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1. NOVAREMED INTERVENTION SPECIFIC APPENDIX (ISA) ADMINISTRATIVE INFORMATION

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1.2 Novaremed ISA Approval Signature Page

Treatment number:

NRD135S.E1

Indication: Painful diabetic peripheral neuropathy

Protocol Number: EN21-01

Study Title:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of 80mg daily of NRD135S.E1 Versus Placebo in Adult and Elderly Participants with Painful Diabetic Peripheral Neuropathy (SERENDIPITY-1).

The undersigned accepts the content of this protocol in accordance with the appropriate regulations and agrees to adhere to it throughout the execution of the study.

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Jessica Robinson-Papp, MD Protocol Principal Investigator Professor of Neurology Icahn School of Medicine, Mount Sinai Health System	**Signature**
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1.3 Investigator Protocol Signature Page

Treatment: NRD135S.E1

Indication: Painful Diabetic Peripheral Neuropathy

Protocol Number: EN21-01

Protocol Version: 8.0, Dated 21 May 2024

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of 80mg daily of NRD135S.E1 Versus Placebo in Adult and Elderly Subjects with Painful Diabetic Peripheral Neuropathy (SERENDIPITY-1).

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study participants (other than those procedures necessary for the well-being of the participants).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval from the cIRB before the study start and obtain signed informed consent from all participants included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the participants (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by Regulatory Authorities or IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all participants or legally designated representatives have understood the nature, objectives, benefits, implications, risks, and inconveniences of participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual participant. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and submission to health authorities worldwide.

Site Name:	
Principal Investigator:	
Signature:	

1.4 List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
AUC	Area Under the Curve (Differences in dose-normalized exposure)
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory – Short Form
CCC	Clinical Coordinating Center
CDE	Common Data Elements
CFR	Code of Federal Regulations
CGIC	Clinician Global Impression of Change
CI	Confidence Interval
cIRB	Central Investigational Review Board
cm	Centimeter
Cmax	Exposure
CRA	Clinical Research Association (also known as Monitor)
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTNI	Clinical Trial Network and Institute
DB	Double Blind
DCC	Data Coordinating Center
DDI	Drug-Drug Interactions
DESS	Discontinuation Emergent Signs and Symptoms
DN4	Douleur Neuropathique en 4 Questions
DNP	Diabetic Neuropathy
DRL	Dr. Reddy's Laboratories Ltd.
DSIS	Daily Sleep Interference Score
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report forms
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EO	Exploratory Objectives
EoDB	End-of-Double-Blind
EoS	End-of-Study
EoT	End-of-Treatment
EPPIC-Net	Early-Phase Pain Intervention Clinical Network

ES	Effect Size
ET	Early Termination
FDA (USFDA)	Food and Drug Administration (US Food and Drug Administration)
g	Gram
GABA	Gamma-Aminobutyric Acid
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GLMM	generalized linear mixed models
hERG	ether-à-go-go-related gene
I/E	Inclusion/Exclusion
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IE	intercurrent events
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISA	Intervention Specific Appendix
ISI	Insomnia Severity Index
ITT	Intent-To-Treat
IXRS	Interactive Web Response System
kg	Kilogram
KRI	Key Risk Indicator
L	Liter
m1	Receptors for Acetylcholine
MAOI	Monoamine Oxidase Inhibitors
MAR	Missing at Random
mg	Milligram
MGH	Massachusetts General Hospital (CCC)
MI	Multiple Imputation
mITT	Modified-Intent-to-Treat
MLA	Marked Laboratory Abnormalities
MM	Medical Monitor
MNAR	Missing-Not-at-Random

MNSI	Michigan Neuropathy Screening Instrument
ms	Millisecond
mTCNS	Modified Toronto Clinical Neuropathy Score
NIH	National Institutes of Health
NIH HEAL Initiative	The Helping to End Addiction Long-term^{SM} Initiative
NINDS	National Institutes of Neurological Disorders and Stroke
NMDA	N-methyl-D-aspartate
NNT	Number-Needed-to-Treat
NOAEL	No-Observed-Adverse-Effect-Level
Norfolk QOL-DN	Norfolk Quality of Life – Diabetic Neuropathy
NPSI	Neuropathy Pain Symptom Inventory
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYU	New York University (DCC)
od	Daily
OUQ	Opioid Use Questionnaire
PCS	Pain Catastrophizing Scale
PD	Pharmacodynamics
PDPN	Painful Diabetic Peripheral Neuropathy
PEG	Pain, Enjoyment, and General activity Scale
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PHQ	Pain Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetics
PP	Platform Protocol
PPI	Protocol Principal Investigator
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	prothrombin time test
QOL	Quality of Life
QTcF	QT interval correction using Fridericia's formula
RBM	Risk Based Monitoring
RBMP	Risk-Based Monitoring Plan
RBQM	Risk-Based Quality Monitoring

SAE	Serious Adverse Event
SB	Single-Blind
SBPWOP	Single-Blind-Placebo-Washout-Phase
SF	Short Form
SF-12	Short Form 12 Questions
SMQ	Standard MedDRA Query
SNRI	Selective Norepinephrine Reuptake Inhibitor
SOE	Schedule of Events
SSRI	Selective Serotonin Reuptake Inhibitor
TAPS	Tobacco, Alcohol, Prescription Medication, and other Substance Use Tool
TCA	Tricyclic Antidepressants
TCNS	Toronto Clinical Neuropathy Score
TEAE	Treatment-Emergent Adverse Event
Tmax	Absorption
TRPA	Transient Receptor Potential channels
UENS	Utah Early Neuropathy Scale
V[#]	Visit [#]
VAS	Visual Analog Scale
WAP	Weekly Average Pain, defined as the mean over a 7-day period of the ratings on the “average daily pain” on NRS
WWP	Weekly Worst Pain, defined as the mean over a 7-day period of the ratings on the “worst daily pain” on NRS
µg	Microgram
µM	Micrometer

1.5 Statement of Compliance

This study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements, including the United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

2. ISA Introduction and Overview

2.1 ISA Introduction

This is the confidential **FULL VERSION** of this ISA to include a blinded Appendix B, to enhance blinding to participating sites. This ISA describes a double-blind Phase II study of the PK/PD,

safety, tolerability, and effect of 12 weeks of NRD135S.E1 (80mg/day) as an ISA within the context of the Platform Protocol to Assess Treatments for Painful Diabetic Peripheral Neuropathy, EN21-PP. The ISA is intended to be read and interpreted within the context of the Platform Protocol and focuses on the description of design features that are specific to NRD135S.E1. While it is not the goal of this study to identify the target of NRD135S.E1, this trial also provides an opportunity to collect clinical samples that could be used to identify or rule out potential targets.

This study is part of Early-Phase Pain Investigator Clinical Network (EPPIC-Net), under The Helping to End Addiction Long-term[SM] Initiative, or NIH HEAL Initiative[SM].

2.2 Sample Size

122 adult participants (18 years and older) with PDPN are expected to be randomized.

2.3 Overview

Key features of this ISA that are necessary to understand its conduct within the Platform Protocol include:

- 12-week parallel-group design with 1:1 randomization to NRD135S.E1 80mg/day administered in the morning orally versus matching placebo.
- Monitoring during the first week of investigational product (IP) administration will include on-site monitored administration of the first dose and one in-person safety visit, followed by the standard follow-up visit structure (i.e. full in-person follow-up visit every 4 weeks).
- A one-week single-blind placebo washout period (considered a withdrawal phase) after the 12 weeks of double-blind treatment to assess for withdrawal symptoms.

2.4 Terminology

- **Double-Blind treatment phase (DB, 12 weeks)** starts at IP Initiation (V3), where neither the participant nor the study team are aware of the treatment arm assigned.
- **End of the Double-Blind treatment phase (EoDB)** is reached on the morning of Visit 8 (V8; Day 84), i.e., the day after the last dose of DB study treatment, or earlier in the case of premature treatment discontinuation.
- **Single-Blind Placebo WashOut Phase (SBPWOP)** starts at the EoDB (V8) with the first dose of placebo treatment after DB and lasts ~7 days, where the participant is unaware of the treatment arm, but the study team knows the assignment is placebo.
- **End of Treatment** (**EoT**) is reached after all assessments have been performed on the day of V9 or completion of an Early Termination (ET) visit.
- **Safety Follow-Up phase** starts at EoDB and lasts 30 days.
- **End of Study** (**EoS**) is defined as the end of participation, either from Early Termination (ET) or completion of the V10 safety follow-up telephone call.

- **"Weekly average pain" (WAP)**, defined as the mean over fixed 7-day periods (anchored to the first day of DB treatment) of the NRS for "average pain during the past 24 hours."
- **"Weekly worst pain" (WWP)**, defined as the mean over fixed 7-day periods (anchored to the first day of DB treatment) of the NRS for "worst pain during the past 24 hours."

2.5 ISA-Specific Assessments/Endpoints

In addition to the measures specified by the Platform Protocol, this ISA adds:

- Patient-Reported Outcome Measures
  - Daily Sleep Interference Score (DSIS), an 11-point pain NRS querying how pain has interfered with sleep
  - Visual Analog Scale (VAS) for average pain over the prior 24 hours
  - Brief Pain Inventory Short Form (BPI-SF), interference items only
  - Clinician Global Impression of Change (CGIC)
  - Short Form 12 (SF-12)
  - Neuropathy Pain Symptom Inventory (NPSI)
  - Insomnia Severity Index (ISI)
- Pharmacokinetic
  - Sparse PK Collection

2.6 ISA-Specific Features of the Study Population

- In addition to the criteria specified in the Platform Protocol, this ISA targets patients with moderate to severe PDPN who are willing to refrain from the use of other pain medications during the trial.
- To date, no embryo-fetal development studies have been completed. Therefore, women of childbearing potential must agree to practice an effective form of **two** types of birth control to be included in the trial.

3. DESCRIPTION OF THE ASSET

3.1 Introduction to NRD135S.E1

The identification of NRD135S.E1 as a potential treatment for moderate to severe painful diabetic peripheral neuropathy (PDPN) is a true "bedside-to-bench" story in modern-day translational medicine. NRD135S.E1 is a fully synthetic derivative of a bacterium that grows on a plant, traditionally used to brew tea to treat a variety of indications, including pain, in a village in Siberia. It has been optimized for its anti-nociceptive effects in multiple animal models of acute and chronic pain, including in the Chung spinal nerve ligation and the streptozotocin-induced diabetic

neuropathic pain models in rats. While the activity of NRD135S.E1 has been extensively studied, its molecular target is not known, though it does not appear to work through any of the opioid receptors or molecular pathways currently targeted by available analgesics. The best evidence suggests it may act, at least in part, through modulating the Lyn kinase signaling pathway.

In clinical studies, NRD135S.E1 has been well tolerated at all dose levels tested in single-dose (up to 1,200 mg) and repeat-dose regimens (up to 300 mg/day over 5 days or 150 mg over 3 weeks), and it has been shown to have predictable pharmacokinetics with dose-dependent increases in exposure. A dose range-finding Phase 2a study was conducted, in which 88 patients with established diabetic neuropathy (DNP) were administered daily oral doses of NRD135S.E1 or placebo for 21 days. NRD135S.E1 showed clinically relevant benefit at 40 and 150 mg/day, the 2 highest doses administered, based on the primary efficacy readout of improved pain scores, as assessed by the 11-point pain numerical rating scale (NRS).

3.2 Non-Clinical Data

3.2.1 Preclinical Pharmacology and Mechanism of Action

NRD135S.E1 showed dose-dependent anti-nociceptive effects in animal models (mouse and rat) for both acute and persistent pain, including tail-flick (acute thermal pain), hot plate (acute thermal pain), Chung's spinal nerve ligation (compression neuropathic pain), and streptozotocin-induced painful neuropathy (diabetic neuropathic pain) models.

The exact mechanism of action and the binding target of NRD135S.E1 is currently not elucidated. NRD135S.E1 does not appear to act directly through any of the mechanisms, receptors, enzymes, or channels known to be associated with pain, such as opioid receptors (mu, delta 2, kappa 1), proteins related to serotonin and norepinephrine reuptake, GABA receptors, NMDA receptors, voltage-gated ion channels (Ca^{2+} and K^{+}, Na^{+}), Transient Receptor Potential channels (e.g., TRPA1-ankyrin ion channels), or receptors for acetylcholine (M1), dopamine or cannabinoids.

In the U87 glioblastoma cell line, it was shown that phosphorylation of Lyn was modified upon treatment with NRD135S.E1 and that these effects were independent of changes in Lyn protein. Lyn kinase signaling is involved in the regulation of P2X4 receptors in pain pathways [Tsuda 2012].

A full summary of the nonclinical pharmacology work can be found in the Investigator's Brochure (IB) [NRD135S.E1 IB].

3.2.2 Drug Metabolism and Pharmacokinetics

In rats and dogs, oral absorption was rapid, exposure increased with increasing dose, either dose-proportionally or in some cases sub-proportionally, and accumulation over time was minimal. The percentage of NRD135S.E1 bound to plasma proteins in humans was 68.7%.

NRD135S.E1 is extensively metabolized before leaving the body. The metabolic products formed are mainly glucuronides of the parent compound.

In a mass balance study in rats, NRD135S.E1-related radioactivity was fully recovered in the urine (39%) and feces (58%) mostly in the form of its metabolites. No binding to melanin-rich tissues occurred.

The oral bioavailability of NRD135S.E1 in animals was incomplete (11–40%) and NRD135S.E1 distributed substantially into tissues, with the highest concentrations found in the stomach, intestine, kidney structures, liver, and bladder wall. NRD135S.E1 is rapidly eliminated in the rat and dog (half-life of 2–5 hours).

In vitro studies were conducted to assess the interaction potential of NRD135S.E1:

- CYP3A4 is the dominant oxidation among the CYP isozymes enzyme metabolizing NRD135S.E1;
- NRD135S.E1 has been determined to be a substrate of P-glycoprotein (P-gp);
- Some potential for induction of CYP3A4 has been shown in human hepatocyte studies;
- NRD135S.E1 inhibited probe substrate transport within relevant concentration ranges set by regulators only with OCT1 – based on the level of inhibition seen, the interaction is expected to be minor.

In vivo and *in vitro* comparison studies of rat, dog and human samples show no evidence of human-specific metabolites.

More detailed information can be found in the Investigator Brochure (IB) [NRD135S.E1 IB].

3.2.3 Toxicology

The current toxicology program includes toxicity studies of up to 13 weeks in rats and dogs. In addition, *in vitro* genotoxicity studies were also conducted.

NRD135S.E1 showed an excellent safety profile in rat and dog safety pharmacology and 3-week and 13-week toxicity, fertility, and embryonic development studies. Both the parental no-observed-adverse-effect level (NOAEL) and the NOAEL for pairing, mating, and fertility performances were considered to be 1000 mg/kg/day, based on the absence of adverse findings at this dose level. NRD135S.E1 did not induce any adverse changes in fertility or early embryonic development study performed in rats assessing dose levels of 100, 300, or 1000 mg/kg/day. No test item-related deaths occurred. In the safety pharmacology in Beagle dogs, no effects on arterial blood pressure, heart rate, and electrocardiography (ECG) were noted after administration of NRD135S.E1 at doses of 6 and 60 mg/kg. At 600 mg/kg, a transient and reversible increase in both systolic and diastolic blood pressure accompanied by a compensatory decrease in heart rate was observed from 0.5–1 hour after dosing only. At 30 µM, NRD135S.E1 did not affect human hERG (ether-à-go-go-related gene) tail currents *in vitro*. No changes in respiratory parameters

related to NRD135S.E1 administration were noted in rats treated with up to 500 mg/kg (highest concentration tested).

NRD135S.E1 was well tolerated up to the highest dose tested in rats (1000 mg/kg/day) and dogs (500 mg/kg/day) with no treatment-related changes after 13 weeks of oral treatment. In each case, the highest dose was considered the NOAEL. In addition, in the rat 13-week toxicity study the stages of spermatogenesis were assessed by histopathology and the morphology, number, and motility of testicular and epididymal sperm. There were no effects on any of the measured parameters up to the highest dose of 1000 mg/kg, indicating that NRD135S.E1 treatment does not affect sperm development number, morphology, or motility.

Based on the exposure (C_{max}) in the male rat at the NOAEL of the 13-week toxicity study, the minimal safety margin to a human dose of 80 mg is 190-fold.

NRD135S.E1 showed no genotoxic potential in bacterial mutagenicity or Chinese hamster ovary cell clastogenicity assays *in vitro* or in a micronucleus assay following oral administration to rats.

To date, no embryo-fetal development studies have been completed. Therefore, women of childbearing potential will have to agree to practice an effective form of **two** types of birth control to be included in the trial. Overall, the nonclinical safety and toxicology data support the conduct of clinical studies for up to a 13-week duration in males and females of non-childbearing potential.

A full summary of the development work is provided in the current version of the IB [NRD135S.E1 IB].

3.3 Clinical Studies

To date, 154 participants (68 healthy volunteers and 86 participants with DNP) have been enrolled in the NRD135S.E1 clinical program. 122 participants (57 healthy volunteers and 65 participants with PDPN) have received at least one dose of NRD135S.E1 and 32 have received placebo. Maximum doses tested were up to 1200 mg/day in single-ascending dose (NRD135S.E1-101), 300 mg/day in multiple doses (NRD135S.E1-102) for 5 days, and 150 mg/day in Phase 2 in DNP for 3 weeks (NRD135S.E1-201).

The human clinical experience with NRD135S.E1 consists of four Phase 1 studies and one Phase 2 study. The following Phase 1 studies were conducted:

- NRD135S.E1-101 was a single ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK) of oral doses of 300, 600, 900, or 1200 mg NRD135S.E1 (or matching placebo) in adult young healthy male participants (N = 32, 8 participants per cohort randomized 3:1) [NRD135S.E1-101].
- NRD135S.E1-102 was a single-center, randomized, double-blind, placebo-controlled, multiple-administration study in healthy adult male participants (9 active and 3 placebo) to evaluate the safety, tolerability, and PK of repeated daily doses of 300 mg NRD135S.E1 administered over 5 days [NRD135S.E1-102].

- NRD135S.E1-103 was a single-center, open-label, randomized (order of treatments), balanced, 2-period, 2-sequence, single-dose cross-over study with administration under fed and fasting conditions. The study was conducted to evaluate the impact of food on the PK characteristics of a single 40-mg dose of NRD135S.E1 in 16 healthy male and female participants [NRD135S.E1-103].
- Study **Error! Reference source not found.** (N = 8) determined single and multiple doses PK of once-daily 80 mg NRD135S.E1 capsule and evaluated the routes/rates of elimination and mass balance recovery after a single oral dose of [^{14}C]-NRD135S.E1 under condition of steady-state exposure to unlabeled NRD135S.E1. Healthy male subjects (30-65 years) received an oral dose of NRD135S.E1 80 mg capsule once daily for 13 days in the morning following a standard breakfast. On Day 7, subjects additionally received a single oral dose of [^{14}C]-NRD135S.E1 in solution (24.35g solution containing 1.61 mg [^{14}C]-NRD135S.E1 in 30% ethanol) administered 30 min after the regular dose of NRD135S.E1 80 mg capsule.

The Phase 1 studies showed that following oral administration NRD135S.E1 PK are characterized by a rapid absorption into the systemic circulation (T_{max} up to 1 hour) followed by the rapid disappearance of the drug as a consequence of distribution to peripheral compartments, or elimination. Thereafter, 6 hours or more after dosing, slower elimination was seen, with secondary peaks in the concentration-time curves, most likely resulting from entero-hepatic recirculation of parent drug and/or metabolites [NRD135S.E1-101, -102, -103, -104].

NRD135S.E1 does not accumulate substantially over the 5 days of dosing (31% increase in AUC_{0-t}) [NRD135S.E1-102 and -104].

When NRD135S.E1 was given with food, the absorption rate decreased as indicated by longer times needed to reach peak concentrations (median T_{max} fasted 0.75 hours, fed 1.50 hours). Mean exposure at maximum plasma concentrations, represented by geometric mean C_{max} values, was about 25% lower under fed conditions. The extent of absorption based on AUC_{0-inf} increased on average by 41% under fed conditions [NRD135S.E1-103]. Variability in absorption parameters (AUC_{0-inf}, $AUC_{0-tlast}$, C_{max}) was similar when NRD135S.E1 was administered with food or without food.

Following a single oral dose of [^{14}C]-NRD135S.E1 in form of a solution, given on Day 7 of the multiple dosing scheme on top of the daily 80-mg capsule dose (steady state), an average of 94.5% of the radioactivity administered was recovered in excreta over a 168 h sampling period with over 74% of the dose already excreted within the first 24h. The majority of TR (81.7% [range 71.4% to 85.8%]) was recovered in the urine, indicating that the drug was well taken up from the gastrointestinal tract into the portal blood and drug-related material then cleared from the systemic blood circulation preferentially by the renal route.

In these four studies, the compound was well tolerated up to and including the dose level of 1200 mg.

Additional details about the PK characteristics and tolerability can be found in the IB.

The phase 2 study (NRD135S.E1-201) was a multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group, proof-of-concept, and dose-finding study of 3 weeks in adults with moderate to severe DNP [NRD135S.E1-201].

After screening and a 1-week treatment-free wash-out period, 88 participants were randomized to NRD135S.E1 10, 40, and 150 mg/day or placebo (1:1:1:1) and underwent a 1 week single-blind (SB) placebo run-in, in an effort to reduce the placebo effect. 86 participants started DB treatment, 21 participants received placebo and, overall, 65 participants received NRD135S.E1 (22, 22, and 21 at 10, 40, and 150 mg/day, respectively), administered once a day in the morning. 80 completed the 3 weeks of DB study treatment.

The main analysis was the change from baseline week to Week 3 in the weekly mean of daily average pain intensity as measured on a numerical rating scale (NRS; an 11-point scale used for participants to self-report pain ranging from 0 “no pain” to 10 “pain as bad as you can imagine”). Two different baselines were used for the analysis: the SB placebo baseline (primary endpoint) and the wash-out baseline (*post hoc*; to allow comparison of the results with published data). The mean placebo-corrected treatment effects from the SB placebo baseline were 0.82 and 0.66 NRS points for the 40 and the 150 mg/day group, respectively, and from the wash-out, the baseline was 1.46 and 1.20 NRS points for the 40 and the 150 mg/day group, respectively.

The efficacy results suggest a clinically relevant reduction of neuropathic pain in participants with DNP treated with a daily dose of 40 or 150 mg/day of NRD135S.E1.

The compound was well tolerated during DB treatment, treatment-emergent adverse events (TEAEs) were reported for 12 (54.5%), 11 (50.0%), and 9 (42.9%) participants on NRD135S.E1 10, 40, and 150 mg/day, respectively, and for 7 (33.3%) participants on placebo. No severe TEAEs were reported. Most of the TEAEs were mild (8/12, 10/11, and 8/9 events on NRD135S.E1 10, 40, and 150 mg/day, respectively, and 6/7 on placebo). Headache was the only TEAE that was more frequent on NRD135S.E1 than placebo (1 [4.5%], 3 [13.6%], and 4 [19.0%] participants on NRD135S.E1 10, 40, and 150 mg/day, respectively, and 1 [4.8%] patient on placebo), and appeared to be possibly dose-related.

No deaths occurred, and the only serious adverse event (SAE; exacerbated chronic obstructive pulmonary disease) occurred during SB placebo treatment.

Most changes in clinical laboratory tests, vital signs, body temperature, ECG parameters, and physical examination findings were small, not clinically relevant, and did not appear related to NRD135S.E1 treatment or dose.

Overall, the study results suggest that a once-daily dose of NRD135S.E1 between 40 and 150 mg/day can induce a clinically relevant reduction in pain and is well tolerated in participants with PDPN.

A detailed summary of the clinical study’s results is provided in the current version of the IB [NRD135S.E1 IB].

4. PURPOSE AND RATIONALE FOR THE STUDY

4.1 Purpose of the Study

The purpose of this study is to investigate the safety and efficacy of the current hard gelatin capsule formulation of NRD135S.E1 80 mg once daily in the treatment of PDPN when administered for 12 weeks.

4.2 Study Rationale

Preliminary data (study NRD135S.1-201) suggests that NRD135S.E1 may be associated with a clinically significant change in pain ratings among participants with moderate to severe PDPN after 3 weeks of treatment with daily doses of 40 mg and 150 mg. Further details are supplied in the Investigational New Drug (IND) 143676, which will be available upon request.

Since PDPN is a chronic indication, it is important to clarify whether longer administration (i.e., 12 weeks) of NRD135S.E1 will provide sustained efficacy.

At the time of writing of the original version of this protocol, three oral drug products had been used in the three Phase 1 studies (NRD135S.E1-101, -102, -103) and the dose-finding Phase 2 study (NRD135S.E1-201). An oral suspension of NRD135S.E1 was administered in study NRD135S.E1-101 (single doses 300, 600, 900, and 1200 mg). Hard gelatin capsules manufactured by Quay Pharmaceuticals Ltd were given in studies NRD135S.E1-102 (multiple dosing 300 mg daily) and NRD135S.E1-201 (multiple dosing 10, 40, and 150 mg daily). These capsules contained a dry powder mix, which is filled semi-automatically. Since this is a challenging process (leading to, for example, potential loss of material during the filling process, potential non-conformity of the filled capsule, etc.) it was decided to develop a new drug product formulation. The goals of the development were: immediate-release formulation, a similar mass of capsules at different dosage strengths, and capsule size 1.

In a food interaction study (NRD135S.E1-103), this 40-mg hard gelatin capsule (current formulation, manufactured by HWI Development GmbH) was administered. The active pharmaceutical ingredient (API) used for the manufacturing of the suspension (administered in study NRD135S.E1-101) and the gelatin capsules (administered in studies NRD135S.E1-102 and -201) was manufactured by Regis Technologies, Inc (Regis). The API used for the 40-mg hard gelatin capsules administered in NRD135S.E1-103, and the capsules proposed for the current study, was manufactured by Dr. Reddy's Laboratories Ltd. (DRL).

To bridge between studies, the magnitude of potential differences in exposure to NRD135S.E1 generated by the different drug products was estimated by model-based methods. Even though concentrations were not measured in study NRD135S.E1-201, likely exposure in that study at the 150-mg dose could be estimated from information derived from the Phase 1 studies NRD135S.E1-101 and NRD135S.E1-102.

The cross-study comparison showed that there are differences in dose-normalized exposure (AUC) when NRD135S.E1 is given in the form of the different drug products. The various models applied predicted exposures for a 40-mg dose of both formulations (suspension or capsule) based on Regis-manufactured API that was consistently within a two-fold band around the exposure actually observed after administration of 40 mg NRD135S.E1 of the current capsule formulation, containing API manufactured by DRL.

Based on this, a daily dose of 80 mg NRD135S.E1 given in form of the current capsule, is expected to produce at the minimum an AUC equivalent to the one achieved by the 40mg daily dose in study NRD135S.E1-201, and at the maximum an AUC not exceeding the one achieved at the highest dose level (150 mg o.d.) in study NRD135S.E1-201.

In study NRD135S.E1-103, an effect of food on the rate and extent of NRD135S.E1 absorption into the systemic circulation could not be excluded. Absorption after fed administration resulted in lower peak concentrations after fed administration (geometric mean 16.4 µg/L [13.9, 19.2 µg/L]) compared with fasted administration (21.2 µg/L [90% CI 17.0, 26.5 µg/L]). The extent of absorption based on $AUC_{0\text{-}inf}$ increased with food on average by 41% [28.07%, 54.52%].

C_{max} values after an 80-mg dose given under fed conditions are expected to remain below the values which had been achieved at the 150-mg dose in study NRD135S.E1-201.

Thus, since in study NRD135S.E1-201 both the 40-mg and 150-mg daily doses induced a clinically significant reduction in pain, an 80-mg daily dose of the current formulation is expected to be well tolerated and to induce a relevant therapeutic effect.

5. STUDY DESIGN

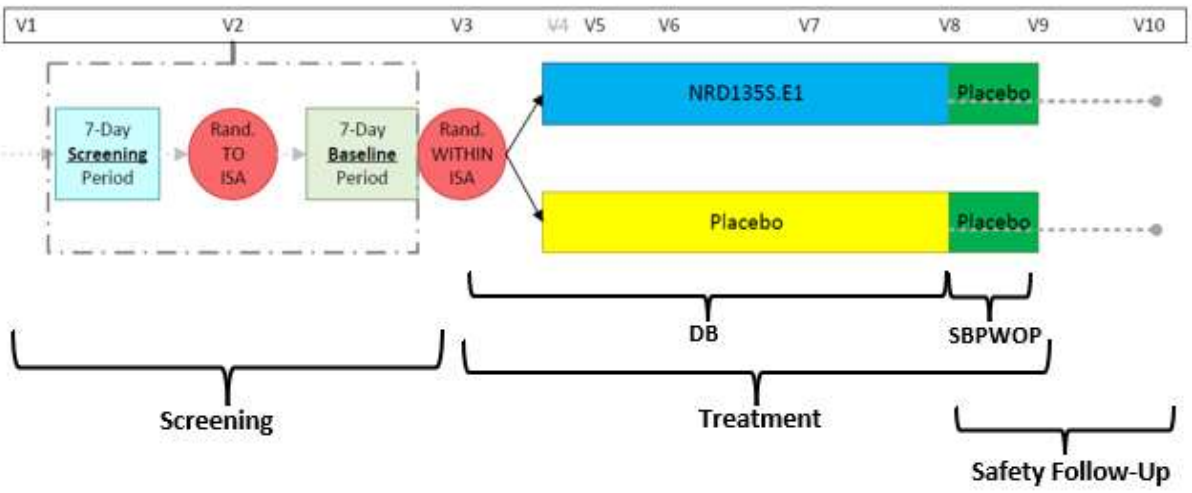
The study will evaluate the safety and efficacy of an oral daily dose of 80 mg NRD135S.E1 for the treatment of confirmed moderate to severe PDPN. The study will also evaluate the potential for a rebound effect of NRD135S.E1 in pain and withdrawal symptoms after IP discontinuation during the SBPWOP period.

In accordance with guidance from the US Food and Drug Administration (FDA) and the European Medicines Agency, a randomized, double-blind, placebo-controlled study design is considered the standard method of determining efficacy in the reduction of neuropathic pain. A treatment duration of 12 weeks is required for the assessment of treatment response and registration in chronic pain conditions. A placebo-controlled design is considered essential as placebo-associated improvements are common in studies in chronic pain (Dworkin et al., 2010). In order to include a placebo group, all participants are allowed to use acetaminophen as needed up to a maximum of 3 g/day.

This study is an interventional, prospective, parallel-group, multicenter, randomized, double-blind, placebo-controlled, Phase 2 study.

The study consists of a screening phase (up to 60 days) which includes a defined 7-day screening period and a defined 7-day baseline period, a double-blind treatment phase (up to 12 weeks), a single-blind placebo washout phase (~1 week), and a safety follow-up phase (~30 days from the end of the double-blind treatment phase) as shown in Figure 1.

Figure 1: Study Design



6. STUDY OBJECTIVES

Common objectives and endpoints are described in the Platform Protocol. This section describes objectives and endpoints specific to this ISA.

6.1 Primary Objective

To demonstrate that NRD135S.E1 80 mg daily is superior to placebo in relieving neuropathic pain associated with PDPN, after 12 weeks' treatment.

6.1.1 Primary Efficacy Endpoint

Change from Baseline to Week 12 in the weekly mean of the daily 24-hour average pain measured by NRS (abbreviated herein as WAP for weekly average pain).

6.1.2 Secondary Efficacy Endpoints

a) Occurrence of 30% reduction of WAP from Baseline to Week 12.

b) Occurrence of 50% reduction of WAP from Baseline to Week 12.

6.2 Safety Objectives

To assess the safety and tolerability of oral administration of NRD135S.E1 80mg/daily in participants with PDPN.

6.2.1 Primary Safety Endpoint

The frequency (i.e. number of participants) with treatment emergent adverse events (TEAEs) reported in the time period defined by first administration of IP (V3) until ~7 days after the last dose of DB IP (EoDB), i.e., the V3/Initiation of IP visit through the V9/Withdrawal Check or ET visit.

6.2.2 Additional Safety Endpoints

1. The frequency during the screening period of:
   a. AEs
   b. SAEs
   c. AEs leading to discontinuation
   d. ECG abnormalities
   e. Marked Laboratory Abnormalities (MLAs)

2. The frequency during the DB treatment periods of:
   a. TEAEs
   b. SAEs
   c. AEs leading to discontinuation
   d. Treatment-emergent ECG abnormalities
   e. Treatment-emergent MLAs

3. The frequency during the SBPWOP of:
   a. TEAEs
   b. SAEs
   c. AEs leading to discontinuation
   d. Treatment-emergent ECG abnormalities
   e. Treatment-emergent MLAs

4. The frequency during safety follow-up of:
   a. Occurrence of SAEs

5. Change from Baseline to the last value and change from Baseline to the worst value (defined as the value resulting in the largest unfavorable change from Baseline) up to and including EoDB and EoT in:
   a. MNSI
   b. Vital signs (systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature)
   c. Body weight

d. ECG parameters
e. Laboratory variables

6. For the C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior during the study will be tabulated.

6.3 Exploratory Objectives

6.3.1 Objectives Related to Platform Protocol Outcome Measures

1. To assess the effect of NRD135S.E1 in comparison to placebo with respect to NIH HEAL Initiative Common Data Elements (CDEs):
    a. Pain, Enjoyment, and General activity Scale (PEG),
    b. Pain Catastrophizing Scale – Short Form 6 (PCS-SF6),
    c. PROMIS Physical Functioning Short-Form 6b,
    d. Patient Health Questionnaire (PHQ-2),
    e. General Anxiety Disorder – 2 item Scale (GAD-2),
    f. Patient Global Impression of Change (PGIC),
    g. Tobacco, Alcohol Prescription Medication Scale (TAPS 1),
    h. Sleep Duration Scale,
    i. PROMIS Sleep Disturbance – 6a,
    j. Opioid Use Questionnaire (OUQ).
2. To assess the effect of NRD135S.E1 in comparison to placebo with respect to secondary outcome measures defined by the platform protocol:
    a. Utah Early Neuropathy Scale (UENS),
    b. Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL-DN),
    c. Michigan Neuropathy Screening Instrument (MNSI).

6.3.2 Objectives Related to Daily NRS at Different Time Points During the Study

3. Compare NRD135S.E1 and placebo in terms of:
    a. The change from Baseline to all study weeks until Week 12 and to the end of SBPWOP with respect to WAP and WWP.
    b. The change from the last 7 days of DB treatment to SBPWOP with respect to WAP and WWP.
    c. The occurrence of 30% and 50% reduction from Baseline at all study weeks for WAP.
    d. The time from the start of DB to the:
        i. First occurrence of a week with 30% and 50% reduction for WAP from Baseline

ii. Confirmed occurrence (i.e., next week's WAP mean being smaller or equal confirms reduction)

iii. Sustained occurrence (if confirmed and still present at Week 12).

iv. Additionally, a cumulative display of the percent pain reduction each week will be generated for both arms.

6.3.3 Objectives Related to the Use of Rescue and Prohibited Medication

4. To compare the use of rescue medication in the NRD135S.E1 and placebo arms in terms of:
    a. Average rescue analgesic consumption by week from Baseline till EoT.
    b. The change from Baseline to all study weeks until Week 12 and to SBPWOP with respect to weekly consumption of rescue analgesic (i.e., total mg of acetaminophen taken per week).
    c. The change from Week 12 to SBPWOP with respect to weekly consumption of rescue analgesic (i.e., total mg of acetaminophen taken per week).
    d. Time to first intake of rescue medication and/or prohibited pain medication (see list of prohibited pain medications) during Weeks 1-12 and SBPWOP separately.
    e. Frequency of any use of rescue medication and/or prohibited pain medication (see list of prohibited pain medications) during Weeks 1-12 and SBPWOP separately.
5. To evaluate the natural direct and indirect effect of NRD135S.E1 on the primary endpoint while considering the use of rescue medication as a mediator.

6.3.4 Objectives Related to ISA-Specific Patient-Reported Outcome Measures

6. Compare NRD135S.E1 and placebo in terms of change from the start of DB to EoDB, start of DB to EoT, and EoDB to EoT in:
    a. 24-hour average pain measured by Visual Analog Scale (VAS),
    b. Neuropathic Pain Symptom Inventory (NPSI),
    c. Brief Pain Inventory – Short Form (BPI-SF) scores (interference items only),
    d. Short form-12 (SF-12)
7. Compare NRD135S.E1 and placebo in terms of change from start of DB to EoDB and to EoT in Insomnia Severity Index (ISI).
8. Compare NRD135S.E1 and placebo in terms of change from Baseline period to last 7 days of DB and to last 7 days of SBPWOP, and from last 7 days of DB to last 7 days of SBPWOP in weekly mean of Daily Sleep Interference Score (DSIS).

9. Compare NRD135S.E1 and placebo in terms of change in Clinician Global Impression of Change (CGIC) at EoDB.

6.3.5 Objectives Related to Withdrawal Symptoms

10. To summarize AEs suggestive of "drug abuse, dependence and withdrawal" using a Standard MedDRA Query (SMQ) for each treatment arm.
11. To evaluate the presence of withdrawal symptoms and rebound effects after abrupt interruption of NRD135S.E1 by comparing NRD135S.E1 and placebo in terms of:
    a. Change of WAP from the Baseline to SBPWOP.
    b. Change of WAP from last 7 days of DB to SBPWOP.
    c. Discontinuation Emergent Signs and Symptoms (DESS-43) score at V9.

6.3.6 Other Objectives

12. To compare NRD135S.E1 to placebo on the 11-point likability scale (0-10).
13. To evaluate and compare the course of symptom severity throughout the 12-week double-blind period for NRD135S.E1 and placebo in terms of longitudinal trajectories.
14. Explore sociodemographic and clinical predictors of response to NRD135S.E1.
15. Characterize activity levels and sleep patterns in participants with PDPN treated with NRD135S.E1 compared to a placebo using actigraphy measures.
16. Characterize the impact of heterogeneity based on pre-trial treatment and pre-trial responsiveness to PDPN medications on the outcome measures.
17. Subgroup analysis to examine the impact of changing in the inclusion criterion for baseline WAP on the primary efficacy WAP outcome for the subgroup of participants whose WAP is 5 or above.

6.4 Pharmacokinetics (PK) Objectives

6.4.1 Sparse PK

The PK objectives are:

- To evaluate the PK of NRD135S.E1 in participants with PDPN.
- To explore the relationship between exposure (concentration of NRD135S.E1) and safety.
- To explore the relationship between exposure (concentration of NRD135S.E1) and pharmacodynamics (PD).

Left-over plasma samples may be used for preliminary NRD135S.E1 metabolite assessment. Results of this preliminary metabolite assessment, if any, will be reported in a separate Research Report.

6.5 Study Population

The study population will consist of adult and elderly participants with moderate to severe PDPN. Vulnerable participants are not eligible since the study can be carried out in a non-vulnerable group of participants and no particular benefit has been anticipated for vulnerable participants which would be different from that in the general population. This protocol is intended for patients with moderate to severe PDPN who are willing to refrain from the use of other pain medications, except acetaminophen, during the trial.

The study will enroll 122 participants. It is expected that approximately 305 participants will need to be screened in order to achieve enrollment of 122. If screen failure rates are higher than projected, enrollment will continue until 122 participants have been randomized.

7. ISA-SPECIFIC INCLUSION AND EXCLUSION CRITERIA

Participants must meet all of the Platform Protocol inclusion criteria and none of the Platform Protocol exclusion criteria. Additional ISA-specific inclusion and exclusion criteria follow.

7.1 ISA-Specific Inclusion Criteria

(To be used in conjunction with Platform Protocol criteria; note, some ISA criteria may be more stringent than Platform criteria; always follow the more stringent criteria when determining eligibility.)

1. Provides written consent for the EN21-01 ISA. Legally Authorized Representatives (LARs) are not allowed, but impartial witnesses may be utilized as needed for visually impaired participants.
2. Patient-reported daily 11-point NRS (for average pain over the last 24 hours) meets the criteria specified in "Appendix B: Blinded Information" during both the 7-day screening and 7-day baseline periods. The algorithm will be assessed centrally.

Waivers to the inclusion criteria will not be allowed.

7.2 ISA-Specific Exclusion Criteria

(To be used in conjunction with Platform Protocol criteria; note, some ISA criteria may be more stringent than Platform criteria; always follow the more stringent criteria when determining eligibility.)

Participants fulfilling any of the following criteria are not eligible for the study.

1. Diagnosis of alcohol or substance abuse or dependence (other than nicotine or caffeine) within the 2 years before the Screening visit. ***This criterion is more stringent than a related Platform Protocol criterion.***
2. Moderate or severe renal impairment, known (documented) or defined as an estimated/calculated creatinine clearance/estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, according to the Chronic Kidney Disease Epidemiology Collaboration formula during the screening process. ***This criterion is more stringent than a related Platform Protocol criterion.***
3. Any of the following conditions related to corrected QT intervals using Fridericia's formula (QTcF):
    a. A QTcF > 500 ms prior to starting IP, up to and including the V3 pre-dose ECG.
    b. A history of the following additional risk factors for torsade de pointes: heart failure, hypokalemia, history or family history of long QT syndrome.
4. History of myocardial infarction, other clinically active significant heart disease, or stroke. ***This criterion is more stringent than a related Platform Protocol criterion.***
5. Participants known to have participated in four or more studies for investigational pain drugs.
6. Participants known to be non-responders to more than three previous neuropathic pain medications at adequate doses over at least 4 weeks. Adequate doses (given as total daily doses) are defined as follows: 1,800 mg gabapentin; 300 mg pregabalin; opioid analgesics 60 mg oxycodone equivalent or 200 mg tramadol; 75 mg amitriptyline or equivalent tricyclic antidepressant; 60 mg duloxetine; 150 mg venlafaxine.
7. Known hypersensitivity or contraindication to any excipients of the study drug formulation.
8. Taking prohibited medications as described in Appendix A, "Prohibited Medications."
9. Major depressive episode within the 6 months before screening and/or a history of diagnosed recurrent major depressive disorder within two years. Any of the following conditions related to suicidality:
    a) Any suicidal ideation with intent, with or without a plan, at screening, i.e., answering "yes" to questions 4 or 5 on the Suicidal Ideation section of the Baseline/Screening version of the Columbia-Suicide Severity Rating Scale (C-SSRS);
    b) Answering "yes" on any item of the Suicidal Behavior Section (except for the "non-suicidal self-injurious behavior") of the C-SSRS if this behavior occurred in the past 2 years;
    c) A lifetime history of suicide attempt (V1).

10. Previous known or possible exposure to NRD135S.E1.

Waivers to the exclusion criteria will not be allowed.

7.3 Failure to Meet Eligibility Criteria

If a participant fails to meet eligibility criteria for the Platform and/or the ISA, all data captured up until the time of the screen fail should be documented in the appropriate electronic case report forms (eCRFs) and any paper source should be uploaded, including the reason for screen failure.

7.3.1 Platform Protocol Screen Failure

Because Platform Protocol eligibility criteria include activities throughout V1, V2, and V3, it is possible that a research participant is randomized to an ISA, but does not meet one or more of the Platform Protocol inclusion and exclusion criteria (e.g. a positive drug test for cocaine at the V3 Baseline visit).

7.3.2 ISA Failure

Eligibility criteria for this ISA include activities from V1, V2, and V3. Sites should carefully review ISA criteria before randomization to an ISA, completed during V2-step 2, to confirm that no ISA-specific exclusions have already been met based on the data collected during V1 or V2-step 1.

Randomization to an ISA when the participant has already failed to meet inclusion criteria and/or met exclusion criteria for Platform Protocol or ISA eligibility will be considered a protocol deviation.

Please refer to the eCRF Completion Guide and the MOP for screen failure data entry instructions at the Platform and ISA levels.

7.4 Rescreening

SF participants may be eligible to rescreen for the Platform Protocol but not at the ISA level. In order to rescreen, there must be evidence to suggest the prior reason(s) for failure no longer apply, such as the appropriate time has elapsed since use of a prohibited medication.

Rescreening activities are dependent on the reason(s) for failure; expectations and procedures are outlined in the Platform Protocol MOP.

8. RANDOMIZATION

Randomization will be completed in a stepwise fashion, via IXRS:

- Step 1: As part of the Platform Protocol, participants will be randomized **to** an ISA, unblinded.
- Step 2: Once all eligibility criteria have been confirmed for both the Platform Protocol and the ISA, the site may proceed to randomization **within** an ISA (randomization to treatment or placebo).

Randomization to treatment assignment will be blinded from study participants, staff from clinical sites, investigators, asset owner, IND sponsors, and/or designees. This blinding will be accomplished by providing identical investigational product and packaging for the NRD135S.E1 and its corresponding control treatment. The use of IXRS will ensure the blinding is accomplished.

Approximately 122 participants will be randomized in a 1:1 ratio according to a central randomization scheme provided by the Almac centralized web-based Interactive Web Response System (IXRS) to the designated study pharmacist (or qualified designee) to the following treatment groups as follows:

1. NRD135S.E1 80 mg/day
2. Matching placebo

Randomization will be stratified by PDPN severity (moderate vs. severe, based on WAP from the baseline period).

8.1 Re-Randomization to an ISA

Participants that screen fail after having been randomized to an ISA, may be able to randomize to another ISA. If the participant is willing, they may be re-randomized between any other current ISAs for which they appear to be potentially eligible. Once randomized to a different ISA, the participant should be consented for that ISA and complete procedures as outlined in that ISA.

9. STUDY ASSESSMENTS

The initial screening visit will be the same for all Platform Protocol participants since they will not yet have been assigned to a particular ISA. This section describes the ISA-specific procedures to be used in addition to screening procedures from the Platform Protocol. The study assessments are summarized in the Schedule of Events (SOE, Table 1) and described in greater detail in the following sections. For all visits, Medable will be used to record the Patient-Reported Outcome (PRO) scales, study medication use, and rescue medication use. CentrePoint will be used to collect and store actigraphy data. All other data will be entered in the electronic data capture (EDC) system, as appropriate, or transferred to the EPPIC-Net Data Coordinating Center (DCC). This includes, but is not limited to, data collected via analog methods (e.g., ECG, central labs, etc.).

In the event of technical difficulties with completion of eCRFs in TrialMaster and/or Medable during the visit, forms should be completed on paper, and the source should be uploaded to Florence. For participant difficulties with completion of the daily PROs and medication diaries in Medable, the participant should be instructed to notify site staff as soon as possible. All technical

issues with eCRF/diary completion should be reported to the CCC contemporaneously. See ISA MOP for instructions on reporting issues and appropriate source documentation.

- For each identified instance of Study Medication Diary and/or Pain NRS non-compliance for remote daily assessments, e.g., Medable email notifications or compliance email alert is received, the site should complete the Adherence Alert Re-Education task in Medable, see ISA MOP for details.

9.1 Schedule of Events

For clarity, the following table shows the full SOE inclusive of events (e.g. V1) which are performed before the participant is assigned to a particular ISA. The initial screening visit will be the same for all Platform Protocol participants since they will not yet have been assigned to a particular ISA. This section describes the ISA-specific procedures to be used in addition to screening procedures from the Platform Protocol.

Table 1: EN21-01 Schedule of Events

	MODULE 1: Screening, Baseline, and daily procedures				**Please note: Visit 4 has been removed from the study**	**MODULE 2: Early safety assessment ***	**MODULE 3: Full follow-up study visits ****			**MODULE 6: Wash out Single blind placebo wash-out (SBPWOP)**	**MODULE 7: Safety follow-up**
Visit number	Daily reporting [a]	V1	V2 [b]	V3	V4	V5	V6	V7	V8/ET/EoDB	V9/EoT	V10/EOS
Timing	Daily	Single Day Between Days -60 to -8	Period of Variable Duration Days -59 to -1	Day 0		Day 7 (+/- 1 day)	Day 28 (+/- 4 days)	Day 56 (+/- 4 days)	Day 84 (+/- 4 days)	Day 91 (+3 days)	Day 114 (+7 days) [u]
Visit short title	Daily reporting	Initial screening	Additional screening	IP initiation		Early safety	Full follow-up visit (week 4)	Full follow-up visit (week 8)	Full follow-up visit (week 12)	Withdrawal check	Final safety check
In-person (I) or remote (R)	R	I	R	I		I	I	I	I	I	R
General procedures											
Informed consent to PP		X									
Informed Consent to ISA			X	X							
Inclusion/ Exclusion [c]		X	X	X							
Medical History & Demographics [d]		X									
Height, weight [e]		X		X			X	X	X	X	
Vital Signs		X		X [f]		X	X	X	X	X	
Physical examination [g]		X		X			X	X	X	X	
Pregnancy test (if applicable)[t]		X		X			X	X	X	X	
Urine drug test [h, i]		X		X			X	X	X	X	
Urinalysis		X		X			X	X	X	X	

Visit number	Daily reporting [a]	V1	V2 [b]	V3		V5	V6	V7	V8/ET	V9	V10/EOS
Neuropathy screening bloodwork		X							X		
Clinical safety bloodwork		X		X			X	X	X	X	
Collection of EPPIC-Net biomarkers (whole blood, plasma, and stool)[j]		X							X		
12-lead ECG[k]		X		X[f]		X	X	X	X	X	
Medable training [l]		X	X								
Develop/review prohibited medication washout plan (if needed)			X								
Distribute devices to subject (actigraphy and Medable device if needed)		X									
Adverse events			X	X		X	X	X	X	X	X
Prior and Concomitant Medications Review		X	X	X		X	X	X	X	X	X
Rescue Medication Review [a, m]			X								
Randomize to ISA			X								
Randomize within ISA				X							

Visit number	Daily reporting [a]	V1	V2 [b]	V3	V4	V5	V6	V7	V8/ET	V9	V10/EOS
IXRS Drug Dispensing				X			X	X	X		
IP Accountability							X	X	X	X	
IP Use Recording [a, m, o]				X							
	NIH HEAL Initiative CDEs for adults with chronic pain										
PEG				X					X		
PROMIS Physical Functioning short Form 6b				X					X		
PROMIS Sleep Disturbance 6a				X					X		
Sleep Duration				X					X		
Pain Catastrophizing Scale - Short Form 6				X					X		
PHQ-2				X					X		
GAD-2				X					X		
Patient Global Impression of Change (PGIC)							X		X		
Opioid Use (OUQ)				X					X		
TAPS 1				X					X		
	Platform Protocol Patient Measures										
11-point Numeric Rating Scale (NRS) for average daily pain [a, m]			X								

Visit number	Daily reporting [a]	V1	V2	V3	V4	V5	V6	V7	V8/ET	V9	V10/EOS
11-point NRS for worst daily pain [a, m]			X								
Neuropathy exam [p]		X		X			X	X	X		
DN4		X									
Norfolk QOL DN				X			X	X	X		
Actigraphy [q]			X				X	X	X	X	
	Any additional procedures										
11-point likability							X	X	X	X	
C-SSRS [r]		X		X		X	X	X	X	X	
DESS-43										X	
VAS for average pain		X		X			X	X	X	X	
Daily Sleep Interference Score (DSIS) [a, m, s]			X								
PK sample				X			X	X	X		
Brief Pain Inventory (BPI) Short Form (interference items only)				X			X	X	X	X	
Clinician Global Impression of Change (CGIC)							X	X	X		
Short Form-12 (SF-12)				X					X	X	

Visit number	Daily reporting [a]	V1	V2	V3	V4	V5	V6	V7	V8/ET	V9	V10/EOS
Neuropathy Pain Symptom Inventory (NPSI)				X			X	X	X	X	
Insomnia Severity Index (ISI)				X					X	X	
Participant Training on Pain Ratings (Placebo Mitigation)		X									
	Additional EOS items										
Collect actigraphy device										X	
Collect Medable device (if applicable)										X	

*ALL procedures from V4 are no longer required; patients will proceed to V5 after completion of V3. **Modules 4 and 5 (see Platform Protocol SOE) are not applicable to this ISA

Notes:

a. Information to be collected daily via Medable includes: time of IP dose, use/timing of any rescue medication, 11-point NRS for average and worst pain, and DSIS. Daily assessments will not be collected after washout (V9). 4 or more missed daily entries on the same form within a 7-day period is considered a protocol deviation and should be reported as such.

b. V2 is a process (rather than a discrete event) which includes: ensuring that inclusion/exclusion processes are complete and the participant is randomized to this ISA; providing any additional education on reporting via Medable; assuring that any medication washout is proceeding according to plan; establishing when the 7d screening Medable recording periods will begin, and reminding the participant to wear actigraphy watch during the 7d prior to V3.

c. All inclusion/exclusion items (e.g. laboratory values) will not be available at the time of the initial screening visit and so this process of establishing eligibility is noted as an activity which takes place over time to allow flexibility (i.e. more than one column in the table above).

d. Includes information on PDPN diagnosis, prior treatments used, and prior surgical and procedural history to be detailed in the CRF.

e. Height to be captured only at the initial screening visit.

f. During the first administration of IP (V3), vital signs and ECG will be collected pre-dose and every 30 minutes for the first 2 hours after IP administration.

g. Physical exam is comprehensive at screening, baseline (V3), and V8 and may be a brief physical exam at other visits.

h. If any urine drug test is positive for an illicit substance (see Platform Protocol for additional details), the participant cannot continue. This will be a screen fail prior to randomization; after randomization the participant should be withdrawn.

i. If a participant tests positive for prescription opioids or marijuana a "second chance" is given (see Platform Protocol for additional details). If the second test is positive, the participant cannot continue. Specifics based on the visit in which the first positive test occurs are as follows:
   V1: The urine drug screen should be repeated prior to beginning the baseline NRS period. If the second test is positive, this is a screen fail.
   V3: The visit must be stopped. However, the test may be repeated once if there is sufficient time remaining in the screening period. If the second test is positive, this is a screen fail.
   All subsequent visits: The patient should be re-educated. If a subsequent test is positive the patient should be withdrawn.

j. Collected only if the subject has consented. Stool kit to be dispensed, the participant may collect stool at home and mail to the biorepository. Whole blood, plasma and stool to be collected at screening visit; plasma only to be collected at V8.

k. If any single ECG, after the introduction of IP, shows a QTcF > 500ms, two additional replicates should be recorded for central review.

l. Participants will complete the first NRS scales during the screening visit (V1) to ensure they understand how to use the Medable system.

m. The participant will report on this daily and study staff should review periodically and at each visit to confirm consistent reporting.

n. Site staff will prospectively select a single-blinded 7-day period during the screening window (days -60 to -8) to use as the screening NRS. The 7-day period immediately preceding the initiation visit (V3) will be used as the baseline NRS. Participants will complete the first NRS scales during the screening visit (V1) to ensure they understand how to use the Medable system.

o. IP use will not be collected prior to IP introduction (V3) nor after Withdrawal Check (V9) or Early Termination (ET).

p. The neuropathy exam includes the UENS, MNSI (part B), TCNS and mTCNS.

q. For all visits in which actigraphy is marked this indicates that the actigraphy device should be worn for the week prior to the visit. For Baseline (V3), the actigraphy device should be worn in the week leading up to the visit, during the baseline period. Participants should be instructed to wear the actigraphy device for the entire week. However, this will not be considered a protocol deviation if the participant takes it off during the designated weeks.

r. C-SSRS – Baseline/Screening version will be given at screening (V1). The Since Last Visit version will be given at all other visits indicated. If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the participant during the administration of the C-SSRS during the treatment period, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the participant's safety. The site should make all efforts to ensure that the participant is evaluated by a licensed physician (or another qualified individual as required by local institutional policy) before leaving the study site. The clinician will determine whether the participant should remain on the study drug.

s. DSIS collection can begin on the day patients are randomized in IXRS to the EN21-01 ISA.
t. Urine pregnancy tests should only be conducted on persons of childbearing potential (POCBP), as described in the Platform Protocol eligibility.
u. If the participant is an ET, the V10 Safety Follow-Up visit should occur 30 days (+7 window) after V8/ET occurs.

*Visit windows are not cumulative over time

9.2 Visit 1 (V1), Initial Screening

The initial screening visit will be the same for all Platform Protocol participants; see Platform Protocol for details.

9.3 Visit 2 (V2), Additional Remote Screening Process & Collection of Baseline Data

The remote V2 processes will be the same for Step 1 and Step 2 for all Platform Protocol participants; see Platform Protocol for details.

V2, Step 1 – Completion of additional screening items

V2, Step 2 – Assignment to regimen (ISA) and washout if needed

Randomization **to** an ISA should be done at least 7 days prior to randomization **within** an ISA at V3/IP Initiation, but must be completed at least 1 day prior to V3.

- Of note, this ISA **does** prohibit concomitant pain medications (as detailed in Appendix A); participants randomized to this ISA will require washout.
    - Bearing in mind that the maximum time between V1 and V3 is limited to 60 days total, if the participant is taking a medication prohibited by the ISA and the patient wishes to discontinue this medication to participate in the study and it is deemed medically safe to do so, a plan will be developed by a qualified member of the research team (typically a physician) in collaboration with the participant to taper this/these medication(s). It is expected that this scenario will arise mainly with participants taking other medications for neuropathic pain. Acetaminophen (up to 3 grams per day) is permitted as a rescue medication.
    - The participant should be allowed sufficient time for pain to stabilize following washout (if applicable) before moving to the next step. It is up to the investigator to determine that sufficient time has elapsed, and that pain has stabilized (based on the participant's daily reports via Medable).

V2, Step 3 – Schedule and prepare for V3

- Schedule V3 and enter planned date in Medable.
- The 7 days prior to V3 will be designated the *baseline* period, once the planned V3 date has been entered in Medable.
    - Report pain NRS daily – eligibility requires completion on at least 5 of 7 days of the NRS during the baseline period.
        - However, a participant should not be deemed a screen failure if NRS data is missing due to technical issues with proper documentation (see MOP Appendix H. Medable Site Readiness and Troubleshooting Guide) Documentation should be filed clarifying the missing data.

- The participant should also be instructed to wear the actigraphy device during these same 7 days (of the baseline period).
- *Report sleep interference symptoms on the DSIS daily – ISA-specific task*

9.4 Visit 3 (V3), Initiation of DB Treatment Phase

This study visit will focus on obtaining baseline outcome measures and administering the first dose of NRD135S.E1 versus placebo under observation. The participant should be instructed to wear the actigraphy device for the 7 days prior to the visit. Safety and outcome assessments will be performed at this visit. If V3 is interrupted before administration of IP, the visit may be resumed on another day, with written approval from the CCC prior to resuming the visit. Contact the CCC/DCC should this occur for further instruction.

V3, Step 1 – Pre-Dose Procedures

The following procedures will be performed prior to dose administration:

- Completion of the informed consent process for this ISA, including the ISA ICF and ISA post-consent checklist
- Vital signs including weight
- Physical Exam
- Urine Drug Test (see Platform Protocol for specifics regarding specific drugs)
    - If a patient has their first positive urine drug test for prescription opioids or marijuana at V3, the visit must be stopped. However, the test may be repeated once if there is sufficient time remaining in the screening period (maximum 60 days between V1 and V3) to do so and repeat the 7-day baseline NRS period (baseline NRS period is repeated because of concern that the values obtained while on opioids or marijuana would not be representative). If a second urine drug screen is positive, the participant should be marked as a screen failure.
    - If the test is positive for illicit drugs (see Platform Protocol for specific details), the participant is a screen failure.
- Urinalysis
- Urine pregnancy test, if applicable
    - Urine pregnancy tests will only be done on persons of childbearing potential (POCBP).
- Clinical Safety Blood Work
- Baseline PK Collection
- 12-lead ECG (pre-treatment). Note that a QTcF >500ms at this time constitutes a screen failure.

- Review of new and ongoing adverse events
- Review of new and ongoing concomitant medications
- Review of rescue medication use
- NIH HEAL Initiative CDEs for chronic pain.
    - Pain, Enjoyment, and General activity scale (PEG)
    - Pain Catastrophizing Scale – Short Form 6 (PCS-SF6)
    - PROMIS Physical Functioning Short-Form 6b
    - Pain Health Questionnaire (PHQ-2)
    - Generalized Anxiety Disorder – 2 item scale (GAD-2)
    - Tobacco, Alcohol, Prescription medication, and other Substance use Tool (TAPS-1)
    - PROMIS Sleep Disturbance – 6A
    - Sleep Duration Scale
    - Opioid Use Questionnaire (OUQ)
- Visual Analog Scale (VAS) for average pain over prior 24 hours
- Neuropathy examination
- Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL DN)
- C-SSRS – Since Last Visit
- Brief Pain Inventory Short Form (BPI-SF) Interference Items only
- Short Form-12 (SF-12)
- Neuropathy Pain Symptom Inventory (NPSI)
- Insomnia Severity Index (ISI)
- After all V3, Step 1 procedures are completed, an investigator must confirm all inclusion criteria and no exclusion criteria are met for both EN21-PP and EN21-01 ISA prior to continuing to V3-Step 2.
    - If eligibility failure is due to EN21-01 ISA criteria (see ISA MOP for instructions), the participant may be eligible to randomize to another active ISA under the Platform Protocol.

V3, Step 2 – Dose Procedures

After the site staff has confirmed eligibility, the participant will be randomized within the IXRS and IP will be dispensed.

The patient reported measures (outlined in V3, Step 1) must be completed prior to the first dose of medication.

The following procedures will be performed as a part of dose administration:

- The first dose will then be administered in the clinic with the time noted. The participant should eat something within 30 minutes before taking the first dose of medication.

V3, Step 3 – Post-Dose Procedures

The following monitoring procedures will then take place over the two hours following administration of the first dose of IP:

- 12-lead ECG every 30 minutes (i.e. at 30, 60, 90, and 120 minutes). Treatment-emergent ECG abnormalities (including but not limited to QTcF > 500 ms) assessed as clinically significant by the investigator will be followed up until resolution, as appropriate to ensure the participant's safety.
    - If QTcF > 500 ms, collect two additional replicate ECGs and submit all three tracings for central review. Additionally, a PK sample should be drawn for each timepoint with a QTcF > 500 ms.
- Vital signs will be monitored every 30 minutes for at least two hours or until any changes assessed as clinically significant by the investigator have been resolved. Changes in vital signs determined by the investigator to be clinically significant will be noted as an AE. If such abnormalities are reported as drug-related AEs of moderate or severe intensity, the participant will have an unscheduled follow-up visit within 1 week (or less, at the investigator's discretion).

At the end of the visit, site staff will remind participants to complete the daily scales (NRS and DSIS) along with documenting IP and rescue medication use in the Medable app.

9.5 Remote Data Collection Between Visits

Sites should advise participants that the following data will be collected remotely, via Medable each day. Missed daily entries will not be considered a protocol deviation unless there are ≥4 consecutive entries of the same form missed in a 7-day period.

- 11-point NRS pain data – daily throughout study
    - Average pain over the prior 24-hours
    - Worst pain over the prior 24-hours
- Use of rescue medication (acetaminophen) – daily throughout study
- DSIS – daily, beginning on the day of randomization to ISA
- Time of IP dose – daily, after IP begins with V3

9.6 Visit 4 (V4), Early Safety Check [Removed]

This visit has been removed, please proceed to Visit 5. All patients will complete V5 after completion of V3.

9.7 Visit 5 (V5), Early Safety Check

- Vital Signs
- 12-lead ECG
    - If QTcF > 500 ms, collect two additional replicate ECGs and submit all three tracings for central review. Additionally, a PK sample should be drawn.
- Review of concomitant medications.
- Review of rescue medications.
- Documentation of adverse events.
- C-SSRS – Since Last Visit

At the end of the visit, site staff will remind participants to complete the daily scales (NRS and DSIS) along with documenting IP and rescue medication use in the Medable app. Additionally, sites should remind participants to wear their actigraphy device for the 7 days leading up to their next visit.

9.8 Visits 6 and 7 (V6, V7), Week 4 and 8, In-Person Follow-Up Visit

The participant should be instructed to wear the actigraphy watch for the 7 days prior to each visit. Safety and outcome assessments will be performed at this visit. The procedures are as follows:

- Vital signs including weight.
- Brief Physical Examination
- Urine Drug Test
- Urinalysis
- Pregnancy test, if applicable
- Clinical safety bloodwork
- Collection of sparse PK. This should be done within 30 minutes of the 12-lead ECG. The order does not matter.
- 12-lead ECG
    - If QTcF > 500 ms, collect two additional replicate ECGs and submit all three tracings for central review.
- Documentation of adverse events
- Review of concomitant medications
- Review of rescue medications
- IXRS Drug Dispensing

- Drug Accountability
- VAS for average pain over prior 24 hours
- Neuropathy examination
- Norfolk QOL-DN
- 11-point likability
- C-SSRS – Since Last Visit
- BPI-SF (interference items only)
- CGIC
- NPSI
- Patient Global Impression of Change (PGIC) (Visit 6 only)

At the end of the visit, site staff will remind participants to complete the daily scales (NRS and DSIS) along with documenting IP and rescue medication use in the Medable app. Additionally, sites should remind participants to wear their actigraphy device for the 7 days leading up to their next visit.

9.9 Visit 8 (V8), 12 Week Follow-Up Visit/Early Termination (ET)

The participant should be instructed to wear the actigraphy watch for the 7 days prior to the visit. The last dose of IP is taken the day before this visit. On the day of this visit, participants will begin a single-blind placebo washout period of ~7 days; however, if the patient does take a dose of the DB IP on the morning of V8, it will not be considered a protocol deviation.

The procedures are as follows:

- Vital signs including weight
- Physical Examination
- Urine Drug Test
- Urinalysis
- Pregnancy test, if applicable
- Clinical safety bloodwork
- Clinical neuropathy bloodwork
- Collection of plasma sample for storage for future EPPIC-Net biomarkers (if participant has consented to this)
- Collection of sparse PK. This should be done within 30 minutes of the 12-lead ECG. The order does not matter.
- 12-lead ECG

    - If QTcF > 500 ms, collect two additional replicate ECGs and submit all three tracings for central review.
- Review of new and ongoing adverse events
- Review of new and ongoing concomitant medications
- Review of rescue medication use
- IXRS Drug Dispensing
    - Single-blind placebo kit
- Drug Accountability
- NIH HEAL Initiative CDEs for chronic pain
    - Pain, Enjoyment, and General activity scale (PEG)
    - Pain Catastrophizing Scale – Short Form 6 (PCS-SF6)
    - PROMIS Physical Functioning Short-Form 6b
    - Pain Health Questionnaire (PHQ-2)
    - Generalized Anxiety Disorder – 2 item scale (GAD-2)
    - Patient Global Impression of Change (PGIC)
    - Tobacco, Alcohol, Prescription medication, and other Substance use Tool (TAPS-1)
    - PROMIS Sleep Disturbance – 6A
    - Sleep Duration Scale
    - Opioid Use Questionnaire (OUQ)
- VAS for average pain over prior 24 hours
- Neuropathy examination
- Norfolk QOL-DN
- 11-point likability
- C-SSRS – Since Last Visit
- BPI-SF (interference items only)
- CGIC
- SF-12
- NPSI
- ISI

At the end of the visit, site staff will remind participants to complete the daily scales (NRS and DSIS) along with documenting IP and rescue medication use in the Medable app. Additionally, sites should remind participants to wear their actigraphy device for the 7 days leading up to their next visit.

10. Early Termination (ET)

Early Termination (ET) procedures should follow the same procedures as V8. Procedures that are refused by the patient at the ET visit will not be considered a protocol deviation. ET participants will not enter the SBPWOP period and will not have the V9 Post-Washout Check, but should complete the V10 Final Safety Follow-Up call, if the participant agrees to do so.

9.10 Visit 9 (V9), Post-washout (Withdrawal) Check

This visit occurs at the end of the SBPWOP. The participant should be instructed to wear the actigraphy watch for the 7 days prior to the visit. The last dose of single-blind placebo should be taken the day before this visit; however, if the patient does take a dose of the DB IP on the morning of V8, it will not be considered a protocol deviation.

The procedures are as follows:

- Vital signs including weight
- Brief Physical Examination
- Pregnancy test, if applicable
- Urine Drug Test
- Urinalysis
- Clinical safety bloodwork
- 12-lead ECG
    - If QTcF > 500 ms, collect two additional replicate ECGs and submit all three tracings for central review.
- Documentation of adverse events
- Review of concomitant medications
- Review of rescue medications
- Drug Accountability
- VAS for average pain over prior 24 hours
- 11-point likability
- C-SSRS – Since Last Visit
- BPI (interference items only)
- SF-12
- NPSI
- ISI

- DESS-43
- Collection of actigraphy device
- Collection of Medable device (if applicable)

9.11 Visit 10 (V10), Final Safety Follow-Up Visit

This is a final check-in which can be performed by audio or video call to assess the participant for any intervening adverse events and review concomitant medications. Following this call, study participation is complete.

9.12 Unscheduled Visits

An unscheduled visit may be performed at any time during the study. The date and reason for the unscheduled visit will be recorded in the eCRF. Depending on the reason for the unscheduled visit, appropriate assessments will be performed based on the judgment of the investigator. The C-SSRS must be performed at each unscheduled visit. In addition, results of conducted assessments including, but not limited to, physical examination, ECG, laboratory assessments, and change in concomitant treatment will be recorded in the eCRF. After an unscheduled visit, the regularly scheduled study visits must continue according to the planned visit and assessment schedule.

Participants with clinically significant vital signs or ECG abnormalities that have been reported by the investigator as drug-related AEs of moderate or severe intensity, must come for an unscheduled visit within one week (or less, according to the investigator's discretion). If a regular study visit is scheduled in this period, that may be used to cover these assessments.

10. ISA-Specific Study Procedures

Many of the assessments and procedures to be performed are listed above in the endpoints sections, particularly those designed to quantify PDPN and its associated symptoms. Key interactions with the participant (e.g. the informed consent process) and procedures to collect other forms of data (e.g. key covariates, safety data) are described below.

Procedures to be implemented across all ISAs are described in the Platform Protocol. This section includes any procedures that are specific to this ISA.

10.1 Consenting

10.1.1 Informed Consent

As a part of the Platform Protocol, participants will complete a Platform ICF that describes the design of the protocol and the potential to be randomized to any of the active ISAs under the Platform Protocol umbrella.

After randomization to an ISA, the participant will need to be consented for that ISA. This consent should be reviewed and signed at the beginning of V3.

Written informed consent for the ISA will be obtained from participants before ISA-specific V3 procedures or assessments are done and after the study objectives, methods, anticipated benefits, and potential hazards are explained. The willingness of the participant to participate in the ISA will be documented in a cIRB approved consent form, which will be signed by the participant.The participant will also be informed that they may refuse entry into the ISA and are free to withdraw from the trial at any time without prejudice to future treatment.

Informed consent will be obtained by the PI or other qualified staff as outlined on the delegation of authority log who are trained on the study and listed on delegation logs as being authorized to obtain consent. The site study staff will be involved in explaining the study and will play a role during the consent process, answering any questions in conjunction with the coordinator and ensuring that the process is carried out correctly. All participants will be offered the opportunity to discuss participation with a licensed physician/Investigator and the participant's decision to accept or decline this opportunity will be documented in the consent form and post-consent checklist. Site study staff performing consent must provide participants adequate information to allow for an informed decision about participation, facilitate the potential participant's understanding of the information, and provide ample time and opportunity to inquire about details of the ISA. The site study staff shall not coerce or unduly influence a potential participant to participate or to continue to participate in the study. Site study staff must continuously provide information as the clinical investigation progresses or as the participant or situation requires.

10.1.2 Post-Consent Checklist

The EN21-01 Post-Consent Checklist should be completed in Medable (or by paper in the event of technical issues) after completion of the EN21-01 ICF as part of V3. For any additional EN21-01 ICFs completed by the participant, including reconsent after amendments, the Post-Consent Checklist must be completed via paper (MOP Appendix G). The checklist documents that the appropriate consenting process was followed, as per FDA/GCP guidelines.

10.2 Prior and Concomitant Medications Review and Documentation Including Use of Prohibited Medications

All concomitant medications taken during the study will be recorded in the Concomitant Medication Log for each patient, along with dosage information (including changes in dosing) and start and stop dates. Medications taken in the 6 months prior to screening and concomitant treatments are captured during the Platform Protocol Screening Visit (V1). Throughout the duration of their participation in the study, new treatments and changes to/discontinuation of ongoing treatments should captured in TrialMaster. Each concomitant drug must be individually

assessed by investigator against all inclusion/exclusion criteria and prohibited medications, as applicable.

A full list of prohibitions and restrictions of concomitant medications is included in Appendix A. For this ISA, only acetaminophen is allowed as a rescue medication for PDPN, up to 3g/day. Use of acetaminophen for any other indications or that exceeds the 3g/day limit should be documented on the concomitant medication log in TrialMaster. If in doubt during screening, the investigator must contact the study Medical Monitor (MM) and a decision agreed upon before randomizing a participant.

In general, participants who report taking prohibited concomitant medications during the trial will be re-educated regarding the importance of adhering to the protocol, and the prohibited medication use will be documented in detail. Further specific instructions, including rules for withdrawing the participant from the study for prohibited medication use, are in Appendix A.

10.2.1 Daily IP Use Review and Documentation

Beginning at IP initiation (V3), participants will record their IP use daily using the Medable app. Designated site staff will receive email notifications from Medable for consecutive missed reporting or consecutive missed doses of IP by a participant. In addition, a listing of triggered notifications is available in Medable for review at any time and should be reviewed regularly. If a notification is triggered, the participant should be reeducated, with documentation completed on the Adherence Alert Re-Education eCRF in Medable.

10.3 ISA Specific 12-Lead ECG Procedures

Single 12-lead ECGs will be performed with ECG machines provided by the study. The Fridericia QT correction formula will be used for clinical decisions related to QTc (QTcF). ECGs will be evaluated by a central cardiologist reviewer with a report provided noting identified abnormalities. The original ECGs and reports will be maintained by the site in the participant record.

Clinically significant abnormal ECG findings (including abnormal ECG findings that were documented at screening that subsequently worsen or progress) should be reported as an AE, unless one of the following is met:

- Finding is explained by an existing event or diagnosis in the participant's medical history,
- Finding is covered by an existing AE that is ongoing.

Participants with clinically significant ECG abnormalities that have been reported by the investigator as drug-related AEs of moderate or severe intensity, must come for an unscheduled visit within one week (or less, according to the investigator's discretion). If a regular study visit is scheduled in this period, that may be used to cover these assessments. A QTcF > 500 ms at V3 prior to initial administration of IP (i.e. pre-dose ECG) will result in a screen failure.

If any single ECG collected after introduction of IP shows a QTcF > 500 ms, two additional replicates should be recorded under continued controlled environmental conditions (participant resting, no interfering procedures to ensure as much as possible a stable heart rate) to confirm the safety findings and copies forwarded to the central ECG lab for assessment.

10.4 Physical Examination

A physical examination will be performed for safety and recorded at the screening visit (V1), IP initiation (V3), Week 4 (V6), Week 8 (V7), Week 12 (V8/ET) and at the withdrawal check visit (V9). The following systems will be examined as part of a comprehensive physical exam: head/neck, eyes, ears, nose and throat, cardiovascular, lungs, abdomen, musculoskeletal, central nervous system, extremities, and skin. A comprehensive physical examination will be done at screening (V1), IP initiation (V3), and Week 12 (V8). A brief physical exam including the examination of general appearance can be substituted at all other applicable visits.

Clinically significant abnormal findings that were present before signing the ICF should be included in the medical history eCRF. Significant findings with onset after the signing of the ICF documented as an AE on the appropriate eCRF.

10.5 Body Weight and Height

Bodyweight will be measured to the nearest 0.1 kilogram (kg)/pound (lb) in indoor clothing, but without shoes .

10.6 Vital Signs

Clinically significant abnormal vital signs (including abnormal vital signs that were documented at screening that subsequently worsen or progress) should be reported as an AE, unless one of the following is met:

- Finding is explained by an existing event or diagnosis in the participant’s medical history, e.g. significantly elevated blood pressure with a documented diagnosis of hypertension.
- Finding is covered by an existing AE that is ongoing, e.g. shortness of breath and corresponding high respiratory rate.

Participants with clinically significant vital sign abnormalities that have been reported by the investigator as drug-related AEs of moderate or severe intensity, must come for an unscheduled visit within one week (or less, according to the investigator’s discretion). If a regular study visit is scheduled in this period, that may be used to cover these assessments.

10.7 Laboratory Procedures

Clinically significant abnormal lab results (including abnormal lab results that were documented at screening that subsequently worsen or progress) should be reported as an AE, unless one of the following is met:

- Finding is an expected part of their diabetes and/or PDPN symptomatology, such as elevated glucose.
- Finding is explained by an existing event or diagnosis in the participant's medical history, e.g. elevated cholesterol with a documented diagnosis of hypercholesterolemia.
- Finding is covered by an existing AE that is ongoing, e.g. elevated white blood cells when the patient is recovering from a cold.
- Additional blood collection for PK monitoring for all randomized participants is required at select visits for this ISA, described in section 10.9.

10.7.1 Blood Collection for Neuropathy Confound Screening

The ISA does not specify cut-off values for abnormalities in blood collection for neuropathy confound or clinical safety screening as exclusion/inclusion criteria, but investigators at their discretion may consider an abnormality an exclusionary neuropathy confound.

10.7.2 Blood Collection for Clinical Safety Laboratory Screening

In addition to the clinical safety lab assessments listed in the Platform Protocol, this ISA requires PT/INR.

10.7.3 Blood Collection for EPPIC-Net Biorepository Storage (Optional)

If the participant consented to the optional collection and storage of samples at the EPPIC-Net biorepository as part of their EN21-PP ICF, whole blood will be collected at screening. Plasma will be collected at screening and with the final blood draw at Week 12 (V8). Samples will be stored and shipped in accordance with EN21-01 MOP Appendix B. Biorepository Manual.

10.7.4 Urine Collection for Clinical Safety Laboratory Screening

Urine is collected at screening (V1), IP initiation (V3), Week 4 (V6), Week 8 (V7), Week 12 (V8/ET), and withdrawal check (V9) for urinalysis (pH, specific gravity, leukocytes, protein, glucose, ketones, bilirubin, nitrite, urobilinogen, blood [hemoglobin], sediment), pregnancy test (if applicable), and urine drug testing.

10.7.5 Urine Drug Testing

During the study, participants found to be positive for illicit drugs (cocaine, ecstasy, methamphetamines, phencyclidine [PCP]; OR amphetamines, benzodiazepines, barbiturates or opioids <u>without a prescription</u>) will be discontinued from the study. Participants found to be positive for a prescribed opioid – buprenorphine, methadone, opiates, or oxycodone – or marijuana – prescribed or recreational – will be counseled and, if willing to cease use, can continue in the study (with appropriate documentation in the eCRF so that use of the prohibited substance can be properly accounted for in statistical analyses). However, if a second urine drug test is positive at

any time during the study (including a first positive at V1 or V3), that participant will be withdrawn.

10.8 Pharmacokinetic (PK) Assessments

10.8.1 PK Procedures for all Participants

Sparse NRD135S.E1 PK samples will be collected from all participants at V3, V6, V7, and V8. Any other blood required for that visit should be drawn at the same time.

PK samples of approximately 2 mL volume will be taken into blood collection tubes with NaF/Na_2EDTA anticoagulant. Batches of the frozen plasma samples will be sent to the NYU Biorepository for batch shipments to the analytical laboratory for analysis.

Further details on sample collection, numbering, processing and shipment can be found in EN21-01 MOP Appendix B. Biorepository Manual.

11. ISA-SPECIFIC PATIENT-REPORTED OUTCOMES

The following patient assessments will be administered as part of this ISA:

- Daily Sleep Interference Score (DSIS)
- Brief Pain Inventory (BPI, interference items only)
- Clinician Global Impression of Change (CGIC)
- Short Form 12 (SF-12)
- Neuropathy Pain Symptom Inventory (NPSI)
- Insomnia Severity Index (ISI)

See Platform Protocol for a full description of patient-reported measures. Questionnaires will be completed by the patient or trained clinician/staff member in the Medable app; see MOP for additional information about training and certification requirements.

12. ISA-SPECIFIC ADVERSE EVENT DEFINITIONS

Adverse events are comprehensively described in the Platform Protocol. A treatment-emergent adverse event (TEAE) is any AE temporally associated with the use of study treatment, whether or not considered by the investigator as related to study treatment. In this ISA, temporal association begins with treatment initiation (V3) and continues through the completion of the V9/Withdrawal Check visit, ~7 days after EoDB.

12.1 Reporting of Pregnancy

See Platform Protocol.

13. TREATMENT

The investigational drug NRD135S.E1 will be provided as capsules of 80 mg. Placebo capsules are matching capsules containing only the excipients. Study treatment supplies must be kept in an appropriate, secure area and stored at 20ºC to 25ºC (68ºF to 77ºF) allowing for excursions between 15°C and 30°C [59°F and 86°F]). Site-specific storage policies that are stricter than this are acceptable.

Study drug will be dispensed by appropriately qualified staff as designated by the investigator's delegation of authority log. Participants will self-administer the study drug following the instructions provided to the participant at the IP initiation study visit (V3). The study PI will complete drug accountability logs in TrialMaster for returned study drug and provide unused study drug to the CCC for review.

The accountability logs in TrialMaster should be auto-filled with study drug bottle number, quantity dispensed, and dispensation date. , Upon return of IP, the site will complete the log with return date and number of pills returned with space to comment on any discrepancies, e.g. missed doses. See ISA MOP for additional details and instructions.

In accordance with local regulatory requirements, the investigator, or designated site staff must document the amount of IP dispensed and/or administered to study participants, the amount returned by the participant, and the amount destroyed. An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The inventory will include details of study drug received and dispensed to participants. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of study drug received and dispensed drug must be reconciled.

The clinical study treatment (active drug product and placebo) will be packed and labeled in bottles, each containing 35 capsules. At V3, V6, and V7, participants will receive one bottle to cover the period until the following visit and a small surplus to avoid running out of medication between visits. At V8 participants will receive one bottle of single-blind study treatment, also containing 35 capsules.

If a bottle is lost or damaged, a replacement bottle can be requested through the IXRS system.

Participants should take one capsule daily in the morning within 30min of eating food. The capsules must be swallowed intact with water and should not be chewed, divided, or crushed. It is recommended that the participant takes the drug around the same time every day. If the dose of study drug is missed within 12 hours of the planned time period, it should be taken immediately. If more than 12 hours have passed since the planned time period, the dose should be skipped and the next dose should be taken at the usual time. The date and time of treatment intake will be recorded daily in the Medable app. The investigator or responsible site personnel must instruct the participant to take the study drug as per protocol.

For information about the manufacturing, label, packaging, or supply of study treatment, see the Platform Protocol. All study treatment supplies are to be used only in accordance with this ISA, and not for any other purpose.

13.1 Study Treatment Dose Adjustments and Interruptions

Study treatment dose adjustments are not permitted. Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. If study treatment is interrupted by the participant for any reason, they should immediately inform the investigator. The study team should also regularly review the participant's daily reporting for IP use and reeducate the participant if consecutive missed doses or missed reporting is identified. For each identified instance of IP non-compliance (e.g., Medable email notifications), a commensurate Re-Education eCRF should be completed; see ISA MOP for details. Interruptions of study treatment must be kept as short as possible and must be recorded appropriately.

If a participant experiences at least one SAE or two severe AEs that are considered to be study drug-related by the investigator, the participant's treatment must be interrupted. The investigator must then discuss with the CCC MM whether it is in the best interests of the participant to be permanently discontinued from the study treatment.

Each bottle and/or kit, if applicable will contain the following information on the label:

- Study number
- Unique bottle and/or kit number
- Drug treatment label
- Route of administration
- Quantity of dose unit
- Directions for use
- Storage conditions
- Space for investigator name, telephone, dispensing date, and participant number
- Space for study participant identifier
- Label statement "Caution: New Drug-Limited by federal law to investigational use"
- Label statement "Caution: Keep out of reach of children"
- Name and address of study drug distribution center

14. DISCONTINUATION OF PROTOCOL ISA

If at least two participants experience drug-related and unexpected SAEs in the same system organ class (SOC), the randomization of new participants will be put on hold until the data has been reviewed by the Medical Monitor, PPI, CCC and DCC and a decision is made to recommend suspending or prematurely terminating the study. For studies that are suspended, while a

determination is being made whether to suspend or terminate, participants in the follow-up phase of a study will be allowed to continue.

If the study is prematurely suspended or terminated, EPPIC-Net SOP 106: Suspension or Early Termination will be followed, including informing the cIRB and FDA.

If the ISA is suspended or prematurely terminated for any reason, the investigator must promptly inform all enrolled participants and ensure their appropriate treatment and follow-up.

The CCC may inform the investigator of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participants' interests.

If the cIRB suspends or terminates its approval/favorable opinion of the ISA at a study site, the investigator must promptly notify the CCC and provide a detailed written explanation of the termination or suspension.

This study may also be discontinued for several other reasons, including but not limited to those listed below:

1. It is determined that continuation would be detrimental to participants' well-being
2. Loss of NIH funding

15. BENEFITS AND RISKS

A favorable risk-benefit ratio for exposure with NRD135S.E1 for up to 13 weeks of treatment is foreseen based on the available safety information combined with the potential of NRD135S.E1 to effectively treat PDPN [Sections 3.2 and 3.3]. Appropriate exclusion criteria [Section 7.2] are defined to ensure the participants' safety and to allow estimation of treatment response with minimal confounding factors for the assessment of neuropathic pain. In addition, the risk for the participants will be minimized by compliance with the planned study procedures, close clinical monitoring, monitoring of TEAEs, and discontinuation of study treatment due to adverse events (AEs) or based on the judgment of the investigator [refer to Platform Protocol].

Participants with PDPN frequently have comorbidities of anxiety, depression, or insomnia. As no drug-drug interactions are foreseen, the study allows treatment for those comorbidities as defined in Appendix A.

To ensure adequate participant safety monitoring, a Risk-Based Monitoring Plan and Medical Monitoring Plan will be in place before the first participant is treated; the plans will define the listings and tabulated blinded summaries that will be reviewed on an ongoing basis to allow adequate participant monitoring. In addition, an independent NINDS Data Safety Monitoring

Board (DSMB; details in the Platform Protocol) will periodically monitor unblinded safety data and make appropriate recommendations to ensure the safety of the participants.

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual participant level, and to discontinue study treatment or the study if, on balance, the investigator believes that continuation would be detrimental to the participant's well-being.

In conclusion, based on available data on NRD135S.E1 and the risk minimization measures mandated by the protocol (stopping rules, DSMB, central review of AEs), the expected risk-benefit assessment supports the conduct of this 13-week (12-week double-blind administration of NRD135S.E1 vs. placebo, plus 1-week of single-blind placebo administration) treatment study in adult and elderly participants with PDPN.

16. MONITORING AND OVERSIGHT

a. Evaluation of Study Sites

Sites selected for this ISA must participate in the Platform Protocol. Selected sites will also be expected to participate in all ISAs currently a part of the Platform Protocol and those added in the future, until the Platform Protocol is closed, or the site discontinues participation in the Platform Protocol. Sites may not choose to participate in some ISAs and not others under the Platform Protocol.

b. Initiation of Sites to ISA

All sites must have appropriate approval and initiation activities completed for the Platform Protocol in order to participate in an ISA.

Before a site is opened for participant enrollment into this ISA, a site initiation visit will be completed to ensure the following: cIRB approval for the ISA has been obtained and documented prior to participant screening, the Investigators and study personnel are appropriately trained and clearly understand the ISA, the Investigators and study personnel accept the obligations incurred in undertaking this ISA.

c. Early Termination of Study Sites

The CCC reserves the right to terminate the participation of individual study sites. If a site is terminated for the Platform Protocol or any of the associated ISAs, the site will be terminated for all associated ISAs. Sites may not participate in a subset of ISAs. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter participants at an acceptable rate.

d. Monitoring Visits

Qualified clinical monitors representing EPPIC-Net will conduct site monitoring visits to ensure that all PIs conduct the study in compliance with the Platform Protocol, the ISA, and applicable regulations. The site will receive notification prior to each monitoring visit during the course of the study. It is expected that the PI and/or Sub-Investigator and other appropriately trained study staff are available during the visit in case any questions might arise.

Periodic monitoring visits will be made in accordance with the approved monitoring plan at all active study sites throughout the clinical study to assure that the PI obligations are fulfilled and all applicable regulations and guidelines are being followed. Visits for the ISA may be completed as standalone visits or combined with other ISAs that fall under the Platform Protocol.

On one or more occasions, the study site may be inspected or audited by an EPPIC-Net representative or a third party. The Investigator will be informed in advance of this visit.

e. Risk-Based Monitoring

EPPIC-Net will employ an ISA-specific Risk-Based Monitoring Plan (RBMP) to ensure a robust quality control method for determining and enabling dynamic management of study risks and facilitating ongoing improvement in the trial conduct and oversight. The Risk-Based Quality Monitoring (RBQM) system uses tools and dashboards to identify Key Risk Indicators (KRIs), which highlight potential issues with such as trial conduct, safety, data integrity, compliance, and enrollment, that may require further monitoring from a qualified contract monitor. In additional to Platform-level Key Risk Indicators (KRIs; described in the Platform Protocol), there will be ISA-specific KRIs which will highlight potential issues with (for example) trial conduct, safety, data integrity, compliance, and enrollment, that may require further monitoring.

17. DATA ANALYSIS

17.1 General Statistical Considerations

A summary of the statistical plan is included here for reference. However, the Statistical Analysis Plan (SAP) should be considered the authoritative document regarding all analyses. The primary analyses will be performed according to the Intent-To-Treat (ITT) principle using a modified Intent-To-Treat set (mITT). This set will include all randomized participants who took at least one dose of double-blind treatment. As described in Section 6.1.1, the primary outcome is the weekly average pain (WAP) obtained by taking the (arithmetic) mean of the daily ratings of "average daily pain" on the 11-point (0-10) NRS scale during a specific week.

The following conventions are used to define several of the analysis endpoints:

1. The week number is the next highest integer after the study day divided by 7 (e.g., days 0-6 are week 1). The numbering of the weeks is independent of the visits.
2. Week 12 is the interval starting on Day 78 and ending on Day 84.

3. Week 0 is the baseline week and includes the last 7 days before randomization to NRD135S.E1 or placebo; it is used as the baseline for the computation of the change in weekly NRS measures from Baseline. For values obtained once on the randomization day (e.g., specific safety measures), this randomization-day value will be the baseline value.
4. EoDB is the morning after the last double-blind drug intake. This may not always be at week 12, for example, if a participant discontinued treatment earlier, or if the scheduling of V8 is delayed.
5. Start of double-blind period is day 0.
6. The SBPWOP (Single-Blind Placebo Washout Phase) is the 7-day period during which the participant receives single-blind placebo treatment. Per protocol, this begins the day after the last double-blind treatment (NRD135S.E1 or placebo) intake. Participants who discontinue treatment early will not have a SBPWOP.
7. EoT (End of Treatment) is defined as the morning after the last placebo intake during the SBPWOP week.

No interim analyses are planned for this ISA. However, it is possible, although unlikely, that exposure of more than 61 participants to NRD135S.E1 (122 total participants including controls) will not occur (e.g. FDA does not allow it or imposes requirements for continuation that would result in unacceptable delay). In this scenario, the clinical trial will be terminated, and the data analyzed.

17.2 Intercurrent Events and the Treatment of Missing Data

All available efficacy data will be used in the analysis except data during the periods when a patient was taking a prohibited pain medication or in the 3 days after last use of a prohibited pain medication (the *latency period*). All days on which prohibited pain medication is used plus a latency period of three days following the last day of use will be considered an intercurrent event. This policy on prohibited medication use applies for participants even if the participant takes a prohibited medication on more than two occasions as long as there are no safety concerns on the use of such medication. Daily efficacy data obtained during the intercurrent event will be set to missing and these missing values will be imputed by carrying the last assessment prior to prohibited pain medication use forward to the end of the latency period. Section 17.3 describes two estimands to be used as supportive analyses using multiple imputation for data set to missing for use of prohibited medication using chained equations (Van Buuren & Groothuis-Oudshoorn, 2011). For the first estimand, the missing values will be imputed under the missing-at-random (MAR) assumption by borrowing information from patients in the same treatment arm. For sensitivity analyses, the second estimand describes the use of multiple imputation that will be conditional on a participant's previously observed outcomes and all baseline characteristics, and borrowing information from patients randomized to placebo, even for participants that were randomized to NRD135S.E1 (i.e., a missing-not-at-random, MNAR, approach).

17.2.1 Missing Data for Reasons Other Than Use of Forbidden Pain Medication

Multiple imputation (MI) will be used to impute missing data for reasons other than use of prohibited pain medication following intensive investigations to ensure reliable and valid MI. Missing data will be multiply imputed assuming MAR.

17.3 Estimands

This section defines the estimands for the supporting analysis for the primary efficacy analysis and sensitivity analyses.

17.3.1 Estimands for Primary Efficacy Objective

The following attributes describe the supporting analysis describing the primary efficacy estimand:

- **Population:** As defined by the Inclusion/Exclusion criteria
- **Endpoint**: The difference in the change from Baseline to Week 12 between randomized groups in the WAP. The arithmetic mean of recorded (or imputed, using day-level data, if missing) NRS for average pain over the 7-days interval (i.e., the WAP) from day 78 to day 84 will be used as end-of-treatment (Week 12) primary pain measure. The baseline WAP corresponds to the 7 days preceding randomization and start of DB treatment.
- **Treatment of interest:** NRD135S.E1 80mg daily or placebo.
- **Handling of intercurrent events (IEs) prior to endpoint assessment**.
    - Intercurrent or interim use of prohibited pain medication including the medication latency period (the 3 days following last use): Available data recorded during such IE will be set to missing.
    - Efficacy data collected during intake of rescue medication will be used for analysis as recorded.
    - Missing data due to any reason will be multiply imputed based on MAR assumption.
        - Policy strategy: All available data will be used (except data collected during an IE as described above). Missing data will be imputed under the MAR assumption by borrowing information from patients in the same treatment arm.
- **Summary measure:** The estimate of the contrast between those randomized to NRD135S.E1 80mg daily versus placebo for the primary endpoint will be obtained from the estimated model (see Section 17.4.1.) which includes only main effects for treatment, baseline WAP, sex, age, and BMI as covariates.

17.3.2 Estimand for the Sensitivity Analysis

This estimand quantifies the treatment effect of NRD135S.E1 80 mg vs placebo at 12 weeks of daily administration while accounting for the IE of prohibited pain medication use and additional IEs leading to study discontinuation prior to Week 12.

A treatment for chronic pain is not efficacious after discontinuation, thus, strategies to handle missing data for participants who do not stay on the treatment for the study duration should not attribute any treatment benefit to participants after discontinuing the treatment. The analysis method under this sensitivity estimand will attribute an outcome similar to placebo to participants who discontinued the treatment (reference-based imputation). This is justified by the relevant placebo effect that is observed in most pain studies.

The following attributes describe the primary estimand:

- **Population:** As defined by the Inclusion/Exclusion criteria
- **Endpoint**: Change from Baseline to Week 12 in the WAP
- **Treatment of interest:** NRD135S.E1 80mg daily or placebo.
- **Handling of intercurrent events (IEs) prior to endpoint assessment**
    - For treatment discontinuations (e.g., for poor tolerability or lack of efficacy); or use of prohibited pain medication (including the 3-day latency period) during Week 12, available data recorded during the IE will be set to missing. Such missing data will be imputed under a MNAR assumption by borrowing information from the placebo arm patients (reference-based imputation).
    - Other missing data, including those set to missing for use of prohibited pain medication before Week 12, will be multiply imputed based on MAR assumption
    - Efficacy data collected during intake of rescue medication will be used for analysis as they are recorded.
- **Summary measure:** The estimate of the contrast between those randomized to NRD135S.E1 80mg daily versus placebo for the primary endpoint will be obtained from the estimated model (see Section 17.4.1.) which includes only main effects for treatment, and baseline WAP, sex, and age as covariates. No interaction term will be included in the model.

For each week, including Week 12, multiple imputation will be performed based on the model covariates and on the values at previous weeks from the patients in the same treatment arm for the first estimand described above for the primary efficacy objective; for the estimand for sensitivity analysis, MI will be performed under the MNAR assumption using data from patients in the placebo arm.

17.4 Primary Objectives

The primary estimand quantifies the treatment effect of NRD135S.E1 80 mg daily as compared to placebo at 12 weeks of daily administration while attributing no relevant role to intercurrent events (IEs) with potential biasing effects and IEs leading to study medication discontinuation prior to the Week 12 assessment.

17.4.1 The Estimator

The endpoint for the primary estimand is the baseline week WAP minus the week 12 WAP.

17.4.2 Primary Efficacy Endpoint: Change from Baseline to Week 12 in WAP

The hypothesis for the primary efficacy endpoint is:

> NRD135S.E1 will be more effective than placebo for treating PDPN with respect to reducing pain as measured by the WAP during Week 12 of treatment.

This hypothesis regarding the treatment effect is equivalent to testing versus in model (1) above. This will be tested using a 2-sided test with significance level.

Sensitivity analysis to investigate the effect of the assumptions underlying the treatment of missing data on the inferences will be conducted as described in Section 17.2.

17.4.3 Secondary Efficacy Endpoint: Occurrence of 30% and 50% Reduction in WAP from Baseline to Week 12

The hypothesis for the secondary efficacy endpoint is:

> NRD135S.E1 will have a higher occurrence of 30% and 50% reductions in WAP from Baseline to Week 12 than placebo.

Improvement in pain is defined as follows: let X_0 denote the WAP during the baseline week and let X_{12} denote the WAP over days 78-84 from randomization. Then $100*(X_0- X_{12})/ X_0$ measures the percent improvement in pain. The following two estimates will be considered for testing:

- Difference between the two treatment groups with respect to proportion of patients with at least 30% improvement in WAP.
- Difference between the two treatment groups with respect to proportion of patients with at least 50% improvement in WAP.

The proportion of patients in the two treatment groups with the respective % improvement will be estimated from raw (observed) proportions including 95% CIs. Chi-square test for independence will be used to test for significance of the unadjusted differences between the two groups.

A gatekeeping approach will be used where statistical inference for 30% improvement will proceed if the test for primary efficacy of NRD135S.E1 compared to placebo is statistically significant at

the 5% significance level. The same approach will be used for 50% improvement provided the hypothesis test for the 30% improvement is statistically significant.

17.4.4 Number-Needed-To-Treat (NNT) Analysis for Secondary Efficacy Endpoints

The number-needed-to-treat (NNT) is defined as the inverse of the absolute risk reduction (i.e., the inverse of the differences in the proportion of participants with 30% [and 50%] percent improvements between NRD135S.E1 and placebo treated participants). Estimates of the NNT (and 95% CI) will be computed for 30% and 50% reductions.

17.5 Safety Objectives

Safety of the NRD135S.E1 80 mg daily treatment will be assessed using the following measures during the double-blind 12-week period and the SBPWOP: TEAEs, SAEs, AEs leading to discontinuation, treatment-emergent ECG abnormalities, treatment-emergent Marked Laboratory Abnormalities (MLAs). The definition of TEAE will also include AEs during the SBPWOP. A separate output, tabulating frequency of AEs occurring only during SBPWOP will be recorded and assessed - this may allow detection of a drift in AE frequency during withdrawal. Also, the change from Baseline to the last value and the change from Baseline to the worst value through Week 12 and end of SBPWOP will be recorded for MNSI, vital signs (systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature), body weight, ECG parameters and laboratory variables. Safety will also be assessed using the occurrence of SAEs at the final safety follow-up visit.

There will be no hypothesis testing under this objective. Instead, summary statistics will be presented separately for each of the two treatment groups and at different time points.

We will compare the two treatment groups with respect to: (a) the proportion of patients with TEAEs; (b) the number of TEAEs; and (c) rate of TEAEs, i.e., the number of TEAEs divided by number of patient-days exposed to the study treatments.

17.6 Exploratory Objectives (EOs)

Similar to the efficacy objectives, for the exploratory objectives, data obtained during the use of prohibited pain medications or the 3-day latency period will be set to missing and the missing data imputed under MAR.

17.6.1 Objectives Related to Common EPPIC-Net General Neuropathy and Pain Outcome Measures

The Exploratory Objectives will be denoted as “EO” in the following.

The Platform Protocol outcome measures include the NIH HEAL Initiative CDEs and neuropathy-specific instruments (UENS, MNSI, Norfolk QOL-DN). We will test the hypotheses that NRD135S.E1 positively impacts the NIH HEAL Initiative CDEs (EO 1) and the neuropathy-

specific instruments (EO 2) as compared to placebo. For outcomes collected only twice (e.g., at Baseline and Week 12), the same approach used for model (1) will be used. For outcomes collected at more than two time points, the outcomes will be modeled as a function of time (with time treated as a factor instead of a continuous variable), treatment and a set of Baseline covariates including age, sex, BMI, and the baseline value of the outcome.

Mixed effects models will be used with random effects for site and participants nested in sites. A likelihood ratio test will be performed to test for an overall mean treatment difference across timepoints for each of the endpoints. A significance level of 5% will be used and we note that the study is not powered for these endpoints. If the test for an overall treatment difference is significant for an objective, 95% confidence intervals will be used to estimate mean treatment difference at each timepoint that the outcome is collected.

17.6.2 Objectives Related to Daily NRS at Different Time Points During the Study (EO 3)

The primary and secondary efficacy endpoints for this study focus on WAP at 12 weeks (as described above in Section 6.1.1 and 6.1.2, respectively). In the analyses described in this section (EO 3), we will explore the effect of NRD135S.E1 compared to placebo at different time points during the study in terms of both WAP and WWP.

17.6.3 Objectives Related to the Use of Rescue and Prohibited Medication (EO 4)

Longitudinal generalized linear mixed models (GLMM) with a Poisson distribution will be used to model the count for participant at week of analgesic consumption per week. This is described further in the SAP.

Additionally, unadjusted analyses will be performed to compare NRD135S.E1 to placebo in terms of rescue medication use throughout the trial by computing: the proportion of participants using rescue medication, the average weekly amount of rescue/participant, number of days/participant (frequency of use, EO4e). Empirical estimates of these quantities will be computed and 95% confidence intervals for differences will be used to compare NRD135S.E1 to placebo. These comparisons will be done for Weeks 1-12 and Week 13 separately.

The Cox proportional hazards model, as described under EO 3d, will be used to model and compare NRD135S.E1 to placebo in terms of time to first intake of rescue medication and/or prohibited pain medication during Weeks 1-12 and Week 13 separately (EO4d). Diagnostic checks will be performed, e.g., examining Schoenfeld residuals, to assess the proportionality assumption for the Cox model.

EO 5. Use of rescue medication as defined in Section 6.3.3 is a post-randomization variable that can be considered as a mediator. Consequently, we will then estimate the natural direct and indirect effect of NRD135S.E1 on change of WAP from Baseline to Week 12. Assuming that standard

mediation analysis assumptions hold and that the endpoint and the mediator are continuous, we will define two linear regression models for 1) the primary endpoint adjusting for an indicator for NRD135S.E1 treatment assignment, the use of rescue medication, their interaction and the vector of baseline covariates that includes sex, age, BMI and the baseline WAP, and 2) the mediator, use of rescue medication (average weekly use of rescue medication), adjusting for NRD135S.E1 and the vector of baseline covariates. Based on the models' estimated parameters, we will then derive the natural direct and indirect effects. Standard errors and confidence intervals will be obtained by using delta method and bootstrap.

17.6.4 Objectives Related to Additional ISA-specific Patient-Reported Outcome Measures (EO 6-9)

The analytical approach to test the exploratory objectives (EO 6-8) for outcomes collected at multiple time points will proceed the same as described in Section 17.6.1. The models will include treatment as the primary factor and baseline score on the measure as a continuous covariate. The models will also control for sex, age, BMI, and baseline value. No adjustment for multiplicity will be made. 95% confidence intervals will be computed for the treatment effect coefficient in each of the models in order to estimate the difference in the outcomes attributed to treatment (NRD135S.E1 versus placebo).

EO 9. The CGIC is measured on a 7-point ordinal scale corresponding to the order responses of the participant's overall status from the start of the study: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) worse, (7) very much worse. We will compare NRD135S.E1 and placebo in terms of CGIC at end of double-blind period using a proportional odds model.

A mixed-effect ordinal logistic model will also be used to explore (longitudinally) differences between NRD135S.E1 and placebo at V6, V7, and V8 which will include a time trend variable, a treatment indicator (and possibly a treatment by time interaction), and a subject-specific random effect.

No imputation for missing data will be performed under this objective.

17.6.5 Objectives Related to Withdrawal Symptoms (EO 9-10) Exploratory Objective 10 (EO 10)

AEs suggestive of drug abuse, dependence and withdrawal will be summarized using a Standard MedDRA Query (SMQ) for each treatment arm.

17.6.6 Exploratory Objective 11 (EO 11)

We will evaluate the presence of withdrawal symptoms and rebound effects after abrupt interruption of NRD135S.E1 by comparing NRD135S.E1 and placebo in terms of: (1) change from the Baseline to SBPWOP in the WAP, (2) change from Week 12 to SBPWOP in the WAP and (3) DESS-43 score at V9. The DESS-43 scores for the occurrence of withdrawal symptoms obtained

at the end of the SBPWOP (V9) week will be summarized for NRD135S.E1 and placebo treated participants. The changes in WWP and WAP between placebo and NRD135S.E1 will be estimated using 95% confidence intervals.

Other Objectives (EO 12-16)

17.6.7 Exploratory Objective 12 (EO 12)

The likability scale is measured on an 11-point scale (0-10) and will be assessed at V6–V9. NRD135S.E1 and placebo will be compared on the likability scale using the approach for endpoints assessed at more than two timepoints, as described in Section 17.6.1. The change in likability scale will also be compared in the same arms across time points via likelihood ratio test by comparing the proposed model with a reduced model constrained to have no change in the likability scores across time points for each arm.

17.6.8 Exploratory Objective 13 (EO 13)

We will evaluate and compare the course of symptom severity throughout the 12-week double-blind period for NRD135S.E1 and placebo in terms of longitudinal trajectories.

No hypotheses are specified for this aim. Longitudinal analyses using the daily NRS pain measures over the 12-week double blind period will be performed in order to explore the pattern of symptom changes over the course of the treatment. Different trend models will be investigated (linear, quadratic and nonparametric). The nonparametric approach permits fitting flexible trajectory shapes using penalized B-splines. The longitudinal models will allow the investigation as to if and when a separation between mean pain levels between NRD135S.E1 and placebo treated participants occurs and the rates of improvement between NRD135S.E1 and placebo groups over the course of treatment. In particular, by comparing and contrasting the trajectories for placebo and NRD135S.E1 treated participants, an evaluation of whether or not placebo effects are maintained or wane throughout the course of treatment can be investigated. The longitudinal approach will also be used to investigate periodic (daily, weekly, seasonable) and complex time trends.

Parametric clustering approaches (Tarpey et al., 2010) will be used to identify commonalities and distinctions in pain trajectory shapes for the NRD135S.E1 and placebo treated participants as well as identify baseline characteristics that align with these groupings.

We will also investigate if enhanced statistical power to test for differences in treatments is achievable by using the full range of longitudinal assessments (instead of just the Baseline and Week 12 mean NRS scores as in the ANCOVA model) by extracting an “average rate of improvement” scalar-valued measure from the outcome trajectories (Tarpey et al., 2021).

17.6.9 Exploratory Objective 14 (EO 14)

We will explore sociodemographic and clinical predictors of response to NRD135S.E1

No formal hypothesis testing will be undertaken in this aim. Under this aim, the relation of sociodemographic and clinical predictors to pain-related outcomes between treatment groups will be explored, such as differences in pain ratings between males and females, differences in outcomes associated with sociodemographic measures, the relation of changes in pain and psychological measures of distress.

17.6.10 Exploratory Objective 15 (EO 15)

We will characterize activity levels in participants with PDPN treated with NRD135S.E1 compared to a placebo using actigraphy measures.

Actigraphy provides a rich source of data to characterize PDPN participants in terms of activity levels. There is currently very active development of statistical and machine learning methodologies for analyzing the complex data arising from actigraphy. Implementing these approaches will allow the investigation of physiological and behavioral measures obtained from actigraphy that are related to pain measures due to PDPN as well as other pain-related measures (e.g., depression, anxiety). The discoveries from these analyses will undergo extensive internal cross-validation and will be reported as exploratory analyses. In particular, these explorations will allow the evaluation of periodic (daily, weekly, seasonal) and temporal trends in activity and its association with pain-related outcome measures. Functional data analysis methods for high-dimensional, correlated data along a time domain will be used to explore these associations.

17.6.11 Exploratory Objective 16 (EO 16)

This EO is to characterize the impact of heterogeneity due to pre-trial treatment for PDPN. This EO will be achieved in 2 parts: (i) explore the impact of whether a participant was on any PDPN treatment or not on a PDPN treatment prior to screening and (ii) for participants on any PDPN treatment prior to screening, the analysis will explore responsiveness to PDPN medications. The same models for primary (and secondary) outcomes will be used, but for (i), an additional indicator variable for any PDPN treatment prior to screening (and its interaction) will be included as a covariate. For (ii), the same models will also be used for participants on any PDPN treatment prior to screening, except an additional covariate will be included in these models defined as the change in pain during the 2 weeks prior to start of the IP (the interaction of this change variable with treatment will also be included in the model). This additional "change in pain" variable is defined as the following difference:

(Pain score from day at first screen visit) – (Pain score at day of randomization).

The same analyses in (ii) will also be done for participants that were not on any PDPN pain treatment prior to screening. Further explorations will investigate heterogeneity due to pre-trial pain treatment by summarizing results based on: the type of medication, the amount of medication that was used pre-screening, and how recently pre-trial pain medication was used prior to screening.

17.6.12 Exploratory Objective 17 (EO 17)

Due to ISA protocol changes in regard to the baseline NRS WAP inclusion criterion cut-off changing from a threshold of 5 to 4, this secondary objective will examine the impact of this subgroup (baseline NRS WAP of 5 or above) on the primary efficacy analysis. This subgroup analysis will be conducted by adding a subgroup indicator variable (and its interaction with treatment group) to the ANCOVA model used for the primary efficacy analysis. Summary statistics will also be generated in order to compare subgroups on the primary outcome. This subgroup analysis will only be conducted if the sample size of the subgroup with baseline WAP score below 5 is greater than 20% of the total sample size.

17.6.13 PK/PD Analyses

The PK evaluation will be performed after database lock and will be described in a dedicated PK protocol. The analysis will be performed on patients from the safety set who have PK data available.

Plasma concentrations of NRD135S.E1 will be summarized by the usual location and scale statistics, and geometric means with Coefficient of Variation and 95% CIs. Individual participant listings will be provided. Participants will be analyzed according to the treatment they received.

Derived PK parameters will include: AUC during dosing interval ($AUC_{0-\tau}$), minimum (= predose) plasma concentration (C_{min}), C_{max}, T_{max}, $T_{½}$, rate constant of terminal period in plasma concentration-time curve () for parent compound.

All kinetic parameters will be determined model-independently for each treatment using Phoenix WinNonlin, software. Pharmacokinetic characteristics will be determined directly from the measured concentrations; actual sampling times will be used for PK evaluation.

Left-over plasma samples may be used for preliminary NRD135S.E1 metabolite assessment. Results of this preliminary metabolite assessment, if any, will be reported in a separate Research Report.

17.6.14 Pharmacodynamic (PD) Endpoints

PD endpoints will be analyzed in the mITT data set from all the selected sites for PK/PD investigation. Individual participant listings will be provided. Participants will be analyzed according to the treatment they received.

17.6.15 Relation of Pharmacokinetic to Pharmacodynamic Endpoints

Analyses concerning the PK/PD relation will be described in the PK/PD protocol. These will include, but may not be limited to:

- The relationship between exposure and the WAP
- The relationship between exposure and safety parameters

17.7 Sample Size

With n=61 per arm, this study will have 80% power to detect an ES of 0.52 (difference of 1.20 between active treatment and placebo, SD 2.35, on NRS change from baseline). The critical value for the test is 0.36 on the SES scale (matching 0.84 ± 2.35 NRS units), i.e., if the estimated SES exceeds 0.36, we would reject the null at a one-sided 0.025 level. Novaremed has provided strong justification for delta 1.20 and SD of 2.35, and the sample size of n=61 per arm was in Novaremed's original FDA-approved protocol.

Simulations were performed to investigate the statistical power under this selected sample size for the primary efficacy hypothesis using the ANCOVA model (1) for a 2-sided significance level of 0.05. Various parameter settings in the simulations were used to assess their impact on statistical power. The power of the test depends on the correlation between the Baseline and Week 12 daily average pain scores and therefore simulations were run for a range of correlations from 0 to 0.80.

Bivariate normal data (representing the Baseline and Week 12 WAP) was generated for the NRD135S.E1 and placebo arms for various values of correlation between Baseline and Week 12, assuming the NRD135S.E1 and placebo arms have the same covariance matrices. The WAP for Baseline was set to 7. Data was generated using the R software. 5000 data sets were simulated for each scenario to estimate power. Cohen's standardized effect size of ES = 0.52 was used to simulate the data which is defined to be a ratio with numerator equal to the difference (placebo minus NRD135S.E1) in the mean differences (Baseline minus Week 12 daily average). This difference is standardized by dividing the standard deviation of the baseline week pain in the placebo arm which was set to 1 in the simulations. For each simulated data set, an ANCOVA model was fit to the data with the difference (Baseline - Week 12) as the outcome and baseline pain and a treatment indicator as covariates. The proportion of p-values (across all simulated data sets) for testing if the treatment indicator differs from zero that are less than 0.05 provides an estimate of the power. The solid black curve in Figure 2 shows a plot of power (versus correlation between Baseline and Week 12 WAP). Also shown in Figure 2 is the power for conducting a 2-sample t-test to compare the change score of NRD135S.E1 to placebo (red dotted curve). The 2-sample t-test is considerably less powerful compared to the ANCOVA approach unless the correlation becomes large. Note that the power estimates in Figure 2 are conservative. For example, adjusting for covariates that explain 10% of the variability gives higher power indicated by the blue dashed curve in Figure 2.

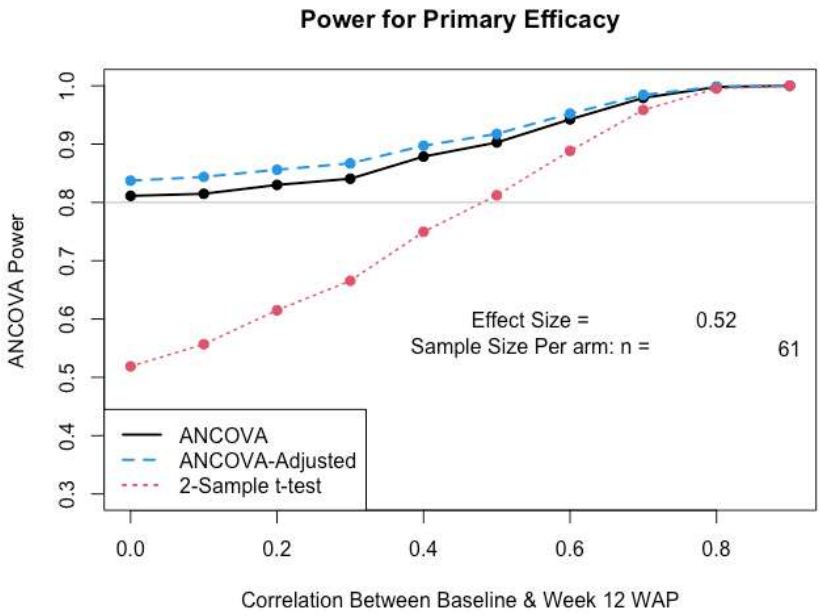


Figure 2: Power versus Correlation for ANCOVA model for the primary efficacy aim.

18. TRIAL REGISTRATION

This ISA is registered on www.ClinicalTrials.gov (NCT05480228). Results will be posted to ClinicalTrials.gov according to applicable regulations.

19. REFERENCES

Additional references can be found in the Platform Protocol.

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Tarpey, T., Petkova, E., Ciarleglio, A., & Ogden, R. T. (2021). Extracting Scalar Measures from Functional Data with Applications to Placebo Response. *Statistics and Its Interface*, *14*, 255–265.

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Van Buuren, S., & Groothuis-Oudshoorn, K. (2011). *Journal of Statistical Software mice: Multivariate Imputation by Chained Equations in R* (Vol. 45). http://www.jstatsoft.org/

20. APPENDICES

A. Prohibited Medications and Food

Participants who use a prohibited medication should be re-educated regarding adherence to study procedures. In addition, use of some medications may require cessation of the study drug as indicated in the table below. Medication category is indicated as "Pain" if the medication is excluded for a possible confounding effect on neuropathic pain.

Medication	Prohibition period	Action taken for study treatment	Medication category
High dose capsaicin patch (8%) use on the feet/distal legs	6 months prior to V1 and for the duration of the study	Discontinue study treatment if medication used	Pain
Another investigational drug	3 months prior to screening and for the duration of the study	Discontinue study treatment if medication used	Pain or Other
Tyrosine kinase inhibitors (e.g., imatinib, lapatinib, idelalisib)	6 weeks prior to V1 and for the duration of the study	None	Other
Any skeletal muscle relaxant (e.g., baclofen, methocarbamol)	2 weeks prior to V1 and for the duration of the study	None	Pain
Mexiletine	2 weeks prior to V1 and for the duration of the study	None	Pain
Dextromethorphan	2 weeks prior to V1 and for the duration of the study	None	Pain
Memantine	2 weeks prior to V1 and for the duration of the study	None	Pain
Alpha-lipoic acid	2 weeks prior to V1 and for the duration of the study	None	Pain
Other anti-epileptic drugs (e.g., valproic acid, carbamazepine, phenytoin)	2 weeks prior to V1 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain

Medication	Prohibition period	Action taken for study treatment	Medication category
Prescription opioids, including tramadol, tapentadol and codeine	At V1 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain
Cannabinoids (e.g., marijuana, CBD)	At V1 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain
Oral or injectable steroids	At V1 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain
NSAID or any other over-the-counter pain medication (including herbal preparations)	At V1 and for the duration of the study	None	Pain
Topical treatment for PDPN, including topical lidocaine	At V1 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain
Antidepressants of the SNRI and TCA classes (e.g. duloxetine, venlafaxine, levomilnacipran, milnacipran, amitriptyline, nortriptyline etc.) *Note: SSRIs are allowed but should be at a stable dose for at least 4 weeks prior to V1.*	3 weeks prior to V3 and for the duration of the study	Discontinue study treatment upon second episode of medication (i.e. SNRI or TCA) use	Pain
MAOIs, anti-psychotics or neuroleptics	3 weeks prior to V3 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain

Medication	Prohibition period	Action taken for study treatment	Medication category
Gabapentinoids	3 weeks prior to V3 and for the duration of the study	Discontinue study treatment upon second episode of medication use	Pain
Strong CYP3A4 inducers or inhibitors: **Inducers**: • Rifampicin • Carbamazepine • St John's Wort **Inhibitors**: • Azole antifungals • Antiviral protease inhibitors (boceprevir, ritonavir, saquinavir, nelfinavir, telaprevir) • Macrolide antibiotics (erythromycin, clarithromycin, telithromycin, azithromycin)	3 weeks prior to V3 and for the duration of the study	None	Other
CYP3A4 substrates with a narrow therapeutic range: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus	3 weeks prior to V3 and for the duration of the study	None	Other

Medication	Prohibition period	Action taken for study treatment	Medication category
Strong modulators of glucuronidation **Inducers**: rifampicin, phenobarbital, phenytoin, efavirenz, telmisartan, fluconazole **Inhibitors**: valproic acid, probenecid, fluconazole	3 weeks prior to V3 and for the duration of the study	None	Other
Grapefruit or Grapefruit Juice	Randomization during Initiation of IP (V3) through 24 hours after EoT (V9)	None	Other

B. Blinded Information

Available upon request.