, pulse measurements, respiratory rate, and temperature. After the patient has been supine for five minutes, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat supine measurements will be made at approximately 1 to 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. After the patient has been standing for 3 minutes, systolic and diastolic blood pressure will be again measured using the above procedure.

[redacted]

Clinically notable vital signs for blood pressure, pulse, and weight are defined in Appendix 1.

### 6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

### 6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Clinically significant abnormalities should be recorded on the Medical History/Adverse Event CRF page as appropriate.

Clinically notable laboratory findings are defined in Appendix 1.

#### 6.5.4.1 Hematology

The following parameters will be collected: standard hematology with differential (red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell morphology, white blood cell differential).

Measures of coagulability to be collected: activated partial thromboplastin time (aPTT), prothrombin time/International Normalized Ratio (PT/INR)

#### 6.5.4.2 Clinical chemistry

The following parameters will be collected: albumin, alkaline phosphatase, amylase, bicarbonate, total bilirubin (direct and indirect bilirubin measured if total bilirubin >1.5 X ULN), calcium, chloride, cholesterol, creatinine, creatine kinase (CK), gamma-glutamyltransferase (γ-GT), glucose, lipase, lactate dehydrogenase, inorganic phosphorus, magnesium, potassium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, triglycerides, urea and uric acid.

At Screening (Visit 1) the following parameters will also be analyzed to determine a patient's eligibility: HIV antibodies, hepatitis B surface antigen, hepatitis C antibodies.

Serum pregnancy will be performed in accordance with Table 6-1

#### 6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be done at the site. If there are any abnormalities present, urine sample should be sent to the central laboratory for microscopy analysis.

[redacted]

[redacted]

#### 6.5.4.5 Urine drug screen

A urine drug screen for drug abuse will include screening for cocaine, amphetamines, barbiturates, cannabinoids (including tetrahydrocannabinol), opiates, phencyclidine, and methadone.

If the results of the Screening urinalysis are positive for a prescribed medications that could be consumed abusively the site may perform a repeat urine drug screen within the screening period.

If the results from the repeat urine drug screen are negative, the patient may be included.

If the repeat results are positive, the patient must be excluded from the study and this patient cannot be re-screened in the future. A second repeat is not admissible. No repeat drug screen will be permitted for recreational drugs.

Urine drug screen will also be performed at Week 4 according to Table 6-1.

### 6.5.5 Electrocardiogram (ECG)

ECGs must be recorded according to the ECG investigator manual. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected with ECG machines supplied by the core laboratory at the visits indicated in Table 6-1. The original ECGs, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. If the single ECG shows a QTcF > 500 ms (males or females), 2 additional ECG replicates should be recorded under continued controlled environmental conditions (patient resting, no interfering procedures to ensure as much as possible stable heart rate) to confirm the safety findings and copies forwarded to the central ECG laboratory for assessment. Shortly after completion of the triplicate ECG recording, a PK sample should be drawn to allow for correlation of PK to the QT/QTc.

If needed clinically significant ECG findings at randomization (pre-dose) may be discussed with the sponsor before administration of study treatment. Clinically significant abnormalities must be recorded on the relevant section of the Medical history/Current medical conditions/AE eCRF page as appropriate.

Detailed instructions concerning the ECG recording will be provided to all Investigators in a separate manual prior to the start of the study.

### 6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

[redacted]

Serum and urine pregnancy tests will be performed according to the schedule in Table 6-1.

### 6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this patient population. Since EMA401 is currently at Phase 2 of clinical development, safety evaluation including hematology and blood chemistry assessments are planned every 2 weeks for close patient monitoring and early detection of any safety signals. [redacted]

## 6.6 Other assessments

### 6.6.1 Patient Reported Outcomes (PRO)

Please refer to Section 6.4 for details on all Patient Reported Outcomes (PRO).

[redacted]

### 6.6.3 Resource utilization

Not applicable.

### 6.6.4 Pharmacokinetics

Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual. The PK collection blood log is given in Appendix 5.

For all patients, PK samples will be collected at Week 8 and Week 12 according to Table 6-1 in order to measure EMA401 blood levels. The first blood sample should be collected after the patients have come to the clinic before taking morning study medication (i.e. EMA401/placebo). The second blood sample should be collected between 1-3 hours after the morning study

[redacted]

medication dose (i.e. EMA401/placebo). The third blood sample should be collected between 4-6 hours after the morning study medication dose (i.e. EMA401/placebo).

For those patients who are also taking pregabalin or gabapentin, an additional pre-dose PK sample will be collected at Baseline, Week 8, and Week 12 before the patient takes their morning dose of pregabalin or gabapentin.

PK sample should also be collected if abnormal ECG result (see Section 6.5.5).

### 6.6.6 Other biomarkers

Not applicable.

# 7 Safety monitoring

## 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing with an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequelae; fatal; or unknown)

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

[redacted]

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 7.2 Serious adverse events

### 7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might

[redacted]

require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

### 7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

## 7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

[redacted]

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate, [redacted]
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- Specialist consultation at the discretion of the investigator.
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, [redacted], imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

## 7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:

[redacted]

  - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3. Specialist consultation may be obtained at the discretion of the investigator.

## 7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

**Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse**

| Treatment error type | Document in Dose Administration (DAR) eCRF (Yes/No) | Document in AE eCRF | Complete SAE form |
|---|---|---|---|
| Unintentional study treatment error | Yes | Only if associated with an AE | Only if associated with an SAE |
| Misuse/Abuse | Yes | Yes | Yes, even if not associated with a SAE |

## 7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

# 8 Data review and database management

## 8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the

accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

## 8.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary (eDiary) by the patient. The system will be supplied by a vendor(s), who will also manage the database.

Patients will fill in their PRO data in a site based electronic tablet. The systems will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

## 8.4 Data Monitoring Committee

An external Data Monitoring Committee (DMC) will be established with the primary goal to perform an ongoing review of safety data from all ongoing EMA401 patient studies. The DMC will consist of external experts who have experience in the management and monitoring of clinical trials and disease area expertise but without any direct involvement in any activities related to EMA401 studies. The DMC will function independently of all other individuals associated with the conduct of the trials, including the investigators, Novartis personnel and other committees overseeing the trials (e.g. ethics committee). Novartis study personnel will not have access to treatment codes or any unblinded data or data summaries prepared for the DMC. Further details will be provided in a DMC charter.

The DMC is responsible for monitoring the safety of the trial participants, ensuring that the EMA401 trials are being conducted with highest scientific and ethical standards and making appropriate recommendations based on the data seen. DMC will conduct quarterly full unblinded safety reviews of cumulative safety data, as well as 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).

Unblinded safety review by the independent DMC will be implemented to stagger patient exposure to the study drug. Randomization of patients to the high dose arm (EMA401 300 mg b.i.d.) in study CEMA401A2201 will only be initiated following an unblinded safety review by the 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 will be conducted 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.

DMC could make the following recommendations:

- Making recommendations regarding changes or adjustments that may be required to ensure patient safety and preserve the trial integrity
- Suggesting modifications to the trial protocols; modifications may include, but are not limited to: changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in trial procedures or trial conduct, or discontinuation of one or more trial treatment groups if applicable
- Recommending continuation of the trials according to the protocols and any relevant amendments OR to discontinue the trials (with provisions for orderly discontinuation in accordance with good clinical practice)

### 8.5 Adjudication Committee

Not required.

## 9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

### 9.1 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.
- 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.

### 9.2 Patient demographics and other baseline characteristics

Demographic and background information will be summarized for the SAF and FAS populations using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

[redacted]

Relevant medical history/current medical conditions will be summarized by system organ class and preferred term of the MedDRA dictionary.

## 9.3 Treatments

Duration (days) of exposure to double-blind study medication will be summarized by treatment group.

Frequency and percentages of patient disposition and reasons for discontinuation of study medication will be presented for both double-blind Treatment epoch and double-blind Treatment withdrawal epoch. Patients who prematurely discontinue the study medication will be listed along with the reason for discontinuation.

The number and percentage of patients who used concomitant medications (coded by World Health Organization [WHO] Anatomic Therapeutic Chemical classification [ATC]) and non-drug therapies will be presented by treatment group. Separate tabulations will be provided for medications taken prior to start of study medication and while a patient is on study drug (i.e. between the first day on study drug and the day of last visit).

The number and percentage of patients who used rescue medication and who used prohibited medications for PHN will also be summarized by treatment.

The analyses will be based on the SAF and FAS populations.

## 9.4 Analysis of the primary variable(s)

### 9.4.1 Primary Variable(s)

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).

To calculate the weekly mean pain intensity score for a given week, each patient will record his/her daily pain intensity score across the preceding 24 hours at a single time point. The daily pain intensity score will then be averaged over 7 days to obtain the mean pain intensity score for a week.

The primary population will be the FAS.

### 9.4.2 Statistical model, hypothesis, 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 an Estimand Charter.

The primary estimation method is based on an Analysis of Covariance (ANCOVA) model including region (e.g. US, EU), treatment, sex, use of concomitant pain medication for PHN (yes/no) as factors and baseline (mean pain intensity) score and age as covariates. The analysis will account for different post-randomization events 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

[redacted]

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 5-2 requiring study treatment discontinuation. 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.

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, 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). More details on the imputation model will be specified in the statistical analysis plan prior to unblinding.
- **Permanent discontinuation of study treatment due to other reasons than AE, LoE and use of prohibited medication:** 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.

The primary objective will be 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 2 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 same ANCOVA model will be applied at the visits prior to Week 12.

[redacted]

Summary statistics by treatment and visit will be provided for the primary efficacy variable.

In the event the EMA401 300 mg b.i.d. dose cannot be initiated, then the dose response characterization 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 hypothesis of superiority of at least one active dose of EMA401 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.

### 9.4.3 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 (See Section 6.4.1). At each visit, 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.

**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 9.4.2 while the imputation procedure for the supplementary analyses is included in Section 9.4.4. The details of these imputation rules will be specified in an Estimand Charter and in the statistical analysis plan prior to unblinding.

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

### 9.4.4 Supplementary Analyses

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

The **first supplementary analysis** will be performed to quantify the treatment effect by considering the discontinuation due to any reason other than the administrative reasons (e.g. technical problems, study terminated by sponsor) and other than pregnancy as unfavorable outcomes (no difference to a placebo patient). The estimation method and handling of post randomization events will be same as for the primary analysis, except that missing data after discontinuation due to any reason other than administrative reason in the EMA401 arms will be multiply imputed according to a “jump-to-reference” assumption.

The **second supplementary analysis** will be performed 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

[redacted]

will be same as for the primary analysis, except that missing data after discontinuation for any reason will be imputed using the MAR assumption.

The **third supplementary analysis** will be performed to quantify the treatment effect of the investigational drug compared to placebo regardless of changes in the dose of concomitant medications for PHN and regardless of use of prohibited medications with potential confounding effect. Such treatment effect corresponds to a "treatment-policy/intention-to-treat" estimand.

### 9.4.5 Sensitivity analyses

The following sensitivity analyses will be performed corresponding to the primary and supplementary estimands.

The same ANCOVA model as for the primary estimation will be adopted. Post randomization events will be handled in the same way as in the primary and three supplementary analyses, respectively. Missing data after discontinuation will in a first step be imputed in the same way as for the primary and three supplementary analyses, respectively. For the EMA401 arms these imputed values will further be worsened in subsequent steps via the application of increasingly large penalties (tipping point analysis, Permute 2015).

## 9.5 Analysis of secondary variables

### 9.5.1 Efficacy variables

The following secondary efficacy variables will be evaluated:

1. 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 hypothesis of superiority of at least one active dose of EMA401 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 closed MCP-Mod procedure. The closed MCP-Mod approach works by applying the maximum contrast test associated with standard MCP-Mod to all intersection hypotheses in a closed testing strategy. As known from standard MCP-Mod the maximum contrast test controls the type I error across multiple dose-response shapes, so it is a valid level alpha test for all intersection hypotheses, and can thus be applied in the context of the closed testing principle.
2. Responder analyses (based on at least a 30% or 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. The responder status for each patient will be calculated based on the continuous weekly score measurements. For patients who prematurely discontinue study treatment, the responder status will be calculated after missing data are multiply imputed according to the approaches specified for the primary and three supplementary analyses. Further analyses will be performed by considering patients who discontinue study treatment due to specific discontinuation reasons as non-responders. Additionally, to study the effect of changes in doses of

[redacted]

concomitant medications for PHN, the use of prohibited medications and rescue medications on the responder criteria, a combined responder status of the patients will be calculated based on their continuous weekly score along with the use of the medications mentioned above. These analyses will be performed on the FAS population. The detail definition of the responder status and the corresponding secondary estimand and its supplementary estimands are defined in detail in an Estimand Charter.

From an analysis point of view, the resulting responder variables 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. 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.

3. Change from baseline to Week 12 in BPI-SF interference total score. This variable will be analyzed according to the same ANCOVA model as the one used for the primary variable.
4. Change from baseline to Week 12 in weekly mean of the 24-hour worst NRS pain score, using an 11-point Numeric Rating Scale (NRS). This variable will be analyzed according to the same ANCOVA model as the one used for the primary variable.
5. PGIC at Week 12. The proportional odds model with the same factors as the ANCOVA model for the primary variable will be used.
6. Change from baseline to 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. The temporal items will be summarized descriptively.
7. Change from baseline to Week 12 in ISI. This variable will be analyzed according to the same ANCOVA model as the one used for the primary variable.

Multiple imputation for the secondary variables will be carried out in a similar fashion as for the primary analysis of the NRS pain score. However, for PGIC no imputation will be performed because it is collected only at one post-baseline visit (Week 12 or Treatment Discontinuation visit). Thus the analysis for PGIC will be performed only on the observed cases. No multiplicity adjustment will be carried out for the secondary variables.

Summary statistics by treatment and visit will be provided for the secondary efficacy variables.

### 9.5.2 Safety variables

Safety analyses will be conducted using the safety (SAF) dataset. Patients will be grouped by the actual treatment received.

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events). Additional safety assessments include laboratory tests, physical examination (including examination of skin), vital sign measures and ECG evaluations. Clinically significant findings in these additional safety assessments will be reported as adverse events and analyzed as such. In addition all safety assessments will be summarized or listed as appropriate. The analyses of additional safety assessments will be defined in the statistical analysis plan.

[redacted]

#### 9.5.2.1 Adverse events

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.

TEAEs will be summarized (number of cases as a percentage of number at risk) by treatment group. 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 epoch. Relationship to study medication will be classified as related ("probably related" and "possibly related") and unrelated ("not related"). Severity will be classified as "mild", "moderate" and "severe". Serious TEAEs, drug related 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.

#### 9.5.2.2 Potential risks and Expected events

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. The search criterion for each of these risks and events will be defined based on MedDRA. The incidence of potential risks and expected events will be summarized. The detailed analysis of potential risks and expected events will be specified in the statistical analysis plan.

#### 9.5.2.3 Laboratory data

The summary of laboratory evaluations will be presented for 3 groups of laboratory tests: Hematology, Chemistry and Urinalysis.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values, and by presenting shift tables using clinically notable ranges (baseline to most extreme post-baseline value). Laboratory data, and specifically liver enzymes, will also be summarized by maximum change from baseline.

For liver enzymes, the number of subjects with newly occurring liver enzymes abnormalities will be summarized by treatment group. Plots related to analysis of laboratory data will be specified in the statistical analysis plan.

Urine pregnancy test results will also be summarized.

#### 9.5.2.4 Vital signs

Vital sign measurements and their change from baseline will be summarized with descriptive statistics (mean, median, standard deviation, min, max) by visit. The number and percentage of subjects with clinically notable vital signs will be presented.

[redacted]

#### 9.5.2.5 ECG evaluations

ECG intervals will be summarized by presenting summary statistics for change from baseline values. The (uncorrected) QT interval will be corrected according to the Bazett's and Fridericia's formulae. The incidence rates of clinically notable ECG abnormalities will be summarized.

[redacted]

#### 9.5.2.7 Other safety evaluations

All clinically significant safety findings based on additional safety evaluations (e.g. ECG or physical examination including assessments of skin, lymph nodes, lung, etc.) must be reported as adverse events on the AE CRF. The statistical analysis of these findings will be done in the analysis of adverse events.

Other safety data will be summarized or listed as appropriate.

### 9.5.3 Resource utilization

Not applicable

### 9.5.4 Pharmacokinetics

EMA401 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. A population PK model will be fitted to the data in order to investigate whether covariates (e.g. age, gender, weight, ethnicity, baseline laboratory values, concomitant medications, etc.) influence the PK of EMA401. The choice of covariates to be included in the final model will be guided by exploratory plots of random effects (inter-individual variability parameters) against covariates. Those that are judged to show evidence of a relationship with the random effects will be tested for entry into the model, using the likelihood-ratio test with $p < 0.05$. The final covariate model will be derived using a rigorous and acceptable model building procedure.

Pregabalin and gabapentin plasma concentration data will be listed and summarized by visit and EMA401 treatment group. Descriptive comparisons between the baseline visit assessments and the post-baseline visit assessments will be made.

[redacted]

[redacted]

[redacted]

### 9.5.6 Biomarkers

Not applicable.

### 9.5.7 PK/PD

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) will be done. All population PK/PD analyses and simulations will be carried out using a non-linear mixed-effects modelling approach.

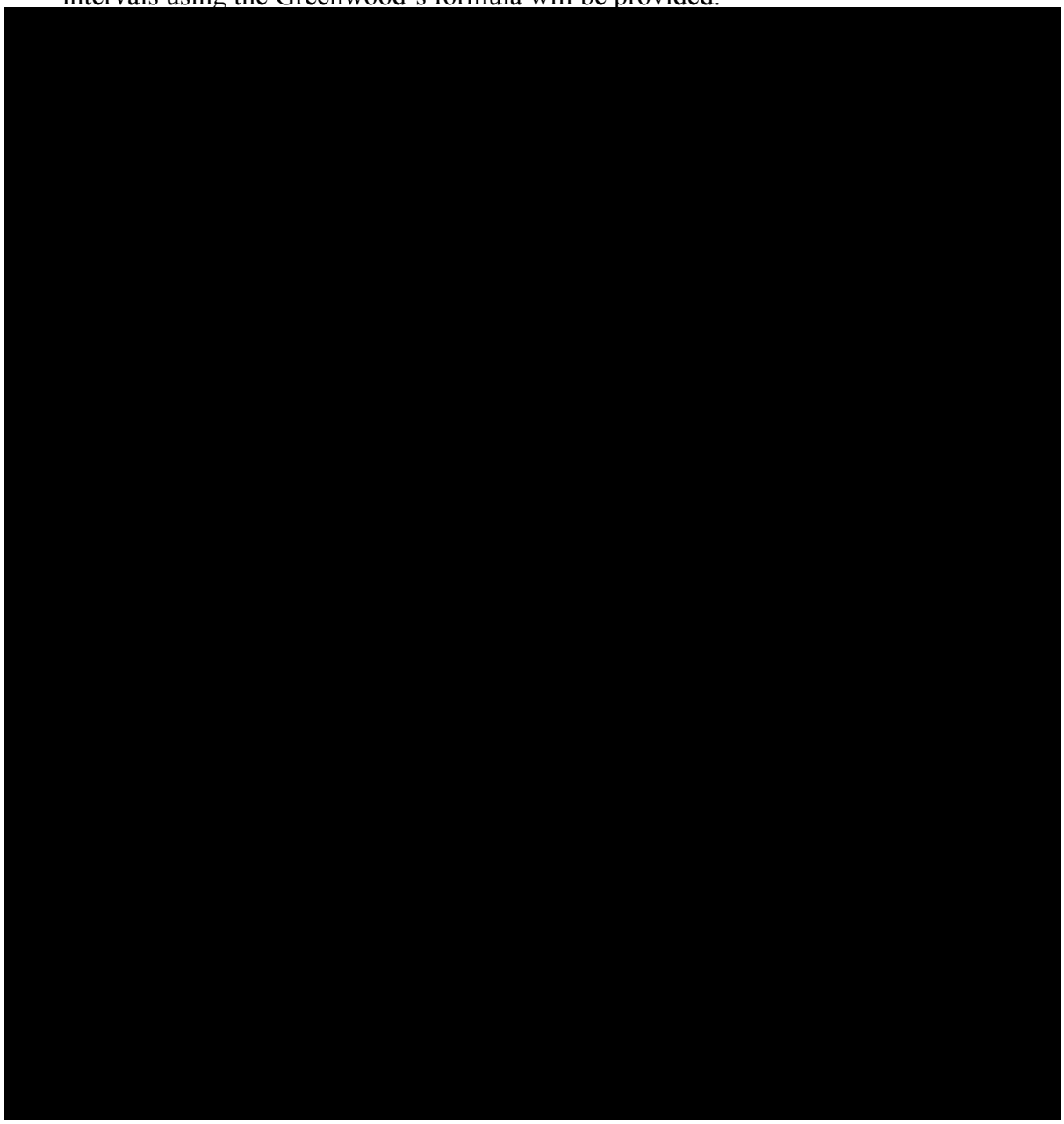
## 9.6 Analysis of exploratory variables

The following exploratory analysis will be performed:

[redacted]

[redacted]

4. 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.
5. The time to first rescue medication intake will be compared between each dose of EMA401 and placebo via a Cox proportional hazard regression model with the same set of covariates used for the primary analysis. The corresponding hazard ratio with the 95% confidence interval will be reported. 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.



## 9.7 Interim analyses

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.

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.) in study CEMA401A2201 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 will be conducted after the completion of 12 weeks exposure of 30 patients in the EMA401 300 mg b.i.d. treatment arm and will determine if 300 mg b.i.d. dosing can be continued as planned.

The DMC will review 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 will be specified in a separate DMC analysis plan.

Since no efficacy evaluation will be performed by DMC, no multiplicity adjustment for the primary efficacy objective is required.

## 9.8 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 (see Section 9.4.2) 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 9.4.2) 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.

[redacted]

# 10 Ethical considerations

## 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

[redacted]

## 10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

[redacted]

## 10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## 10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

# 11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

## 11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

[redacted]

# 12 References

References are available upon request.

[redacted]

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.

Chaparro LE, Wiffen PJ, Moore RA, et al (2012) Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev; 7:CD008943.

Cunningham AL, Dworkin RH (2000) The management of post-herpetic neuralgia. Br Med J; 321(7264):778–9.

Dworkin RH, Turk DC, Peirce-Sandner S, et al (2010) Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain;149: 177-193.

European Medicines Agency (2015) Report from Dose Finding Workshop. EMA/117491/2015 (Internet) Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/04/WC500185864.pdf> (Accessed 25 Jan 2017).

European Medicines Agency, Committee for Medicinal Products for Human Use (2015) Guideline on the clinical development of medicinal products intended for the treatment of pain. EMA/CHMP/970057/2011, Corr. 1 (Internet) Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199242.pdf> (Accessed 12 Dec 2016).

Finnerup NB, Attal N, Haroutounian S, et al (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol; 14(2):162-73.

Finnerup NB, Haroutounian S, Kamerman P (2016) Neuropathic pain: An updated grading system for research and clinical practice. Pain; 157 (8):1599-1606.

Food and Drug Administration, Center for Drug Evaluation and Research (2014) Guidance for Industry Analgesic Indications: Developing Drug and Biological Products, Draft guidance (Internet) Available from: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf> (Accessed 12 Dec 2016).

Food and Drug Administration, Center for Drug Evaluation and Research (2004) Approval package for application number NDA 21-273, Medical Review. (Internet) Available from: <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021723s000_LyricaCaps_medr.pdf> (Accessed 12 Dec 2016).

Hempenstall K, Nurmikko TJ, Johnson RW et al (2005) Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med; 2(7):628–44.

Johnson RW, Rice AS (2014) Clinical practice. Postherpetic neuralgia. N Engl J Med; 371:1526–1533.

Kravit A, Kuranz S (2015) Neuropathic Pain. Decision Resources Group. 2015 DR/Decision Resources, LLC.

[redacted]

Mixcoatl-Zecuatl T, Calcutt NA (2013) Biology and Pathophysiology of Painful Diabetic Neuropathy. in: E. Lawson, M. Backonja (Eds.) Painful Diabetic Polyneuropathy: A Comprehensive Guide for Clinicians. 1st ed. Springer-Verlag, New York:13–26.

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.

Rice A, Dworkin R, McCarthy T, et al (2014) EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: a randomised, double-blind, placebo-controlled phase 2 clinical trial. Lancet; 383(9929):1637-47.

Smith M, Muralidharan A (2015) Targeting angiotensin II type 2 receptor pathways to treat neuropathic pain and inflammatory pain. Expert Opin Ther Targets; 19(1):25-35.

[redacted]

[redacted]

[redacted]

# 13 Appendix 1: Clinically notable laboratory values and vital signs

**Table 13-1 Clinically notable values for vital signs and weight changes**

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

bpm= beats per minute

### Clinically notable laboratory values

Notable laboratory values will be specified in the laboratory manual with specific alert values. Both the Novartis clinical team and the investigator will be notified for all types of alerts.

[redacted]

# 14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

**Table 14-1 Liver Event and Laboratory Trigger Definitions**

| | Definition/ threshold |
|---|---|
| LIVER LABORATORY TRIGGERS | • 3 x ULN < ALT / AST ≤ 5 x ULN<br>• 1.5 x ULN < TBL ≤ 2 x ULN |
| LIVER EVENTS | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• TBL > 2 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity* |

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

**Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| Potential Hy's Law case[a] | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) [redacted] |
| **ALT or AST** | | |
| > 8 × ULN | • Discontinue the study treatment immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) [redacted] |
| > 3 × ULN and INR > 1.5 | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) [redacted] |

[redacted]

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| > 5 to ≤ 8 × ULN | • Repeat LFT within 48 hours<br>• If elevation persists, continue follow-up monitoring<br>• If elevation persists for more than 2 weeks, discontinue the study drug<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>[redacted] |
| > 3 × ULN accompanied by symptoms[b] | • Discontinue the study treatment immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>[redacted] |
| > 3 to ≤ 5 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks |
| **ALP (isolated)** | | |
| > 2 × ULN (in the absence of known bone pathology) | • Repeat LFT within 48 hours<br>• If elevation persists, establish causality<br>• Complete liver CRF | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit<br>[redacted] |
| **TBL (isolated)** | | |
| > 2 × ULN (in the absence of known Gilbert syndrome) | • Repeat LFT within 48 hours<br>• If elevation persists, discontinue the study drug immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)<br>[redacted] |
| > 1.5 to ≤ 2 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| Jaundice | • Discontinue the study treatment immediately<br>• Hospitalize the patient<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>[redacted] |
| Any AE potentially indicative of a liver toxicity* | • Consider study treatment interruption or discontinuation<br>• Hospitalization if clinically appropriate | Investigator discretion<br>[redacted] |

[redacted]

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| | • Establish causality<br>• Complete liver CRF | collected at the time of event, after 48 hours, after 96 hours if liver enzymes are still rising, and at resolution |

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

# 15 Appendix 3: Specific Renal Alert Criteria and Actions

**Table 15-1 Specific Renal Alert Criteria and Actions**

| | |
|---|---|
| **Serum Event** | |
| Serum creatinine increase<br>25 – 49% compared to baseline | Confirm 25% increase after 24-48h<br>Follow up within 2-5 days |
| Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline | Follow up within 24-48h if possible<br>Consider study treatment interruption<br>Consider patient hospitalization /specialized treatment |
| **Urine Event** | |
| New dipstick proteinuria ≥1+<br>Albumin- or Protein-creatinine ratio increase ≥2-fold<br>Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol;<br>Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol | Confirm value after 24-48h<br>Perform urine microscopy<br>Consider study treatment interruption / or discontinuation |
| New dipstick glycosuria ≥1+ not due to diabetes | Blood glucose (fasting)<br>Perform serum creatinine, ACR |
| New dipstick hematuria ≥1+ not due to trauma | Urine sediment microscopy<br>Perform serum creatinine, ACR |
| **For all renal events:** | |
| Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed<br>Monitor patient regularly (frequency at investigator's discretion) until either:<br>Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or<br>Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. | |

# 16 Appendix 4: Proprietary screening algorithm for assessing eligibility

Available upon request of health authorities and IRB/IECs.

[redacted]

# 17 Appendix 5: PK sample log - Time schedule for blood sampling for PK assessments

**Table 17-1 Time schedule for blood sampling for PK assessments (all patients)**

| Plasma EMA401 concentration | | | | |
|---|---|---|---|---|
| Week | Scheduled time | Dose reference ID | Sample number | Blood volume |
| 8 | Prior to morning study medication (i.e. EMA401/placebo) dose | 1 | 101 | 3 mL |
| | 1-3 hours after morning study medication (i.e. EMA401/placebo) dose | 1 | 102 | 3 mL |
| | 4-6 hours after morning study medication (i.e. EMA401/placebo) | 1 | 103 | 3 mL |
| 12 | Prior to morning study medication (i.e. EMA401/placebo) dose | 2 | 104 | 3 mL |
| | 1-3 hours after morning study medication (i.e. EMA401/placebo) dose | 2 | 105 | 3 mL |
| | 4-6 hours after morning study medication (i.e. EMA401/placebo) | 2 | 106 | 3 mL |
| Total amount of blood for PK assessments | | | | 18 mL |

**Table 17-2 Time schedule for blood sampling for PK assessments (additional sampling for patients taking pregabalin or gabapentin)**

| Plasma concentration of pregabalin/gabapentin | | | | |
|---|---|---|---|---|
| Week | Scheduled time | Dose reference ID | Sample number | Blood volume |
| 0 | Prior to morning pregabalin/gabapentin dose | 3 | 201 | 3 mL |
| 8 | Prior to morning pregabalin/gabapentin dose | 4 | 202 | 3 mL |
| 12 | Prior to morning pregabalin/gabapentin dose | 5 | 203 | 3 mL |
| Total amount of blood for PK assessments | | | | 9 mL |

[redacted]

# 18 Appendix 6: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria for Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   **Note:** Do not include symptoms that are clearly attributable to another medical condition.

   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

   **Note:** Criteria A–C represent a major depressive episode (MDE).

   **Note:** Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of

[redacted]

a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in an MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of an MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of an MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in an MDE. In grief, self-esteem is generally preserved, whereas in an MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in an MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

**Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

[redacted]

# 19 Appendix 7: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) diagnostic criteria for Substance Use Disorders

The diagnosis of a substance use disorder can be applied to all 10 classes except caffeine (alcohol; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants; tobacco; and other (or unknown) substances). For certain classes some symptoms are less salient, and in a few instances not all symptoms apply (e.g., withdrawal symptoms are not specified for phencyclidine use disorder, other hallucinogen use disorder, or inhalant use disorder).

**Diagnostic Criteria**

A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following criteria, occurring within a 12-month period:

1. The individual may take the substance in larger amounts or over a longer period than was originally intended.
2. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use.
3. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home.
6. The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities may be given up or reduced because of substance use.
8. Recurrent substance use in situations in which it is physically hazardous.
9. The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    - Requiring a markedly increased dose of the substance to achieve the desired effect
    - A markedly reduced effect when the usual dose is consumed.
11. Withdrawal, as manifested by either of the following:
    - A syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the

[redacted]

substance. Withdrawal symptoms vary greatly across the classes of substances, and separate criteria sets for withdrawal are provided for the drug classes.

- The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

A mild substance use disorder is suggested by the presence of two to three symptoms, moderate by four to five symptoms, and severe by six or more symptoms.

[redacted]