COVER PAGE

Official Title:	A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients With Diabetic Peripheral Neuropathic Pain
NCT Number:	NCT05895552
Document Date:	09 May 2024

901-C-2102

A PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RTA 901 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN

RTA 901

VERSION 4.0 – 9 MAY 2024

SIGNATURE PAGE

Protocol 901-C-2102 was approved by:

_____ _____

[redacted], MD Date *(DD-MMM-YYYY)*

[redacted]

Biogen

INVESTIGATOR'S AGREEMENT

I have read the 901-C-2102 protocol and agree to conduct the study as outlined. I have received and read the Investigator's Brochure for RTA 901. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical Monitor and Study Medical Lead	[redacted]	Medical Director, [redacted] Biogen | 225 Binney Street | Cambridge, MA | 02142 Email: [redacted] Tel: [redacted] Cell: [redacted]
Clinical Trial Lead	[redacted]	CYPRESS Clinical Trial Lead Biogen | 225 Binney Street | Cambridge, MA | 02142 Email: [redacted] Tel: [redacted] Cell: [redacted]
Serious Adverse Event Reporting	[redacted] Fax: [redacted] Email: [redacted]	

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Study Drug:
RTA 901

Title of Study:
A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients with Diabetic Peripheral Neuropathic Pain

Study center(s): Approximately 75 study centers in the United States

Studied period:	**Phase of development:**
Estimated date first subject first visit: Jun 2023 Estimated date last subject last visit: Oct 2025	2

Objectives:

Primary:

Efficacy:

- To assess the efficacy of RTA 901 based on change from baseline in the average daily pain intensity score using the Numeric Pain Rating Scale (NPRS) after 12 weeks of treatment

Safety:

- To assess the safety and tolerability of RTA 901 during and following the Treatment Period

Secondary:

- To assess the efficacy of RTA 901 in achieving at least 30% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the efficacy of RTA 901 in achieving at least 50% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the percentage of subjects using rescue medication for diabetic peripheral neuropathic pain (DPNP) treatment during the Treatment Period, as well as the quantity and timing of such medication use during the Treatment Period
- To assess the Daily Sleep Interference Scale (DSIS) score after 12 weeks of treatment

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

Endpoints:

Primary, secondary, exploratory, [redacted] endpoints will be evaluated for each dose of RTA 901 compared to placebo.

Primary:

Efficacy:

- Change from baseline in the average daily NPRS pain intensity score during Week 12

Safety:

- Frequency, intensity, and relationship to study drug of adverse events and serious adverse events and change from baseline in the following assessments: physical examinations, vital sign measurements, electrocardiograms, clinical laboratory measurements, and body weight.

Secondary:

- Proportion of subjects who achieve at least a 30% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of subjects who achieve at least a 50% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of subjects using rescue medication for DPNP, as well as the quantity and timing of such medication use during the Treatment Period
- Change from baseline in the average DSIS score during Week 12

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

Methodology:

This is a 2-part, randomized, placebo-controlled, double-blind, Phase 2 study to evaluate the safety, tolerability, efficacy, [redacted] of RTA 901 in qualified subjects with DPNP. While on the study, subjects will take only 1 prescribed standard-of-care (SOC) pain medication (duloxetine, pregabalin, or gabapentin) at a stable dose (Section 7.8.1) and a single rescue medication, as needed, to treat DPNP (Section 7.8.3).

The duration of each part of the study will be approximately 20 weeks, including a Screening Period of up to 2 weeks, a Run-in Period of 2 weeks, a Treatment Period of 12 weeks, and a Follow-up Period of 4 weeks. All subjects in Part 1 and Part 2 of the study will follow the same visit and assessment schedule. Procedures will be performed according to the Schedule of Assessments.

Screening Period (Days -28 to -15): Includes 1 clinic visit up to 2 weeks prior to the Run-in Period (within 28 [± 2] days prior to Day 1). Daily NPRS and DSIS will be collected using an e-diary from Screening to the end-of-study visit. Washout from prohibited medications is allowed if the Investigator deems it medically appropriate; the washout period must cover 5 half-lives of the prohibited medication and must be completed prior to the end of the Screening Period, or in the case of NSAIDs for DPNP, washout must be completed prior to the last 7 days of Screening.

Run-in Period (Days -14 to -1): Includes 1 clinic visit which must occur during a 14 (± 2)-day period prior to Day 1. Subjects who continue to successfully meet the Run-in eligibility criteria will receive single-blind placebo once daily in the morning in addition to their SOC pain medication. All study drug should be administered in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and for 1 hour following study drug administration. Daily NPRS scores will continue to be collected using the e-diary. Pain intensity and rescue medication use will also continue to be recorded daily at bedtime in the e-diary. Subjects will also complete the DSIS upon waking.

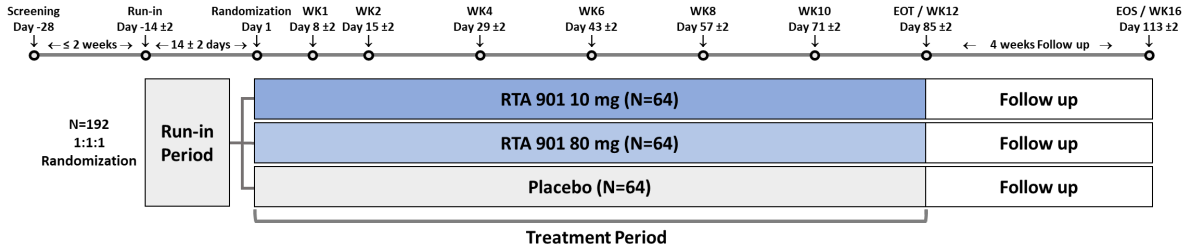
- Subjects in Part 1 who remain eligible after the Run-in period will be randomized 1:1:1 to either RTA 901 (10 or 80 mg) or placebo at Day 1 (randomization),
- Subjects in Part 2 who remain eligible after the Run-in period will be randomized 1:1:1 to either RTA 901 (Dose 1 or Dose 2) or placebo at Day 1 (randomization).

Treatment Period (Day 1 to Week 12): Includes 8 clinic visits over 12 weeks. Within each study part (ie, Part 1 or Part 2), subjects who successfully meet the randomization eligibility criteria will be randomized using randomization and trial supply management and stratified by SOC pain medication on Day 1. Post randomization, study drug will be dispensed according to the Schedule of Assessments. All study drug should be administered in an early fasted state (as described above).

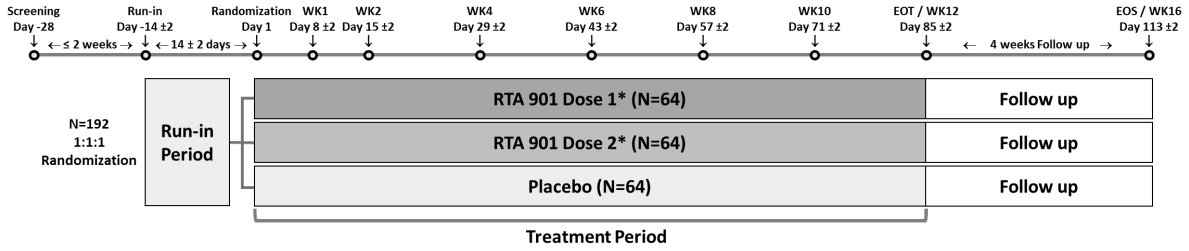
Follow-up/end of study (Week 16): Includes 1 clinic visit on Day 113 ± 2, which must occur approximately 4 weeks following the end of treatment visit.

Study Schema

Part 1



Part 2



*The Dose Selection Committee will select 2 doses of RTA 901 (1 to 80 mg) to be used in Part 2 of the study.

Abbreviations: EOS=end of study; EOT=end of treatment; Wk=Week

A Dose Selection Committee (DSC) will select the 2 doses of RTA 901 for Part 2 using data from Part 1 based on E-R analysis. E-R analysis will be conducted using efficacy data up to Week 12 of treatment with all subjects in Part 1 to provide a dosing recommendation for Part 2 to the DSC.

Subjects enrolled in Part 1 will not be eligible for enrollment in Part 2.

Number of subjects (planned):

Approximately 384 subjects are expected to be randomized across Part 1 and Part 2 (approximately 192 subjects per part, with 64 subjects per treatment arm within each part).

Diagnosis and main criteria for inclusion:

Run-in Inclusion Criteria:

1. Adult male and female subjects ≥ 18 years of age upon study consent;
2. Diagnosis of type 1 diabetes mellitus or type 2 diabetes mellitus at least 1 year prior to Screening;
3. Clinical diagnosis of DPNP defined as symptomatic distal symmetric polyneuropathy (secondary to diabetes) in the lower extremities, which may include symptoms of pain that is burning, lancinating, tingling, or shooting (electric shock–like). Pain in the lower extremities may occur with paresthesia or dysesthesia (unpleasant sensations of burning). Neuropathic pain may be accompanied by an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by light touch or contact, eg, with socks, shoes, and bedclothes (allodynia);
4. Currently taking only 1 allowed prescribed SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 4 weeks prior to Screening (Section 7.8.1);

5. Stable glycemic control as indicated by hemoglobin A1C values over the 3 months prior to Screening;
6. NPRS pain intensity score ≥ 4 on an 11-point scale at Screening;
7. A score ≥ 2.5 on the Michigan Neuropathy Screening Instrument Part B;
8. Body mass index < 45 kg/m^2;
9. A history of chronic pain related to DPNP present for at least 6 months prior to Screening;
10. Estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 at Screening using the Chronic Kidney Disease Epidemiology Collaboration equation;
11. Willing to sign and date an informed consent document indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any study-mandated procedures;
12. A negative COVID-19 test result during Screening.

Run-in Exclusion Criteria:

1. Has neuropathy from a cause other than type 1 diabetes mellitus or type 2 diabetes mellitus;
2. Has a condition other than DPNP that could confound the assessment of pain (eg, fibromyalgia or regional pain caused by lumbar or cervical compression);
3. Hemoglobin A1C > 11% at Screening;
4. Diabetic foot ulceration or infection within 90 days prior to Screening;
5. Has had more than 1 episode of ketoacidosis or hyperosmolar state requiring hospitalization within 90 days prior to Screening;
6. Has had more than 3 episodes of hypoglycemia requiring medical assistance within 90 days prior to Screening;
7. Any acute or chronic medical condition, or concurrent therapy (pharmaceutical or otherwise) which, in the opinion of the Investigator could potentially adversely impact subject safety, response to study drug, or interfere with study assessments;
8. Clinically significant and severe ophthalmologic disease, including but not limited to retinopathy, or visual field impairment which, in the opinion of the Investigator could potentially preclude enrollment in the study;
9. Serum aminotransferase (alanine aminotransferase or aspartate aminotransferase) levels > 1.5× the upper limit of normal at Screening;
10. Has HIV or active hepatitis B or C virus infection;
11. History of malignancy within 3 years prior to Screening, except for non-melanoma skin tumor, cervical carcinomas in situ, or successfully treated malignancies in remission;
12. Unwilling to practice a protocol-specified acceptable method of birth control (both males who have partners of child-bearing potential and females of child-bearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested (Section 6.7);
13. Females who are pregnant or breastfeeding;
14. Subject is, in the opinion of the Investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;
15. Known hypersensitivity to any component of the study drug;
16. Systolic blood pressure < 90 mmHg after a period of rest at Screening;
17. Pneumonia due to COVID-19 within 6 months prior to Screening or a history of COVID-19–related hospitalization within 6 months prior to Screening;

18. Known or suspected active drug or alcohol abuse, per Investigator judgement;
19. Use of the following medications:
    a. Use of another investigational drug or participation in an investigational study within 30 days or 5 half-lives of that investigational drug (whichever is longer), prior to Screening;
    b. Prior participation in a study with RTA 901;
    c. Neuroleptics, monoamine oxidase inhibitors, N-methyl-D-aspartate receptor ligand for pain (ketamine, amantadine, dextromethorphan [except low dose intermittent use for cough], memantine, methadone, dextropropoxyphene, and/or ketobemidone), and/or alpha-lipoic acid within 7 days prior to Screening;
    d. Tricyclic antidepressants and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); and/or 5-HT3 receptor antagonists, within 7 days prior to Screening;
    e. Exposure of drugs or chemicals that may cause neuropathy and interfere with clinical evaluation. Agents include but are not limited to pyridoxine, hydralazine, metronidazole, phenytoin, dapsone, amiodarone, nitrofurantoin, paclitaxel, vinblastine, vincristine, cisplatin, etoposide, didanosine, disulfiram, suramin, zalcitabine, anti-tuberculosis medications (eg, isoniazid, rifampin, ethambutol, ethionamide), heavy metals, and industrial solvents, within 7 days prior to Screening;
    f. Strong or moderate cytochrome P450 – isotype 3A4 inhibitors or inducers and P-glycoprotein inhibitors, within 14 days prior to Screening;
    g. Topical pain medications intended to treat pain associated with DPNP (including but not limited to lidocaine 5% patch, over-the-counter capsaicin, amitriptyline, and/or isosorbide dinitrate spray) within 7 days prior to Screening;
    h. Prescription patch containing 8% capsaicin use within 6 months prior to Screening;
    i. Opioid use at a dose of ≥ 30 morphine milligram equivalents on 3 or more days per week in the 30 days prior to Screening; or planned treatment with opioid or opioid-based drugs, including but not limited to tapentadol and/or tramadol from Screening throughout the course of the study;
    j. Central nervous system active drugs detected in the urine such as cocaine, amphetamines, and cannabinoids (marijuana);
    k. Oral prednisolone or equivalent within 7 days prior to Screening.
20. Use of the following devices or procedures:
    a. Transcutaneous electrical nerve stimulation unit for the treatment of DPNP within 30 days prior to Screening;
    b. Implanted neurostimulators;
    c. Nerve decompression surgery or plans for such surgery for treatment of DPNP;
    d. Steroid or local anesthetic nerve blocks within the last 12 months prior to Screening;
    e. Cryotherapy, intrathecal/epidural opioids, or botulinum toxin if administered within the last 6 months prior to Screening;
    f. Alternative medicine products or treatments (eg, acupuncture, naturopathy, homeopathy, etc.) within 7 days prior to Screening;
    g. Major surgery within 30 days prior to Screening or planned to occur during the course of the study.

Randomization Inclusion Criteria:

1. Subject has an average NPRS pain intensity score ≥ 4 on an 11-point NPRS calculated from pain assessments during the last 7 days prior to randomization. A minimum of 5 measurements must be recorded;
2. Subject must have a ≤ 3-point decline in NPRS pain intensity score during Run-in, which will be calculated using the average score during the last 7 days of Screening compared to the average score during the last 7 days of Run-In;
3. If subject is on insulin treatment to maintain glycemic control, the subject must have a relatively stable insulin dose with no drastic changes during Screening per the Investigator's judgement;
4. If subject is taking oral anti-diabetic medication, the subject must have a < 50% change of routine oral anti-diabetic agent dose from Screening oral anti-diabetic agent dose to Day 1;
5. Currently taking only 1 allowed prescribed SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 8 weeks prior to Day 1 with no anticipated changes to dose(s) during study (Section 7.8.1);
6. Has had a complete diabetic eye exam within the 12 months prior to randomization, as per SOC.

Randomization Exclusion Criteria:

1. Pneumonia due to COVID-19 or COVID-19–related hospitalization during Screening or Run-in;
2. Use of the following medications during Screening or Run-in:
   a. Neuroleptics, monoamine oxidase inhibitors, N-methyl-D-aspartate receptor ligand for pain (ketamine, amantadine, dextromethorphan [except low dose intermittent use for cough], memantine, methadone, dextropropoxyphene, and/or ketobemidone), and/or alpha-lipoic acid;
   b. Tricyclic antidepressants and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); and/or 5-HT3 receptor antagonists;
   c. Exposure of drugs or chemicals that may cause neuropathy and interfere with clinical evaluation. Agents include but are not limited to pyridoxine, hydralazine, metronidazole, phenytoin, dapsone, amiodarone, nitrofurantoin, paclitaxel, vinblastine, vincristine, cisplatin, etoposide, didanosine, disulfiram, suramin, zalcitabine, anti-tuberculosis medications (eg, isoniazid, rifampin, ethambutol, ethionamide), heavy metals, and industrial solvents;
   d. Strong or moderate cytochrome P450 – isotype 3A4 inhibitors or inducers and P-glycoprotein inhibitors;
   e. Topical pain medications intended to treat pain associated with DPNP (including but not limited to lidocaine 5% patch, over-the-counter capsaicin, amitriptyline, and/or isosorbide dinitrate spray);
   f. Prescription patch containing 8% capsaicin;
   g. Opioid use at a dose of ≥ 30 morphine milligram equivalents on 3 or more days per week during Screening or Run-in; or planned treatment with opioid or opioid-based drugs, including but not limited to tapentadol and/or tramadol throughout the course of the study;
   h. Central nervous system active drugs detected in the urine such as cocaine, amphetamines, and cannabinoids (marijuana);
   i. Oral prednisolone or equivalent.

3. Use of the following devices or procedures during Screening:
    a. Transcutaneous electrical nerve stimulation unit for the treatment of DPNP;
    b. Implanted neurostimulators;
    c. Nerve decompression surgery or plans for such surgery for treatment of DPNP;
    d. Steroid or local anesthetic nerve blocks;
    e. Cryotherapy, intrathecal/epidural opioids, or botulinum toxin;
    f. Alternative medicine products or treatments (eg, acupuncture, naturopathy, homeopathy, etc.);
    g. Major surgery during Screening or planned to occur during the course of the study.

Study drug, dosage, and mode of administration:

Part 1: RTA 901 capsules (10 mg or 80 mg) will be administered orally once daily

Part 2: RTA 901 capsules (2 doses selected from dose range of 1 to 80 mg) will be administered orally once daily

Duration of treatment:

14 weeks, when including 2-weeks single-blind Run-In

Reference therapy, dosage, and mode of administration:

Matching placebo will be administered orally once daily

Statistical methods:

This study will be conducted in 2 parts. A total of approximately 192 subjects (64 subjects per treatment arm) are planned for randomization in Part 1, and approximately 192 subjects (64 subjects per treatment arm) are planned for randomization in Part 2, for a total of 384 subjects to be randomized. This sample size is based on a dose-ranging scheme to evaluate initial safety, efficacy, [redacted] of RTA 901 in this subject population. The primary comparisons for efficacy are between each of the RTA 901 treatment groups and the placebo treatment group. The overall Type I error rate will be controlled at the 0.05 significance level using a hierarchical testing strategy that will be defined in the Statistical Analysis Plan. Power calculations are based on a 2-sample t-test with no adjustments for multiple comparisons. The study assumes a mean difference in NPRS pain intensity of 1.2 between each RTA 901 treatment group and placebo and a standard deviation of 2.4.

If doses selected for Part 2 do not include doses studied in Part 1, then an analysis by dose group for Part 1 or Part 2 doses will be performed following completion of each study part. With 64 subjects per treatment group, each study part has 80% power to compare treatment groups to placebo.

If doses selected for Part 2 include any doses studied in Part 1 (ie, 10 or 80 mg), then an analysis by dose group will be performed using Part 1 and Part 2 combined, following completion of the study. The dose group that is enrolled in both parts will have 128 subjects. With 128 placebo subjects compared to 128 subjects in the RTA 901 dose group, there is 98% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4). RTA 901 dose groups that are enrolled in only 1 part will have 64 subjects. With 128 placebo subjects compared to 64 subjects in each RTA 901 dose group, there is 90% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4).

The intent-to-treat analysis set is defined as all randomized subjects categorized by their randomized treatment group (whether or not they received study drug). The analysis population for the efficacy endpoints is the intent-to-treat population. Mixed-model repeated measures analyses will be used to analyze the primary efficacy endpoints. A detailed Statistical Analysis Plan will be developed prior to database lock.

The safety analysis set includes all randomized subjects who receive at least 1 dose of randomized study drug. The safety analysis set will be used for evaluation of safety variables. Subjects who receive at least 1 dose of RTA 901 will be classified in the RTA 901 group. Subjects who are randomized and receive at least 1 dose of placebo and no dose of RTA 901 will be classified in the placebo group. Subjects in the Run-in phase who fail to randomize into the Treatment Period will not be included in the placebo group.

Safety and tolerability will be evaluated by adverse events, serious adverse events, clinical laboratory test results, vital signs, electrocardiogram findings, physical examinations, and weight. All analyses of the safety data will be performed using the safety analysis set. Descriptive statistics will be presented by treatment group assignment in the safety analysis set. No formal statistical testing is planned for safety analyses.

An exposure-response (E-R) analysis for efficacy is planned for Part 1 using efficacy data up to Week 12 including all Part 1 subjects. Results from this E-R analysis will be used to determine the doses of RTA 901 to be studied in Part 2. Details of the E-R analysis for efficacy will be described in a separate analysis plan and the results will be reported in a separate standalone report, outside the clinical study report.

[redacted]

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LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CRA	clinical research associate
CS	clinically significant
CSR	clinical study report
CYP3A4	cytochrome P450 – isotype 3A4
DMC	Data Monitoring Committee
DPN	diabetic peripheral neuropathy
DPNP	diabetic peripheral neuropathic pain
[redacted]	[redacted]
DSC	Dose Selection Committee
DSIS	Daily Sleep Interference Scale
DSPN	distal symmetric polyneuropathy

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
E-R	exposure-response
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
HbA1c	Hemoglobin A1C
Hsp70	heat shock protein 70
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
LSM	least squares mean
MAD	multiple ascending dose
MMRM	mixed model repeated measures
MNSI	Michigan Neuropathy Screening Instrument
NCS	not clinically significant
[redacted]	[redacted]
NPRS	Numeric Pain Rating Scale
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
P-gp	P-glycoprotein
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	patient-reported outcome

Abbreviation or Specialist Term	Explanation
QD	once daily
RTSM	randomization and trial supply management
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	standard-of-care
[redacted]	[redacted]
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TENS	transcutaneous electrical nerve stimulation
[redacted]	[redacted]

1. INTRODUCTION

RTA 901, an orally bioavailable novobiocin derivative, is a potent C-terminal inhibitor of heat shock protein 90 (Hsp90) and is also an inducer of heat shock protein 70 (Hsp70) and the cytoprotective heat shock response. Activities of Hsp70 include, but are not limited to, support of the bioenergetic functions of mitochondria and direct involvement in the downregulation of inflammatory pathways controlled by nuclear factor-kappa B (NF-κB) signaling. Because of the sensitivity of the central and peripheral nervous system to inflammation and mitochondrial dysfunction, Hsp70 plays a critical role in models of neuronal injury (Ma, 2015; Ran, 2004; Lee, 2001; Park, 2012). RTA 901 has demonstrated marked activity in several animal models involving insensate and painful diabetic neuropathy, a model of L5+L6 (lumbar) spinal nerve ligation-induced painful neuropathy, a model involving motor dysfunction associated with neuronal inflammation and demyelination (ie, the experimental autoimmune encephalomyelitis [EAE] model of multiple sclerosis), as well as a model of c-jun driven demyelinating neuropathy (ie, a model of Charcot–Marie–Tooth disease and chronic inflammatory demyelinating polyneuropathy) (Zhang, 2018). The neuroprotective activities of RTA 901 have been shown to be dependent on Hsp70, as RTA 901 does not produce any effects in studies conducted in Hsp70-knockout mice (Ma, 2015; Zhang, 2018).

Given the preclinical data, Reata Pharmaceuticals, Inc. (hereinafter referred to as Reata or the Sponsor) is interested in pursuing further clinical development of RTA 901.

1.1. Clinical Experience

The safety, tolerability, [redacted] of oral RTA 901 have been evaluated in a first-in-human Phase 1 clinical study in healthy volunteers (Study 901-C-1503). This study was a randomized, single-center study that was conducted in 2 parts. Forty-eight subjects (n=36 RTA 901 versus n=12 Placebo) participated in Part 1, which consisted of a double-blind assessment of the safety, tolerability, [redacted] of single ascending dose (SAD) RTA 901 administered orally. Thirty subjects (n=24 RTA 901 versus n=6 Placebo) participated in Part 2, which consisted of a double-blind assessment of the safety, tolerability, [redacted] of multiple ascending dose (MAD) RTA 901 administered orally once daily for 14 days. Therefore, a total of 60 healthy volunteers have received oral RTA 901 over a dose range of 10 to 160 mg. [redacted] This study found that administration of single and multiple ascending doses of RTA 901 was generally safe and well tolerated.

The safety, tolerability, [redacted] of oral RTA 901 were also evaluated in 2 additional recently completed Phase 1 clinical studies:

- [redacted]

- [redacted]

1.1.1. Safety and Tolerability

Overall, RTA 901 oral capsules were well tolerated in healthy volunteers who took a single dose (10 to 160 mg) and multiple doses (10 to 80 mg) in a 14-day Phase 1 study (Study 901-C-1503). No serious adverse events (SAEs) or treatment-emergent adverse events (TEAEs) reportedly lead to study drug discontinuation, or were considered related to RTA 901. Of the unrelated TEAEs, most were Grade 1 in severity. No deaths were reported during the study.

During Part 1 (SAD) of Study 901-C-1503, the most common TEAE was contact dermatitis, which occurred in 2 subjects in the RTA 901 capsule cohorts (1 [16.7%] subject in the 120-mg cohort and 1 [16.7%] subject in the 160-mg cohort) and 1 (8.3%) subject in the pooled placebo cohort. Of note, the Investigator attributed the contact dermatitis TEAEs in the subjects who received RTA 901 to the electrocardiogram (ECG) electrode pads. No other specific TEAEs occurred in more than 1 subject. All TEAEs in Part 1 (SAD) were Grade 1 in severity.

One subject who received placebo with the RTA 901 120-mg cohort during Part 1 (SAD) of the study had a Grade 1 TEAE of ECG QT prolonged. The event resolved on Study Day 1 and the subject continued in the study. To determine if the occurrence of this TEAE would impact the safety and dosing of future cohorts, the subject's treatment assignment was unblinded during the study and identified as placebo. The Investigator did not change the original causality assessment of the TEAE following unblinding of the subject. There were no other clinically relevant ECG findings during Part 1 (SAD) of the study.

The TEAEs reported during Part 2 (MAD) of the study were Grade 4 blood creatine phosphokinase increased (RTA 901 10-mg cohort), Grade 1 myalgia (RTA 901 10-mg cohort), and Grade 1 contact dermatitis (RTA 901 40-mg cohort); however, no specific TEAEs occurred in more than 1 subject.

One subject in the RTA 901 10-mg cohort in Part 2 (MAD) of the study had a Grade 4 TEAE of blood creatine phosphokinase increased that began on Study Day 24 (10 days after completion of the 14-day dosing regimen). The event was assessed as unrelated to study drug by the Investigator. The subject completed the study following resolution of the TEAE at an Unscheduled Visit on Study Day 37. As a result of this TEAE, clinically relevant increases in mean creatine kinase at Study Day 24 and a mean change in creatine kinase from baseline to Study Day 24 were noted in the RTA 901 10-mg cohort in Part 2 (MAD) of the study. There

were no other clinically relevant mean or individual changes in laboratory parameters during Part 2 (MAD) of the study.

More detailed information about the known and expected benefits and risks of RTA 901 capsules may be found in the Investigator's Brochure (IB).

- [redacted]
- [redacted]
- [redacted]

[redacted]

1.2. Study Rationale

Diabetic neuropathy is the most common neurologic complication of diabetes mellitus and often used as a synonym of distal symmetric polyneuropathy (DSPN). Duration of diabetes mellitus and how well it is managed are important risk factors for the development of diabetic peripheral neuropathy (DPN) in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). It gradually affects the longest nerve fibers, with symptoms beginning distally and symmetrically in toes and feet. It may be present in at least 10% to 15% of patients newly diagnosed with T2DM with rates increasing to 50% after 10 years of disease duration (Pop-Busui, 2017). Treatment of diabetic peripheral neuropathic pain (DPNP) involves effective glycemic control, education and counseling on foot care and safety measures, and symptomatic treatment of pain. The pathogenesis of DPNP involves multiple differentially regulated pathways ultimately converging to mitochondrial dysfunction with bioenergetic failure and oxidative damage of axons, especially at the most distal portion.

Although there are several approved therapies for this condition, they are limited by efficacy and tolerability. Many treatments are discontinued, suggesting low levels of satisfaction and/or poor tolerability (Yang, 2015). Given this, and the large and growing population of patients with diabetes, a significant unmet medical need remains. Nonclinical data suggest that RTA 901 is able to improve dysfunction resulting from pathogenic demyelination of sensory fibers, along with mitigation of mitochondrial dysfunction. In addition, the potent pharmacological effects of RTA 901 shown in animal models support the hypothesis that RTA 901 may have potential therapeutic benefit to treat the central pathology underlying the development of DPNP.

Therefore, the current study is designed to investigate the efficacy and safety of multiple doses of RTA 901 in subjects with DPNP, when RTA 901 is added to the standard-of-care (SOC) pain medication. RTA 901 doses of 10 mg and 80 mg once daily (QD) will be investigated in Part 1 of this study. Based on an exposure-response (E-R) analysis for efficacy in Part 1, 2 doses of

RTA 901 between 1 to 80 mg QD will be investigated in Part 2 of the study. This will allow the Sponsor to determine the optimal dose(s) for future development.

1.3. Rationale for Study Population

Diabetic peripheral neuropathic pain is a common condition seen in both T1DM and T2DM. Neuropathic pain can lead to interference with daily activities, disability, psychosocial impairment, [redacted]. It may be associated with hyperalgesia and allodynia. Although there are approved therapies for this condition, they are limited by efficacy and tolerability. Many treatments are discontinued, suggesting low levels of satisfaction and/or poor tolerability (Yang, 2015). Given this, and the large and growing population of subjects with diabetes, a significant unmet medical need remains.

According to the Centers for Disease Control National Diabetes Statistics Report (2022), 37.3 million Americans have diabetes. The most common neuropathy associated with diabetes is DSPN (Pop-Busui, 2017). Although estimates of its incidence and prevalence vary, data suggests that DSPN occurs in at least 20% of subjects with T1DM after 20 years of disease. It may be present in at least 10% to 15% of subjects newly diagnosed with T2DM with rates increasing to 50% after 10 years of disease duration. Neuropathic pain, specifically DPNP, is present in up to 25% of subjects with DSPN.

The development of DPNP is associated with a small-fiber neuropathy resulting from dysfunction of unmyelinated or thinly myelinated sensory fibers and the gradual degeneration of larger myelinated fibers. Further, although numerous pathologic mechanisms contribute to DPNP (Farmer, 2012), increased oxidative stress and mitochondrial dysfunction appear to be a central facilitator in its development (Fernyhough, 2010). Nonclinical data suggest that RTA 901 is able to improve dysfunction resulting from pathogenic demyelination of sensory fibers, along with mitigation of mitochondrial dysfunction. Taken together, the potent pharmacological effects of RTA 901 shown in animal models support the hypothesis that RTA 901 may have potential therapeutic benefit to treat the central pathology underlying the development of DPNP.

1.4. Dose Rationale

Dose selection for Part 1 was based on the established safety profile from the first-in-human study in healthy subjects (Study 901-C-1503), [redacted], no observed adverse effect levels established in 3-month good laboratory practice (GLP) toxicity studies in mice and monkeys, and exposures required to produce efficacy in rodent models of DPN.

RTA 901 was generally safe and well tolerated following single doses of up to 160 mg and multiple daily doses (for 14 days) of up to 80 mg (Study 901-C-1503) [redacted] Additionally, at the highest proposed dose of 80 mg QD, there is at least a 40-fold safety margin based on the data from the 3-month GLP toxicity studies in mice and monkeys (Table 8 of the IB).

[redacted]

In summary, at the proposed doses for Part 1, RTA 901 is predicted to have efficacious and safe exposure in subjects with DPNP, with a 10 mg dose anticipated to be an efficacious dose and 80 mg the highest feasible dose with potentially maximal efficacy and an acceptable safety profile. However, based on the exposures associated with efficacy in the nonclinical models, it is possible that a dose lower than 10 mg may need to be explored to identify the minimally effective dose in subjects with DPNP and thereby enable a robust phase 2 dose ranging study. Therefore, a planned E-R analysis for efficacy from the all subjects in Part 1 of this study will be incorporated to recommend the optimal doses for investigation in Part 2. Eligible doses for selection in Part 2 will be limited to a dose range of 1 to 80 mg. Part 2 doses will not exceed 80 mg, at which there is at least a 40-fold safety margin based on the data from the 3-month GLP toxicity studies in mice and monkeys.

1.5. Risk/Benefit

There may be side effects and discomforts that are not yet known nor seen in previous studies. There may be risks or side effects that are related to the study drug and that are unknown at this time.

The potent pharmacological effects of RTA 901 seen in preclinical data demonstrate marked therapeutic activity in rodent models of insensate and painful diabetic neuropathy and support the hypothesis that RTA 901 may have potential therapeutic benefit to treat the central pathology underlying the development of DPNP.

Therefore, the risk-benefit profile for participating in the current study appears to be favorable.

2. STUDY OBECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Efficacy

- To assess the efficacy of RTA 901 based on change from baseline in the average daily pain intensity score using the Numeric Pain Rating Scale (NPRS) after 12 weeks of treatment

2.1.1.2. Safety

- To assess the safety and tolerability of RTA 901 during and following the Treatment Period

2.1.2. Secondary Objectives

- To assess the efficacy of RTA 901 in achieving at least 30% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the efficacy of RTA 901 in achieving at least 50% decrease in the NPRS pain intensity score after 12 weeks of treatment
- To assess the percentage of subjects using rescue medication for DPNP treatment during the Treatment Period, as well as the quantity and timing of such medication use during the Treatment Period
- To assess the Daily Sleep Interference Scale (DSIS) score after 12 weeks of treatment

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

2.2. Study Endpoints

The primary, secondary, exploratory, [redacted] endpoints will be evaluated for each dose of RTA 901 compared to placebo.

2.2.1. Primary Endpoints

2.2.1.1. Efficacy

- Change from baseline in the average daily NPRS pain intensity score during Week 12

2.2.1.2. Safety

- Frequency, intensity, and relationship to study drug of adverse events (AEs) and SAEs and change from baseline in the following assessments: physical examinations, vital sign measurements, ECGs, clinical laboratory measurements, and body weight

2.2.2. Secondary Endpoints

- Proportion of subjects who achieve at least a 30% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of subjects who achieve at least a 50% decrease from baseline in the Week 12 average NPRS pain intensity score
- Proportion of subjects using rescue medication for DPNP, as well as the quantity and timing of such medication use during the Treatment Period
- Change from baseline in the average DSIS score during Week 12

[redacted]

3. INVESTIGATIONAL PLAN

Study procedures will follow the Schedule of Assessments (Table 4).

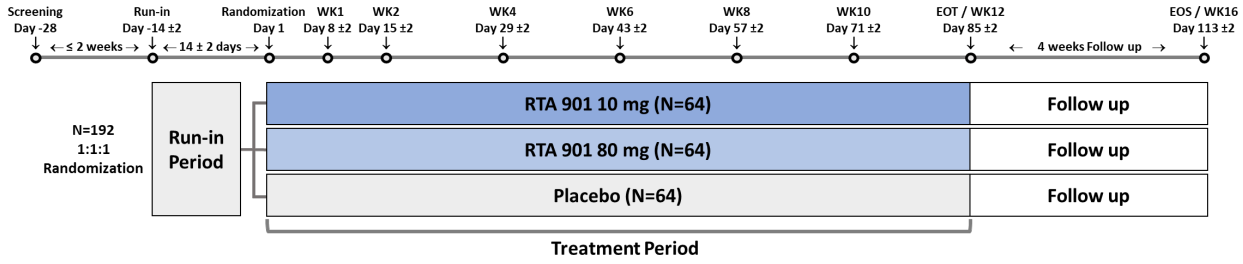
3.1. Study Design

This is a 2-part, randomized, placebo-controlled, double-blind, Phase 2 study to evaluate the safety, tolerability, efficacy, [redacted] of RTA 901 in qualified subjects with DPNP. Approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 1, and approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 2, for a total of 384 subjects randomized. Randomization within each part will be stratified by SOC pain medication using randomization and trial supply management (RTSM). A total of approximately 75 sites in the United States will be included in this study.

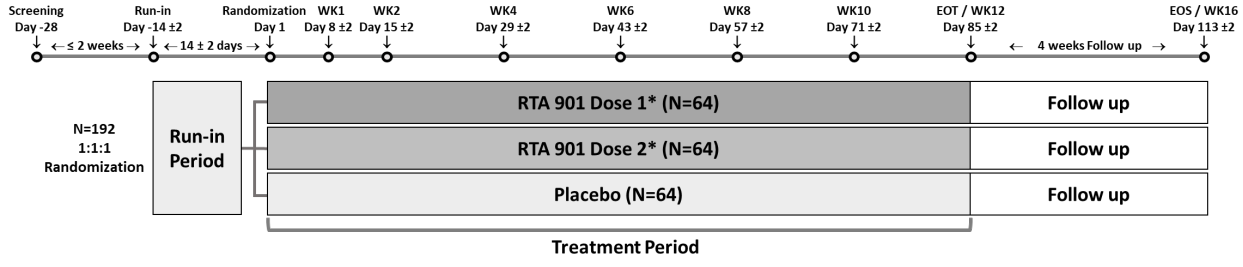
The duration of each part of the study will be approximately 20 weeks, including a Screening Period of up to 2 weeks, a Run-in Period of 2 weeks, a Treatment Period of 12 weeks, and a Follow-up Period of 4 weeks. All subjects in Part 1 and Part 2 of the study will follow the same visit and assessment schedule.

Figure 1: Study Design

Part 1



Part 2



*The Dose Selection Committee will select 2 doses of RTA 901 (1 to 80 mg) to be used in Part 2 of the study.

Abbreviations: EOS=end of study; EOT=end of treatment; Wk=Week

3.2. Screening Period (Days -28 to -15)

The Screening Period includes 1 clinic visit, up to 2 weeks prior to the Run-in Period (within 28 days prior to Day 1, approximately, as the visit has a ± 2-day window). Upon Institutional Review Board (IRB) approval of the protocol, potential subjects will be required to sign a written informed consent form (ICF) for the study before any study-specific screening procedures are performed. See Section 10.4 for details on informed consent. Subjects who meet the Run-in

inclusion criteria (Section 4.1) and none of the exclusion criteria are considered eligible to proceed to Run-in. Washout from prohibited medications is allowed during the Screening Period if the Investigator deems it medically appropriate; the washout period must cover 5 half-lives of the prohibited medication and must be completed prior to the end of the Screening Period, Or, in the case of NSAIDs for DPNP, the washout must be completed prior to the last 7 days of screening.

Subjects will be given access to an e-diary at Screening and will be trained on how to use it. Subjects will be directed to complete the NPRS and record their rescue medication usage in the e-diary at bedtime. Subjects will also complete the DSIS via their study-issued e-diary daily upon waking. Subjects who have been diagnosed with T1DM or T2DM at least 1 year prior to Screening, with hemoglobin A1c (HbA1c) ≤ 11% and who have been suffering from painful diabetic peripheral neuropathy in the lower extremities for at least 6 months, will be screened for diabetic polyneuropathy using the Michigan Neuropathy Screening Instrument (MNSI) Part B, and will be included if a score ≥ 2.5 is obtained. Subjects must have a score ≥ 4 on the 11-point NPRS for average pain intensity over the past 24 hours at Visit 1, denoting moderate to severe pain.

Additional procedures [redacted] assessments are to be completed according to the Schedule of Assessments (Table 4).

The rescreening process is described in Section 4.4.3.

3.3. Run-in Period (Days -14 to -1)

The Run-in Period includes 1 clinic visit, which must occur during a 14 (± 2)-day period prior to Day 1. Subjects who continue to successfully meet the Run-in eligibility criteria will be enrolled and receive single-blind placebo once daily in the morning. All study drug should be administered in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and 1 hour following study drug administration. Since the first dose will be taken in-clinic at the Run-in visit, subjects should fast for 2 hours prior to the visit.

During the Run-in Period, NPRS and rescue medication use will continue to be recorded daily at bedtime in the e-diary. Subjects will also complete the DSIS upon waking. The baseline score will be calculated as the mean of the pain scores recorded daily by the subject within the last 7 days prior to randomization (the average value is to be rounded to 1 decimal point). Fluctuations in the pain score are allowed. A minimum of 5 measurements must be recorded. Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).

The subjects should be reminded not to take the single-blinded study drug on the morning of the treatment Day 1 visit.

If changes in the subject's health occur during the Screening and Run-in Periods before randomization, including changes in medication affecting the status of the subject, the Medical Monitor should be notified. The Medical Monitor will advise the Investigator regarding any assessments that should be repeated to ensure eligibility requirements are met.

3.4. Treatment Period (Day 1 to Week 12)

The Treatment Period includes 8 clinic visits over 12 weeks. Within each part of the study, subjects who successfully meet the Randomization eligibility criteria will be randomized using RTSM and stratified by SOC pain medication on Day 1, see Section 4.5. Post randomization, study drug will be dispensed, according to the Schedule of Assessments (Table 4). Once daily, subjects will self-administer 1 capsule from each bottle included in their study drug kits orally, according to Section 7.5. All study drug should be administered in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and 1 hour following study drug administration. [redacted] Subjects should also fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16). Additional study procedures and assessments will be performed according to the Schedule of Assessments (Table 4).

Subjects will be instructed to use rescue medication as needed for DPNP per Section 7.8.3. Subjects will be directed to continue completing the NPRS and recording their rescue medication usage in the e-diary at bedtime. Upon waking, subjects will be asked to complete the DSIS. Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).

Week 12/Day 85 will be the end of treatment (EOT) visit.

3.5. Follow-up/End of Study (Week 16)

The Follow-up Period includes 1 clinic visit on Day 113 ± 2, which must occur approximately 4 weeks following the EOT visit. Procedures will be performed according to the Schedule of Assessments (Table 4). Completion of this visit concludes the subject's participation in the study.

Subjects will be directed to continue completing the NPRS and recording their rescue medication usage in the e-diary at bedtime. Upon waking, subjects will be asked to complete the DSIS. Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).

3.6. Part 2 Dose Selection Process

A Dose Selection Committee (DSC) comprised of Sponsor personnel and an external pharmacometrics consultant will select the 2 doses of RTA 901 for Part 2 using data from Part 1. An E-R analysis for efficacy will be conducted with efficacy data from all subjects up to Week 12 of treatment in Part 1 and provide a dosing recommendation for Part 2 to the DSC. The selected doses will be documented in a Note-to-File to the Investigators and IRBs (as appropriate) and will not require a protocol amendment.

It is possible that enrollment in Part 2 of the study may begin while some Part 1 subjects are completing their remaining study visits. Subjects enrolled in Part 1 will not be eligible for enrollment in Part 2.

Details of the membership, objectives, and process to be followed by the DSC will be described in a separate charter. Additionally, a separate data management and analysis plan supporting this activity will be created. Results will be reported in a separate standalone report, outside the clinical study report (CSR).

4. STUDY POPULATION

4.1. Run-in Eligibility

4.1.1. Run-in Inclusion Criteria

1. Adult male and female subjects ≥ 18 years of age upon study consent;
2. Diagnosis of T1DM or T2DM at least 1 year prior to Screening;
3. Clinical diagnosis of DPNP defined as symptomatic distal symmetric polyneuropathy (secondary to diabetes) in the lower extremities, which may include symptoms of pain that is burning, lancinating, tingling, or shooting (electric shock–like). Pain in the lower extremities may occur with paresthesia or dysesthesia (unpleasant sensations of burning). Neuropathic pain may be accompanied by an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by light touch or contact, eg, with socks, shoes, and bedclothes (allodynia);
4. Currently taking only 1 allowed prescribed SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 4 weeks prior to Screening (Section 7.8.1);
5. Stable glycemic control as indicated by HbA1c values over the 3 months prior to Screening;
6. NPRS pain intensity score ≥ 4 on an 11-point scale at Screening;
7. A score ≥ 2.5 on the MNSI Part B;
8. Body mass index < 45 kg/m^2;
9. A history of chronic pain related to DPNP present for at least 6 months prior to Screening;
10. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 at Screening using the Chronic Kidney Disease Epidemiology Collaboration equation;
11. Willing to sign and date an informed consent document indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any study-mandated procedures;
12. A negative COVID-19 test result during Screening.

4.1.2. Run-in Exclusion Criteria

1. Has neuropathy from a cause other than T1DM or T2DM;
2. Has a condition other than DPNP that could confound the assessment of pain (eg, fibromyalgia or regional pain caused by lumbar or cervical compression);
3. HbA1c > 11% at Screening;
4. Diabetic foot ulceration or infection within 90 days prior to Screening;
5. Has had more than 1 episode of ketoacidosis or hyperosmolar state requiring hospitalization within 90 days prior to Screening;

6. Has had more than 3 episodes of hypoglycemia requiring medical assistance within 90 days prior to Screening;
7. Any acute or chronic medical condition, or concurrent therapy (pharmaceutical or otherwise) which, in the opinion of the Investigator could potentially adversely impact subject safety, response to study drug, or interfere with study assessments;
8. Clinically significant and severe ophthalmologic disease, including but not limited to retinopathy, or visual field impairment which, in the opinion of the Investigator could potentially preclude enrollment in the study;
9. Serum aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) levels > 1.5× the upper limit of normal at Screening;
10. Has HIV or active hepatitis B or C virus infection;
11. History of malignancy within 3 years prior to Screening, except for non-melanoma skin tumor, cervical carcinomas in situ, or successfully treated malignancies in remission;
12. Unwilling to practice a protocol-specified acceptable method of birth control (both males who have partners of child-bearing potential and females of child-bearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested (Section 6.7);
13. Females who are pregnant or breastfeeding;
14. Subject is, in the opinion of the Investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;
15. Known hypersensitivity to any component of the study drug;
16. Systolic blood pressure < 90 mmHg after a period of rest at Screening;
17. Pneumonia due to COVID-19 within 6 months prior to Screening or a history of COVID-19–related hospitalization within 6 months prior to Screening;
18. Known or suspected active drug or alcohol abuse, per Investigator judgement;
19. Use of the following medications:
    a. Use of another investigational drug or participation in an investigational study within 30 days or 5 half-lives of that investigational drug (whichever is longer), prior to Screening;
    b. Prior participation in a study with RTA 901;
    c. Neuroleptics, monoamine oxidase inhibitors, N-methyl-D-aspartate receptor ligand for pain (ketamine, amantadine, dextromethorphan [except low dose intermittent use for cough], memantine, methadone, dextropropoxyphene, and/or ketobemidone), and/or alpha-lipoic acid within 7 days prior to Screening;
    d. Tricyclic antidepressants and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); and/or 5-HT3 receptor antagonists, within 7 days prior to Screening;
    e. Exposure of drugs or chemicals that may cause neuropathy and interfere with clinical evaluation. Agents include but are not limited to pyridoxine, hydralazine, metronidazole, phenytoin, dapsone, amiodarone, nitrofurantoin, paclitaxel,

vinblastine, vincristine, cisplatin, etoposide, didanosine, disulfiram, suramin, zalcitabine, anti-tuberculosis medications (eg, isoniazid, rifampin, ethambutol, ethionamide), heavy metals, and industrial solvents, within 7 days prior to Screening;

f. Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors, within 14 days prior to Screening;
g. Topical pain medications intended to treat pain associated with DPNP (including but not limited to lidocaine 5% patch, over-the-counter capsaicin, amitriptyline, and/or isosorbide dinitrate spray) within 7 days prior to Screening;
h. Prescription patch containing 8% capsaicin use within 6 months prior to Screening;
i. Opioid use at a dose of ≥ 30 morphine milligram equivalents on 3 or more days per week in the 30 days prior to Screening; or planned treatment with opioid or opioid-based drugs, including but not limited to tapentadol and/or tramadol from Screening throughout the course of the study;
j. Central nervous system active drugs detected in the urine such as cocaine, amphetamines, and cannabinoids (marijuana);
k. Oral prednisolone or equivalent within 7 days prior to Screening.

20. Use of the following devices or procedures:

a. Transcutaneous electrical nerve stimulation (TENS) unit for the treatment of DPNP within 30 days prior to Screening;
b. Implanted neurostimulators;
c. Nerve decompression surgery or plans for such surgery for treatment of DPNP;
d. Steroid or local anesthetic nerve blocks within the last 12 months prior to Screening;
e. Cryotherapy, intrathecal/epidural opioids, or botulinum toxin if administered within the last 6 months prior to Screening;
f. Alternative medicine products or treatments (eg, acupuncture, naturopathy, homeopathy, etc.) within 7 days prior to Screening;
g. Major surgery within 30 days prior to Screening or planned to occur during the course of the study.

4.2. Randomization Eligibility

4.2.1. Randomization Inclusion Criteria

1. Subject has an average NPRS pain intensity score ≥ 4 on an 11-point NPRS calculated from pain assessments during the last 7 days prior to randomization. A minimum of 5 measurements must be recorded;
2. Subject must have a ≤ 3-point decline in NPRS pain intensity score during Run-in, which will be calculated using the average score during the last 7 days of Screening compared to the average score during the last 7 days of Run-In;
3. If subject is on insulin treatment to maintain glycemic control, the subject must have a relatively stable insulin dose with no drastic changes during Screening per the Investigator's judgement;
4. If subject is taking oral anti-diabetic medication, the subject must have a < 50% change of routine oral anti-diabetic agent dose from Screening oral anti-diabetic agent dose to Day 1;

5. Currently taking only 1 allowed prescribed SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 8 weeks prior to Day 1 with no anticipated changes to dose(s) during study (Section 7.8.1);
6. Has had a complete diabetic eye exam within the 12 months prior to randomization, as per SOC.

4.2.2. Randomization Exclusion Criteria

1. Pneumonia due to COVID-19 or COVID-19–related hospitalization during Screening or Run in;
2. Use of the following medications during Screening or Run-in:
   a. Neuroleptics, monoamine oxidase inhibitors, N-methyl-D-aspartate receptor ligand for pain (ketamine, amantadine, dextromethorphan [except low dose intermittent use for cough], memantine, methadone, dextropropoxyphene, and/or ketobemidone), and/or alpha-lipoic acid;
   b. Tricyclic antidepressants and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); and/or 5-HT3 receptor antagonists;
   c. Exposure of drugs or chemicals that may cause neuropathy and interfere with clinical evaluation. Agents include but are not limited to pyridoxine, hydralazine, metronidazole, phenytoin, dapsone, amiodarone, nitrofurantoin, paclitaxel, vinblastine, vincristine, cisplatin, etoposide, didanosine, disulfiram, suramin, zalcitabine, anti-tuberculosis medications (eg, isoniazid, rifampin, ethambutol, ethionamide), heavy metals, and industrial solvents;
   d. Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors;
   e. Topical pain medications intended to treat pain associated with DPNP (including but not limited to lidocaine 5% patch, over-the-counter capsaicin, amitriptyline, and/or isosorbide dinitrate spray);
   f. Prescription patch containing 8% capsaicin;
   g. Opioid use at a dose of ≥ 30 morphine milligram equivalents on 3 or more days per week during Screening or Run-in; or planned treatment with opioid or opioid-based drugs, including but not limited to tapentadol and/or tramadol throughout the course of the study;
   h. Central nervous system active drugs detected in the urine such as cocaine, amphetamines, and cannabinoids (marijuana);
   i. Oral prednisolone or equivalent.
3. Use of the following devices or procedures during Screening:
   a. TENS unit for the treatment of DPNP;
   b. Implanted neurostimulators;
   c. Nerve decompression surgery or plans for such surgery for treatment of DPNP;
   d. Steroid or local anesthetic nerve blocks;
   e. Cryotherapy, intrathecal/epidural opioids, or botulinum toxin;
   f. Alternative medicine products or treatments (eg, acupuncture, naturopathy, homeopathy, etc.);

g. Major surgery during Screening or planned to occur during the course of the study.

4.3. Protocol Waivers

Protocol waivers are not allowed. If there is an immediate hazard to a subject, the Investigator may deviate from the protocol using his/her best medical judgment to ensure the subject's safety. If such a deviation occurs, the site must notify the Sponsor and IRB within 48 hours.

4.4. Retesting and Rescreening

4.4.1. Retesting

Retesting is defined as repeating abnormal laboratory tests within the same study part.

Subjects who fail to qualify for the study based on an abnormal laboratory test may have any individual laboratory test retested once within the same study part at the discretion of the Investigator.

4.4.2. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently assigned to the study drug or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in accordance with Section 4.4.3.

4.4.3. Rescreening

Subjects who fail to meet all Run-in inclusion/exclusion criteria may be considered for rescreening at the discretion of the Investigator after consultation with the Medical Monitor. These subjects will be considered Screen Failures.

Subjects may repeat Screening once to qualify for the study. If a subject is approved to rescreen, they will be given a new subject number and all screening procedures will be repeated.

Subjects who participate in the Run-in Period but fail to meet the Randomization criteria will not be allowed to rescreen for the study. These subjects will be considered Randomization Failures.

4.5. Subject Enrollment and Randomization

Following a Screening Period of up to 2 weeks, eligible subjects will be enrolled and enter a single-blind placebo Run-in Period (14± 2 days). Subjects in Part 1 who remain eligible (according to Randomization eligibility criteria) will be randomized 1:1:1 to either RTA 901 (10 or 80 mg) or placebo at Day 1, and subjects in Part 2 who remain eligible will be randomized 1:1:1 to either RTA 901 (Dose 1 or Dose 2) or placebo at Day 1 (see Table 3). Approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 1, and approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 2. Randomization within each part will be stratified using RTSM into 2 strata based on approved

SOC pain medication. One stratum will include subjects taking duloxetine, while the other stratum will include subjects taking pregabalin or gabapentin.

Table 3: Treatment Arms by Study Part

Study Part	Treatment Arms		
Part 1 (N=192)	10 mg RTA 901 (N=64)	80 mg RTA 901 (N=64)	Placebo (N=64)
Part 2 (N=192)	Dose 1 RTA 901 (N=64) (selected from dose range of 1 to 80 mg)[a]	Dose 2 RTA 901 (N=64) (selected from dose range of 1 to 80 mg)[a]	Placebo (N=64)

Abbreviations: E-R=exposure-response

[a] Dose selection in Part 2 will be determined by a Dose Selection Committee and based off an E-R analysis for efficacy from all subjects in Part 1.

4.5.1. Methods for Ensuring Blinding

In this 2-part, randomized, placebo-controlled, double-blind study, all subjects, Investigators, site personnel, and laboratories (except the bioanalytical laboratory) with direct involvement in the conduct of the study or their designees will be blinded to randomized treatment assignments. Subjects will be blinded throughout the study. Investigators will not be blinded in the single-blind Run-in Period but will be blinded in the double-blind Treatment Period of the study. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the subjects and personnel mentioned previously. To maintain the blind, Investigators will distribute blinded study drug kits to subjects as assigned by the RTSM (Section 7.3). The Data Monitoring Committee (DMC) will review unblinded safety data and make recommendations as appropriate. Members of the DSC will be unblinded to recommend Part 2 doses of RTA 901, respectively.

4.5.2. Methods for Unblinding

For subject unblinding, the Investigator is encouraged to contact the Medical Monitor to discuss situations in which he or she believes that the blind should be broken, but ultimately the Investigator has the right to break the blind (eg, in the event of a serious or life-threatening medical situation). If unblinding is required, the Investigator will utilize RTSM to perform the unblinding. If a study drug assignment is unblinded, the Investigator must describe the event that required unblinding in the subject's source documents. Subjects must discontinue taking the study drug if their treatment assignment has been unblinded to the Investigator (or designee). Such subjects must undergo the same study discontinuation procedures as those subjects who discontinue taking study drug for other reasons. Subject treatment assignments must not be unblinded in the case of an AE or SAE except as described above.

4.5.2.1. Unblinding for Regulatory Submission

In situations where regulation requires unblinding and reporting of a particular SAE, the appropriate bodies (eg, IRBs, regulatory agencies) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to any Investigator, site personnel or subject; therefore, this type of unblinding does not necessitate

that the subject discontinues taking study drug. In cases when unblinded information must be conveyed to local health authorities, the Clinical Program Operations and Data Management teams must be excluded.

4.5.2.2. Data Monitoring Committee

An independent DMC will review the accumulating unblinded safety [redacted] data throughout the study and make recommendations as appropriate.

The DMC will consist of external experts supported by an independent statistical group which will prepare unblinded analyses for the DMC and will have no role in the Statistical Analysis Plan (SAP) after the study has started enrolling subjects. A separate statistical group not associated with the DMC will be responsible for producing and finalizing the SAP and executing the final data analysis of the study.

The DMC will be governed by a charter that will describe the following:

- Roles and responsibilities of the DMC members and the independent statistical group;
- Meeting format and frequency;
- Communication channels between the DMC, the independent statistical group, the Sponsor, and the blinded study statisticians;
- Voting process and requirements (eg, requirement of consensus for issuance of a termination recommendation);
- Provisions governing conflict of interest and confidentiality.

Briefly, the DMC will review the progress of the study and the accumulating unblinded safety data while the study is ongoing. The DMC will make recommendations to Sponsor representatives following each meeting. The DMC may recommend that the study continue as is, be modified to protect subject safety, or be terminated for safety. The DMC can make recommendations for the study based specifically on the analysis of the primary endpoint.

4.5.2.3. Dose Selection Committee

The DSC will be comprised of Sponsor personnel and an external pharmacometrics consultant. The E-R analysis will be conducted for efficacy using unblinded data from all subjects in Part 1, which is the basis for dosing recommendation of Part 2 to DSC. Eligible doses for selection in Part 2 will be limited to a dose range of 1 to 80 mg of RTA 901. The selected doses will be documented in a Note-to-File to the Investigators and IRBs (as appropriate) and will not require a protocol amendment.

Details of the membership, objectives, and process to be followed by the DSC will be described in a separate charter. Additionally, a separate data management and analysis plan supporting this activity will be created. Results will be reported in a separate standalone report, outside the CSR.

4.6. Study Drug Discontinuation, Interruption, and Subject Termination

4.6.1. Discontinuation of Study Drug

Discontinuation from study drug does not mean discontinuation from the study. Subjects who discontinue the study drug early for any reason should complete the procedures associated with the Week 12/EOT visit at the closest study visit. If the subject discontinued study drug during a study visit, the EOT procedures should be performed during that study visit. If the subject discontinues study drug in between visits, he/she will perform the EOT procedures at the next scheduled study visit. The subject will then complete the procedures associated with the Week 16/end of study (EOS) visit 4 weeks after discontinuation.

If a clinically significant (CS) finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

4.6.2. Resuming Study Drug after Interruptions

The term interruption generally refers to a temporary halt in study drug administration. This can be either at the direction of the site, or by the subject's decision or non-compliance. An interruption from the study drug based on the subject's decision or non-compliance will be defined as missing at least 3 consecutive days of study drug administration. There is no minimum timeframe for a site directed interruption.

If study drug has been interrupted, the Investigator should conduct an evaluation to determine whether the subject is still eligible to receive study drug, and, if so, how to resume the assigned treatment. This should include a confirmation that the reason for discontinuation was not a per protocol specified reason (see Section 4.6.3) and that the subject's circumstances have not changed in a manner that would prohibit administration of the study drug (eg, the subject is now taking a prohibited medication).

4.6.3. Subject Discontinuation and Termination

Subjects are free to withdraw from participation in the study at any time upon request. Subjects who wish to withdraw from the study should complete the procedures associated with the Week 12/EOT visit at the nearest study visit and the Follow-up Week 16/EOS visit 4 weeks later.

At their discretion, an Investigator may discontinue or withdraw a subject. Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- Withdrawal by subject;
- Investigator decision;
- Adverse event;
- Death;
- Pregnancy;
- Protocol deviation;

- Study terminated by Sponsor;
- Significant study non-compliance, as per Run-in Exclusion Criteria 14 and Section 7.6;
- Lost to follow-up; or
- Other (specify).

The term discontinuation refers to a *permanent* halt in study drug administration.

The reason for subject discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF). A comprehensive physical examination, body weight, vital signs measurement, ECG, laboratory analysis, urine pregnancy test for females of child-bearing potential, urine sample for urinalysis, and an assessment of concomitant medications and AEs will be performed at the closest study visit, according to Section 4.6.1. [redacted]

Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to AEs; the clock time, time in relation to dose, and date the sample was taken will be recorded.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

If a positive result is obtained on a pregnancy test for a subject, or a subject reports that they or their female partner become(s) pregnant during the study, the subject must be discontinued immediately. The Investigator must report the pregnancy within 1 business day of the site being aware, as described in Section 6.6.

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

4.6.4. Termination of the Study

Although the Sponsor intends to complete the study, the Sponsor reserves the right to terminate the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor terminates the study, all study drug will be discontinued, and the Investigator will be provided guidance on how to close out participation of all subjects enrolled in the study.

5. STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as outlined in the Schedule of Assessments (Table 4). However, it is anticipated that from time to time there may be circumstances outside the control of the Investigator that may make it unfeasible to perform a test. In these cases, the Investigator must take all necessary steps to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the Investigator will document the reason for the missed test and any corrective and preventative actions which were taken to ensure that the required procedures are adhered to as soon as possible. The Study Management Team must be informed of these incidents in a timely manner.

5.1. Administrative Procedures

5.1.1. Informed Consent

Written informed consent (Section 10.4) must be obtained from the subject before any study-related procedures are performed. Re-consenting will be required when there is an update or change in the study procedures, safety information, or any other information that may affect the subject's willingness to participate.

5.1.2. Inclusion/Exclusion

Both the Run-in and Randomization inclusion and exclusion criteria must be reviewed as indicated in Section 4.1 and Section 4.2. Subjects must meet all inclusion and no exclusion criteria for entry into the study and randomization on Day 1. Investigators should contact the Medical Monitor with any questions regarding randomization eligibility prior to randomizing the subject on Day 1.

5.1.3. Demographics

Demographic data including date of birth, age, sex, ethnicity, and race will be collected as indicated in Table 4.

5.1.4. Medical History

A complete medical history, including surgical history, alcohol, tobacco, and nicotine-containing product use histories for the past 5 years, will be taken at Screening. All relevant changes throughout the study after Screening will be recorded in the subject's source document and eCRF as AEs.

5.1.5. Prior and Concomitant Medications

The name, dose, and frequency must be recorded for all medications that the subject is taking. All allowed and excluded medications should be recorded including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used where possible. Prior and concomitant medications (ie, medications that the subject is taking or has taken within 30 days prior to Screening) will be reviewed per Table 4 and all changes throughout the study after Screening will be recorded in the subject's source

document and eCRF. Prior opioid use to manage DPNP will be recorded for the past 5 years prior to Screening.

5.1.6. Adverse Events

Investigators and study staff are responsible for detecting, documenting, and reporting AEs and SAEs. For each subject, reporting of AEs and SAEs begins after written informed consent/assent is provided. Throughout the study, subjects will be provided opportunities to report AEs. For more information on AEs, see Section 6.3.

5.1.7. Electronic Diary Set-up

During Screening, subjects deemed likely to be eligible for the study will be given access to an e-diary and trained on how to record daily pain scores from Screening up to Day 1. The results will be reviewed on Day 1 to confirm that the subject is eligible for the study. The use of an e-diary will improve consistency and reliability of scoring for NPRS and DSIS, and timing of dosing and rescue medication.

Subjects will be instructed to report the NPRS number that best indicates the average intensity of pain over the last 24 hours throughout the study daily at bedtime. Subjects will also complete the DSIS via their e-diary daily upon waking. Non-compliance is defined as recording less than 70% of expected PROs during any evaluation period (visit to visit).

[redacted], treatment administration, and rescue medication usage will also be recorded in the e-diary.

5.2. Clinical Procedures/Assessments

5.2.1. Height Measurement

Height will be measured only at Screening; the subject will not wear shoes during the measurement of height.

5.2.2. Weight Measurement

Body weight will be measured at the times indicated in Table 4. Weight should be taken with no shoes, hats, and outerwear. Body mass index will be calculated at Screening for eligibility.

5.2.3. Comprehensive Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 4 and as documented within the medical record. The comprehensive physical examination must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological.

Assessments of any specific signs or symptoms reported by the subject must also be performed and documented along with any other findings of note. Clinically significant findings at Screening must be addressed in medical history (ie, findings should be attributable to a diagnosis recorded in medical history). The physical examination performed at Screening will serve as the baseline physical examination for clinical assessments. Following the examination at Screening,

new or changed physical examination findings meeting the definition of an AE must be reported as an AE. If possible, the same individual should perform each physical examination on a subject during the study.

5.2.4. Targeted Physical Examination

Targeted physical examinations are symptom-directed examinations and involve the organ system(s) associated with the symptoms exhibited or reported. Targeted physical examinations are to be performed at visits indicated in Table 4.

5.2.5. Electrocardiogram

The 12-lead ECGs will be recorded at the times indicated in Table 4.

The ECGs will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, or sleeping) during the rest period.

Triplicate ECGs, approximately 1 minute apart, for the QT/QTc using Fridericia's correction formula review will be obtained at the required nominal time points.

Baseline for clinical assessments will be those measurements obtained prior to study drug administration on Day 1. Another ECG will be performed approximately 1-hour postdose on Day 1.

Each ECG will be printed and evaluated by an appropriately qualified Investigator at the study site (the "local reader"). The local reader will sign and date each ECG and provide a global interpretation using the following categories or equivalent:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – CS
- Unable to evaluate

The local reader evaluations of the triplicate ECGs will be entered into the electronic source documents or eCRFs. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (eg, sinus bradycardia, arrhythmia). Only overall diagnosis CS Abnormal ECG findings will be reported as AE.

All original ECG tracings will be retained as source documentation in the subject's records at the study site.

5.2.6. Vital Sign Measurements

Vital signs, including blood pressure, heart rate, respiration rate, and body temperature, will be assessed on the study days indicated in Table 4 or at early discontinuation. The vital sign measurements obtained just prior to study drug administration on Day 1 will serve as the baseline measurements for clinical assessments. Blood pressure and heart rate will be measured after the subject has been sitting for at least 5 minutes. Three blood pressure recordings will be

obtained and recorded at each assessment; each recording should be a minimum of 2 minutes apart. The average of the second and third readings will be calculated and assessed.

5.2.7. Michigan Neuropathy Screening Instrument

The distal symmetrical peripheral neuropathy will be evaluated at Screening using MNSI.

The MNSI is widely used for the evaluation of distal symmetrical peripheral neuropathy in diabetes (Herman, 2012). It has 2 parts: 1) history (subject portion) and 2) physical examination findings (clinician's portion). The first part (Part A) is a 15-item self-administered questionnaire, and the second part (Part B) is a lower extremity examination that includes inspection and assessment of vibratory sensation and ankle reflexes and is scored by assigning points for abnormal findings. Scores vary from 0 to 1 for each abnormality in the foot appearance, Achilles reflexes presence and vibratory by tuning fork and monofilament testing.

To be eligible for randomization, subjects must have a score ≥ 2.5 on MNSI Part B only; Part A will not be used in this study. The MNSI (Part B) will be assessed by the Investigator per Table 4.

5.3. Laboratory Procedures/Assessments

Samples will be obtained at a minimum for the clinical laboratory tests at the times indicated in Table 4. Samples will be stored under conditions stipulated in the Central Laboratory Manual until they are transported for measurement. Samples will be transported and measured by a central laboratory. The laboratory results will be reviewed, signed, and dated by an Investigator.

- Clinical laboratory tests may be repeated at the discretion of the Investigator to verify any out-of-range value;
- The Investigator will follow the CS, out-of-range value to a satisfactory clinical resolution or until the out-of-range value becomes NCS; and
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE.

5.3.1. Pregnancy Tests for Females of Child-bearing Potential

A serum or urine pregnancy test will be performed at the times indicated in Table 4. A serum pregnancy test will be performed at Screening for females of child-bearing potential or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs.

5.3.2. Follicle-Stimulating Hormone

Follicle-stimulating hormone (FSH) will only be assessed at Screening for female subjects who have been post-menopausal for at least 1 year and are not surgically sterile (e.g., not had bilateral tubal ligation, bilateral oophorectomy, or a hysterectomy). The investigator, based on the available information (including the FSH result), uses their clinical judgment to determine whether or not the participant is of child-bearing potential.

5.3.3. Serology

5.3.3.1. Hepatitis Screen

Subjects will have blood tested for the presence of hepatitis B surface antigen and hepatitis C virus antibody at Screening. Only those subjects with negative results for the presence of hepatitis B surface antigen and hepatitis C virus antibody will be allowed to enroll in the study.

5.3.3.2. HIV Screen

Subjects will have blood tested for the presence of anti-HIV antibodies (HIV-1/HIV-2) at Screening. Only those subjects with negative results for the presence of antibodies will be allowed to enroll in the study. The results of the HIV antibody testing will be retained by the clinical unit under confidential restriction with the exception of reporting to government authorities as required by law.

5.3.4. COVID-19 Test

A COVID-19 test will be performed at the times indicated in Table 4 for all subjects.

5.3.5. Drugs of Abuse and Cotinine Screen

A urine screen for drugs of abuse and cotinine will be performed at Screening. The panel for drugs of abuse will minimally include cannabinoids, opiates, 3,4-methylenedioxymethamphetamine, methadone, methamphetamine, oxycodone, phencyclidine, tricyclic antidepressants, barbiturates, amphetamines, cocaine, and benzodiazepines. Results of all tests will be retained by the investigative site.

5.3.6. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses as indicated in Table 4 ferritin, creatine kinase, blood urea nitrogen, enzymatic creatinine, eGFR, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, amylase, lipase, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin, lactate dehydrogenase, magnesium, chloride, bicarbonate, and gamma-glutamyl transferase.

5.3.6.1. Estimated Glomerular Filtration Rate Equation

The equation used to calculate the eGFR is the Chronic Kidney Disease Epidemiology Collaboration equation:

$$\text{eGFR (mL/min/1.73 m}^2) = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

Where S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ or 1 and max indicates the maximum of S_{cr}/κ or 1. Age indicates age at time of serum creatinine lab collection.

5.3.7. International Normalized Ratio

Samples will be collected for international normalized ratio as indicated in Table 4.

5.3.8. Hematology

Samples will be collected for the following hematology assessments as indicated in Table 4: hematocrit, hemoglobin, red blood cell count, white blood cell count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected), absolute platelet count, mean corpuscular hemoglobin , mean corpuscular volume, and mean corpuscular hemoglobin concentration.

5.3.9. Urinalysis and Microscopy

Samples will be collected for the following urinalysis and microscopy assessments as indicated in Table 4: specific gravity, ketones, pH, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and a microscopic examination (if indicated based on laboratory results).

[redacted]

5.3.11. Hemoglobin A1c

Samples will be collected for HbA1c as indicated in Table 4. Detailed instructions on collection, storage, and shipment of the samples will be provided in the Central Laboratory Manual provided to the Investigator.

5.3.12. Fasting Lipid Profile

Samples will be collected for the following lipid assessments as indicated in Table 4: total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides. Subjects should

fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16).

5.4. Patient Reported Outcome Assessments

5.4.1. Pain Evaluation

Diabetic polyneuropathy is a common neurologic complication of diabetes and one of the most common causes of peripheral neuropathy. It is primarily a distal symmetric sensory polyneuropathy and early signs reflect the gradual loss of integrity of both large myelinated (loss of vibratory sensation and proprioception and reduced ankle reflexes) and small myelinated and unmyelinated nerve fibers (impairment of pain, light touch, and temperature sensation). Most sensory axons are unmyelinated, thus making them more susceptible to damage. In other words, distal portions of the longest myelinated and unmyelinated sensory axons are initially involved, with relative sparing of motor axons. Thus, symptoms begin presenting distally and symmetrically in the toes and feet and later, sensory loss ascends to the hands causing the typical "stocking-glove" sensory loss.

Approximately 50% of subjects with diabetes experience DPN and around 15 to 20% of subjects with diabetic neuropathy have pain in the feet. Alleviation of pain is the is a primary goal and cornerstone of subject management. The approved treatments for DPNP include 3 oral medications (duloxetine, pregabalin, and tapentadol) and a topical patch (containing 8% capsaicin). Of these, tapentadol (an opioid medication) and the 8% capsaicin patches are prohibited per protocol, see Section 7.8.4. The approved medications are suboptimal and both effective pain relief and tolerability remain elusive. Thus, a large unmet need remains for the treatment of DPNP.

The development of specific easy to use questionnaires for neuropathic pain-based essentially on verbal self-reporting of qualitative aspects of pain has improved the diagnosis and management of DPNP in the past decade. These instruments can serve 2 different purposes, for screening and assessing DPNP. They can be used in clinical and research settings to detect neuropathic pain and monitor treatment response. In addition, they are quick, easy to use and understandable for most subjects. Demonstration of effectiveness for pain reduction assessed via a PRO measure and interpretability, meaningfulness, and clinical significance on the pain scores are essential for approval of new pain treatments.

5.4.1.1. Numeric Pain Rating Scale

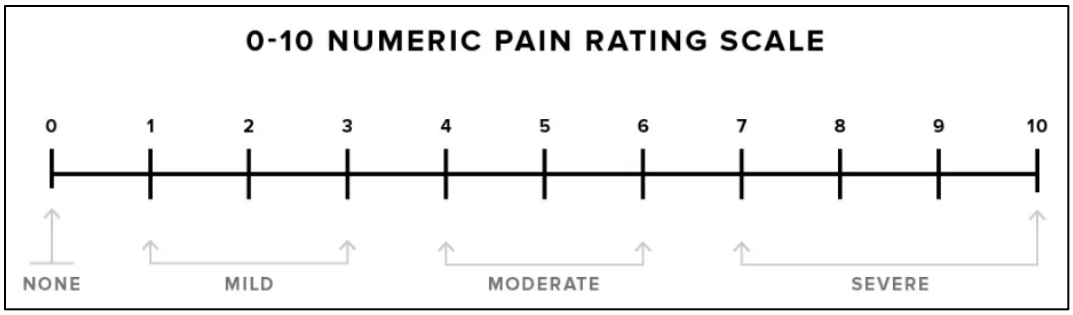
In order to highlight how people experience pain sensations differently and how the unpleasant aspects of pain can differ from pain intensity, subjects will report how they perceive their average pain intensity, worst pain intensity, and other characteristics of their pain during the past 24 hours at bedtime, using the 11-point NPRS as per Table 4.

The NPRS of pain intensity is a numeric scale, ranging from 0 (representing no pain at all) to 10 (representing the worst pain imaginable) (Figure 3). The subject selects a whole number (0 to 10) that best indicates the intensity of his/her pain in the past 24 hours.

Subjects must have a score ≥4 on the NPRS at Screening and an average NPRS pain intensity score ≥4 during the last 7 days prior to randomization with a minimum of 5 measurements

(Section 4.2.1). The results from this PRO will be used to determine the efficacy of RTA 901 in achieving at least a 30% or a 50% decrease in pain scores after 12 weeks of treatment.

Figure 2: Numeric Pain Rating Scale

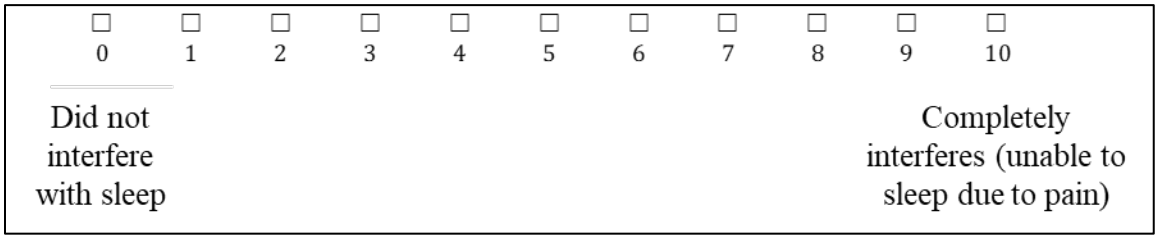


5.4.1.2. Daily Sleep Interference Scale

Often felt during the night, DPNP causes substantial interference in sleep and quality of life. The DSIS is a PRO that was developed to quantify sleep interference due to pain. The DSIS will be completed daily by subjects upon waking (3-minute self-administered questionnaire), preferably in the morning, to accurately capture variability in sleep interference due to pain, thus minimizing recall bias. Using the e-diary, subjects will assess how pain has interfered with their sleep during the past 24 hours as per Table 4.

The DSIS is a numeric scale, ranging from; 0 representing no interference with sleep to 10 representing complete inability to sleep (Figure 3, Vernon, 2008). The subject selects a whole number (0 to 10) that best indicates his/her ability to sleep in the past 24 hours.

Figure 3: Daily Sleep Interference Scale



[redacted]

[redacted]

5.5. Schedule of Assessments

Table 4 lists the overall schedule of assessments for the study.

Table 4: Schedule of Assessments (Part 1 & 2)

Study Period	Screening Period[a]	Run-in Period[b]	Treatment Period								Follow-up Period
Study Visit	Screening	Run-in	Day 1[c]	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 / EOT	Week 16 / EOS[d]
Study Day	Day -28 to -15	Day-14 to -1 (± 2)	Day 1	Day 8 (± 2)	Day 15 (± 2)	Day 29 (± 2)	Day 43 (± 2)	Day 57 (± 2)	Day 71 (± 2)	Day 85 (± 2)	Day 113 (± 2)
Administrative Procedures:											
Informed Consent	X										
Run-in Inclusion/Exclusion[e]	X	X									
Demographics	X										
Medical History	X										
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[f]	X	X	X	X	X	X	X	X	X	X	X
Electronic Diary Set-up	X										
Clinical Procedures/Assessments:											
Height Measurement[g]	X										
Weight Measurement[h]	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Physical Examination	X		X							X	X
Targeted Physical Examination[i]		X		X	X	X	X	X	X		
ECG	X		X[j]	X						X	X
Vital Sign Measurements	X	X	X	X	X	X	X	X	X	X	X
MNSI	X										
Laboratory Procedures/Assessments:											
Pregnancy Tests for Females of Child-bearing Potential[k]	X		X	X	X	X	X	X	X	X	X
FSH[l]	X										
Serology (Hepatitis and HIV Screening)	X										
COVID-19 Test	X		X								
Drug of Abuse and Cotinine Screen	X										
Clinical Chemistry	X		X	X	X	X	X	X	X	X	X
INR	X		X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X
Urinalysis and Microscopy	X		X	X	X	X	X	X	X	X	X
HbA1c	X					X		X		X	X
Fasting Lipid Profile[n]	X					X		X		X	X

Study Period	Screening Period[a]	Run-in Period[b]	Treatment Period								Follow-up Period
Study Visit	Screening	Run-in	Day 1[c]	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 / EOT	Week 16 / EOS[d]
Study Day	Day -28 to -15	Day-14 to -1 (± 2)	Day 1	Day 8 (± 2)	Day 15 (± 2)	Day 29 (± 2)	Day 43 (± 2)	Day 57 (± 2)	Day 71 (± 2)	Day 85 (± 2)	Day 113 (± 2)
Study Drug Procedures:											
Randomization Inclusion/Exclusion			X								
Randomization			X								
Dispense Study Drug		X	X			X		X			
Study Drug Administration[o]		X	X[p]	X	X	X	X	X	X	X	
Collect / Review Study Drug			X			X		X		X	
Patient Reported Outcome Assessments:											
NPRS[q]	X	X	X	X	X	X	X	X	X	X	X
DSIS[r]	X	X	X	X	X	X	X	X	X	X	X
[redacted]											

Abbreviations: [redacted] DSIS=Daily Sleep Interference Scale; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; [redacted] FSH=follicle-stimulating hormone; HbA1c=Hemoglobin A1c; INR=International Normalized Ratio; IRB=Institutional Review Board; MNSI=Michigan Neuropathy Screening Instrument; [redacted]; NPRS=Numeric Pain Rating Scale; [redacted]

[a] The Screening Period includes 1 clinic visit up to 2 weeks prior to the Run-in Period (within approximately 28 days prior to Day 1), see Section 3.2.

[b] The Run-in Period includes 1 clinic visit and must occur during a 14 (± 2) day period prior to the Day 1 first dose, see Section 3.3.

[c] Day 1 includes the first dose administration, and all procedures must be performed before study drug administration, except for adverse events, 1-hour postdose ECG, [redacted].

[d] Subjects who discontinue study drug early for any reason should complete the procedures associated with the Week 12/EOT visit at the nearest study visit and the Follow-up Week 16/EOS visit 4 weeks later.

[e] Run-in eligibility procedures do not need to be repeated at the Run-in visit; however, a review of any changes in eligibility criteria should be evaluated prior to Run-in visit procedures.

[f] Adverse event assessments should be performed after the informed consent has been signed.

[g] Height should be measured with no shoes.

[h] Weight should be measured with no shoes, hats, or outerwear.

[i] Investigator will evaluate if a targeted physical examination is needed, based on any symptomatology reported to the study team.

[j] ECG on Day 1 should be recorded at predose and 1-hour postdose.

[k] A serum pregnancy test will be performed at Screening for females of child-bearing potential or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs.

[l] FSH will only be assessed at Screening for female subjects who have been post-menopausal for at least 1 year and are not surgically sterile.

[redacted]

[n] Subjects should fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16).

[o] All study drug administration should be performed in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and for 1 hour following study drug administration. Since the first dose will be taken in-clinic and there are no [redacted] or fasting lipids taken at the Run-in visit, subjects should fast for 2 hours prior to the visit.

[p] On visits containing both labs with fasting and study drug administration, the longer fasting guidance (8 hours) is to be followed, these are not additive.

[q] Subjects will complete the NPRS in the e-diary daily at bedtime.

[r] Subjects will complete the DSIS in the e-diary daily upon waking.

5.6. Unscheduled Visits

Unscheduled visits may be performed at any time and for any reason, including those not specifically mentioned in this section, as deemed necessary by the Investigator.

Unscheduled visits conducted for the following reasons should include collection of AEs, clinical chemistry, hematology, concomitant medication collection, and vital signs:

- Management of an AE or SAE;
- Performance of additional laboratory tests for clinically abnormal laboratory test values or to confirm a possible pregnancy;
- Subject safety evaluation.

Unscheduled visits conducted for the following reasons do not require additional assessments unless deemed necessary by the Investigator:

- Study drug dispensation;
- Any operational need that would require the subject to return to the site between scheduled visits.

6. SAFETY REPORTING, MEDICAL MANAGEMENT, AND OVERSIGHT

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety assessments. Safety parameters include vital sign measurements, ECG results, AEs, SAEs, weight, and laboratory test results.

6.1. Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a subject regardless of its causal relationship to study drug. An AE can be any unfavorable and unintended sign (including any CS abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

The definition above, provided for in the good clinical practice (GCP) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6, is being extended for the purpose of Reata studies to include any events, intercurrent diseases and accidents observed while the subject is on study, ie, during the actual Treatment Period, as well as during drug-free, pre- and post-Treatment Periods.

All AEs observed or reported by the subject during the study (from the time of consent until the final visit or 30 days following final study dose for subjects who terminate early) must be reported, regardless of their relationship to study drug or their clinical significance. All conditions present prior to time of consent should be documented as medical history.

6.1.1. Definition of Non-treatment-emergent Adverse Event

Adverse events that present after signing of the ICF and prior to the initiation of study drug will be categorized as non-TEAEs and considered “not applicable” for the causality assessment with study drug.

6.1.2. Definition of Treatment-emergent Adverse Event

Adverse events that present, or worsen in intensity or frequency, following the initiation of study treatment will be categorized as TEAEs.

6.2. Definitions of Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital anomaly or birth defect in an offspring of a subject taking study drug
- Is an important medical event

The term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of consent until the final visit). Certain pregnancy outcomes will require submission as an SAE (Section 6.6).

6.3. Recording of Adverse Events

At every study visit, subjects must be asked a standard, non-directed question, such as, "How do you feel?" or "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses should be recorded in the source documents.

In addition to subject observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, ECG abnormalities, or other documents that are relevant to subject safety.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Pre-existing conditions (present before the start of the AE collection period, prior to signed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication (except disease progression) should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Elective procedures (surgeries or therapies) scheduled prior to the start of AE collection should not be recorded as AEs but rather documented in the subject's source documents as elective (eg, elective periodontal surgery). However, if a preplanned procedure is performed early (eg, as an emergency) because of a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

While an AE is ongoing, changes in the severity (eg, worsening or improving) should be noted in the source documents but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF. Adverse events characterized as intermittent require documentation of onset and duration.

6.3.1. Adverse Events Based on Signs and Symptoms

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s).

6.3.2. Adverse Events Based on Tests or Examinations

Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged by the Investigator to be CS (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation).

If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

6.3.3. Follow-up of Unresolved Adverse Events

All drug-related (Section 6.3.4) AEs, including CS abnormal laboratory test results reported or observed during the study, must be followed to resolution (either return to baseline or within normal limits). All other AEs or non–drug-related abnormal laboratory results will be followed through the final visit (ie, EOS or early termination). Information to be collected includes type of event, date of onset, date of resolution, Investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

6.3.4. Assessment of Causality

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug but could have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with study drug administration seems likely.

Definitely: This relationship suggests that a definite causal relationship exists between the study drug administration and the AE, and other conditions (eg, concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Not Applicable: AE occurred prior to administration of first dose of study drug.

6.3.5. Assessment of Severity

The Investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

Mild: Symptoms causing no or minimal interference with usual social and functional activities

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities

Severe: Symptoms causing inability to perform usual social and functional activities

6.4. Reporting of Serious Adverse Events

Initial Reports

Any AE, occurring from the time of consent until the final visit or 30 days following final study dose for subjects who terminate early, that meets the criteria of serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event. To report the SAE, fax or email the completed SAE form along with any supporting documentation (eg, subject discharge summary or autopsy reports) to [redacted] (fax number and email listed below in Table 5) within 24 hours of awareness.

Table 5: Serious Adverse Event Reporting Contact Information

[redacted]
E-mail: [redacted]

For questions regarding SAE reporting, contact your Study Manager, Monitor, or Medical Monitor at [redacted].

Follow-up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (eg, subject discharge summary or autopsy reports), should be faxed or emailed to Sponsor/designee (Table 5).

The Sponsor or its designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible, but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other

SAEs that do not meet the fatal or life-threatening unexpected criteria but are reported to be associated with the study drug, the Sponsor or its designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. The Sponsor or its designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the Investigators for their information and submission to their IRB, as appropriate.

Investigators are responsible for informing their IRB of any SAEs at their site, as appropriate. The DMC will review all safety data in an unblinded manner throughout the study and make recommendations as appropriate. All SAE correspondence with regulatory authorities or IRBs must be submitted to the Sponsor or its designee for recording in the study file.

6.5. Overdose

An overdose is defined as a subject administering any dose as non-compliant (more than 120% of expected study drug visit to visit). Overall, the RTA 901 toxicity program has identified the liver and kidney as target organs at doses producing systemic exposures (based on AUC) at least 50-fold above those observed in humans at the highest planned clinical dose of 80 mg. The adverse effects on liver and kidney identified in GLP toxicity studies were associated with readily monitorable and standard clinical pathology evaluations and were reversible after drug discontinuation. Overall, safety margins of > 40-fold were established, based on systemic exposures (ie, AUCs) at the no observed adverse effect levels from the 3-month GLP toxicity studies in mice and monkeys and the systemic exposure (ie, AUC) at the highest dose in human subjects (ie, 80 mg).

Any overdose is required to be reported within 24 hours either as an AE or SAE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious and meet the serious criteria (Section 6.2), the event must be reported as an SAE according to Section 6.4.

6.6. Pregnancy

During the study, all female subjects must be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, late or missed menstrual period). Male subjects must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant.

If a subject or Investigator suspects that the subject may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the subject must discontinue taking study drug and be discontinued from the study (Section 4.6.3).

Pregnancy in a study subject must be reported to the responsible safety party within 1 business day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. The Investigator must follow a pregnant subject or the pregnant female partner of a male subject (if consenting) and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. The Sponsor or its designee may contact the Investigator to request additional information throughout the course of the pregnancy.

Pregnancy in a study subject is not considered an AE. However, the following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form:

- Congenital anomaly/birth defect;
- Stillbirth; or
- Spontaneous miscarriage.

6.7. Methods of Birth Control

During Screening, while taking study drug, and until 30 days following administration of the final dose of study drug, females of child-bearing potential must practice 1 of the following highly effective methods of birth control:

- Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal, or transdermal) as prescribed;
- Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed);
- Use of an intrauterine hormone-releasing system as prescribed;
- Vasectomized partner (with vasectomy performed at least 6 months prior to Screening with the appropriate post-procedure documentation of surgical success). Partner *must* be the sole partner for that subject;
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

In addition, female participants should not donate eggs for the duration of the study and for at least 30 days after their last dose of study treatment.

During Screening, while taking study drug, and until 30 days after the final dose of study drug, fertile males who have female partners of child-bearing potential must practice 1 of the following methods of birth control:

- Partner contraception methods; *must* be the sole partner for that subject:
  - Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed);
  - Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal or transdermal) as prescribed;
  - Use of an intrauterine hormone-releasing system as prescribed;
  - Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (eg, x-ray, ultrasound);
  - Reproductive potential has been terminated by radiation;

  - Postmenopausal (defined as no menses for at least 1 year without an alternative medical cause).

- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

In addition, male participants should not donate sperm for the duration of the study and for at least 90 days after their last dose of study treatment.

6.8. Management of Elevated Aminotransferase Levels (ALT and/or AST)

If a subject's aminotransferases are elevated, follow the instructions outlined in Table 6.

Table 6: Management of Elevated Aminotransferase Levels (ALT and/or AST)

ALT and/or AST Level(s)	Dose Discontinuation (Yes/No)
> 8× ULN	Yes
> 5× ULN for more than 2 weeks	
> 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)	
> 3× ULN and (TBL > 2× ULN **or** INR > 1.5)	
> 3× ULN	No

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; TBL=total bilirubin; ULN=upper limit of normal

6.9. Management of Study Drug-Related Toxicities

In the case of serious toxicities, the Investigator may choose to interrupt study drug administration. See Section 4.6.2 for details on resuming study drug after interruptions.

7. STUDY DRUG

7.1. Dose and Treatment Regimens

Study drug is defined as either RTA 901 or placebo. During the Run-in Period, subjects will be administered single-blind placebo once daily in the morning. During the Treatment Period, subjects will be administered double-blind study drug QD in the morning according to their randomized assignment (Table 3).

7.2. Identity of Study Drug

RTA 901 drug product information is shown in Table 7. Information about the placebo is shown in Table 8.

Table 7: Part 1 RTA 901 Drug Product Information

Description	RTA 901 capsule (10 mg size #4, 40 mg size #0)
Ingredients	Active Ingredients: RTA 901 [redacted] Inactive Ingredients: Lactose Monohydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose Capsule Shell
Route of Administration	Oral

Table 8: Placebo Information

Description	Placebo for RTA 901 capsule (size #4, size #0)
Ingredients	Active Ingredients: N/A Inactive Ingredients: Lactose Monohydrate, Microcrystalline Cellulose, Magnesium Stearate, Hypromellose Capsule Shell
Route of Administration	Oral

7.3. Study Drug Packaging and Labeling

The study drug will be supplied in tamper-evident kits containing high-density polyethylene bottles. Each bottle will utilize foil induction-seal liners and a child-resistant closure. In Part 1, each bottle of study drug will contain 30 capsules of 10 mg or 40 mg strength RTA 901 or the matching placebo capsules. In Part 2, each bottle of study drug will contain 30 capsules of RTA 901 or matching placebo capsules, depending on the doses of RTA 901 recommended by the DSC (see Section 3.6).

In Part 1, the study drug kits will contain a combination of bottles, each containing active or placebo capsules in varying strengths to make up each dosing regimen. Table 9 shows the combination of bottles that will be used to comprise the dose for each treatment arm, while maintaining the study blind in Part 1. Kit configurations for Part 2 will depend on the doses recommended by the DSC. As in Part 1, the kits for each treatment arm will contain the same

number of bottles and the same configuration of capsule sizes necessary to maintain the study blind.

Table 9: Study Drug Kit Configurations – Part 1

Treatment Arm	Bottles of 10 mg Size #4 RTA 901	Bottles of Size #4 Placebo	Bottles of 40 mg Size #0 RTA 901	Bottles of Size #0 Placebo
Placebo	0	1	0	2
RTA 901 10 mg	1	0	0	2
RTA 901 80 mg	0	1	2	0

The label on each bottle will contain, at minimum, the following information:

- Medication ID number;
- Protocol 901-C-2102;
- Expiry date;
- Contains 30 capsules;
- Study Drug Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use. Keep out of reach of children;
- Control or lot number;
- Store at 15°C to 25°C (59°F to 77°F);
- Reata Pharmaceuticals, Inc., Plano, TX 75024

7.4. Study Drug Storage

Clinical study sites must store the study drug in a secure location at 15° to 25°C (59° to 77°F) and maintain a temperature excursion log of the storage conditions. Temperature excursion logs must be available for review at each monitoring visit. If the study drug is stored outside of the designated conditions for 24 hours or more, a temperature excursion notification should be submitted to the Sponsor for review and approval for use of the affected study drug.

7.5. Study Drug Administration

Subjects must self-administer 1 capsule orally from each of the bottles included in their study drug kit QD, beginning at Run-in through the end of the Treatment Period, as indicated in Table 4. Each dose of study drug should be administered at approximately the same time each day and will be recorded in the e-diary. All doses should be taken in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and 1 hour following study drug administration. [redacted]

A vomited dose must not be replaced. A double dose (eg, missed dose from previous day and dose for current day) must not be taken.

It is the responsibility of the Investigator or designee to provide clear instructions to the subject regarding the number and type of capsules to be ingested at each study drug administration timepoint listed in Table 4. Subjects must be instructed to continue taking study drug once daily through Week 12 unless:

1. The subject has been otherwise instructed by the Investigator, or
2. The subject has been formally discontinued from study drug.

7.6. Treatment Compliance

The Investigator or his/her designated and qualified representatives will only dispense study drug to subjects enrolled in the study in accordance with the protocol. Subjects should administer study drug exactly as instructed by the site. Non-compliance is defined as taking less than 80% or more than 120% of expected study drug during any evaluation period (visit to visit).

Subjects should record in the e-diary all administered and missed doses of study drug. The reason for a missed dose should be recorded in the e-diary. A missed dose includes drug holidays and temporary study drug discontinuations. Subjects will be asked to return all unused study drug (study drug bottles and any unused capsules).

Refer to Section 5.1.7 for compliance related to PRO completion via the e-diary.

7.7. Study Drug Accountability

The Investigator, or designee, will maintain a record of all study drug received, dispensed, and returned to the Sponsors' designee. An Investigator or his/her designated representatives will administer the study drug only to subjects enrolled in the study. A current (running) and accurate inventory of study drug will be kept by each Investigator and will include shipping invoices and the date on which study drug is dispensed/administered to the subject. An overall accountability of the study drug will be performed and verified by the study monitor throughout the study and at the closeout visit. Upon completion or termination of the study, all original containers (containing unused study drug) will be returned to the Sponsor or its designee, according to instructions from the Sponsor and according to local regulations. Labels must remain attached to the containers. Local study drug destruction is only allowed with prior Sponsor approval.

7.8. Concomitant and Other Treatments

7.8.1. Standard of Care Pain Medications

Subjects are required to take only 1 SOC pain medication for neuropathic pain (consistent with regional or local SOC guidelines for DPNP) at a stable dose (defined as < 50% change in total dose) that does not exceed the maximum dose in the prescribing information for approximately 4 weeks prior to Screening. Allowed SOC pain medications include duloxetine, pregabalin, and gabapentin. Attempts should be made to maintain the stable dose of pain therapy. If changes to the dose are necessary, the Investigator should discuss with the Medical Monitor. However, dose

level should not be above the maximum prescribed dose as instructed in the medication's dosage and administration section of the prescribing information.

7.8.2. Allowed Medications

The following medications and therapeutics are allowed during the study:

- Benzodiazepine, zolpidem, diphenhydramine, or related drugs for insomnia if the subject is on a stable dose for 3 months prior to entry and it is not anticipated to change during the study;
- SSRI (selective serotonin reuptake inhibitor) for depression if the subject is on a stable dose for 3 months prior to entry and it is not anticipated to change during the study;
- NSAIDs prescribed for conditions other than DPNP.
- Aspirin ≤325 mg/day for cardiac prophylaxis.
- Rescue medication, see Section 7.8.3.

7.8.3. Rescue Medication

Rescue medication for DPNP is in addition to standard of care medication (gabapentin, pregabalin or duloxetine) for DPNP. Rescue medication is intended to treat temporary elevations in a subject's DPNP and is intended to be used occasionally and not meant to be used for prolonged periods of time.

Subjects who enter screening after implementation of protocol Version 4.0 may only use acetaminophen as a rescue medication for DPNP as needed. If rescue medication is needed for DPNP, subjects will be instructed to take acetaminophen 500 mg every 4 to 6 hours as needed (not to exceed 3000 mg per day).

Subjects currently in the study at the time of implementation of protocol Version 4.0 using ibuprofen as rescue medication for DPNP may switch their rescue medication to acetaminophen (i.e., no longer use ibuprofen as a rescue medication for DPNP) or continue to use as rescue medication for DPNP ibuprofen 200 to 400 mg every 4 to 6 hours as needed (not to exceed 600 mg/day) for up to 3 days in a 7-day period (not calendar week). Subjects unable to comply with these conditions will need to discontinue study treatment and withdraw from the study; some or all of such subjects may be replaced at the discretion of the Sponsor.

The daily maximum dosages stated in this section are inclusive of those used outside of treatment for DPNP. Any questions related to rescue medications should be directed to the Medical Monitor prior to administration when possible.

7.8.4. Prohibited Medications

The following medications and therapeutics are prohibited during the study:

- Neuroleptics, monoamine oxidase inhibitors, N-methyl-D-aspartate receptor ligand for pain (ketamine, amantadine, dextromethorphan [except low dose intermittent use for cough], memantine, methadone, dextropropoxyphene, and/or ketobemidone), and/or alpha-lipoic acid;

- Tricyclic antidepressants and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); and/or 5-HT3 receptor antagonists;
- Drugs or chemicals that may cause neuropathy and interfere with clinical evaluation. Agents include but are not limited to pyridoxine, hydralazine, metronidazole, phenytoin, dapsone, amiodarone, nitrofurantoin, paclitaxel, vinblastine, vincristine, cisplatin, etoposide, didanosine, disulfiram, suramin, zalcitabine, anti-tuberculosis medications (eg, isoniazid, rifampin, ethambutol, ethionamide), heavy metals, and industrial solvents;
- Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors;
- Topical pain medications intended to treat pain associated with DPNP (including but not limited to lidocaine 5% patch, over-the-counter capsaicin, amitriptyline, and/or isosorbide dinitrate spray);
- Prescription patch containing 8% capsaicin;
- Opioid or opioid based drugs;
- Central nervous system active drugs such as cocaine, amphetamines, and cannabinoids (marijuana);
- Oral prednisolone or equivalent are excluded during the Screening and Run-in Periods;
- NSAIDs for DPNP (applies only to subjects who enter the study following implementation of protocol Version 4.0) (see Section 7.8.2 for NSAIDs prescribed for conditions other than DPNP);
- Muscle relaxers.

7.8.5. Prohibited Devices/Procedures

- TENS unit for the treatment of DPNP;
- Implantation of neurostimulators;
- Nerve decompression surgery for treatment of DPNP;
- Steroid or local anesthetic nerve blocks;
- Cryotherapy, intrathecal/epidural opioids, or botulinum toxin;
- Alternative medicine products or treatments (eg, acupuncture, naturopathy, homeopathy, etc.).

7.8.6. Recording of Concomitant Treatment

Concomitant medications include those being taken at Screening or at any point throughout the study, up to and including the Week 16/EOS visit. Instructions to discontinue any medication to comply with the study protocol should take place only after the subject has signed the ICF. Concomitant medication will be recorded on eCRFs by their trade and/or generic name and will include dose and duration of treatment. Subjects requiring excluded medications will not be

eligible for the study. Planned deviations from the eligibility criteria, with regard to excluded medications, will not be approved. Subjects will be instructed to consult with the Investigator or other site personnel before taking any newly prescribed medications, over-the-counter medications, or supplements/herbal preparations. If a subject requires use of a prohibited medication during the study, the Medical Monitor should be contacted to determine whether an alternative drug is feasible and if not, how to handle dosing with study drug while the prohibited medication is being used. Documentation of these discussions must be maintained in the subject's source records.

8. STATISTICS

8.1. Sample Size Estimate

This study will be conducted in 2 parts. A total of approximately 192 subjects (64 subjects per treatment arm) are planned for randomization in Part 1 and approximately 192 subjects (64 subjects per treatment arm) are planned for randomization in Part 2, for a total of 384 subjects to be randomized. This sample size is based on a dose-ranging scheme to evaluate initial safety, efficacy, [redacted] of RTA 901 in this population. The primary comparisons for efficacy are between each of the 2 RTA 901 treatment groups and the placebo treatment group. The overall Type I error rate will be controlled at the 0.05 significance level. A hierarchical testing strategy to control the overall Type I error will be defined in the SAP. Power calculations are based on a 2-sample t-test with no adjustments for multiple comparisons. The study assumes a difference in NPRS pain intensity means of 1.2 between each RTA 901 treatment group and the placebo treatment group and a standard deviation of 2.4.

If doses selected for Part 2 do not include doses studied in Part 1, then an analysis by dose group for Part 1 or Part 2 doses will be performed following completion of each study part. Within each Part, with 64 subjects per treatment group, each study part has 80% power to compare treatment groups to placebo.

If doses selected for Part 2 include any doses studied in Part 1 (ie, 10 or 80 mg), then an analysis by dose group will be performed using Part 1 and Part 2 combined, following completion of the study. The dose group that is enrolled in both parts will have 128 subjects. With 128 placebo subjects compared to 128 subjects in the RTA 901 dose group, there is 98% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4). RTA 901 dose groups that are enrolled in only 1 part will have 64 subjects. With 128 placebo subjects compared to 64 subjects in each RTA 901 dose group, there is 90% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4).

8.2. Definitions of Analysis Sets

A detailed SAP will be developed prior to database lock.

8.2.1. Intent-to-Treat Analysis Set

The intent-to-treat analysis set is defined as all randomized subjects categorized by their randomized treatment group (whether or not they received study drug). The analysis population for the efficacy endpoints is the intent-to-treat population.

8.2.2. Safety Analysis Set

The safety analysis set includes all randomized subjects who receive at least 1 dose of randomized study drug. The safety analysis set will be used for evaluation of safety variables. Subjects who receive at least 1 dose of RTA 901 will be classified in the RTA 901 group. Subjects who are randomized and receive at least 1 dose of placebo and no dose of RTA 901 will be classified in the placebo group. Subjects in the Run-in phase who fail to randomize into the Treatment Period will not be included in the placebo group.

Safety and tolerability will be evaluated by AEs, SAEs, clinical laboratory test results, vital signs, ECG findings, physical examinations, and weight. All analyses of the safety data will be performed using the safety analysis set. Descriptive statistics will be presented by treatment group assignment in the safety analysis set. No formal statistical testing is planned for safety analyses.

[redacted]

8.3. Endpoints and Objectives

The SAP will describe in detail the methods used for the primary, safety, secondary, and exploratory endpoints and will serve as the final arbiter of all statistical analyses. The study endpoints are listed in Section 2.2.

Data will be summarized using descriptive statistics. Continuous data will be summarized with statistics such as mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using frequency counts and percentages.

If doses selected for Part 2 include any doses studied in Part 1 (ie, 10 or 80 mg), then the final analysis by dose group will be performed following final study database lock. Otherwise, if doses selected for Part 2 do not include doses studied in Part 1 then final analysis by dose group for Part 1 or Part 2 doses will be performed following the Part 1 or Part 2 database lock, respectively.

8.4. Methods for Statistical Analyses

8.4.1. Hypotheses

Primary hypothesis: There will be a greater mean reduction from baseline in NPRS pain intensity for the RTA 901-treated groups compared with placebo after 12 weeks of double-blind treatment.

8.4.2. Closed Testing Procedure

The overall Type I error rate will be controlled at the 0.05 significance level. A hierarchical testing strategy to control the overall Type I error will be defined in the SAP.

8.4.3. Analysis of the Primary Variable(s)

The primary analysis will be performed using mixed model repeated measures (MMRM), and detail of the MMRM model will be specified in the SAP. Within the framework of the MMRM model, estimate and 95% CIs will be calculated for the mean changes within each treatment group as well as for the differences in mean changes relative to the placebo.

8.4.4. Analysis of the Secondary Variables

The secondary endpoints will be summarized, and analyses will be described in the SAP.

8.4.5. Subgroup Analysis

Subgroup analysis will be described in the SAP.

8.4.6. Interim Analysis

No interim analysis for efficacy or safety is planned.

8.4.7. Sensitivity Analysis

Sensitivity analyses will be described in the SAP.

8.4.8. Analysis of Safety Variables

The number and percent of subjects with an AE will be summarized for each treatment group. Changes from baseline to each scheduled time point for physical examinations, vital sign measurements, ECGs, clinical laboratory measurements, and body weight will be summarized by treatment group.

In addition, the number and percent of subjects with a predefined abnormality in clinical laboratory tests will be summarized by treatment group.

8.4.9. Exploratory Analysis

The exploratory endpoints will be summarized and described in the SAP.

9. STUDY AND DATA MANAGEMENT

9.1. Training of Study Site Personnel

Prior to the start of the study, the Sponsor will review the protocol, eCRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with each investigative site (Investigator, Sub-Investigator, and relevant study site personnel). It is the responsibility of the Investigator to ensure all staff are appropriately qualified and trained to perform study responsibilities, prior to the conduct of any study procedures, and as outlined on the delegation of authority log. Training will be documented, and relevant training records will ultimately be stored in the Trial Master File.

9.2. Monitoring of the Study

The study monitor, as a representative of the Sponsor, is obligated to follow the study conduct closely. In doing so, the monitor will visit the Investigator and study facilities periodically and will maintain necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the Investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigators and staff.

The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the ICH guideline E6(R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

Each Investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for study-related monitoring and internet during the visit.

9.2.1. Risk-Based Quality Management

The Sponsor or its designee will monitor all aspects of the study for quality and risk management with respect to E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry and current standard operating procedures.

The quality management system and risk management procedures help ensure the monitoring of the study is proportionate to the risks inherent in the study and the importance of the information collected. Full details for risk-based quality management will be outlined in a Risk Management Plan, or equivalent document.

In case study sites are closed for any visitors and monitors over a certain period of time, a risk-based approach to monitoring will be taken, focusing on certain sites, certain data points, and certain processes that are critical to ensure the rights, safety, and well-being of study participants and the integrity of the study (and study data). The results of adjusted monitoring/review measures and their impact will be reported to the Sponsor in monitoring reports and in the CSR, where applicable. Adjusting monitoring activities may include a combination of on-site and off-site monitoring, where permitted by local regulations. Remote source data verification may also be taken into consideration, where permitted by local regulations.

9.2.2. Source Data

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Examples of source documents include e-diary, hospital records, clinical and office charts, laboratory notes, memoranda, signed ICF, evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, and information initially recorded in an electronic format. The Sponsor may provide source documentation worksheets to record pertinent information.

Data collection is the responsibility of the clinical study staff at each site under the supervision of the site Investigator. Each Investigator should ensure the accuracy, completeness, and timeliness of the data reported in the electronic data capture (EDC) and all other required reports. Data reported in the EDC, that are derived from other source documents, should be consistent with the source documents or the discrepancies should be explained. Any missing data must be explained. An audit trail will be maintained by the EDC system. Each Investigator should retain records of the changes and corrections to paper source documents.

Subject completed forms are also considered to be source data. In no instance should an Investigator or study site personnel record any data or make changes to subject completed forms. Each Investigator or designee should review subject completed forms during study visits for completeness and accuracy. If an entry is found to be illegible or a mistake is found (eg, incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, and dating and initialing the change.

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs per the study Monitoring Plan utilizing the original source documentation and will query discrepant findings. Each Investigator and study site personnel will be responsible for answering all queries.

Details regarding procedures used for data review, database cleaning, and issuing and resolving queries will be outlined in the Monitoring Plan and Data Management Plan.

A copy of the complete subjects' eCRFs and PROs for the site will be provided to each Investigator at the conclusion of the study, and the Investigator must ensure these data are stored in a secure place.

9.2.3. Study Agreements

The Sponsor will secure agreement from all involved parties to ensure direct access (Section 9.2.1) to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. Agreements, made by the Sponsor with each Investigator/institution and any other parties involved with the clinical study, will be in writing, as part of the protocol or in a separate agreement.

9.2.4. Archiving of Study Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

The Investigator/institution should maintain the study documents as specified in Essential Documents for the ICH E6 Section 8 and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for at least 2 years after the marketing approval for the drug or as required by regulatory authorities.

9.3. Study Timetable and End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

9.4. Data Management

9.4.1. Data Handling

Data will be reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

The CRA will verify the e-diary completion.

9.4.2. Computer Systems

All eCRF, e-diary, and lab data will be processed using a validated computer system conforming to regulatory requirements.

9.4.3. Data Entry

Data must be recorded using the EDC system and e-diary as the study is in progress. All site personnel must log into the EDC system using their secure username and password to enter,

review, or correct study data. Subjects must log into the e-diary using their secure username and password.

These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

In the event subject data are transferred from source documentation to eCRF, the Investigator will verify that all the information is accurately recorded on the eCRF by providing an electronic signature. Data transferred from source documents to eCRF must be traceable back to the source documents.

9.4.4. Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

9.4.5. Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by an Investigator.

9.5. Clinical Study Insurance

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, ICH E6 GCP, the Declaration of Helsinki (2008), and all other applicable regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

10.2. Subject Data Protection

All laboratory evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.3. Ethics and Regulatory Review

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. Each site must provide the Sponsor or its designee a signed and dated statement that the protocol and ICF have been approved by the IRB before consenting subjects. Prior to study initiation, each Investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities as required.

The IRB chairperson or their designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, the date approval, and/or if a favorable opinion was granted.

Each Investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The Investigator must supply the Sponsor or its designee with written documentation of reviews of the clinical research.

10.4. Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

An Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. An Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed ICF must be maintained by an Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

10.5. Changes to the Protocol and Informed Consent Form

Any changes that arise after the approval of the protocol must be documented as protocol amendments. The FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the Investigator, and the IRB. In cases when the protocol is modified to enhance subject safety, changes may be implemented, and the amendment must be immediately submitted to the IRB.

Amendment number and date of the amendment will be recorded on the title page of the protocol.

Changes to the ICF will be managed in accordance with the Sponsor's Standard Operating Procedures.

The Investigator is responsible for informing the IRB of all problems involving risks to subjects according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify the FDA in accordance with United States CFR Title 21.

10.6. Audits and Inspections

Investigators and institutions involved in the study will permit study-related monitoring, audits, and IRB review, and regulatory inspections, by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, and other relevant regulatory authorities access to all study records.

The Investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

11. LIST OF REFERENCES

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AMENDMENT SUMMARY

Biogen Protocol 901-C-2102

A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients with Diabetic Peripheral Neuropathic Pain

Version 4.0

Date: 09 May 2024

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 901-C-2102 are:

- To update the language of rescue medicine use to address recommendations from the Data Monitoring Committee (DMC).

- To update the language regarding interim exposure-response (E-R) analysis (an E-R analysis including all participants will be performed at the completion of Part 1 instead of an interim analysis when 96 subjects complete treatment through Week 12 of Part 1).

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 7.8.3, Rescue Medication

Now reads:

~~Subjects may use a single rescue medication (NSAID or acetaminophen) to treat DPNP as needed during study participation, in addition to their standard of care medication. Subjects may not alternate between NSAIDs and acetaminophen. The rescue medication of choice should remain consistent throughout the study. If rescue medication is needed, subjects will be instructed to take acetaminophen 500 mg every 4 to 6 hours as needed (not to exceed 3000 mg per day) or ibuprofen 200 to 400 mg every 4 to 6 hours as needed (not to exceed 1200 mg per day).~~

~~This does not exclude the use of these rescue medications in other forms for other uses outside of treatment for DPNP. Subjects taking one form of rescue medication can take a medication containing the other form solely for use outside of DPNP. The daily maximum dosages are inclusive of those used outside of treatment for DPNP. Subjects should be encouraged NOT to take cough syrups or sleep aids containing NSAIDs (eg, Nyquil for cold/flu, or Tylenol PM for sleep), but if they do then it should be recorded as concomitant medication. The use of NSAIDs for cardiovascular health is allowed and should be documented as a concomitant medication. The daily maximum dosages of each medication should still be maintained. Any questions related to rescue medications should be directed to the Medical Monitor prior to administration when possible.~~

Rescue medication for DPNP is in addition to standard of care medication (gabapentin, pregabalin or duloxetine) for DPNP. Rescue medication is intended to treat temporary elevations in a subject's DPNP and is intended to be used occasionally and not meant to be used for prolonged periods of time.

Subjects who enter screening after implementation of protocol Version 4.0 may only use acetaminophen as a rescue medication for DPNP as needed. If rescue medication is needed for DPNP, subjects will be instructed to take acetaminophen 500 mg every 4 to 6 hours as needed (not to exceed 3000 mg per day).

Subjects currently in the study at the time of implementation of protocol Version 4.0 using ibuprofen as rescue medication for DPNP may switch their rescue medication to acetaminophen (i.e., no longer use ibuprofen as a rescue medication for DPNP) or continue to use as rescue medication for DPNP ibuprofen 200 to 400 mg every 4 to 6 hours as needed (not to exceed 600 mg/day) for up to 3 days in a 7-day period (not calendar week). Subjects unable to comply with these conditions will need to discontinue study treatment and withdraw from the study; some or all of such subjects may be replaced at the discretion of the Sponsor.

The daily maximum dosages in stated in this section are inclusive of those used outside of treatment for DPNP. Any questions related to rescue medications should be directed to the Medical Monitor prior to administration when possible.

Rationale: The rescue medication language was updated in response to a DMC concern regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a rescue medication in the target diabetic population. The DMC provided the following recommendations:

- Newly enrolled subjects cannot use NSAIDs as rescue medication for DPNP.
- Subjects in screening who had been using NSAIDs for DPNP pain must wash out before starting study medication.
- Currently enrolled participants taking NSAIDs as rescue for DPNP will be asked to switch to acetaminophen or keep the NSAID dose within a cap of 600mg/day for no more than 2-3 days per week. If the participants are unable to abide by those limits or are exceeding them, they would have to exit the study or switch to acetaminophen.
- New and continuing subjects can use NSAIDs if these are prescribed for conditions other than DPNP. As the Rx would be coming from a non-study MD, there would be no specific number of days the NSAID could be used for a condition other than DPNP.

To implement the DMC recommendations, rescue medication language was updated.

This change also affects the following sections:

- Protocol Synopsis, Objectives
- Protocol Synopsis, Endpoints
- Section 2.1.2, Secondary Objectives
- Section 2.2.2, Secondary Endpoints
- Section 3.2, Screening Period (Days -28 to -15)
- Section 3.4, Treatment Period (Day 1 to Week 12)

- Section 7.8.2, Allowed Medications
- Section 7.8.4, Prohibited Medications

Section 3.6, Part 2 Dose Selection Process

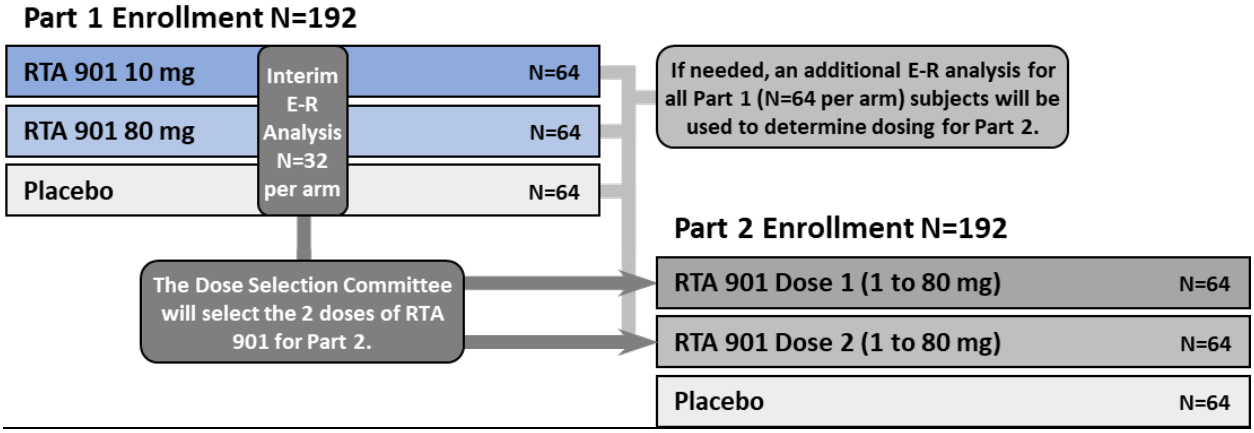
Now reads:

A Dose Selection Committee (DSC) comprised of Sponsor personnel and an external pharmacometrics consultant will select the 2 doses of RTA 901 for Part 2 using data from Part 1. **An E-R analysis for efficacy will be conducted with efficacy data from all subjects up to Week 12 of treatment in Part 1 and provide a dosing recommendation for Part 2 to the DSC**. ~~Once the first 96 subjects in Part 1 complete treatment through Week 12, the external pharmacometrics consultant will conduct the interim E-R analysis for efficacy using unblinded data and provide a dosing recommendation for Part 2 to the Sponsor personnel. The doses of RTA 901 for Part 2 will be selected from a dose range of 1 to 80 mg by the DSC based on this analysis. If the DSC determines that the interim E-R analysis for efficacy (N=approximately 32 per arm) does not provide sufficient RTA 901 E-R information to make dose recommendations for Part 2, then an additional E-R analysis for efficacy will be conducted with all subjects in each treatment arm in Part 1 who completed treatment through Week 12.~~ The selected doses will be documented in a Note-to-File to the Investigators and IRBs (as appropriate) and will not require a protocol amendment.

It is possible that enrollment in Part 2 of the study may begin while some Part 1 subjects are completing their remaining study visits. Subjects enrolled in Part 1 will not be eligible for enrollment in Part 2.

Details of the membership, objectives, and process to be followed by the DSC will be described in a separate charter. Additionally, a separate data management and analysis plan supporting this activity will be created. Results will be reported in a separate standalone report, outside the clinical study report (CSR).

~~**Figure 1: Part 2 Dose Selection Process**~~



~~Abbreviations: E-R=exposure-response~~

Rationale: The original intent of the protocol was to conduct an interim E-R analysis after the first 96 participants completed Part 1 of the study to inform dose selection for Part 2 of the study. The updated language and removal of Figure 2 reflect the plan not to conduct an interim E-R analysis during Part 1 and instead to base dose selection decisions on an E-R analysis for efficacy conducted with data from all subjects up to Week 12 of treatment in Part 1.

This change also affects the following sections:

- Protocol Synopsis, Study Schema
- Protocol Synopsis, Statistical Methods
- Section 1.2, Study Rationale
- Section 1.4, Dose Rationale
- Section 4.5, Subject Enrollment and Randomization
- Section 4.5.2.3, Dose Selection Committee
- Section 8.4.6, Interim Analysis
- [redacted]

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Protocol Synopsis

The Protocol Synopsis was revised to reflect changes made throughout the protocol.

Section 5.3.2, Follicle-Stimulating Hormone

Change: Added more information regarding assessment of child-bearing potential.

Now reads:

Follicle-stimulating hormone (FSH) will only be assessed at Screening for female subjects who have been post-menopausal for at least 1 year and are not surgically sterile **(e.g., not had bilateral tubal ligation, bilateral oophorectomy, or a hysterectomy). The investigator, based on the available information (including the FSH result), uses their clinical judgment to determine whether or not the participant is of child-bearing potential**.

Rationale: To provide additional clarity regarding the assessment of child-bearing potential in the study.

Section 6.7**,** Methods of Birth Control

Change: The description of the allowed methods of contraception was updated from "acceptable" to "highly effective." Text noting restrictions on egg and sperm donation for participants is added.

Now reads:

During Screening, while taking study drug, and until 30 days following administration of the final dose of study drug, females of child-bearing potential must practice 1 of the following ~~acceptable~~ **highly effective** methods of birth control:

- Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal, or transdermal) as prescribed;
- Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed);
- Use of an intrauterine hormone-releasing system as prescribed;
- Vasectomized partner (with vasectomy performed at least 6 months prior to Screening with the appropriate post-procedure documentation of surgical success). Partner *must* be the sole partner for that subject;

- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

In addition, female participants should not donate eggs for the duration of the study and for at least 30 days after their last dose of study treatment.

During Screening, while taking study drug, and until 30 days after the final dose of study drug, fertile males who have female partners of child-bearing potential must practice 1 of the following methods of birth control:

- Partner contraception methods; *must* be the sole partner for that subject:
  - Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed);
  - Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal or transdermal) as prescribed;
  - Use of an intrauterine hormone-releasing system as prescribed;
  - Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (eg, x-ray, ultrasound);
  - Reproductive potential has been terminated by radiation;
  - Postmenopausal (defined as no menses for at least 1 year without an alternative medical cause).
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

In addition, male participants should not donate sperm for the duration of the study and for at least 90 days after their last dose of study treatment.

Rationale: The wording "highly effective" aligns with the Clinical Trials Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials guidance terminology. The added language on egg/sperm donation reflects the latest changes in the Investigator's Brochure and the Patient Safety Information.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Protocol version history was removed.
- The Signature Page was updated to align with the applicable protocol template.
- The Page of Contacts in Case of Emergency was updated.
- Minor inconsistencies and formatting were corrected.

AMENDMENT CHANGE SUMMARY DOCUMENT

CLINICAL STUDY PROTOCOL 901-C-2102

Study Title: A PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RTA 901 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN

Protocol History
Version 1.0 – 28 April 2022
Version 2.0 – 27 September 2022
Version 3.0 – 8 February 2023

CONFIDENTIALITY STATEMENT

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 2 to produce the text of Version 3. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the current amended version of the protocol.

Section	Version 3	Rationale
Title Page	~~RTA 901~~ 901-C-2102 A PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RTA 901 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN ~~(DPNP)~~ ~~CYPRESS~~ RTA 901 VERSION ~~2~~ 3.0– ~~27 SEP 2022~~ 8 FEB 2023	The abbreviation "DPNP" was removed from the study title. The study name was removed from the title page, in lieu of the study title. The version and date were updated.
Footer	Version ~~2~~3.0 – ~~USA –~~ ~~27 Sep 2022~~8-FEB-2023	The country was removed from the footer since this study will only be performed in the USA. The date was updated.
SIGNATURE PAGE	[redacted], MS [redacted] Reata Pharmaceuticals, Inc.	Clarification of [redacted] title.
SIGNATURE PAGE	[redacted], MPH	Clarification of [redacted] credentials and middle initial.
SIGNATURE PAGE	{See Appended Electronic Signature Page} [redacted], PharmD, PhD [redacted] Reata Pharmaceuticals, Inc.	Addition of [redacted] as a signatory
1. INTRODUCTION	Given the preclinical data, Reata Pharmaceuticals, Inc. (hereinafter referred to as Reata or the Sponsor) is interested in pursuing further clinical development of RTA 901.	Clarification of the terms used to refer to Reata Pharmaceuticals
1.1. Clinical Experience	The formulation used in this study was [redacted] of RTA 901 [redacted].	Providing additional detail on the form of the study drug
1.1. Clinical Experience	The safety, tolerability, [redacted] of oral RTA 901 ~~is currently being~~ were also evaluated in 2 additional recently completed Phase 1 clinical studies: • [redacted]	Additional detail was provided on prior clinical studies conducted with RTA 901.

Section	Version 3	Rationale
	[redacted]	
1.1. Clinical Experience	• [redacted]	Additional detail was provided on prior clinical studies conducted with RTA 901.
1.1.1. Safety and Tolerability	Overall, RTA 901 oral capsules were well tolerated in healthy volunteers ~~following single~~ who took a single dose (10 to 160 mg) and multiple doses (10 to 80 mg) in a 14-day ~~multiple ascending dose~~ Phase 1 study (Study 901-C-1503). No serious adverse events (SAEs) or treatment-emergent adverse events (TEAEs) ~~leading~~ reportedly lead to study drug discontinuation ~~were reported. No deaths were reported during the study. Administration of RTA 901 during the study (Part 1 [SAD] and Part 2 [MAD]) was generally safe and well tolerated, with no SAEs~~, or ~~TEAEs that~~ were considered related to RTA 901 ~~study drug. Also~~. Of the unrelated TEAEs, most ~~TEAEs~~ were Grade 1 in severity ~~and.~~ No deaths were ~~assessed as unrelated to~~ reported during the study ~~drug by the Investigator~~.	This text was edited grammatically for clarity.

Section	Version 3	Rationale
[redacted]		

Section	Version 3	Rationale
[redacted]		

Section	Version 3	Rationale
[redacted]		

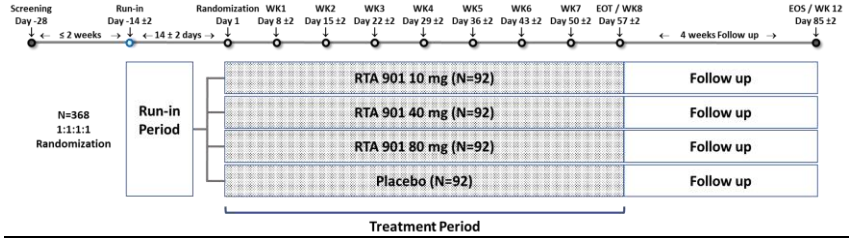
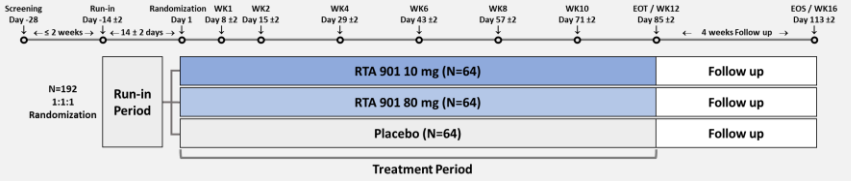
Section	Version 3	Rationale
[redacted]		
1.2. Study Rationale	Therefore, the current study is designed to investigate the efficacy and safety of multiple doses of RTA 901 in ~~DPNP~~ subjects with DPNP, when RTA 901 is added to the standard-of-care (SOC) pain medication. RTA 901 doses of 10 mg, ~~40 mg,~~ and 80 mg once daily (QD) will be investigated in Part 1 of this study~~, so that~~. Based on an interim exposure-response (E-R) analysis for efficacy in Part 1, 2 doses of RTA 901 between 1 to 80 mg QD will be investigated in Part 2 of the study. This will allow the Sponsor to determine the optimal dose(s)for future development ~~can be selected based on the efficacy and safety data from this study~~.	The study design was modified to better determine the optimal dose of RTA 901 for future studies. The study will be conducted in 2 parts with differing treatment arms in each part.
1.3. Rationale for Study Population	1.3. Rationale for Study Population Diabetic peripheral neuropathic pain is a common condition seen in both T1DM and T2DM. Neuropathic pain can lead to interference with daily activities, disability, psychosocial impairment, and	This text was moved from Section 3.7 of the protocol.

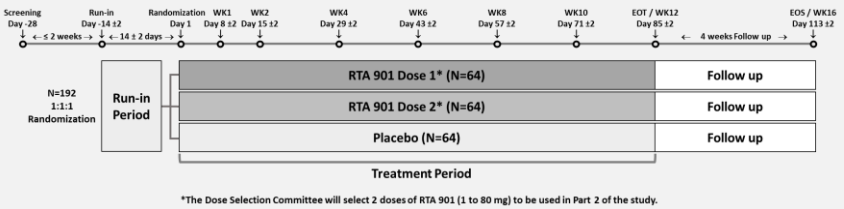
Section	Version 3	Rationale
	[redacted] It may be associated with hyperalgesia and allodynia. Although there are approved therapies for this condition, they are limited by efficacy and tolerability. Many treatments are discontinued, suggesting low levels of satisfaction and/or poor tolerability (Yang, 2015). Given this, and the large and growing population of subjects with diabetes, a significant unmet medical need remains. According to the Centers for Disease Control National Diabetes Statistics Report (2022), 37.3 million Americans have diabetes. The most common neuropathy associated with diabetes is DSPN (Pop-Busui, 2017). Although estimates of its incidence and prevalence vary, data suggests that DSPN occurs in at least 20% of subjects with T1DM after 20 years of disease. It may be present in at least 10% to 15% of subjects newly diagnosed with T2DM with rates increasing to 50% after 10 years of disease duration. Neuropathic pain, specifically DPNP, is present in up to 25% of subjects with DSPN. The development of DPNP is associated with a small-fiber neuropathy resulting from dysfunction of unmyelinated or thinly myelinated sensory fibers and the gradual degeneration of larger myelinated fibers. Further, although numerous pathologic mechanisms contribute to DPNP (Farmer, 2012), increased oxidative stress and mitochondrial dysfunction appear to be a central facilitator in its development (Fernyhough, 2010). Nonclinical data suggest that RTA 901 is able to improve dysfunction resulting from pathogenic demyelination of sensory fibers, along with mitigation of mitochondrial dysfunction. Taken together, the potent pharmacological effects of RTA 901 shown in animal models support the hypothesis that RTA 901 may have potential therapeutic benefit to treat the central pathology underlying the development of DPNP.	
1.4. Dose Rationale	1.4. Dose Rationale Dose selection for Part 1 was based on the established safety profile from the first-in-human study in healthy subjects (Study 901-C-1503), [redacted], no observed adverse effect levels established in 3-month good laboratory practice (GLP) toxicity studies in mice and	This text was moved from Section 3.8 of the protocol with additional updates to provide justification for planned interim analysis for efficacy in Part 1 of the study.

Section	Version 3	Rationale
	monkeys, and exposures required to produce efficacy in rodent models of DPN. RTA 901 was generally safe and well tolerated following single doses of up to 160 mg and multiple daily doses (for 14 days) of up to 80 mg (Study 901-C-1503) using [redacted] RTA 901 [redacted] Additionally, at the highest proposed dose of 80 mg QD, there is at least a 40-fold safety margin based on the data from the 3-month GLP toxicity studies in mice and monkeys (Table 8 of the IB). Based on the clinical multiple dose study (901-C-1503), [redacted] These exposures are similar to or above the exposures at the efficacious doses in the rodent models of diabetic neuropathy [redacted] In summary, at the proposed doses for Part 1, RTA 901 is predicted to have efficacious and safe exposure in subjects with DPNP, with a 10 mg dose anticipated to be an efficacious dose and 80 mg the highest feasible dose with potentially maximal efficacy and an acceptable safety profile. However, based on the exposures associated with efficacy in the nonclinical models, it is possible that a dose lower than 10 mg may need to be explored to identify the minimally effective dose in subjects with DPNP and thereby enable a robust phase 2 dose ranging study. Therefore, a planned interim E-R analysis for efficacy from the first 96 subjects in Part 1 of this study has been incorporated to recommend the optimal doses for investigation in Part 2. Eligible doses for selection in Part 2 will be limited to a dose range of 1 to 80 mg. Part 2 doses will not exceed 80 mg, at which there is at least a 40-fold safety margin based on the data from the 3-month GLP toxicity studies in mice and monkeys.	
2.1.1. Primary Objectives	2.1.1. Primary Objectives 2.1.1.1. Efficacy • To assess the efficacy of RTA 901 based on change from baseline in	Subheadings were added to denote the primary efficacy and safety objectives of the study.

Section	Version 3	Rationale
	the average daily pain score using the Numeric Pain Rating Scale (NPRS) after ~~8~~12 weeks of treatment 2.1.1.2. Safety • To assess the safety and tolerability of RTA 901 during and following the Treatment Period	Additional detail was included on the method for determining the primary efficacy objective based upon recommendation from the FDA. The Treatment Period of the study was lengthened to 12 weeks.
2.1.2. Secondary Objectives	• To assess the efficacy of RTA 901 in achieving at least 30% decrease in the ~~Numeric Pain Rating Scale (~~NPRS~~)~~ pain intensity score after ~~8~~12 weeks of treatment • To assess the efficacy of RTA 901 in achieving at least 50% decrease in the NPRS pain intensity score after ~~8~~12 weeks of treatment • To assess the Daily Sleep Interference Scale (DSIS) score after ~~8~~12 weeks of treatment	The pain intensity score on the NPRS is the data point used for these objectives. The Treatment Period of the study was lengthened to 12 weeks.
[redacted]		
2.2. Study Endpoints	The primary, secondary, exploratory, [redacted] endpoints will be evaluated for each dose of RTA 901 compared to placebo.	This text was added to describe the endpoints of the study.
2.2.1. Primary Endpoints	2.2.1.1. Efficacy • Change from baseline in the average ~~pain intensity as assessed by~~	Subheadings were added to denote the primary efficacy and safety

Section	Version 3	Rationale
	~~the~~ daily NPRS pain intensity ~~at~~ score during Week ~~8~~ 12 2.2.1.2. Safety • Frequency, intensity, and relationship to study drug of AEs and SAEs and change from baseline in the following assessments: physical examinations, vital sign measurements, ~~12-lead~~ ECGs, clinical laboratory measurements, and body weight.	endpoints of the study. Additional detail was included on the method for determining the primary efficacy endpoint based upon recommendation from the FDA. The Treatment Period of the study was lengthened to 12 weeks. The description of the 12-lead ECGs was redundant with later text and was removed.
2.2.2. Secondary Endpoints	• Proportion of subjects who achieve at least a 30% decrease ~~in the NPRS score~~ from baseline ~~to~~ in the Week ~~8~~ 12 average NPRS pain intensity score • Proportion of subjects who achieve at least a 50% decrease ~~in the NPRS score~~ from baseline ~~to~~ in the Week ~~8~~ 12 average NPRS pain intensity score • Change from baseline in the average DSIS ~~at~~ score during Week ~~8~~ 12	The treatment period of the study was lengthened to 12 weeks. The pain intensity score on the NPRS is the data point used for these endpoints. Additional detail was included on the method for determining the secondary endpoint based upon recommendation from the FDA.
[redacted]		

Section	Version 3	Rationale
3.1. Study Design	This is a 2-part, randomized, placebo-controlled, double-blind, Phase 2 study to evaluate the safety, tolerability, efficacy, [redacted] of RTA 901 in qualified subjects with ~~Diabetic Peripheral Neuropathic Pain (DPNP). The duration of the study will be approximately 16 weeks, including a Screening Period of up to 2 weeks, a Run-in Period of 2 weeks, a Treatment Period of 8 weeks, and a Follow-up Period of 4 weeks. Following the Run-in Period, subjects who remain eligible will be randomized 1:1:1:1 to either RTA 901 (10, 40, or 80 mg) or placebo at Day 1 (randomization).~~. Approximately ~~368~~ 192 eligible subjects (~~92~~ 64 subjects per treatment arm) will be enrolled, ~~and randomization~~ in Part 1, and approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 2, for a total of 384 subjects randomized. Randomization within each part will be stratified by SOC pain medication using randomization and trial supply management (RTSM). A total of approximately 75 sites in the United States will be included in this study. The duration of each part of the study will be approximately 20 weeks, including a Screening Period of up to 2 weeks, a Run-in Period of 2 weeks, a Treatment Period of 12 weeks, and a Follow-up Period of 4 weeks. All subjects in Part 1 and Part 2 of the study will follow the same visit and assessment schedule.	The study design was modified to better determine the optimal dose of RTA 901 for future studies. The study will be conducted in 2 parts with differing treatment arms in each part. The Treatment Period of the study was lengthened to 12 weeks.
Figure 1: Study Design		The study design was replaced with the 2-part design and extended Treatment Period.
Figure 1: Study Design	**Part 1** 	The study design was updated with the 2-part design and extended Treatment Period.

Section	Version 3	Rationale
	Part 2  Abbreviations: EOS=end of study; EOT=end of treatment; Wk=Week	
~~3.2. Informed Consent~~	~~3.2. Informed Consent~~ ~~The informed consent form (ICF) must be signed prior to the initiation of any Screening or study-specific procedures. See Section 10.4 for details on informed consent.~~	Redundant text was consolidated to Section 10.4.
3.2. Screening Period (Days -28 to -15)	The Screening Period includes 1 clinic visit, up to 2 weeks prior to the Run-in Period (within ~~approximately~~ 28 days prior to Day 1, approximately, as the visit has a ±2-day window). Upon Institutional Review Board (IRB) approval of the protocol, potential subjects will be required to sign a written informed consent form (ICF) for the study before any study-specific screening procedures are performed. See Section 10.4 for details on informed consent. Subjects who meet the Run-in inclusion criteria (Section 4.1) and none of the exclusion criteria are considered eligible to proceed to Run-in. Washout from prohibited medications is allowed during the Screening Period if the Investigator deems it medically appropriate~~. The~~; the washout period must cover 5 half-lives of the prohibited medication and must be completed prior to the end of the Screening Period.	Added clarity around the timing of the Day 1 visit relative to the Screening visit. Text added to clarify that the washout must be completed during the Screening Period.
3.2. Screening Period (Days -28 to -15)	Subjects will be given access to an e-diary at Screening and will be trained on how to use it. ~~Daily pain score/status utilizing~~ Subjects will be directed to complete the NPRS ~~will be collected in the e-diary for 2 consecutive weeks. Starting after this visit, pain intensity~~ and record their rescue medication ~~use will be recorded daily~~ usage in the e-diary at bedtime ~~in the e-diary~~. ~~Subjects will enter their average pain intensity, worst pain intensity, pain on walking, and whether rescue medication was used during the past 24 hours.~~ Subjects will also complete the DSIS via their study-issued e-diary daily upon waking~~, preferably in the morning~~.	Text was modified for clarity and repeated text was deleted.

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3.2. Screening Period (Days -28 to -15)	Subjects must have a score ~~of~~ ≥ 4 on the 11-point NPRS for average pain intensity over the past 24 hours at Visit 1, denoting moderate to severe pain. Additional procedures ~~during Screening (Visit 1) will include the administration of the following~~ [redacted] ~~(Section 5.4.2):~~ [redacted] are to be completed according to the Schedule of Assessments (Table 4).	The pain intensity score on the NPRS is the data point used for this criterion. [redacted]
3.3. Run-in Period (Days -14 to -1)	Since the first dose will be taken in-clinic at the Run-in visit, subjects should fast for 2 hours prior to the visit. During the Run-in Period, ~~daily~~ NPRS ~~scores will continue to be collected using the e-diary. Pain intensity~~ and rescue medication use will also continue to be recorded daily at bedtime in the e-diary. Subjects will also complete the DSIS upon waking~~, preferably in the morning.~~. The baseline score will be calculated as the mean of the pain scores recorded daily by the subject within the last 7 days prior to randomization (the average value is ~~not~~ to be rounded~~).~~ to 1 decimal point). Fluctuations in the pain score are allowed. A minimum of 5 measurements must be recorded. ~~The other~~ Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).	Additional guidance on fasting prior to the Run-in visit was provided. Redundant text was removed. The DSIS average will be rounded to 1 decimal point.
3.4. Treatment Period (Day 1 to Week 12)	The Treatment Period includes ~~9~~8 clinic visits over ~~8~~12 weeks. ~~Subjects~~ Within each part of the study, subjects who successfully meet the Randomization eligibility criteria will be randomized using RTSM and stratified by SOC pain medication ~~with 3 groups (duloxetine, pregabalin/gabapentin, or other)~~ on Day 1, see Section 4.5.	The Treatment Period of the study was adjusted to 8 visits in 12 weeks.
3.4. Treatment Period (Day 1 to Week 12)	Subjects should also fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16). Additional study procedures and assessments will be performed according to the Schedule of Assessments (Table 4). Subjects will also be instructed to use rescue medication for DPNP if needed and reminded not to exceed 3000 mg/day of acetaminophen or 1200 mg/day of NSAIDs. Subjects will be directed to continue ~~entering~~ completing the aver~~age of pain intensity, worst pain intensity,~~ NPRS and ~~pain upon walking and whether they needed to use~~ recording their rescue medication~~,~~ usage in the e-diary at	Additional guidance was provided for fasting on days when fasting lipids would be taken. Text was modified for clarity and repeated text was deleted.

Section	Version 3	Rationale
	bedtime. Upon waking ~~in the morning~~, subjects will be asked to complete the DSIS. Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).	
3.4. Treatment Period (Day 1 to Week 12)	~~The other~~ Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4). Week ~~8~~12/Day ~~57~~85 will be the end of treatment (EOT) visit.	The Treatment Period of the study was lengthened to 12 weeks.
3.5. Follow-up/End of Study (Week 16)	3.5. Follow-up/End of Study (Week ~~12~~16) The Follow-up Period includes 1 clinic visit on Day 113 ± 2, which must occur approximately 4 weeks following the EOT visit ~~on Day 85 ± 3~~. Procedures will be performed according to the Schedule of Assessments (Table 4). Completion of this visit concludes the subject's participation in the study. Subjects will be directed to continue ~~entering~~ completing the ~~average of pain intensity, worst pain intensity,~~ NPRS and ~~pain upon waking and whether they needed to use~~ recording their rescue medication~~,~~ usage in the e-diary at bedtime. Upon waking ~~in the morning~~, subjects will be asked to complete the DSIS. Additional procedures [redacted] are to be completed according to the Schedule of Assessments (Table 4).	The follow-up visit is now on Week 16. Text was modified for clarity and repeated text was deleted.
3.6. Part 2 Dose Selection Process	A Dose Selection Committee (DSC) comprised of Sponsor personnel and an external pharmacometrics consultant will select the 2 doses of RTA 901 for Part 2 using data from Part 1. Once the first 96 subjects in Part 1 complete treatment through Week 12, the external pharmacometrics consultant will conduct the interim E-R analysis for efficacy using unblinded data and provide a dosing recommendation for Part 2 to the Sponsor personnel. The doses of RTA 901 for Part 2 will be selected from a dose range of 1 to 80 mg by the DSC based on this analysis. If the DSC determines that the interim E-R analysis for efficacy (N=approximately 32 per arm) does not provide sufficient RTA 901 E-R information to make dose recommendations for Part 2, then an additional E-R analysis for efficacy will be conducted with all subjects in each treatment arm in Part 1 who completed treatment through Week 12. The selected doses will be documented in a Note-to-File to the Investigators and IRBs (as appropriate) and will not require a protocol amendment. It is possible that enrollment in Part 2 of the study may begin while some Part 1 subjects are completing their remaining study visits. Subjects enrolled in Part 1 will not be eligible for enrollment in Part 2.	Text from other sections of the protocol was merged into this new section.

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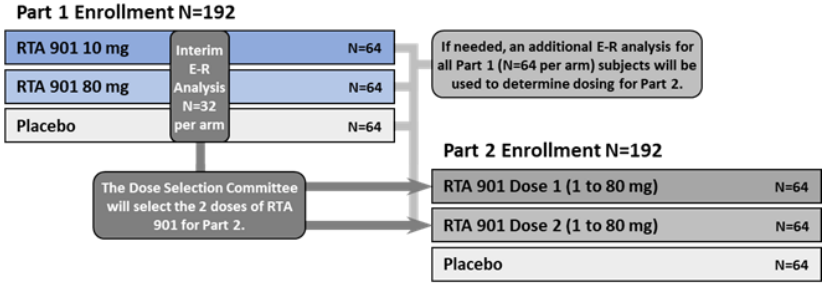
	Details of the membership, objectives, and process to be followed by the DSC will be described in a separate charter. Additionally, a separate data management and analysis plan supporting this activity will be created. Results will be reported in a separate standalone report, outside the clinical study report (CSR).	
Figure 2: Part 2 Dose Selection Process	 Abbreviations: E-R=exposure-response	This figure was added to illustrate the dose selection process for Part 2.
~~3.7. Rationale for Study Population~~	~~3.7. Rationale for Study Population~~ ~~DPNP is a common condition seen in both T1DM and T2DM. Neuropathic pain can lead to interference with daily activities, disability, psychosocial impairment,~~ [redacted] ~~It may be associated with hyperalgesia and allodynia. Although there are approved therapies for this condition, they are limited by efficacy and tolerability. Many treatments are discontinued, suggesting low levels of satisfaction and/or poor tolerability (Yang, 2015). Given this, and the large and growing population of subjects with diabetes, a significant unmet medical need remains.~~ ~~According to the Centers for Disease Control National Diabetes Statistics Report (2022), 37.3 million Americans have diabetes. The most common neuropathy associated with diabetes is DSPN (Pop-Busui, 2017). Although estimates of its incidence and prevalence vary, data suggests that DSPN occurs in at least 20% of subjects with T1DM after 20 years of disease. It may be present in at least 10% to 15% of subjects newly diagnosed with T2DM with rates increasing to 50% after 10 years of disease duration. Neuropathic pain, specifically DPNP, is present in up to 25% of subjects with DSPN.~~ ~~The development of DPNP is associated with a small-fiber neuropathy resulting from dysfunction of unmyelinated or thinly~~	This text was moved to Section 1.3 of the protocol.

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	~~myelinated sensory fibers and the gradual degeneration of larger myelinated fibers. Further, although numerous pathologic mechanisms contribute to DPNP (Farmer, 2012), increased oxidative stress and mitochondrial dysfunction appear to be a central facilitator in its development (Fernyhough, 2010). Nonclinical data suggest that RTA 901 is able to improve dysfunction resulting from pathogenic demyelination of sensory fibers, along with mitigation of mitochondrial dysfunction. Taken together, the potent pharmacological effects of RTA 901 shown in animal models support the hypothesis that RTA 901 may have potential therapeutic benefit to treat the central pathology underlying the development of DPNP.~~	
~~3.8. Dose Rationale~~	~~3.8. Dose Rationale~~ ~~Dose selection was based on the established safety profile from the first-in-human study in healthy subjects (Study 901-C-1503), no-observed-adverse-effect levels (NOAELs) established in 3-month good laboratory practice (GLP) toxicity studies in mice and monkeys, and exposures required to produce efficacy in rodent models of diabetic peripheral neuropathy.~~ ~~RTA 901 was generally safe and well tolerated following single doses of up to 160 mg and multiple once a daily dose (for 14 days) of up to 80 mg (Study 901-C-1503). Additionally, at the highest proposed dose of 80 mg QD, there is at least a 40-fold safety margin based on the data from the 3-month GLP toxicity studies in mice and monkeys (Table 8 of the Investigator's Brochure).~~ ~~Based on the clinical multiple dose study (901-C-1503),~~ [redacted] ~~These exposures are similar to or above the exposures at the efficacious doses in the rodent models of diabetic neuropathy~~ [redacted] ~~In summary, at the proposed doses, it is predicted to have efficacious and safe exposure in the subjects with DPNP with 10 mg anticipated to be the minimum efficacious dose and 80 mg the highest feasible dose with optimal efficacy and acceptable safety profile.~~	This text was moved to Section 1.4 of the protocol.

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4.1.1. Run-in Inclusion Criteria	4. Currently taking ≤ only 1 allowed prescribed ~~standard of care~~ SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 4 weeks prior to Screening (Section 7.8.1); ~~or failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications;~~	The subjects must be taking only 1 SOC pain medication. Refractory subjects are now excluded.
4.1.1. Run-in Inclusion Criteria	5. Stable glycemic control as indicated by ~~Hemoglobin A1C (~~HbA1c~~) value ≤ 11% at~~ values over the 3 months prior to Screening;	Inclusion criterion modified based on recommendation from the FDA.
4.1.2. Run-in Exclusion Criteria	3. HbA1c > 11% at Screening;	This exclusion criterion was moved from the Run-in Inclusion criteria.
4.1.2. Run-in Exclusion Criteria	12. Unwilling to practice ~~methods~~ a protocol-specified acceptable method of birth control (both males who have partners of childbearing potential and females of child-bearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested (Section 6.7);	Added clarity to denote the protocol-approved methods of birth control.
4.1.2. Run-in Exclusion Criteria	f. ~~Chronic treatment with s~~ Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors, within 14 days prior to Screening;	Any treatment with CYP3A4 or P-gp inhibitors within 14 days of Screening is excluded.
4.2.1. Randomization Inclusion Criteria	2. Subject must have a ≤ 3-point decline in NPRS pain intensity score during Run-in, which will be calculated using the average score during the last 7 days of Screening compared to the average score during the last 7 days of Run-In;	Additional detail added to describe how the decline in NPRS will be measured.
4.2.1. Randomization Inclusion Criteria	5. Currently taking ≤ only 1 allowed prescribed SOC pain medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 8 weeks prior to Day 1 with no anticipated changes to dose(s) during study (Section 7.8.1)~~, or failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications;)~~;	The subjects must be taking only 1 SOC pain medication. Refractory subjects are now excluded.
4.2.2. Randomization Exclusion Criteria	d. ~~Chronic treatment with s~~ Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors;	Any treatment with CYP3A4 or P-gp inhibitors is excluded.
4.4.1. Retesting	Retesting is defined as repeating abnormal laboratory tests within the same ~~Screening Period.~~ study part.	The repeated testing is to be performed during the same part

<table>
<tr><th>Section</th><th>Version 3</th><th>Rationale</th></tr>
<tr><td></td><td>Subjects who fail to qualify for the study based on an abnormal laboratory test may have any individual laboratory test retested once within the same ~~Screening Period~~ study part at the discretion of the Investigator.</td><td>of the study, not limited to the Screening Period.</td></tr>
<tr><td>4.5. Subject Enrollment and Randomization</td><td>Following a Screening Period of up to 2 weeks, eligible subjects will be enrolled and enter a ~~14-day~~ single-blind placebo Run-in Period (14± 2 days). ~~During Run-~~ Subjects in, ~~subjects will be administered single-blind placebo study drug once daily in the morning. All study drug should be administered in a fasted state, defined as having no food within 2 hours prior to study drug administration and for 1 hour following study drug administration. Following the Run-in Period, subjects~~ Part 1 who remain eligible (according to Randomization eligibility criteria) will be randomized 1:1:1~~:1~~ to either RTA 901 (10~~, 40~~, or 80 mg) or placebo at Day 1~~.~~, and subjects in Part 2 who remain eligible will be randomized 1:1:1 to either RTA 901 (Dose 1 or Dose 2) or placebo at Day 1 (see Table 3). Approximately ~~368~~192 eligible subjects (~~92~~ 64 subjects per treatment arm) will be enrolled~~, and randomization~~ in Part 1, and approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 2. Randomization within each part will be stratified ~~by~~ using RTSM into 2 strata based on approved SOC pain medication ~~with 3 groups (~~. One stratum will include subjects taking duloxetine, while the other stratum will include subjects taking pregabalin~~/~~ or gabapentin~~, or other) using RTSM. The "other" stratification group includes subjects who failed treatment, could not tolerate/are unable to take on-label medications for DPNP, or use only an NSAID or acetaminophen as a treatment option. For additional detail on the use of rescue medications, see Section 7.8.3.~~.</td><td>The study design was modified to better determine the optimal dose of RTA 901 for future studies. The study will be conducted in 2 parts with differing treatment arms in each part. Additional detail on the number of subjects in each group was provided.

The study will now be stratified into 2 strata, subjects taking duloxetine and subjects taking pregabalin or gabapentin. Refractory subjects are now excluded.</td></tr>
<tr><td>Table 3: Treatment Arms by Study Part</td><td><table>
<tr><td>Study Part</td><td colspan="3">Treatment Arms</td></tr>
<tr><td>Part 1 (N=192)</td><td>10 mg RTA 901 (N=64)</td><td>80 mg RTA 901 (N=64)</td><td>Placebo (N=64)</td></tr>
<tr><td>Part 2 (N=192)</td><td>Dose 1 RTA 901 (N=64)</td><td>Dose 2 RTA 901 (N=64)</td><td>Placebo (N=64)</td></tr>
</table></td><td>This table was included to describe the possible treatment arms in each part of the study.</td></tr>
</table>

Section	Version 3	Rationale
	<table><tr><td></td><td>(selected from dose range of 1 to 80 mg)[a]</td><td>(selected from dose range of 1 to 80 mg)[a]</td><td></td></tr></table> Table 3: Treatment Arms by Study Part Abbreviations: E-R=exposure-response [a]Dose selection in Part 2 will be determined by a Dose Selection Committee and based off an interim E-R analysis for efficacy with approximately 32 subjects from each treatment arm in Part 1.	
4.5.1. Methods for Ensuring Blinding	In this 2-part, randomized, placebo-controlled, double-blind study, all subjects, Investigators, site personnel, and laboratories (except the bioanalytical laboratory) with direct involvement in the conduct of the study or their designees will be blinded to randomized treatment assignments. Subjects will be blinded throughout the study. Investigators will not be blinded in the single-blind Run-in Period but will be blinded in the double-blind Treatment Period of the study. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the subjects and personnel mentioned previously. To maintain the blind, Investigators will distribute blinded study drug kits to subjects as assigned by the RTSM~~, see~~ (Section 7.3). ~~The study drug kits will contain a combination of three bottles of capsules, each containing active or placebo capsules in varying strengths to make up each dosing regimen. Table 11 shows the combination of bottles that will be used to comprise the dose for each treatment arm, while maintaining the study blind. Subjects will be blinded throughout the study. Investigators will not be blinded in the single-blind Run-in Period but will be blinded in the double-blind Treatment Period of the study.~~ The Data Monitoring Committee (DMC) will review unblinded safety data and make recommendations as appropriate. Members of the DSC will be unblinded to recommend Part 2 doses of RTA 901, respectively.	The bioanalytical lab will be unblinded. Text was moved from later in the paragraph. Redundant text regarding study drug was removed. The DMC and specific members of the DSC are unblinded.
4.5.2.2. Data Monitoring Committee	An independent ~~Data Monitoring Committee (~~DMC~~)~~ will review the accumulating unblinded safety [redacted] data throughout the study and make recommendations as appropriate.	The DMC will also review the [redacted] data as needed.
4.5.2.3. Dose Selection Committee	4.5.2.3. Dose Selection Committee The DSC will be comprised of Sponsor personnel and an external pharmacometrics consultant. The external pharmacometrics consultant will conduct the interim E-R analysis for efficacy using unblinded data	Section added to describe the DSC used to select the dose for Part 2.

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	from the first 96 subjects in Part 1 (approximately 32 subjects per treatment arm) who complete treatment through Week 12 and provide a dosing recommendation for Part 2 to Sponsor personnel. Eligible doses for selection in Part 2 will be limited to a dose range of 1 to 80 mg of RTA 901. If the DSC determines that the interim E-R analysis with the first 96 subjects from Part 1 does not a provide sufficient RTA 901 E-R information to make dose recommendations for Part 2, then an additional E-R analysis will be conducted with all subjects per treatment arm in Part 1 who complete treatment through Week 12, see Figure 2. The selected doses will be documented in a Note-to-File to the Investigators and IRBs (as appropriate) and will not require a protocol amendment. Details of the membership, objectives, and process to be followed by the DSC will be described in a separate charter. Additionally, a separate data management and analysis plan supporting this activity will be created. Results will be reported in a separate standalone report, outside the CSR.	
4.6.1. Discontinuation of Study Drug	Discontinuation from study drug does not mean discontinuation from the study. ~~Subjects who discontinue study drug early should be encouraged to continue participation in the study.~~ Subjects who discontinue the study drug early for any reason should complete the procedures associated with the Week ~~8~~12/EOT visit at the closest study visit. If the subject discontinued study drug during a study visit, the EOT procedures should be performed during that study visit. If the subject discontinues study drug in between visits, he/she will perform the EOT procedures at the next scheduled study visit. The subject will then complete the procedures associated with the Week ~~12~~16/end of study (EOS) visit 4 weeks after discontinuation.	Subjects who discontinue study drug early will then proceed to the EOT and EOS visits. The Treatment Period of the study was lengthened to 12 weeks. The follow-up visit is now on Week 16.
4.6.3. Subject Discontinuation and Termination	Subjects who wish to withdraw from the study should complete the procedures associated with the Week ~~8~~ 12/EOT visit at the nearest study visit and the Follow-up Week ~~12~~ 16/EOS visit 4 weeks later.	The treatment period of the study was lengthened to 12 weeks. The follow-up visit is now on Week 16.
4.6.3. Subject Discontinuation and Termination	The term discontinuation ~~generally~~ refers to a *permanent* halt in study drug administration. The reason for subject discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF). A ~~complete~~ comprehensive physical examination, body weight, vital	Subjects who discontinue study drug early will not be required to do [redacted] procedures.

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	signs measurement, ~~12-lead~~ ECG, laboratory analysis, urine pregnancy test for females of child-bearing potential, urine sample for urinalysis, [redacted]~~,~~ and an assessment of concomitant medications and AEs will be performed at the closest study visit, according to Section 4.6.1. [redacted]	
5.1.3. Demographics	5.1.3. Demographics Demographic data including date of birth, age, sex, ethnicity, and race will be collected as indicated in Table 4.	A demographics section was added to align with the Schedule of Assessments.
5.1.4. Medical History	5.1.4. ~~Demographic/~~Medical ~~and Surgical~~ History A complete medical history, including surgical history, alcohol, tobacco, and nicotine-containing product use histories for the past 5 years, will be taken at Screening ~~for the last 5 years~~. All relevant changes throughout the study after Screening will be recorded in the subject's source document and ~~electronic case report form (~~eCRF~~)~~ as AEs.	Demographics were moved to Section 5.1.3. to align with the Schedule of Assessments. Only relevant changes from baseline will be recorded as AEs.
5.1.5. Prior and ~~Current~~ Concomitant Medications	Prior opioid use to manage DPNP will be recorded for the past 5 years prior to Screening.	Collecting additional details on history of opioid use.
~~5.1.5. Safety Assessments~~	~~5.1.5. Safety Assessments~~ ~~Overall safety and tolerability will be assessed by the incidence of TEAEs and SAEs and by evaluations of change from baseline in physical examination, vital signs, 12-lead ECGs, and clinical chemistry, hematology, coagulation, and urinalysis lab tests.~~	This section was replaced with Section 5.1.6. Adverse Events.
5.1.6. Adverse Events	5.1.6. Adverse Events Investigators and study staff are responsible for detecting, documenting, and reporting AEs and SAEs. For each subject, reporting of AEs and SAEs begins after written informed consent/assent is provided. Throughout the study, subjects will be provided opportunities to report AEs. For more information on AEs, see Section 6.3.	This section is to replace Section 5.1.5. Safety Assessments to align with the Schedule of Assessments.
5.1.7. Electronic Diary Set-up	Subjects will also complete the DSIS via their e-diary daily upon waking~~, preferably in the morning~~.	Redundant text was removed.
5.2. Clinical Procedures/Assessments	5.2.1. Height ~~and Weight~~ Measurement Height will be measured only at Screening; the subject will not wear	Height and weight were separated into 2 sections to align with the

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	shoes during the measurement of height. 5.2.2. Weight Measurement Body weight will be measured at the times indicated in Table 4. Weight should be taken with no shoes, hats, and outerwear. Body mass index will be calculated at Screening for eligibility.	Schedule of Assessments.
5.2.3. Comprehensive Physical Examination	5.2.3. Comprehensive Physical Examination	Physical Examination was separated into 2 sections to align with the Schedule of Assessments.
5.2.4. Targeted Physical Examination	5.2.4. Targeted Physical Examination	Physical Examination was separated into 2 sections to align with the Schedule of Assessments.
5.2.5. Electrocardiogram	Baseline for clinical assessments will be those measurements obtained prior to study drug administration on Day 1. Another ECG will be performed approximately 1-hour postdose on Day 1.	An additional ECG at 1-hour postdose was added based upon recommendation from the FDA.
5.2.6. Vital Signs Measurements	The average of the second and third readings will be assessed and calculated as part of the submission data processing and assessed.	Additional detail was removed, as this will be covered in the SAP.
5.3. Laboratory Procedures/Assessments	Samples will be stored under conditions stipulated in the Central Laboratory Manual until they are transported for measurement. Samples will be transported and measured by a central laboratory.	Additional guidance provided for the care of lab samples.
5.3.1. Pregnancy Tests for Females of Child-bearing Potential	5.3.1. Pregnancy Tests for Women Females of Child-bearing Potential A serum and or urine pregnancy test will be performed at the times indicated in Table 4. A serum pregnancy test will be performed at Screening for women females of child-bearing potential (WOCBP) or at any point in time if a pregnancy is suspected.	The word "woman" was replaced by "female" throughout the protocol for consistency.
5.3.6. Clinical Chemistry	Samples will be collected for the following clinical chemistry analyses as indicated in Table 4: ferritin, creatine kinase, blood urea nitrogen , enzymatic creatinine, eGFR, total bilirubin , direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (, AST), alkaline phosphatase , amylase, lipase, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin, lactate dehydrogenase , magnesium, chloride,	Amylase and lipase will now be included in the clinical chemistries.

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	bicarbonate, and gamma glutamyl transferase.	
~~5.3.7. Hemoglobin A1c~~	~~5.3.7. Hemoglobin A1c~~ ~~Samples will be collected for HbA1c as indicated in Table 6. Detailed instructions on collection, storage, and shipment of the samples will be provided in the Central Laboratory Manual provided to the Investigator.~~	This text was moved to Section 5.3.11. of the protocol.
~~5.3.8. Fasting Lipid Profile~~	~~5.3.8. Fasting Lipid Profile~~ ~~Samples will be collected for the following lipid assessments as indicated in Table 6: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.~~	This text was moved to Section 5.3.12. of the protocol.
[redacted]		
5.3.11. Hemoglobin A1c	5.3.11. Hemoglobin A1c Samples will be collected for HbA1c as indicated in Table 4. Detailed instructions on collection, storage, and shipment of the samples will be provided in the Central Laboratory Manual provided to the Investigator.	This text was moved from Section 5.3.7. of the protocol.
5.3.12. Fasting Lipid Profile	5.3.12. Fasting Lipid Profile Samples will be collected for the following lipid assessments as indicated in Table 4: total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides. Subjects should fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16).	This text was moved from Section 5.3.8. of the protocol. Additional guidance on fasting was provided,
~~5.4.1. Rescue Medication~~	~~5.4.1. Rescue Medication~~ ~~Allowed rescue medication includes NSAIDs or acetaminophen to be used as needed and not to exceed the maximum dose stipulated in this protocol (Section 7.8.3). Subjects will be instructed to take no more than 3000 mg per day of acetaminophen (eg, 500 mg every 4 to 6 hours and not exceeding the daily limit) or 1200 mg/day of ibuprofen (eg, 200-400 mg every 4 to 6 hours as needed and not exceeding the daily limit).~~	This text also included in Section 7.8.3. The duplicated text was removed.

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5.4.1. Pain Evaluation	~~Diabetic peripheral neuropathy (DPN) occurs in approximately~~ Approximately 50% of subjects with diabetes experience DPN and ~~at~~ around 15~~-~~ to 20% of subjects with diabetic neuropathy have pain in the feet. Alleviation of pain is the is a primary goal and cornerstone of subject management. ~~Treatment is available and to date there are three~~ The approved treatments for DPNP include 3 oral medications ~~to treat DPNP~~ (duloxetine, pregabalin, and tapentadol) and a topical patch (containing 8% capsaicin~~), though~~). Of these, tapentadol (an opioid medication) and the 8% capsaicin patches are prohibited per protocol, see Section 7.8.4. The approved medications are suboptimal and both effective pain relief and ~~suboptimal effectiveness and~~ tolerability remain elusive ~~and is~~. Thus, a large unmet ~~medical~~ need remains for the treatment of DPNP.	This text was edited to clarify that although tapentadol and 8% capsaicin patches are approved to treat DPNP, they are prohibited per the protocol.
5.4.1.1. Numeric Pain Rating Scale	In order to highlight how people experience pain sensations differently and how the unpleasant aspects of pain can differ from pain intensity, subjects will report how they perceive their average pain intensity, worst pain intensity, and ~~pain upon walking~~ other characteristics of their pain during the past 24 hours at bedtime, using the 11-point NPRS as per Table 4. The NPRS of pain intensity is a numeric scale, ranging from 0 (representing no pain at all) to 10 (representing the worst pain imaginable) (Figure 3). The subject selects a whole number (0 to 10) that best indicates the intensity of his/her pain in the past 24 hours. Subjects must have a score ~~of at least~~ ≥4 on the NPRS at Screening and an average NPRS pain intensity score of at least ≥4 during the last 7 days prior to randomization~~.~~ with a minimum of 5 measurements (Section 4.2.1). The results from this PRO will be used to determine the efficacy of RTA 901 in achieving at least a 30% ~~and~~ or a 50% decrease in pain scores after ~~8~~ 12 weeks of treatment.	The description of the NPRS was edited for clarity. The treatment period of the study was lengthened to 12 weeks.
5.4.1.2.Daily Sleep Interference Scale	The DSIS ~~is~~ will be completed daily by subjects upon waking (3-minute self-administered questionnaire), preferably in the morning, to accurately capture variability in sleep interference due to pain, thus minimizing recall bias.	Repeated text about DSIS was consolidated into this section.
[redacted]		

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[redacted]		
Table 4: Schedule of Assessments (Part 1 & 2)	~~Week 3~~ Week 4 ~~Week 5~~ Week 6 ~~Week 7~~ Week 8 Week 10 ~~Week 8~~ Week 12 / EOT Week ~~12~~ 16 / EOS[d]	The treatment period of the study was lengthened to 12 weeks. The

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	~~Day 22 (±2)~~ | Day 29 (±2) | ~~Day 36 (±2)~~ | Day 43 (±2) | ~~Day 50 (±2)~~ | Day 57 (±2) | Day 71 (±2) | Day 57~~85~~ (±2) | Day ~~85~~ 113 (±2)	visits on Weeks 3, 5, and 7 were removed and additional visits were included on Weeks 10 and 16. The EOT visit will now by at Week 12 and the follow-up visit is now on Week 16.
Table 4: Schedule of Assessments (Part 1 & 2)	Adverse events were added to the Screening visit.	Adverse events were included in the Screening visit, as AEs are collected after the ICF is signed.
[redacted]		
Table 4: Schedule of Assessments (Part 1 & 2)	[c] Day 1 includes the first dose administration, and all procedures must be performed before study drug administration, except for adverse events, 1-hour postdose ECG, [redacted].	An additional ECG at 1-hour postdose was added based upon recommendation from the FDA.
Table 4: Schedule of Assessments (Part 1 & 2)	[d] Subjects who discontinue study drug early for any reason should complete the procedures associated with the Week ~~8~~12/EOT visit at the nearest study visit and the Follow-up Week ~~12~~16/EOS visit 4 weeks later.	The treatment period of the study was lengthened to 12 weeks. The follow-up visit is now on Week 16.
Table 4: Schedule of Assessments (Part 1 & 2)	[g] Height should be measured with no shoes.	The height should be measured without shoes.
Table 4: Schedule of Assessments (Part 1 & 2)	[j] ECG on Day 1 should be recorded at predose and 1-hour postdose.	An additional ECG at 1-hour postdose was added based upon recommendation from the FDA.
Table 4: Schedule of Assessments (Part 1 & 2)	[n] Subjects should fast for at least 8 hours prior to clinic visits where fasting lipids are taken (Screening, Week 4, Week 8, Week 12, and Week 16).	Additional guidance provided for fasting on days where fasting lipids are measured.
Table 4: Schedule of Assessments (Part 1 & 2)	[o] All study drug administration should be performed in an early fasted state, defined as having no food within at least 2 hours prior to study drug administration and for 1 hour following study drug administration. Since the first dose will be taken in-clinic and there	Additional guidance for fasting prior to visits was provided.

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	are no [redacted] fasting lipids taken at the Run-in visit, subjects should fast for 2 hours prior to the visit.	
Table 4: Schedule of Assessments (Part 1 & 2)	[p] On visits containing both labs with fasting and study drug administration, the longer of the fasting guidance (8 hours) is to be followed, these are not additive.	Additional guidance provided for managing fasting based on the visit.
Table 4: Schedule of Assessments (Part 1 & 2)	[q] Subjects will complete the NPRS in the e-diary daily at bedtime. [r] Subjects will complete the DSIS in the e-diary daily upon waking.	Additional guidance to denote the PROs performed daily on the e-diary.
6.3.2. Adverse Events Based on Tests or Examinations	~~In the first-in-human SAD/MAD study for RTA 901 (901-C-1503), study drug was generally safe and well tolerated. In Part 1 (SAD) there were no clinically relevant mean or individual changes in laboratory parameters.~~ ~~In Part 2 (MAD), one subject in the RTA 901 10mg cohort of the study had a Grade 4 TEAE (preferred term) of blood creatine phosphokinase increased that began on Study Day 24. The event was assessed as unrelated to study drug by the investigator. The subject completed the study following resolution of the TEAE at an Unscheduled Visit on Study Day 37. As a result of this TEAE, clinically relevant increases in mean creatine kinase (CK or CPK) at Study Day 24 and mean change in creatine kinase from baseline to Study Day 24 were noted in the RTA 901 10 mg cohort in Part 2 (MAD) of the study. There were no other clinically relevant mean or individual changes in laboratory parameters during Part 2 (MAD) of the study. Elevated CPK levels leading to study drug interruptions should be recorded. However, elevated CPK levels which require more frequent laboratory testing without study drug interruptions should be reported as AEs.~~	Duplicated text from the Introduction Section was removed.
6.6. Pregnancy	During the study, all female subjects must be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, late or missed menstrual period). Male subjects must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant. If a subject or Investigator suspects that the subject may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the subject must discontinue taking study drug and be	This text was moved from Section 6.7.1. of the protocol.

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	discontinued from the study (Section 4.6.3).	
6.6. Pregnancy	Pregnancy in a study ~~subject or the female partner of the~~ subject must be reported to the responsible safety party within 1 business day of the site becoming aware of the pregnancy. ~~Subjects who become pregnant or whose female partner becomes pregnant during the study must be discontinued (Section 4.6.3).~~ Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. ~~Pregnancy is not considered an adverse event; however, the~~ The Investigator must follow a pregnant subject or the pregnant female partner of a male subject (if consenting) and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. ~~Reata Pharmaceuticals, Inc.~~The Sponsor or its designee may contact the Investigator to request additional information throughout the course of the pregnancy.	Clarified guidance for pregnancy in study subjects and female partners of subjects.
6.6. Pregnancy	Pregnancy in a study subject is not considered an ~~adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to the responsible safety party within 24 hours of the site becoming aware of the event.~~AE. However, the following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form: • Congenital anomaly/birth defect; • Stillbirth; or • Spontaneous miscarriage.	Clarified guidance for pregnancy in study subjects and female partners of subjects. This text was moved from Section 6.7.1. of the protocol.
6.7. Methods of Birth Control	• ~~Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (eg, contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);~~ • Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal, or transdermal) as prescribed ~~for at least 60 days prior to start of study drug administration~~; • Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed);	Additional detail was provided on the approved female birth control methods.

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	• Use of an intrauterine ~~device~~ hormone-releasing system as prescribed;	
6.7. Methods of Birth Control	• ~~Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (eg, contraceptive sponge, spermicidal jelly or cream, diaphragm [always used with spermicidal jelly/cream]);~~ • Partner contraception methods; must be the sole partner for that subject: — ~~Use of an intrauterine device;~~ — Use of a non-hormonal intrauterine device with appropriate re-insertion period (as prescribed); — Use of hormonal contraceptives associated with inhibition of ovulation (oral, parenteral, intravaginal or transdermal) as prescribed ~~for at least 60 days prior to start of study drug administration~~; — Use of an intrauterine hormone-releasing system as prescribed;	Additional detail was provided on the approved male birth control methods.
~~6.7.1. Maternal exposure~~	~~6.7.1. Maternal exposure~~ ~~During the study, all female subjects must be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, late or missed menstrual period). Male subjects must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant.~~ ~~If a subject or Investigator suspects that the subject may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the subject must discontinue taking study drug and be discontinued from the study. The Investigator must immediately report a pregnancy associated with study drug exposure and record the event.~~ ~~Pregnancy is not considered an adverse event; however, the Investigator must follow a pregnant subject or the pregnant female partner of a male subject (if consenting) and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata Pharmaceuticals, Inc. or its designee may contact the Investigator to~~	Duplicated text was consolidated to Section 6.6.

<table>
<tr><th>Section</th><th>Version 3</th><th>Rationale</th></tr>
<tr><td></td><td>~~request additional information throughout the course of the pregnancy.~~
~~The following pregnancy outcomes must be considered SAEs and will require additional reporting in the CRF and on an SAE form:~~
~~• Congenital anomaly/birth defect;~~
~~• Stillbirth; or~~
~~• Spontaneous miscarriage.~~</td><td></td></tr>
<tr><td>Table 6: Management of Elevated Aminotransferase Levels (ALT and/or AST)</td><td>
<table>
<tr><th>ALT and/or AST Level(s)</th><th>Dose ~~Interruption~~ <u>Discontinuation</u> (Yes/No)</th><th>~~Procedure~~</th></tr>
<tr><td>> 8x ULN</td><td rowspan="4">Yes</td><td rowspan="4">~~Discontinue study drug temporarily~~
~~Contact the medical monitor~~
~~The study drug may be restarted with Sponsor approval after all the following criteria are met:~~
~~Ultrasound or MRI of the hepatobiliary tree*;~~
~~ALT and AST returned to ≤ ULN;~~
~~TBL is within normal range;~~
~~Other relevant labs (eg, albumin, INR, PT) are within normal range;~~
~~No clinical signs or symptoms of liver injury are present.~~
~~*Based on imaging results, if additional tests/studies are warranted, this should be discussed with the medical monitor.~~</td></tr>
<tr><td>> 5x ULN for more than 2 weeks</td></tr>
<tr><td>> 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia <u>(>5%)</u></td></tr>
<tr><td>> 3x ULN <u>and</u> (TBL > 2x ULN <u>or</u> INR > 1.5)</td></tr>
<tr><td>> 3x ULN</td><td>No</td><td>~~Check aminotransferase levels (as well as TBL, GGT, ALP), and INR within 48 to 72 hours~~</td></tr>
</table>
</td><td>Updated guidance for the management of elevated aminotransferases. Study drug cannot be resumed following a drug interruption due to elevated aminotransferases.

List of abbreviations moved to the general text in Section 6.8.</td></tr>
</table>

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	~~Continue testing for ALT/AST every 72 to 96 hours until aminotransferase levels are below 3x the ULN for at least one week~~ ~~Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase; INR=international normalized ratio; MRI=magnetic resonance imaging; PT=prothrombin time; TBL=total bilirubin; ULN=upper limit of normal~~	
6.8. Management of Elevated Aminotransferase Levels (ALT and/or AST)	Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; PT=prothrombin time; TBL=total bilirubin; ULN=upper limit of normal	This text was moved from Table 6.
6.8. Management of Elevated Aminotransferase Levels (ALT and/or AST)	~~The hepatobiliary tree must be assessed by ultrasound or magnetic resonance imaging (MRI) for subjects who meet temporary discontinuation criteria. Based on imaging results, if study drug additional tests/studies are warranted, this should be discussed with the medical monitor.~~	Updated guidance for the management of elevated aminotransferases. Study drug cannot be resumed following a drug interruption due to elevated aminotransferases.
6.9. Management of Study Drug-Related Toxicities	See Section 4.6.2 for details on resuming study drug after interruptions.	Reference added for additional details.
7.1. Dose and Treatment Regimens	~~Approximately 368 eligible subjects (92 subjects per treatment arm) will be randomized 1:1:1:1 to either RTA 901 (10, 40, or 80 mg) or placebo at Day 1 (randomization) and will remain on the assigned treatment arm through Week 8.~~ Study drug is defined as ~~administration of~~ either RTA 901 or placebo. During the Run-in Period, subjects will be administered single-blind placebo once daily in the morning. During the Treatment Period, subjects will be administered double-blind study drug QD in the morning according to their randomized assignment (Table 3).	Text updated to match the revised study design and remove duplicated text.
Table 8: Placebo Information	Placebo for RTA 901 capsule (~~10 mg~~ size #4, ~~40 mg~~ size #0)	Text updated to match the revised study design.
7.3. Study Drug Packaging and Labeling	The study drug will be supplied in tamper-evident kits containing ~~three~~ high-density polyethylene bottles. Each bottle will utilize foil induction-seal liners and a child-resistant closure. ~~Each~~ In Part 1, each bottle of study drug will contain 30 capsules of 10 mg or 40 mg	Text updated to match the revised study design.

<table>
<tr><th>Section</th><th>Version 3</th><th>Rationale</th></tr>
<tr><td></td><td>strength RTA 901 or the matching placebo capsules. In Part 2, each bottle of study drug will contain 30 capsules of RTA 901 or matching placebo capsules, depending on the doses of RTA 901 recommended by the DSC (see Section 3.6).
~~The~~ In Part 1, the study drug kits will contain a combination of ~~three~~ bottles, each containing active or placebo capsules in varying strengths to make up each dosing regimen. ~~The following table (~~Table 9~~)~~ shows the combination of bottles that will be used to comprise the dose for each treatment arm, while maintaining the study blind~~.~~ in Part 1. Kit configurations for Part 2 will depend on the doses recommended by the DSC. As in Part 1, the kits for each treatment arm will contain the same number of bottles and the same configuration of capsule sizes necessary to maintain the study blind.</td><td></td></tr>
<tr><td>Table 9: Study Drug Kit Configurations – Part 1</td><td>Table 9: Study Drug Kit Configurations – Part 1
<table>
<tr><th>Treatment Arm</th><th>Bottles of 10 mg Size #4 RTA 901</th><th>Bottles of ~~10 mg~~ Size #4 Placebo</th><th>Bottles of 40 mg Size #0 RTA 901</th><th>Bottles of ~~40 mg~~ Size #0 Placebo</th></tr>
<tr><td>Placebo</td><td>0</td><td>1</td><td>0</td><td>2</td></tr>
<tr><td>RTA 901 10 mg</td><td>1</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>~~RTA 901 40 mg~~</td><td>~~0~~</td><td>~~1~~</td><td>~~1~~</td><td>~~1~~</td></tr>
<tr><td>RTA 901 80 mg</td><td>0</td><td>1</td><td>2</td><td>0</td></tr>
</table></td><td>Text updated to match the revised study design.</td></tr>
<tr><td>7.5. Study Drug Administration</td><td>Subjects must be instructed to continue taking study drug once daily through Week ~~8~~ 12 unless:</td><td>The treatment period of the study was lengthened to 12 weeks.</td></tr>
<tr><td>7.7. Study Drug Accountability</td><td>A current (running) and accurate inventory of study drug will be kept by each Investigator and will include shipping invoices and the date on which study drug is dispensed/administered to the subject. An overall accountability of the study drug will be performed and verified by the study monitor throughout the study and at the closeout visit. Upon completion or termination of the study, all original containers (containing unused study drug) will be returned to ~~Reata~~ the Sponsor or its designee, according to instructions from ~~Reata~~ the Sponsor and according to local regulations. Labels must remain attached to the containers. Local study drug destruction is only allowed with prior Sponsor approval.</td><td>Sponsor approval is required for local IP destruction.</td></tr>
</table>

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7.8.1. Standard of Care Pain Medications	Subjects are ~~allowed~~ required to ~~enter the study with a maximum of~~ take only 1 SOC pain medication for neuropathic pain (consistent with regional or local ~~standard of care~~ SOC guidelines for DPNP) ~~that has been taken~~ at a stable dose (defined as < 50% change in total dose) that does not exceed the maximum dose in the prescribing information for approximately 4 weeks prior to Screening. Allowed SOC pain medications include: duloxetine, pregabalin, and gabapentin. Attempts should be made to maintain the stable dose of ~~SOC~~ pain therapy. If changes to the dose are necessary, the Investigator should discuss with the Medical Monitor. However, dose level should not be above the maximum prescribed dose as instructed in the medication's dosage and administration section of the prescribing information. ~~Subjects who failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications are also allowed.~~	Clarified text on SOC pain medications.
7.8.2. Allowed Medications	The following medications and therapeutics are allowed during the study: • Benzodiazepine, zolpidem, diphenhydramine, or related drugs for insomnia~~,~~ if subject is ~~anticipated to be~~ on a stable dose for 3 months prior to entry and it ~~will~~ is not anticipated to change during the study; • SSRI (selective serotonin reuptake inhibitor) for depression~~,~~ if the subject is ~~anticipated to be~~ on a stable dose for 3 months prior to entry and it ~~will~~ is not anticipated to change during the study; • Analgesics, see Section 7.8.3.	Clarified text on allowed medications.
7.8.3. Rescue Medication	Subjects may use a single rescue medication (NSAID or acetaminophen) to treat DPNP as needed during study participation, in addition to their standard-of-care medication.	Clarified text on rescue medications.
7.8.6. Recording of Concomitant Treatment	Concomitant medications include those being taken at Screening or at any point throughout the study, up to and including the Week ~~12~~ 16/EOS visit.	The follow-up visit is now on Week 16.
8.1. Sample Size Estimate	This study will be conducted in 2 parts. A total of ~~368 subjects (92 subjects~~ approximately 192 subjects (64 subjects per treatment arm) are planned for randomization~~.~~ in Part 1 and approximately 192 subjects (64 subjects per treatment arm) are planned for randomization in Part 2, for a total of 384 subjects to be randomized. This sample size is based on a dose-ranging scheme to evaluate initial	The study design was modified to better determine the optimal dose of RTA 901 for future studies. The study will be conducted in 2 parts with differing treatment arms in each part.

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	safety, efficacy, [redacted] of RTA 901 in this population. The primary comparisons for efficacy are between each of the ~~3~~2 RTA 901 treatment groups and the placebo treatment group. ~~Each comparison between RTA 901 and placebo will be at the 0.019 level from Dunnett's adjustment so that the~~ The overall Type I error rate will be controlled at the 0.05 significance level. ~~With 92 subjects per treatment group, there is 80% power to detect~~ A hierarchical testing strategy to control the overall Type I error will be defined in the SAP. Power calculations are based on a 2-sample t-test with no adjustments for multiple comparisons. The study assumes a difference in NPRS pain intensity means of 1.2 between each RTA 901 treatment group and the placebo treatment group~~, assuming~~ and a standard deviation of 2.4 ~~and a missing data rate of 10%~~.	Additional detail was provided for the statistics analyses of the revised of the study design.
8.1. Sample Size Estimate	~~8.1.1. Blinded Sample Size Recalculation~~ ~~In order to maintain sufficient study power to detect the pre-specified treatment effect for the primary efficacy endpoint (i.e., change from baseline in NPRS of 1.2 points) a sample size recalculation may be performed to evaluate on a blinded basis the study assumptions (variability and drop-out rate) used to calculate sample size. A Sample Size Recalculation Committee (SRC), comprised of Sponsor personnel and the study's blinded statistician, will be established to recalculate sample size based on blinded assessment of study assumptions. The SRC will review available data (e.g., baseline characteristics, study drug discontinuations, variability in NPRS change from baseline) when approximately 70% of the subjects have been enrolled in the study. The Sponsor may increase the sample size of the study up to 468 subjects. There will be no sample size decrease under this procedure. An increase of sample size within this range will be documented in a Note-to-File (NTF) to the Investigators and IRBs (as appropriate) and will not require a protocol amendment. Because these analyses will be based on pooled, blinded data they will not impact the Type I error rate. A Blinded Sample Size Recalculation Plan will present details regarding the planned recalculation of sample size.~~	The sample size recalculation section was removed from the study. Additional detail was provided for the statistics analyses of the revised of the study design.

Section	Version 3	Rationale
	If doses selected for Part 2 do not include doses studied in Part 1, then an analysis by dose group for Part 1 or Part 2 doses will be performed following completion of each study part. Within each Part, with 64 subjects per treatment group, each study part has 80% power to compare treatment groups to placebo. If doses selected for Part 2 include any doses studied in Part 1 (ie, 10 or 80 mg), then an analysis by dose group will be performed using Part 1 and Part 2 combined, following completion of the study. The dose group that is enrolled in both parts will have 128 subjects. With 128 placebo subjects compared to 128 subjects in the RTA 901 dose group, there is 98% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4). RTA 901 dose groups that are enrolled in only 1 part will have 64 subjects. With 128 placebo subjects compared to 64 subjects in each RTA 901 dose group, there is 90% power to detect the same difference (1.2 NPRS points) assuming the same standard deviation (2.4).	
8.2. Definitions of Analysis Sets	A detailed SAP will be developed prior to database lock.	This text was moved from Section 8.2.1.
8.2.1. Intent-to-Treat Analysis Set	~~Mixed-model repeated measures (MMRM) analyses will be used to analyze the primary efficacy endpoints. A detailed SAP will be developed prior to database lock.~~	This text was consolidated to Section 8.4.3. and duplicated text was removed.
8.2.2. Safety Analysis Set	The safety analysis set includes all randomized subjects who receive~~d~~ at least 1 dose of randomized study drug. The safety analysis set ~~is~~ will be used for evaluation of safety variables. Subjects who receive~~d~~ at least 1 dose of RTA 901 will be classified in the RTA 901 group. Subjects who ~~will be~~ are randomized and receive at least 1 dose of placebo and no dose of RTA 901 will be classified in the placebo group. Subjects in the Run-in phase who fail to randomize into the Treatment phase will not be included in the placebo group.	Subjects who are not eligible for randomization will not be included in the placebo group of the safety analysis set.
[redacted]	[redacted]	[redacted]
8.3. Endpoints and Objectives	The SAP will describe in detail the methods used for the primary, safety, secondary, and exploratory endpoints and will serve as the final arbiter of all statistical ~~analysis~~ analyses. The study endpoints are listed in Section 2.2.	Additional detail was provided for the statistics analyses of the revised of the study design.

Section	Version 3	Rationale
	Data will be summarized using descriptive statistics. Continuous data will be summarized with statistics such as mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using frequency counts and percentages. If doses selected for Part 2 include any doses studied in Part 1 (ie, 10 or 80 mg), then the final analysis by dose group will be performed following final study database lock. Otherwise, if doses selected for Part 2 do not include doses studied in Part 1 then final analysis by dose group for Part 1 or Part 2 doses will be performed following the Part 1 or Part 2 database lock, respectively.	
8.4.1. Hypotheses	Primary hypothesis: There will be a greater mean reduction from baseline in NPRS pain intensity for the RTA 901-treated groups compared with placebo after ~~8~~12 weeks of double-blind treatment.	The pain intensity score on the NPRS is the data point used for this analysis. The treatment period of the study was lengthened to 12 weeks.
8.4.2. Closed Testing Procedure	~~For primary analysis, each comparison between RTA 901 (10, 40, 80 mg) and placebo will be at the 0.019 level from Dunnett's adjustment so that t~~The overall Type I error rate will be controlled at the 0.05 significance level. A hierarchical testing strategy to control the overall Type I error will be defined in the SAP.	Additional detail was provided for the statistics analyses of the revised of the study design.
8.4.6. Interim Analysis	~~No formal interim analysis is planned for this study.~~ An interim E-R analysis for efficacy is planned for the Part 1 interim E-R analysis cohort (ie, the first 96 subjects in Part 1 (approximately 32 subjects per treatment arm) who complete treatment through Week 12). Results from this interim E-R analysis will be used to determine the doses of RTA 901 in Part 2. An additional E-R analysis for efficacy may also be conducted with all subjects who complete treatment through Week 12 in Part 1 (approximately 64 subjects per treatment arm) of the study to determine the doses of RTA 901 in Part 2 if the results from the interim E-R analysis using the first 96 subjects who complete treatment through Week 12 from Part 1 do not provide sufficient RTA 901 E-R information to make dose recommendations for Part 2. Details of the interim E-R analysis will be described in a separate analysis plan and the results will be reported separately from the CSR. No formal interim analysis for efficacy or safety by dose is planned.	Additional detail was provided for the planned interim E-R analysis(es) for efficacy of the revised study design.

Section	Version 3	Rationale
8.4.8. Analysis of Safety Variables	The number and percent of subjects with an AE will be summarized for each treatment group. Changes from baseline to each scheduled time point for ~~each~~ physical examinations, vital sign measurements, ECGs, clinical laboratory ~~test, blood pressure~~ measurements, and ~~heart rate~~ body weight will be summarized by treatment group.	Analysis updated to match the Primary Safety Endpoint.
[redacted]		

AMENDMENT CHANGE SUMMARY DOCUMENT

CLINICAL STUDY PROTOCOL 901-C-2102

Study Title: A PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RTA 901 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN (DPNP)

CYPRESS

Protocol History
Version 2.0 – 27 September 2022
Version 1.0 – 28 April 2022

CONFIDENTIALITY STATEMENT

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 1 to produce the text of Version 2. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are notdescribed.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 2	Rationale
SIGNATURE PAGE & CONTACTS IN CASE OF EMERGENCY	[redacted] Office: [redacted]	Reata personnel change
[redacted]		
3.3. Screening Period (Days -28 to -15)	The Screening Period includes 1 clinic visit, w~~hich should not occur more than~~ up to 2 weeks prior to the Run-in Period (within approximately 28 days prior to Day 1).	To clarify that the Screening Period can be less than 2 weeks
3.3. Screening Period (Days -28 to -15)	Michigan Neuropathy Screening Instrument Part B, and will be included if a score ≥ ~~3.0~~ 2.5 is obtained.	The MNSI inclusion criteria was lowered to 2.5 to ensure that patients with early neuropathy are not excluded
3.3. Screening Period (Days -28 to -15)	Additional procedures during Screening (Visit 1) will include the administration of the following [redacted]	To avoid duplication of the instructions as both the DSIS and NPRS were mentioned in the previous paragraph.
3.4. Run-in Period (Days -14 to -1)	[redacted]	Direction to Table 6, SOA to look at [redacted]
3.5. Treatment Period (Day 1 to Week 8)	~~Other scales~~ The [redacted] are to be completed ~~on Day 1 of randomization~~ according to the Schedule of Assessments (Table 6). [redacted]	Direction to Table 6, SOA to look at [redacted]
3.6. Follow-up/End of Study (Week 12)	Subjects will be directed to continue entering the average of pain intensity, worst pain intensity, and pain upon walking and whether they needed to use rescue medication, in the e-diary at bedtime. Upon waking in the morning, subjects will be asked to complete the DSIS. [redacted]	[redacted]

Section	Version 2	Rationale
4.1.1. Run-in Inclusion Criteria	4. Currently taking ≤ 1 allowed prescribed standard-of-care medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 4 weeks prior to Screening (Section 7.8.1); failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications;	To specify that the stable dose of the standard of care drug taken must be within the maximum dose of the drug's prescribing information and the SOC refers to medications approved for DPNP
4.1.1. Run-in Inclusion Criteria	7. A score of ≥ ~~3.0~~ 2.5 on the Michigan Neuropathy Screening Instrument (MNSI) Part B;	The MNSI inclusion criteria was lowered to 2.5 to ensure that patients with early neuropathy are not excluded
4.1.1. Run-in Inclusion Criteria	11. Willing to sign and date an informed consent document indicating that the subject ~~(or a legally acceptable representative)~~ has been informed of all pertinent aspects of the study prior to initiation of any ~~subject~~ study-mandated procedures;	Removal of the consent of a legally acceptable representative for consistency with Reata standard
4.1.1. Run-in Inclusion Criteria	12. A negative COVID-19 ~~Polymerase Chain Reaction (PCR)~~ test result during Screening.	To specify the COVID-19 test will be a rapid COVID-19 antigen test
4.1.2. Run-in Exclusion Criteria	d. Tricyclic antidepressants ~~(other than amitriptyline)~~ and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); 5-HT3 receptor antagonists, within 7 days prior to Screening;	Amitriptyline is no longer allowed. To allow the usage of Triptans for causes other than DPNP
4.1.2. Run-in Exclusion Criteria	f. Chronic treatment with strong or moderate cytochrome P450 isotype 3A4 (CYP3A4) inhibitors or inducers and P-glycoprotein (P-gp) inhibitors, within 14 days prior to Screening;	To exclude the use of P-gp inhibitors based on DDI study data
4.2.1. Randomization Inclusion Criteria	5. Currently taking ≤ 1 allowed prescribed SOC medication for managing DPNP at a stable dose (not exceeding the maximum dose in the prescribing information) for approximately 8 weeks prior to Day 1 with no anticipated changes to dose(s) during study (Section 7.8.1), or failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications;	To specify that the stable dose of the standard of care drug taken must be within the maximum dose of the drug's prescribing information and the SOC refers to medications approved for DPNP
4.2.2. Randomization Exclusion Criteria	b. Tricyclic antidepressants ~~(other than amitriptyline)~~ and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); 5-HT3 receptor antagonists;	Amitriptyline is no longer allowed. To allow the usage of Triptans for causes other than DPNP

Section	Version 2	Rationale
4.2.2. Randomization Exclusion Criteria	d. Chronic treatment with strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors;	To exclude the use of P-gp inhibitors based on DDI study data
4.4.3. Rescreening	Subjects who fail to meet all Run-in inclusion/exclusion criteria may be considered for rescreening at the discretion of the Investigator after consultation with the Medical Monitor. These subjects will be considered Screen Failures. Subjects may repeat Screening once to qualify for the study. If a subject is approved to rescreen, they will be given a new subject number and all screening procedures will be repeated. Subjects who participate in the Run-in Period but fail to meet the Randomization criteria will not be allowed to rescreen for the study. These subjects will be considered Randomization Failures.	To clarify the nomenclature for Screen Failures and Randomization Failures
4.5. Subject Enrollment and Randomization	The "other" stratification group includes subjects who failed treatment, could not tolerate/are unable to take on-label medications for DPNP, or use only an NSAID or acetaminophen as a treatment option. For additional detail on the use of rescue medications, see Section 7.8.3.	To clarify the "other" stratification group
4.6. Study Drug Discontinuation, Interruption, and Subject Termination	4.6. Study Drug ~~Subject~~ Discontinuation, Interruption, and Subject Termination	Updating section title to match new sub-sections
4.6.1. Discontinuation of Study Drug	Discontinuation from study drug does not mean discontinuation from the study. Subjects who discontinue study drug early should be encouraged to continue participation in the study~~, completing all study visits, including Week 8/EOT and Week 12/EOS, according to the Schedule of Assessments (Table 6)~~. Subjects who discontinue the study drug early for any reason should complete the procedures associated with the Week 8/EOT visit at the closest study visit. If the subject discontinued study drug during a study visit, the EOT procedures should be performed during that study visit. If the subject discontinues study drug in between visits, they will perform the EOT procedures at the next scheduled study visit. The subject will then complete the procedures associated with the Week 12/end of study (EOS) visit 4 weeks after discontinuation. ~~The subject should continue to follow the remaining study scheduled visits, including Week 8/EOT and Week 12/EOS.~~	To clarify that a patient discontinuing the study should only do the EOT and EOS visits, not the entire remaining schedule.

Section	Version 2	Rationale
4.6.2. Resuming Study Drug after Interruptions	The term interruption generally refers to a temporary halt in study drug administration. This can be either at the direction of the site, or by the patient's decision or non-compliance. An interruption from the study drug based on the patient's decision or non-compliance will be defined as missing at least 3 consecutive days of study drug administration. There is no minimum timeframe for a site directed interruption.	To add clarity on the definition of a study drug interruption
4.6.3. Subject Discontinuation and Termination	Subjects are free to withdraw from participation in the study at any time upon request. Subjects who wish to withdraw from the study should complete the procedures associated with the Week 8/EOT visit at the nearest study visit and the Follow-up Week 12/EOS visit 4 weeks later.	To clarify the procedures done at the EOT visit
4.6.3. Subject Discontinuation and Termination	If a positive result is obtained on a pregnancy test for a subject, or a subject reports that they or their female partner become(s)~~ing~~ pregnant during the study, the subject must be discontinued immediately.	Clarifying that a patient whose female partner becomes pregnant must also discontinue the study
5.1.3. Demographic/Medical and Surgical History	A complete medical history, including alcohol, tobacco, and nicotine-containing product use histories, will be taken at Screening for the last 5 years.	To specify the time period of the medical history
5.1.4. Prior and Current Concomitant Medications	Prior and concomitant medications (ie, medications that the subject is taking or has taken within 30 days prior to Screening ~~Day 1~~) will be reviewed per Table 6 and all changes throughout the study after Screening will be recorded in the subject's source document and eCRF.	Adjusting timeframe for consistency with Inclusion/Exclusion Criteria
5.1.6. Electronic Diary	During Screening, subjects deemed likely to be eligible for the study will be given access to an e-diary and trained on how to record daily pain scores from ~~Visit 1~~ Screening up to ~~Visit 3~~Day 1. The results will be reviewed on Day 1 ~~(Visit 3)~~ to confirm that the subject is eligible for the study.	To clarify reference to the visit name instead of the visit number

Section	Version 2	Rationale
5.2.1. Height and Weight	Height will be measured only at Screening; the subject will not wear shoes during the measurement of height. ~~The physical examination performed on Day 1 will serve as the baseline physical examination for clinical assessments. Any clinically significant physical examination findings after study drug administration will be recorded as AEs.~~ Body weight will be measured at the times indicated in Table 6. Weight should be taken ~~at the same time each day,~~ with no shoes, hats, and outerwear. ~~BMI~~ Body mass index will be calculated at Screening for eligibility.	To move the reference to the physical exam to section 5.2.2. Physical Examination There will not be daily weights taken on this study
5.2.2. Physical Examination	The physical examination performed on Day 1 will serve as the baseline physical examination for clinical assessments.	Moving the physical examination text from section 5.2.1 Height and Weight to section 5.2.2 Physical Examination
5.2.4. Vital Signs	Vital signs, including blood pressure, heart rate, respiration rate, and body temperature, will be assessed on the study days indicated in Table 6 or at early discontinuation.	Including respiration rate in the vital signs
5.2.5. Michigan Neuropathy Screening Instrument (MNSI)	To be eligible for randomization, subjects must have a score of ≥ ~~3.0~~ 2.5 on MNSI Part B only; Part A will not be used in this study.	The MNSI inclusion criteria was lowered to 2.5 to ensure that patients with early neuropathy are not excluded
5.3.4. COVID-19 Test	5.3.4. COVID-19 ~~PCR~~ Test A COVID-19 ~~PCR~~ test will be performed at the times indicated in Table 6 for all subjects.	To specify the COVID-19 test will be a rapid COVID-19 antigen test
5.3.5. Drugs of Abuse, and Cotinine Screen	5.3.5. Drugs of Abuse, ~~Alcohol,~~ and Cotinine Screen A urine screen for drugs of abuse and cotinine, ~~and alcohol test,~~ will be performed at Screening.	There will not be an alcohol test
[redacted]		

Section	Version 2	Rationale
5.4.1. Rescue Medication	~~The percentage of subjects using rescue medication for DPNP during the Treatment Period, including baseline and average weekly and cumulative dose, as well as the quantity and timing of such medication intake must be recorded for posterior analysis. Thus, subjects will be trained to enter the use of rescue therapy daily at bedtime.~~	Removing repeated text
Table 6: Schedule of Assessments	Week 8 / EOT	To clarify the visit names
Table 6: Schedule of Assessments	Day 8 (±~~3~~2) Day 15 (±~~3~~2) Day 22 (±~~3~~2) Day 29 (±~~3~~2) Day 36 (±~~3~~2) Day 43 (±~~3~~2) Day 50 (±~~3~~2) Day 57 (±~~3~~2) Day 85 (±~~3~~2)	The visit windows will be ±2 days
Table 6: Schedule of Assessments	COVID-19 ~~PCR~~ Test	To specify the COVID-19 test will be a rapid COVID-19 antigen test
Table 6: Schedule of Assessments	Drug and~~,~~ Cotinine~~, and Alcohol~~ Screen	There will not be an alcohol test
Table 6: Schedule of Assessments	Study Drug Administration	Adding an "x" to the table to indicate study drug will be administered during Run-in
Table 6: Schedule of Assessments	Numeric Pain Rating Scale (NPRS) (at home) Daily Sleep Interference Score (DSIS) (at home)	To indicate that the NPRS and DSIS will be performed at home
Table 6: Schedule of Assessments	[a] The Screening Period includes 1 clinic visit ~~and should not occur more than~~ up to 2 weeks prior to the Run-in Period (within approximately 28 days prior to Day 1), see Section 3.3.	To clarify that the Screening Period can be less than 2 weeks
Table 6: Schedule of Assessments	[d] ~~Subjects who discontinue treatment early should be encouraged to complete all study visits, including Week 8/EOT and Week 12/EOS.~~ Subjects who discontinue ~~the~~ study drug early for any reason should complete the procedures associated with the Week 8/EOT visit at ~~discontinuation~~ the nearest study visit and the Follow-up Week 12/EOS visit 4 weeks later.	To clarify that a patient discontinuing the study should only do the EOT and EOS visits, not the entire remaining schedule.
Table 6: Schedule of Assessments	[f] Weight should be taken ~~at the same time each day (~~with no shoes, hats, and outerwear~~)~~.	There will not be daily weights taken

Section	Version 2	Rationale
Table 6: Schedule of Assessments	[redacted]	[redacted]
5.6. Unscheduled Visits	5.6. Unscheduled Visits Unscheduled visits may be performed at any time and for any reason, including those not specifically mentioned in this section, as deemed necessary by the investigator. Unscheduled visits conducted for the following reasons should include collection of AEs, clinical chemistry, hematology, concomitant medication collection, and vital signs: • Management of an AE or SAE; • Performance of additional laboratory tests for clinically abnormal laboratory test values or to confirm a possible pregnancy; • Patient safety evaluation. Unscheduled visits conducted for the following reasons do not require additional assessments unless deemed necessary by the investigator: • Study drug dispensation; • Any operational need that would require the patient to return to the site between scheduled visits.	Included new section on unscheduled visits
6.1.2. Definition of Treatment Emergent Adverse Event	Adverse events that present, or worsen in intensity or frequency, following the initiation of study treatment will be categorized as TEAEs.	Inclusion of missing text
6.2. Definitions of Serious Adverse Event	Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of ~~first dose of study drug~~ consent until the final visit).	Clarification pregnancies will be tracked from consent, not from first dose of study drug

Section	Version 2	Rationale
6.3.2. Adverse Events Based on Tests or Examinations	Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged by the Investigator to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). ~~except for the following laboratory test values which should be considered AEs regardless of their clinical significance:~~	Removal of text to facilitate clarity on how the PI should evaluate an AE based on changes in laboratory test values
6.6. Pregnancy	Pregnancy in a study subject or the female partner of the subject must be reported to the responsible safety party within 1 business day of the site becoming aware of the pregnancy. Subjects who become pregnant or whose female partner becomes pregnant during the study must be discontinued (Section 4.6.3).	Clarifying that a patient whose female partner becomes pregnant must also discontinue the study
6.8. Management of Elevated Aminotransferase Levels (ALT and/or AST)	6.8. Management of Elevated ~~Transaminase~~ Aminotransferase Levels (ALT and/or AST) ~~Some subjects may experience more rapid increases in ALT/AST values than others during the dose titration period. Investigators may consider extending the time between each dose increase to manage ALT/AST elevations.~~ If a subject's ~~transaminases~~ aminotransferases are elevated, follow the instructions outlined in Table 8.	Removed reference to dose titration Transaminases were renamed to aminotransferases
7.5. Study Drug Administration	[redacted]	To add detail [redacted]

Section	Version 2	Rationale
7.8.1. Standard of Care Medications	Subjects are allowed to enter the study with a maximum of 1 SOC medication for neuropathic pain (consistent with regional or local standard of care guidelines for DPNP) that has been taken at a stable dose (defined as < 50% change in total dose) for approximately 4 weeks prior to Screening. Allowed SOC medications include: duloxetine, pregabalin, and gabapentin~~, amitriptyline, and venlafaxine~~. Attempts should be made to maintain the stable dose of SOC therapy. If changes to the dose are necessary, the Investigator should discuss with the Medical Monitor. However, dose level should not be above the maximum prescribed dose as instructed in the medication's dosage and administration section of the prescribing information. Subjects who failed to respond or tolerate SOC (approved medications for DPNP) and are receiving alternative pain medications~~, or are treatment naïve,~~ are also allowed.	Amitriptyline and venlafaxine are excluded as these medications are not FDA approved for DPNP To specify that the stable dose of the standard of care drug taken must be within the maximum dose of the drug's prescribing information Treatment naïve patients are not allowed
7.8.2. Allowed Medications	• SRI for depression, subject is anticipated to be on a stable dose 3 months prior to entry and it will not change during the study; • Analgesics ~~that are non-opioid, non-sedative and do not interfere with subject's pain reporting.~~, see Section 7.8.3.	To clarify the allowed stable dose
7.8.3. Rescue Medication	This does not exclude the use of these rescue medications in other forms for other uses outside of DPNP. Subjects taking one form of rescue medication can take a medication containing the other form solely for use outside of DPNP. The daily maximum dosages are inclusive of those used outside of DPNP. Subjects should be encouraged NOT to take cough syrups or sleep aids containing NSAIDs (eg, Nyquil for cold/flu, or Tylenol PM for sleep), but if they do then it should be recorded as concomitant medication. NSAIDs taken for cardiovascular health are allowed and should be documented as a concomitant medication. The daily maximum dosages of each medication should still be maintained.	Allowing the use of NSAIDs or acetaminophen in other forms outside of treating DPNP symptoms
7.8.4. Prohibited Medications	Tricyclic antidepressants ~~(other than amitriptyline~~) and other tricyclic drugs including cyclobenzaprine and promethazine; triptans (prescribed usage outside of DPNP allowed); 5-HT3 receptor antagonists;	Amitriptyline is no longer allowed To allow the usage of Triptans for causes other than DPNP

Section	Version 2	Rationale
7.8.4. Prohibited Medications	Strong or moderate CYP3A4 inhibitors or inducers and P-gp inhibitors;	To prohibit the use of P-gp inhibitors based on DDI study data
7.8.4. Prohibited Medications	Muscle relaxers.	To prohibit the use of muscle relaxers as this is a confounding factor for pain improvement
8.1.1. Blinded Sample Size Recalculation	8.1.1. Blinded Sample Size Recalculation In order to maintain sufficient study power to detect the pre-specified treatment effect for the primary efficacy endpoint (i.e., change from baseline in NPRS of 1.2 points) a sample size recalculation may be performed to evaluate on a blinded basis the study assumptions (variability and drop-out rate) used to calculate sample size. A Sample Size Recalculation Committee (SRC), comprised of Sponsor personnel and the study's blinded statistician, will be established to recalculate sample size based on blinded assessment of study assumptions. The SRC will review available data (e.g., baseline characteristics, study drug discontinuations, variability in NPRS change from baseline) when approximately 70% of the subjects have been enrolled in the study. The Sponsor may increase the sample size of the study up to 468 subjects. There will be no sample size decrease under this procedure. An increase of sample size within this range will be documented in a Note-to-File (NTF) to the Investigators and IRBs (as appropriate) and will not require a protocol amendment. Because these analyses will be based on pooled, blinded data they will not impact the Type I error rate. A Blinded Sample Size Recalculation Plan will present details regarding the planned recalculation of sample size.	To include a blinded sample size recalculation to maintain the study assumptions for variability and drop-out rate and detect the effect for primary efficacy endpoint.
8.2.1. Intent to Treat Analysis Set (ITT)	The intent-to-treat (ITT) analysis set is defined as all enrolled ~~randomized~~ subjects categorized by their randomized treatment group (whether they received study drug).	To clarify the ITT population includes randomized patients