NOVARTIS

Global Clinical Development - General Medicine

EMA401

Clinical Trial Protocol CEMA401A2202 / NCT03297294

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

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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
ATC	Anatomic Therapeutic Chemical classification
AUC	Area under the Curve
AV Block	Atrioventricular block
b.i.d.	twice a day
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
C_{max}	Maximum concentration
CNS	Central Nervous System
COA	Clinical Outcome Assessment
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form
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
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
[redacted]	[redacted]
DN4	Douleur Neuropathique en 4 Questions
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	Ethics Committee
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

[redacted]

eDiary	Electronic diary
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoT	End of Trial
ePRO	Electronic Patient Reported Outcome
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GT	gamma-glutamyltransferase
[redacted]	[redacted]
HbA1c	Glycated hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
[redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISI	Insomnia Severity Index
J2R	Jump to reference
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
MCSFR1	Macrophage colony-stimulating factor 1 receptor
MCV	Mean Corpuscular Volume
MDE	Major Depressive Episode
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
MTD	Maximum Tolerated Dose

[redacted]

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
PerfO	Performance Outcomes
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
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety set
[redacted]	[redacted]
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
TENS	Transcutaneous Electrical Nerve Stimulation
TEAE	Treatment-Emergent Adverse Events
UGT	Uridine Diphosphate Glycosyltransferase
ULN	Upper limit of Normal
US	United States
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. 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.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
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 consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	CEMA401A2202
Full Title	A double-blind, placebo-controlled, randomized trial to determine the safety and efficacy of EMA401 100 mg b.i.d. in reducing 24-hour average pain intensity score in patients with painful diabetic neuropathy (EMPADINE)
Brief title	Safety and efficacy of EMA401 in patients with painful diabetic neuropathy (PDN)
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate safety and efficacy of EMA401 100 mg b.i.d. compared to placebo in patients with painful diabetic neuropathy (PDN).
Primary 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 EMA401 100 mg b.i.d vs. placebo
Key secondary Objective	To compare the efficacy of EMA401 vs. placebo in Neuropathic Pain Symptom Inventory (NPSI) total score by testing the superiority of EMA401 100 mg b.i.d vs. placebo
Secondary Objectives	• Objective 1: 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 • Objective 2: 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 • Objective 3: To evaluate the efficacy of EMA401 compared to placebo, on the Patient Global Impression of Change (PGIC) at Week 12 • Objective 4: 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 • Objective 5: To evaluate the effect of EMA401 compared to placebo on the Insomnia Severity Index (ISI) at Week 12 • Objective 6: To evaluate the safety and tolerability of EMA401 compared to placebo in PDN 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 • Objective 7: To evaluate the pharmacokinetics (PK) of EMA401 and exposure-response (decrease in pain intensity) relationship for EMA401 throughout the study • Objective 8: To evaluate the proportion of patients who need rescue medication separately for the double blind treatment epoch and treatment withdrawal epoch and the time to first intake of rescue medication during the double blind treatment epoch.
Study design	The study is interventional, randomized, parallel, placebo-controlled,

[redacted]

	double-blind treatment.
Population	The study population will consist of approximately 400 randomized male and female patients (≥ 18 years old) with PDN

Key Inclusion criteria	• At the time of Screening, have documented diagnosis of Type I OR Type II diabetes mellitus (DM) with painful distal symmetrical sensorimotor neuropathy (for example ICD-10 code G63.2) of more than 6 months duration with any one or more of the following:
	  • Neuropathic symptoms (e.g. numbness, non-painful paresthesias or tingling, non-painful sensory distortions or misinterpretations, etc.)
	  • Decreased distal sensation (e.g. decreased vibration, pinprick sensation, light touch, etc.)
	• Be assessed as suffering from moderate to severe neuropathic pain across the Screening epoch (NRS ≥ 4)
	• A score of ≥ 4 on the Douleur Neuropathique en 4 Questions (DN4) questionnaire at Screening

Key Exclusion criteria	• History or current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study • 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 • Have evidence of significant renal insufficiency or pre-existing liver condition • 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 • Participants whose glycemic control has been unstable within 3 months immediately prior to screening (e.g., ketoacidosis requiring hospitalization, any recent episode of hypoglycemia requiring assistance through medical intervention, uncontrolled hyperglycemia) • Patients with any differential diagnosis of PDN including but not limited to other neuropathies (e.g. Vitamin B12 deficiency, Chronic Inflammatory Demyelinating Polyneuropathy), polyradiculopathies, central disorders (e.g. demyelinating disease), or rheumatological disease (e.g., foot arthritis, plantar fasciitis) • Patient is unwilling or unable to complete daily eDiary
Study treatment	EMA401 and placebo
Efficacy assessments	• 11-point Numeric Rating Scale (NRS) • Neuropathic Pain Symptom Inventory (NPSI) • Brief Pain Inventory-Short Form (BPI-SF) • Patient Global Impression of Change (PGIC) • Insomnia Severity Index (ISI)
Key safety assessments	• Adverse event monitoring • Physical examinations and vital signs • Monitoring of laboratory markers in blood and urine • ECGs • [redacted]

[redacted]

	• Withdrawal and rebound effect
Other assessments	• Pharmacokinetics (PK) [redacted]
Data analysis	The primary objective of the study will be achieved if the active dose (EMA401 100 mg b.i.d.) is statistically significant versus placebo in terms of 24-hour average pain intensity score at Week 12, using an 11 point Numeric Rating Scale (NRS). Similarly, key secondary objective of the study will be achieved if the active dose (EMA401 100 mg b.i.d.) is statistically significant versus placebo in terms of Neuropathic Pain Symptom Inventory (NPSI) total score. While comparing EMA401 100 mg b.i.d. versus placebo, for the primary and key secondary endpoints the statistical testing will be carried out using the graphical testing procedure to preserve the family-wise error rate at the 2.5% level. The estimation of the treatment effect will be performed based on an Analysis of Covariance (ANCOVA) model including region (e.g. US, EU), treatment, sex, use of concomitant pain medication for PDN (yes/no) as factors and baseline score and age as covariates. The analysis will account for different post-randomization events, such as changes in doses of concomitant medication for PDN, 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.
Key words	Painful diabetic neuropathy, neuropathic pain, angiotensin II type 2 receptor antagonist

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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).

Diabetic neuropathy is a common and disabling complication of diabetes mellitus (DM) and has been recognized as a leading cause of non-traumatic amputations secondary to foot ulceration (Vinik et al 2000; Mahmood et al 2009). The typical diabetic neuropathy is a chronic, symmetrical, length-dependent sensory-motor polyneuropathy. Though the precise etiology of diabetic neuropathy remains to be elucidated, it develops on a background of long-standing metabolic dysfunction associated with diabetes (including polyol flux, hyperglycemia, accumulation of advanced glycation end products, oxidative stress, and lipid alterations among other metabolic abnormalities) and cardiovascular risk factors (Dyck et al 1999; Tesfaye et al 2005; Dyck et al 2006). The neuropathy in diabetes can affect the peripheral (painful diabetic neuropathy; PDN) nervous system or the autonomic nervous system (diabetic autonomic neuropathy); the current study focuses exclusively on the former.

Pain is a common complication of diabetic neuropathy and the condition, PDN, has few validated treatments. The patient complains of pain which is distal, symmetrical, often associated with nocturnal exacerbations, and commonly described as prickling, deep aching, sharp, like an electric shock, or burning with hyperalgesia and frequently allodynia upon examination (Apfel et al 2001; Boulton et al 2004).

Recent recommendations of Neuropathic Pain Special Interest Group (NeuPSIG) for the pharmacotherapy of neuropathic pain include use of tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors (i.e. duloxetine), 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

[redacted]

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 treatment discontinuation rates and thus may substantially limit the utility of such combinations (Chaparro et al 2012). Given the prevalence and severity of PDN, 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 seven 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 evaluate safety and efficacy of EMA401 100 mg b.i.d. (i.e. 200 mg/day) compared to placebo in patients with painful diabetic neuropathy (PDN).

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) • To compare the efficacy of EMA401 vs. placebo in 24-hour average pain intensity score at Week 12, using an 11 point Numeric Rating Scale (NRS) by testing the superiority of EMA401 100 mg b.i.d. vs. placebo	**Endpoint(s) for primary objective(s)** • Change in weekly mean 24-hour average pain score (using the 11 point NRS) from Baseline to Week 12
Key Secondary Objective(s) • To compare the efficacy of EMA401 vs. placebo in Neuropathic Pain Symptom Inventory (NPSI) total score by testing the superiority of EMA401 100 mg b.i.d. vs. placebo	**Endpoint(s) for key secondary objective(s)** • Change in Neuropathic Pain Symptom Inventory (NPSI) total score from Baseline to Week 12
Secondary Objective(s) • To evaluate the efficacy of EMA401 compared to placebo, as measured by the Brief Pain Inventory-Short Form (BPI-SF) interference total score at Week 12 • To evaluate the efficacy of EMA401 compared to placebo, as measured by	**Endpoint(s) for secondary objective(s)** • Change in BPI-SF interference total score from Baseline to Week 12 • Change in weekly mean of the 24-hour worst pain score, using an 11-point NRS,

Objective(s)	Endpoint(s)
the weekly mean of the 24-hour worst pain intensity score, using an 11-point Numeric Rating Scale (NRS) at Week 12	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
• 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 safety and tolerability of EMA401 compared to placebo in PDN 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
• To evaluate the proportion of patients who need rescue medication separately for the double blind treatment epoch and treatment withdrawal epoch and the time to first intake of rescue medication during the double blind treatment epoch.	• Proportion of patients who need rescue medication separately for the double blind treatment epoch and treatment withdrawal epoch, the time to first intake of rescue medication during the double blind treatment epoch

[redacted]

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

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

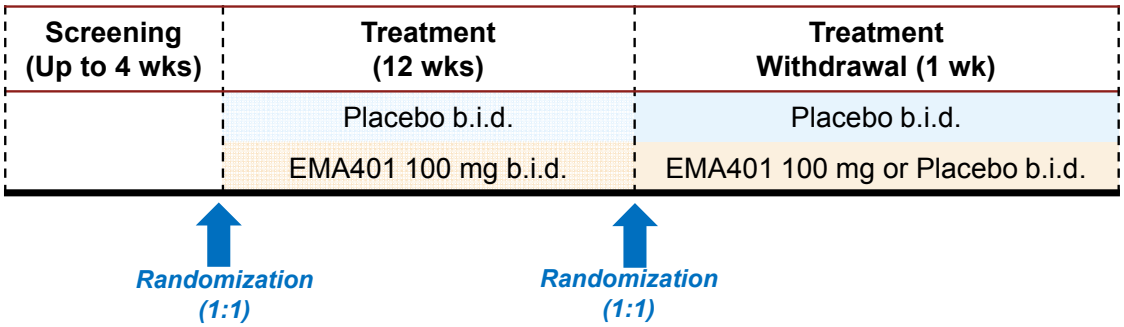
The study will consist of a Screening epoch (up to 4 weeks), a double-blind Treatment epoch (12 weeks), and a double-blind Treatment withdrawal epoch (1 week). Concomitant use of pregabalin or duloxetine at stable doses is allowed (Section 5.5.7). Based on historical data study will enroll approximately 50% of patients on concomitant pregabalin or duloxetine.

- Patients will be randomized in a 1:1 ratio to treatment with placebo or EMA401 100 mg b.i.d.

Overall approximately 400 patients will be enrolled in the study (i.e. approximately 200 patients will be enrolled in each treatment arm). End of Trial (EoT) will occur when the last patient completes last visit (LPLV).

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

Figure 3-1 Study design



Screening epoch (Up to 4 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,

[redacted]

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.

During Screening, site staff must ensure that the patient is not taking any prohibited concomitant medications or combination therapy for neuropathic pain treatment. Patients who pass preliminary Screening assessments will receive their electronic patient reported outcome (ePRO) diary (eDiary) device. Patients completing their 7 day baseline 24-hour pain intensity scores will return to the study site at Visit 101 (i.e. Baseline).

The patient's final eligibility will be based on an assessment of their average pain intensity scores using a proprietary screening algorithm (Appendix 4) prior to randomization.

General principles of the algorithm 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.

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 at the Baseline visit (V101). Patients will visit the study site for assessments that are outlined in the visit assessment schedule (Table 6-1). At each scheduled visit Investigators/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, retraining the patient 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 site staff can assess patient's compliance with the dosing regimen. Patients should bring their duloxetine (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)

For patients who complete the 12 week 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

[redacted]

either stop treatment (i.e. receive placebo) or to continue the active treatment assigned during the double-blind Treatment epoch.

3.2 Rationale for study design

This study will evaluate the safety and efficacy of EMA401 100 mg b.i.d. in the treatment of PDN.

The aim is to estimate the treatment effect of the investigational drug (EMA401 100 mg b.i.d.) 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 evaluating safety and efficacy 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, as indicated in Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. The quarterly unblinded DMC review of safety data, together with clinical assessments every two weeks will ensure patient safety, according to the DMC Charter.

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

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

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).

The dose planned to be studied in this study is EMA401 100 mg b.i.d. (i.e. 200 mg per day).

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).

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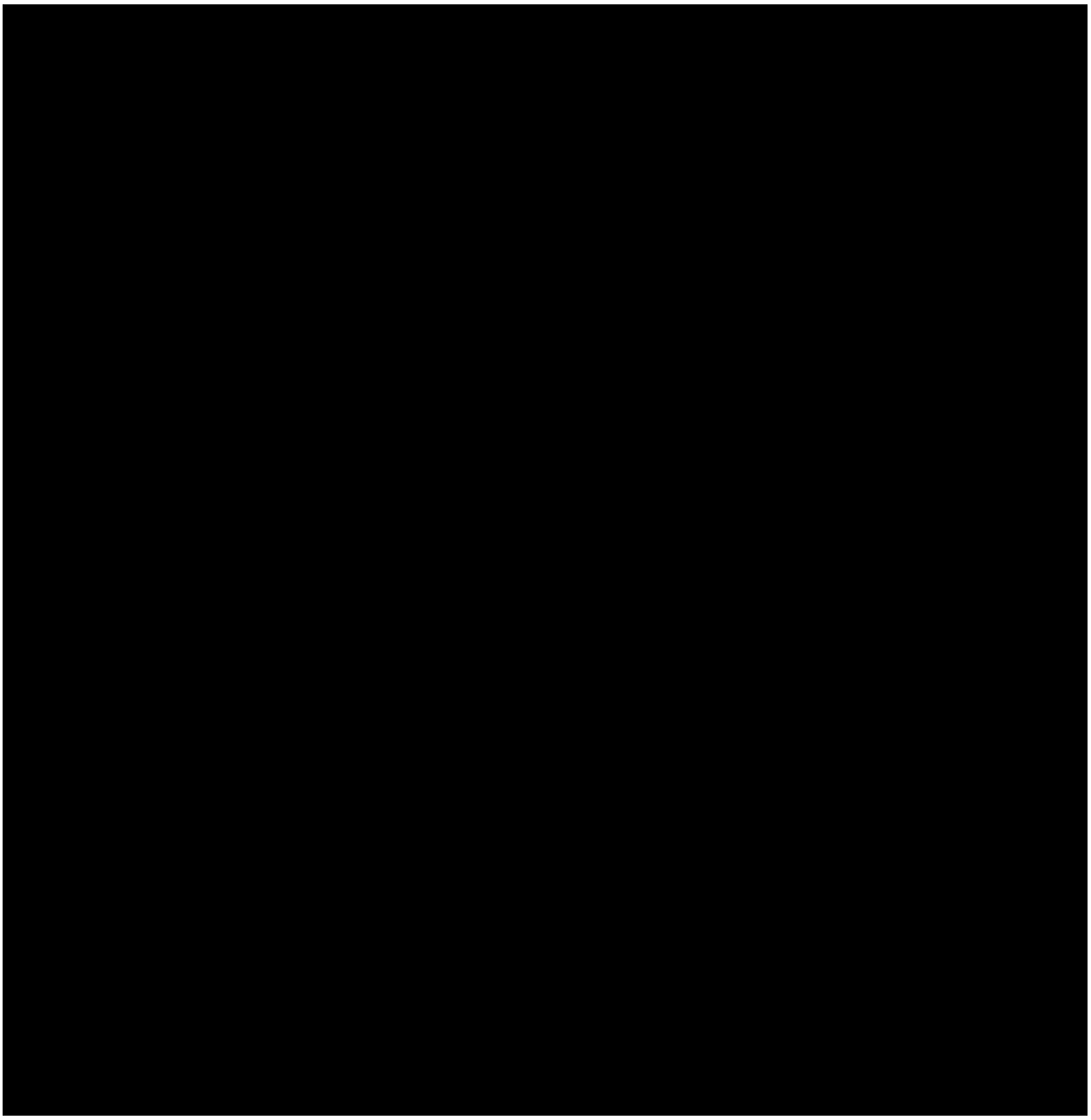


3.3.3 Non-Clinical Safety

The non-clinical program of EMA401 include safety pharmacology studies, toxicology studies in three species (dogs up to 4-week duration, rats and monkeys up to 13-week duration), mechanistic studies and preliminary embryo-fetal toxicity studies in two species (rat and rabbit). Together, these non-clinical studies support the conduct of clinical trials of up to 13-week in duration up to the highest daily clinical dose of 600 mg (300 mg b.i.d.) including in women of child-bearing potential. In the 13-week rat toxicity study, mortality and excessive toxicity was noted at doses ≥ 500 mg/kg/day (≥ 250 mg/kg b.i.d.). The various inflammatory changes gastrointestinal tract and nasal turbinate) noted at doses ≥ 150 mg/kg/day (75 mg/kg b.i.d) and hepatocyte lipid vacuolation noted at doses ≥ 30 mg/kg/day (15 mg/kg b.i.d) were demonstrated to be clinically-irrelevant. In the 13-week toxicity study

in monkeys, oral administration of EMA401 sporadically resulted in abnormal feces and/or post-dose emesis and vomitus at doses ≥ 100 mg/kg/day (50 mg/kg b.i.d). Those clinical signs were not adverse because they were transient, did not result in decreased body weight/body weight gain and did not affect the overall health of the animals. There were no target organ of toxicity. A summary of completed non-clinical studies and their results can be found in the Investigator's Brochure.

3.3.4 Clinical Safety

As of 05-Aug-2017, a total of 556 subjects (342 subjects from clinical pharmacology studies and 214 patients) have been enrolled into the EMA401 clinical program (inclusive of Phase 1 and Phase 2), of which 373 subjects (250 healthy subjects, 92 patients with PHN, and 31 patients with CINP) have received EMA401 and 183 subjects (92 healthy subjects and 91 patients with PHN) have received placebo. 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 at the time of protocol finalization.

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.

The Ethnic Sensitivity Study (EMA401A1101) with the new formulation has recently been conducted to characterize pharmacokinetics, safety and tolerability of EMA401 after single ascending oral doses administered in Japanese (N=40) and Caucasian healthy adult subjects (N=20) and multiple oral doses administered in Japanese healthy elderly subjects (N=12). The safety part of the EMA401A1101 study is already analyzed.

Single and multiple oral doses of EMA401 were safe and well-tolerated in Caucasian healthy subjects as well as in Japanese healthy adult and elderly subjects enrolled in EMA401A1101 study. There were no deaths, no SAEs, and no discontinuation due to AEs. Gastrointestinal AEs (e.g. diarrhea) were the most significant AEs in subjects who received EMA401 in the

seven complete phase 1 studies. Overall AE profile is consistent with previous experience in EMA401 studies in healthy subjects.

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 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: Suspected Unexpected Serious Adverse Reactions (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 duloxetine) and other comorbid diseases at stable doses is therefore allowed, as no safety concerns are foreseen.

4 Population

The study population will consist of male and female patients (≥ 18 years old) with painful diabetic neuropathy (PDN). The goal is to randomize a total of approximately 400 patients in approximately 100 centers worldwide. Since a 40% screening failure rate is expected, approximately 675 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.

[redacted]

3. At the time of Screening, have documented diagnosis of Type I OR Type II diabetes mellitus (DM) with painful distal symmetrical sensorimotor neuropathy (for example ICD-10 code G63.2) of more than 6 months duration with any one or more of the following:
    a) Neuropathic symptoms (e.g. numbness, non-painful paresthesias or tingling, non-painful sensory distortions or misinterpretations, etc.)
    b) Decreased distal sensation (e.g. decreased vibration, pinprick sensation, light touch, etc.)
4. 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 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.
5. A score of ≥ 4 on the Douleur Neuropathique en 4 Questions (DN4) questionnaire at Screening.

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.
3. History or current diagnosis of 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. 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 recurrence or metastases.
6. 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]

8. Pregnant or nursing (lactating) women.
9. 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.
   - 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 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.
10. 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).
11. 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).
12. Positive urine drug screen at Screening.
13. Evidence of pre-existing liver condition as defined as any of the following:
    - Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 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
    - Known gallbladder or bile duct disease
    - Acute or chronic pancreatitis
14. Have platelets $\leq 100 \times 10^9$/L, or neutrophil count $< 1.2 \times 10^9$/L (or equivalent), or hemoglobin ≤ 100 g/L for women or hemoglobin ≤ 110 g/L for men at Screening.

[redacted]

15. Participants whose glycemic control has been unstable within 3 months immediately prior to screening (e.g., ketoacidosis requiring hospitalization, any recent episode of hypoglycemia requiring assistance through medical intervention, uncontrolled hyperglycemia).
16. Patients with any differential diagnosis of PDN including but not limited to other neuropathies (e.g. Vitamin B12 deficiency, Chronic Inflammatory Demyelinating Polyneuropathy), polyradiculopathies, central disorders (e.g. demyelinating disease), or rheumatological disease (e.g., foot arthritis, plantar fasciitis).
17. Other than pain as a result of PDN:
    - 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, other chronic pain conditions (e.g. osteoarthritis, fibromyalgia), that in the opinion of the Investigator, precludes participation in the study or may interfere with the study objectives and assessment of change in neuropathic pain
    - Had a clinically significant illness or operative procedure within four weeks of Screening (e.g., influenza, myocardial infarction)
18. Have undergone neurolytic or neurosurgical therapy or use a neuro stimulating device for PDN within 3 months of Screening or are using/ plan to use Transcutaneous Electrical Nerve Stimulation (TENS).
19. Patient is unwilling or unable to complete daily eDiary.

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:

- 50 mg

EMA401 and placebo will be identical in appearance.

5.1.2 Additional treatment

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

5.2 Treatment arms

Patients will be assigned at Baseline (Visit 101) to one of the following 2 treatment arms in the ratio of 1:1.

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

[redacted]

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
Placebo b.i.d.	Placebo b.i.d.	2
EMA401 100 mg b.i.d.	EMA401 100 mg b.i.d.	1
EMA401 100 mg b.i.d.	Placebo b.i.d.	1

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 PDN (yes/no) in order to achieve balance of treatment allocation within the stratification factors.

For the primary analysis at Week 12, the overall study randomization ratio will be 1:1 for the treatment arms placebo and EMA401 100 mg b.i.d. (refer to Section 9.8).

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

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

[redacted]

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 database 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 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.

[redacted]

Patients may NOT be re-screened if the reason for screen failure was due to not meeting the requirements of the proprietary screening algorithm based on assessment of their 24-hour average pain intensity scores recorded in the eDiary device.

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 every study visit and 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.

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 duloxetine if applicable) prior to arriving at the site and completing the necessary assessments.** Patients should bring their duloxetine (if applicable) with them to the study visits where PK is collected so it may be administered after the PK assessment, 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 4 times per day) for unacceptable pain due to any reason during the study.

The patients will be instructed to fill out the electronic pain diary (eDiary) before intake of acetaminophen/paracetamol. Use of acetaminophen/paracetamol must be recorded in the eDiary.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after enrolling into the study. All medications including antidiabetic 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.

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.

1. Patients will be allowed to take **only one** of the following prescribed medications for managing their PDN, provided the dose level has been stable for at least 2 weeks prior to the Screening Visit (Visit 1) and must remain at stable doses throughout the study (PRN (as needed) use is not allowed):
   - Pregabalin
   - Duloxetine
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.

[redacted]

- 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 duloxetine) must be stable for at least 2 weeks prior to the Screening visit, and must remain stable throughout the study. **Any change to a different standard of care medication from baseline (e.g. switch from pregabalin to duloxetine) will be treated as prohibited medication.**

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 Screening Visit and throughout study		
Any skeletal muscle relaxant (e.g. baclofen, orphenadrine, methocarbamol)	2 weeks prior to Screening and after Screening	None
Mexiletine	2 weeks prior to Screening and after Screening	None
Dextromethorphan	2 weeks prior to Screening and after Screening	None
Memantine	2 weeks prior to Screening and after Screening	None
Alpha-lipoic acid	2 weeks prior to Screening and after Screening	None
Other anti-epileptic drugs (e.g. valproic acid, carbamazepine, phenytoin)	2 weeks prior to Screening and after Screening	Discontinue study treatment upon 2nd episode of medication use
Antiviral medications (e.g. valacyclovir, acyclovir, amantadine, anti-HIV)	2 weeks prior to Screening and after Screening	None
High dose capsaicin patch (8%)	6 months prior to Screening and after Screening	Discontinue study treatment
Prohibited after Screening Visit and throughout study		
Oral or injectable steroids	After Screening	Discontinue study treatment upon 2nd episode of medication use
Monoamine oxidase inhibitors or any other antidepressants (except stable dosage of SSRI)	After Screening	Discontinue study treatment upon 2nd episode of medication use
Antipsychotic or neuroleptic medications	After Screening	Discontinue study treatment upon 2nd episode of medication use
Cannabinoids (e.g. marijuana)	After Screening	Discontinue study treatment upon 2nd episode of medication use
Prescribed opioids, including codeine	After Screening	Discontinue study treatment

[redacted]

Medication	Prohibition period	Action taken for study treatment
		upon 2nd episode of medication use
Prescription systemic pain medication, or *topical* treatment for PDN, including lidocaine plaster	After Screening	Discontinue study treatment upon 2nd episode of medication use
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or any other over-the-counter pain medications	After Screening	None
Any non-drug therapies that could modulate the perception of pain either directly or indirectly (i.e. transcutaneous electrical nerve simulation (TENS) or surgery)	After Screening	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)	After Screening	None

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

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 the 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 6.5.6 and Section 7.6)
- Use of prohibited treatment that requires study treatment discontinuation as described in Table 5-2
- 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:
    - Skin rash – In the event a skin rash occurs while on study medication, initial evaluation by a qualified clinician is required. Identified common dermatologic conditions (i.e. insect bites, poison ivy etc.) can be evaluated and treated per standard of care by investigator. In cases of suspected allergic dermatitis does not respond to treatment, consultancy with an independent dermatologist for follow-up is required

[redacted]

with appropriate documentation in patient's source. Study treatment should be interrupted if allergic dermatitis is suspected. The following assessments should be done at the time of determination and recorded in the appropriate CRF: body temperature, blood chemistry (including Liver Function Tests (LFTs) and Complete Blood Cell Count (CBC)). Study treatment can be started again following recommendation of the dermatologist and investigator. Study treatment must be permanently discontinued thereafter if allergic dermatitis 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 testing 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 x 10^9/L
  - Absolute neutrophil count <1.0 x 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 on the Dosage Administration 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.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the abbreviated study visit schedule.

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

[redacted]

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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.

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

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

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.

Patients must be seen for all visits on the designated day, or as close to it as possible. 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

[redacted]

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]	X	X								X	X
Urine pregnancy test		X			X		X		X		
Hematology/Blood chemistry[2]	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
DN4 screening questionnaire	X										
Dispense ePRO eDiary device	S										
Complete pain eDiary 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

S = assessment to be recorded on source documentation only; TD = Study Treatment Discontinuation visit; X = assessment to be recorded on clinical data base

[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

[1]Collected as part of the blood chemistry.

[2]HbA1c will be collected at Baseline and Week 12/TD

[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]

[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 and pre-dose single ECG →Vital signs → Pre-dose PK and 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 duloxetine according to the schedule detailed in Table 17-2. Patients should be instructed not to take their morning dose of duloxetine prior to arriving at the site and completing the necessary assessments. Patients should bring their duloxetine (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 eDiary daily (NRS)	X	X	X	X	X	X	X
BPI-SF, NPSI			X		X		X
PGIC							X
[redacted]							
Treatment epoch disposition							X

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

[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. In addition, previous/ongoing PDN medication(s) use will be collected (i.e. the latest dosing information of each medication and corresponding start/end dates).

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 should 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 study medication 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 patient, 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 eDiary device or an electronic tablet. Detailed training on use of the devices 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.

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 according to 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 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,

[redacted]

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.

6.4.3 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 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.

6.4.6 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] are recommended for assessing the patient's perception of the impact of disease and treatment on

[redacted]

daily life physical, psychological and social functioning and well-being. The Patient Global Impression of Change is a useful supportive indicator of the overall perceived benefit of treatment in chronic pain trials. Therefore BPI-SF and PGIC are included.

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

Sleep disturbance may change pain perception and might affect efficacy assessments. Furthermore, pharmacodynamic effects of EMA401 may influence these comorbidities. ISI will be used to access impact on perceived insomnia severity.

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, and extremities, vascular and neurological.

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. The repeat supine measurements will be made at approximately 1 to 2 minute intervals and the mean of the three measurements will be used. After the patient has been standing for 3 minutes, systolic and diastolic blood pressure will be again measured using the above procedure.

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.

At Baseline and Week 12/TD, glycated hemoglobin (HbA1c) will also be collected.

Serum pregnancy will be performed according to Table 6-1.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, albumin, 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.

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, the site may perform a

single repeat urine drug screen within the screening period after the Screening visit. 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. A second repeat is not admissible.

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 preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected with ECG machines supplied by the central vendor at the visits indicated in Table 6-1. The original ECGs, appropriately signed, should be 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.

Clinically significant ECG findings at randomization (pre-dose) must 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.

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]

[redacted]

6.6 Other assessments

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Patient Reported Outcomes (PRO)

The impact of PDN on various aspects of patient's health status will be assessed by the following measures:

Douleur Neuropathique 4 (DN4)

The Douleur Neuropathique 4 (DN4) is a clinician administered questionnaire that can be useful in diagnosing neuropathic pain (Bouhassira et al 2005).

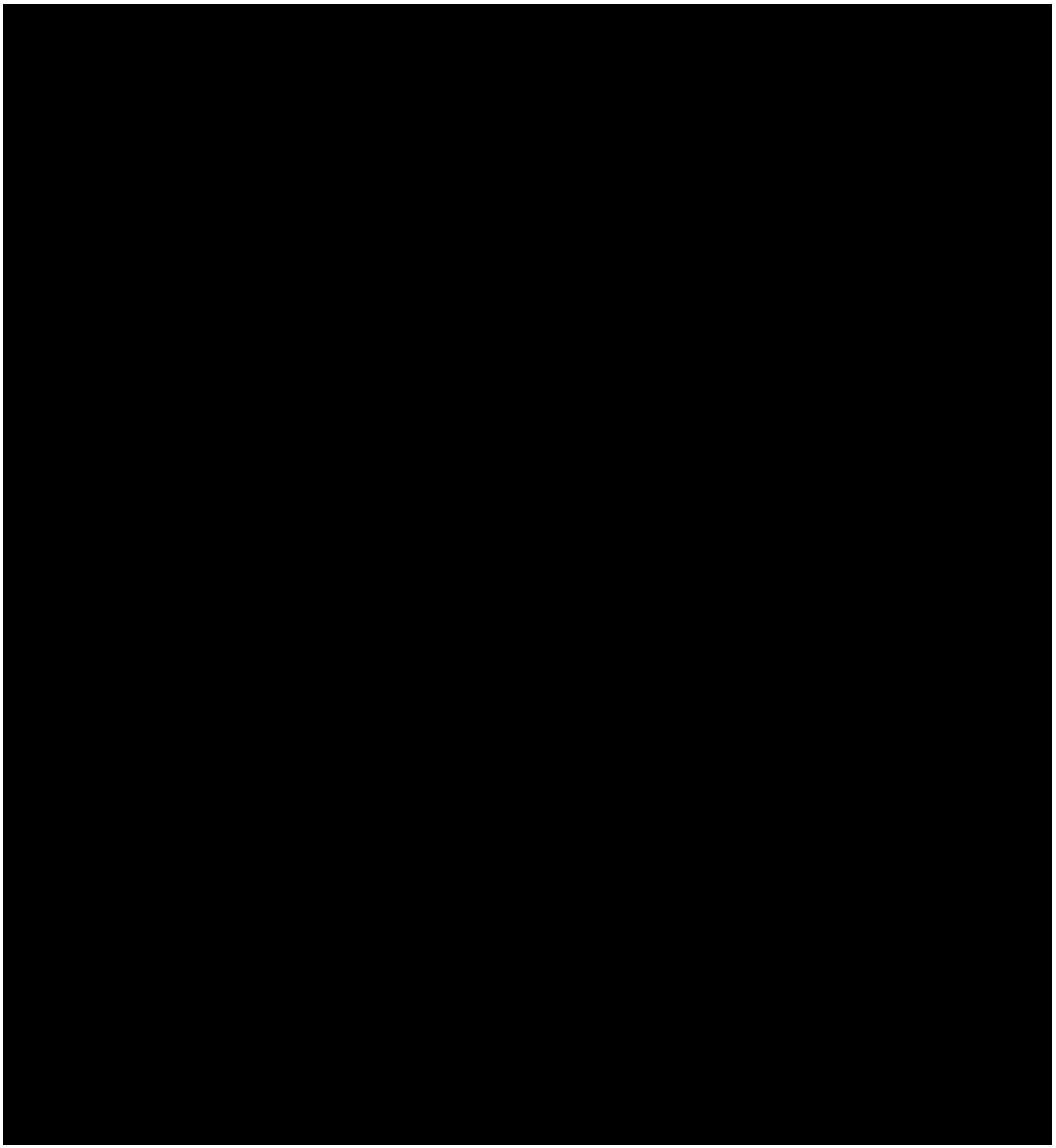
The DN4 consists of 10 items. Seven items are related to pain quality (i.e. sensory and pain descriptors) and are based on an interview with the patient, and 3 items are based on the clinical examination. The clinical examination assesses whether there is reduced sensation (hypoesthesia) to touch or pinprick, and whether light brushing increases or causes pain (allodynia).

The DN4 will be administered by the clinician at Screening and recorded in the electronic tablet at the site.

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.

At Baseline, the clinical 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.



[redacted]

[redacted]

6.6.2 Resource utilization

Not applicable.

6.6.3 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 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).

[redacted]

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

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

[redacted]

6.6.5 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:

[redacted]

- 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 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.

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

[redacted]

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 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

[redacted]

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.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

[redacted]

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.

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.

[redacted]

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:
  - confirmed (after ≥ 24 h) 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 dose administration record (DAR) 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 Record (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 for up to 12 months after birth.

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.

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).

[redacted]

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.

[redacted]

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.

[redacted]

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).

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) comprises all subjects to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization.
- The Safety Set (SAF) includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received.

The primary efficacy analysis will be performed on 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). Relevant medical history/current medical conditions will be summarized by system organ class and preferred term of the MedDRA dictionary.

[redacted]

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 PDN will also be summarized by treatment.

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

9.4 Analysis of the primary variable and key secondary variable

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 recorded his/her daily pain intensity score across the preceding 24 hours at a single time point. The daily pain intensity score was then averaged over 7 days to obtain the mean pain intensity score for a week.

The key secondary efficacy variable will be the change from baseline to Week 12 in the Neuropathic Pain Symptom Inventory (NPSI) total score which is calculated as the sum of 10 descriptors outcome measure (as defined in Section 6.4.2) out of the 12 items measured in the NPSI.

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 for NRS are detailed in an Estimand Charter. The definitions of the estimands for the key secondary variable NPSI will also be detailed in an Estimand Charter.

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

[redacted]

The primary estimation method for the both primary and key secondary efficacy variable will be based on an Analysis of Covariance (ANCOVA) model including region (e.g. US, EU), treatment, sex, use of concomitant pain medication for PDN (yes/no) as factors and baseline score of the corresponding scale and age as covariate in an univariate fashion. The analysis will account for different post-randomization events as follows:

- **Changes in doses of concomitant medication for PDN:** Efficacy observations collected during the period of changes in doses of concomitant medication for PDN (compared to baseline) and the 3-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 imputed via multiple imputation method 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 imputed via multiple imputation method 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, Lack of efficacy (LoE) and use of prohibited medication:** If retrieved drop-out data are available, these will be used for analysis. If no data was retrieved after study treatment discontinuation, missing data will be multiply imputed based on placebo arm data, i.e. “jump to reference” (J2R) assumption for the EMA401 arm, missing at random assumption for placebo arm (Carpenter et al 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 imputed via multiple imputation using the MAR assumption.

The multiple imputations for the primary efficacy variable (NRS) will be carried out on the weekly mean pain score.

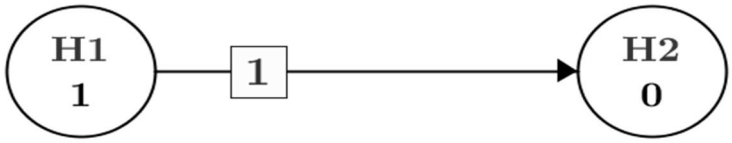
The primary objective will be achieved if the EMA401 100 mg b.i.d. dose is statistically significant versus placebo in terms of the primary efficacy variable after multiplicity adjustment.

The key secondary objective will be achieved if the EMA401 100 mg b.i.d. dose is statistically significant versus placebo in terms of NPSI total score after multiplicity adjustment.

[redacted]

The primary population will be the FAS. To preserve the family-wise error rate at the 2.5% level when comparing the EMA401 100 mg b.i.d. dose versus placebo on the two endpoints NRS and NPSI, statistical testing will be carried out using the following sequentially rejective, weighted Bonferroni-type test using the graphical approach (Bretz et al 2009) mentioned in Figure 9-1.

Figure 9-1 Sequentially rejective, weighted Bonferroni-type test using the graphical approach



In the graphical testing procedure given in Figure 9-1, H1 and H2 denote the two null hypotheses of no treatment difference of EMA401 100 mg b.i.d. vs. placebo for the primary efficacy variable NRS and key secondary efficacy variable NPSI total score. The corresponding alternative hypotheses will be EMA401 100 mg b.i.d. is superior to placebo for the NRS and NPSI respectively. In the Figure 9-1 the number in the circle represents the proportion of alpha level to be assigned at the initial stage among the two null hypotheses. The direction and the number in the arrow represent the proportion of the alpha to be propagated to the next hypothesis.

Initially, H1 will be tested at the full alpha level (1 sided) 0.025. If H1 is rejected then H2 will be tested also at the full alpha level (1 sided) 0.025.

The same ANCOVA model will be applied at the visits prior to Week 12. Multiplicity adjustment at visits prior to Week 12 will not be carried out.

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.

[redacted]

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

9.4.4 Supplementary analyses

The supplementary analyses to the primary analysis for NRS will be performed on the FAS population. The supplementary estimands corresponding to these supplementary analyses are described in detail in an Estimand Charter.

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 arm will be imputed via multiple imputation 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 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 PDN 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 for NRS will be performed corresponding to each of the primary and supplementary analyses.

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 two supplementary analyses, respectively. Missing data after discontinuation will in a first step be imputed in the same way as for the primary and two supplementary analyses, respectively. For the EMA401 arm these imputed values will further be worsened in subsequent steps via the application of increasingly large penalties (tipping point analysis, Permutt 2015).

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The following secondary efficacy variables will be evaluated:

1. 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

[redacted]

patients who prematurely discontinue study treatment, the responder status will be calculated after missing data are imputed via multiple imputation according to the approaches specified for the primary and two 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 concomitant medications for PDN, 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.

2. 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.
3. 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.
4. PGIC at Week 12. The proportional odds model with the same factors as the ANCOVA model for the primary variable will be used.
5. The temporal items of NPSI will be summarized descriptively.
6. 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.
7. The proportion of patients who need rescue medication (at each visit and at least once during the study) will be evaluated separately for the double blind treatment epoch and treatment withdrawal epoch. 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.
8. The Kaplan-Meier estimates of the proportion of patients with rescue medication intake during the double blind treatment epoch, along with the associated 95% confidence intervals using the Greenwood's formula will be provided The time to first rescue medication intake during the double blind treatment epoch 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.

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.

[redacted]

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.

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 and suicidality will be summarized during the double-blind Treatment epoch and treatment withdrawal epoch. The search criterion for each of these events will be defined based on MedDRA. The drug abuse-related adverse events will be summarized for the double-blind Treatment withdrawal epoch to assess the potential for withdrawal effect.

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, expected events and the events of special interest 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.

[redacted]

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values, and by presenting shift tables to compare a patient's baseline laboratory evaluation relative to minimum (when applicable) and maximum values post baseline For the shift tables, the reference ranges provided in the laboratory manual will be used to evaluate whether the most-extreme post baseline laboratory test value is normal, low, or high relative to whether or not the baseline value is normal, low, or high.

Incidence of newly occurring liver enzymes abnormalities and renal events will be summarized using number and percentage of patients by treatment group. Plots related to analysis of laboratory data will be specified in the statistical analysis plan.

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.

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.

[redacted]

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.

Duloxetine 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]

9.5.6 Biomarkers

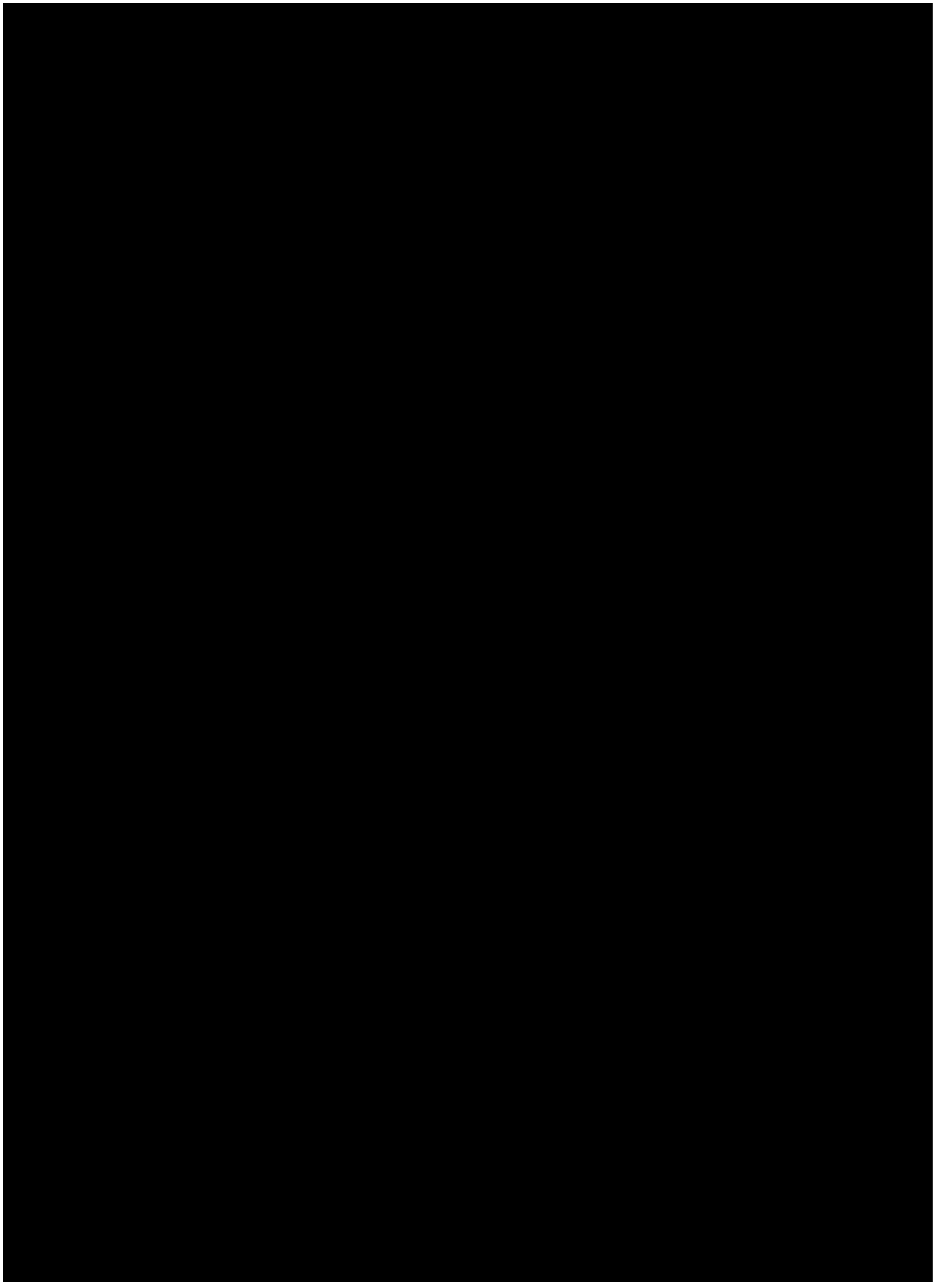
Not applicable.

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.

[redacted]

[redacted]



9.7 Interim analyses

No interim analysis will be performed for the efficacy evaluation, therefore no multiplicity adjustment for the primary efficacy objective is required. An external Data Monitoring Committee (DMC) is established for the EMA401 program with the primary goal to perform an ongoing review of safety data (Section 8.4).

The details of the analysis required for DMC will be specified in a separate DMC statistical analysis plan.

9.8 Sample size calculation

The calculation of power for the testing procedure mentioned in Figure 9-1 is based on the following assumptions:

- The treatment difference of 100 mg b.i.d. vs. placebo was assumed as 0.7, 0.8 and 0.9 points, for the primary efficacy variable (weekly mean of the 24-hour average pain score). A treatment difference of 0.7 points was observed for the 100 mg b.i.d. dose vs. placebo for weekly mean of the 24-hour average pain score (NRS) in the Study EMA401-003 during a 4-week treatment period. The standard deviation is 2.6 points (based on data from pregabalin historical trials – see FDA Approval Package Medical Review, 2004) is assumed for the primary efficacy variable. In Study EMA401-003 in PHN patients, 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. It is also assumed that the same standard deviation holds for the PDN population.

- Treatment differences of 5 points for Pregabalin and 10 points for Duloxetine on NPSI total score were observed via an indirect comparison using the results from Tesfaye (2013) which is an active control study (Pregabalin vs Duloxetine) and Kalliomaki (2013) which is a placebo controlled study (AZD2423 vs placebo). The standard deviation was derived as 16 points using the results from Kalliomaki (2013). A correlation of approximately 0.2 was observed between the baseline scores of NRS and NPSI total score in Freeman et al (2014). The power of the study was calculated assuming correlation coefficient values of 0 and 0.2. Since the power values obtained for correlation values of 0.2 and 0 are similar, in a conservative scenario the results reported herein are for correlation value of 0.

  Since the NPSI has not been studied in the EMA401-003 study, to mitigate the risk of uncertainty on the value of treatment difference and standard deviation, the effect size (treatment difference/ standard deviation) of NPSI total score has been considered for the calculation of power. The power of the study was calculated for different effect sizes ranging in 0.1, 0.5 for NPSI total score corresponding to 100 mg.

Under the assumptions of a 0.8 point treatment difference between 100 mg b.i.d. and placebo, a standard deviation as 2.6 for the primary efficacy variable and an effect size of 0.4 for 100 mg b.i.d. for the key secondary variable, N=200 patients per treatment arm will provide approximately 85% power to show that 100 mg b.i.d. is statistically significant over placebo for the primary efficacy variable, using the testing procedure mentioned in Figure 9-1. The power of showing the statistical significance of 100 mg b.i.d. dose in terms of the key secondary variable will be 84% under the same scenario. If we assume the treatment difference of 0.7 for the NRS as observed in the 4-week PoC study and the effect size for NPSI as 0.35, then the power for the primary objective will be 77% and that for the key secondary objective will be 72%. If the treatment difference between 100 mg b.i.d. and placebo is 0.9 for the NRS, and effect size is 0.45 for 100 mg b.i.d. for the NPSI, the power increases to 94% for the primary objective. The corresponding power for the key secondary objective increases to 93%.

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.

[redacted]

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (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. 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.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

[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.

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

[redacted]

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/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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]

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[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 50 bpm	and an and a	increase of ≥ 15 bpm decrease of ≥ 15 bpm
Systolic blood pressure	180 mm Hg 90 mm Hg	and an and a	increase of ≥ 20 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	105 mm Hg 50 mm Hg	and an and a	increase of ≥ 15 mm Hg decrease of ≥ 15 mm Hg
Weight	Baseline weight (kg)	and an and a	increase of ≥ 7% decrease of ≥ 7%

bpm= beats per minute

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 • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • 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) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • 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 • Hospitalize, if clinically appropriate • Establish causality • 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 • Hospitalize if clinically appropriate • Establish causality • 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 • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) [redacted]
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours	ALT, AST, TBL, Alb, PT/INR, ALP and

[redacted]

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

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	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.

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy 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 Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or 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.

[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	6 mL
	1-3 hours after morning study medication (i.e. EMA401/placebo) dose	1	102	6 mL
	4-6 hours after morning study medication (i.e. EMA401/placebo)	1	103	6 mL
12	Prior to morning study medication (i.e. EMA401/placebo) dose	2	104	6 mL
	1-3 hours after morning study medication (i.e. EMA401/placebo) dose	2	105	6 mL
	4-6 hours after morning study medication (i.e. EMA401/placebo)	2	106	6 mL
Total amount of blood for PK assessments				36 mL

Table 17-2 Time schedule for blood sampling for PK assessments (additional sampling for patients taking duloxetine)

Plasma concentration of duloxetine				
Week	Scheduled time	Dose reference ID	Sample number	Blood volume
0	Prior to morning duloxetine dose	3	201	3 mL
8	Prior to morning duloxetine dose	4	202	3 mL
12	Prior to morning duloxetine 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

[redacted]

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 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]