COVER PAGE

Official Title:	A Phase 2 Study to Evaluate the Safety and Efficacy of RTA 901 in Patients With Diabetic Peripheral Neuropathic Pain
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STATISTICAL ANALYSIS PLAN-STUDY 901-C-2102 PART 1

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Study Title: A phase 2 study to evaluate the safety and efficacy of RTA 901 in patients with diabetic peripheral neuropathic pain

Name of Study Treatment: RTA 901 (BIIB143)

Protocol No.: 901-C-2102

Study Phase: Phase 2

Confidential Information

APPROVAL

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Study Medical Lead	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0		NA

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
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
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
MMRM	mixed model repeated measures
MNSI	Michigan Neuropathy Screening Instrument
[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
QD	once daily
RTSM	randomization and trial supply management
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

Study 901-C-2102 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). Approximately 192 eligible subjects (64 subjects per treatment arm) will be enrolled in Part 1. Randomization within each part will be stratified by SOC pain medication using randomization and trial supply management (RTSM). The doses for Part 2 will be selected based on Part 1 data. Potential changes with study design for Part 2 may also apply pending the Part 1 results.

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses for Part 1 safety, tolerability, efficacy, [redacted] of RTA 901 up to the Part 1 end of study visit (Week 16). A separate statistical analysis plan will be prepared for Part 2.

This SAP is based on Version 4 of the protocol, dated 9 MAY 2024. All references to the protocol refer to Version 4. This SAP will cover the planned analysis only for Part 1.

2. Study Overview

2.1. Study Objectives and Endpoints

Study Primary Objectives

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

Study Primary Endpoints

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 assessment: physical examinations, vital sign measurement, electrocardiograms, clinical laboratory measurements, and body weight.

Study 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 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

Study 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]

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

[redacted]

- [redacted]

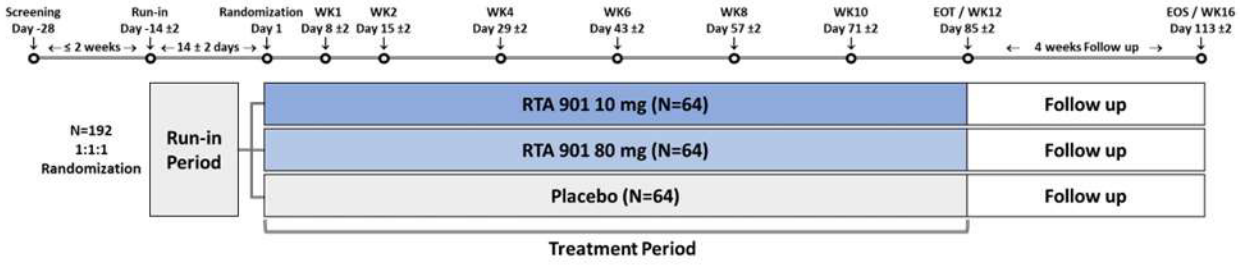
- [redacted]
- [redacted]

2.2. Study Design

Study 901-C-2101 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.

Part 1 of the study includes screening period of up to 2 weeks, a run-in period of 2 weeks, a treatment period of 12 weeks and a safety follow-up period of 4 weeks (see Figure 1). Approximately 192 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 stratified by SOC pain medication (duloxetine or pregabalin/gabapentin).

Figure 1 Study Design



2.3. Schedule of Activities

Table 1 Schedule of Assessments

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 Childbearing 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										

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)
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
[redacted]											
HbA1c	X					X		X		X	X
Fasting Lipid Profile[n]	X					X		X		X	X
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 of the study protocol
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 Section3.3 of the study protocol.
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] 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.

2.4. Sample Size Considerations

This sample size for Part 1 is based on a dose-ranging scheme to evaluate initial safety, efficacy, [redacted] of RTA 901 in patients with DPNP. The primary comparisons for efficacy are between each of the 2 RTA 901 treatment groups and the placebo treatment group. With assumed treatment difference of 1.2 and standard deviation of 2.4 in NPRS pain intensity, 64 subjects per arm approximately provides 80% power with two-sided alpha of 0.05. The purpose of Part 1 is to provide dose selection information for Part 2.

3. Definitions

3.1. Dates and Points of Reference

3.1.1. Definition of Baseline

The randomization visit for the study takes place after the 2-weeks run-in period. Unless stated otherwise, baseline data are defined as the last data collected prior to the time and/or on the date of first randomized dose, which is usually the same day as the Day 1 Predose/Baseline Visit for scheduled measurements. If baseline data at Day 1 predose/Baseline visit are missing, the last non-missing data prior to dosing (including data from Screening) will be used as baseline.

The data collected in the single-blind placebo run-in period will not be analyzed unless they are considered baseline data for randomized patients. For NPRS and DSIS, the baseline data are defined as the weekly mean prior to the first randomized dose.

3.1.2. Study Day

Study Day 1 is defined as the date of receiving the first randomized dose.

- Study Day
  - For a date on or after Study Day 1

    Study Day = (Date of Interest) – (Study Day 1) + 1
  - For a date before Study Day 1

    Study Day = (Date of Interest) – (Study Day 1)

The quantity ‘days since the first randomized dose’ is defined as:

- days since first dose = visit (or event) date – Study Day 1 + 1

The quantity ‘days since the last randomized dose’ is defined as:

- days since last dose = visit (or event) date - date of last dose

For summaries that present distribution of time expressed in weeks and months, weeks are defined as days divided by 7 and months are defined as days divided by 30.4375.

3.1.3. Analysis Visit Windows

Data from early termination visits and unscheduled visits will be assigned to an appropriate scheduled postbaseline visit using a windowing scheme for assessments that are tabulated or summarized by visit. Scheduled visits will not be windowed.

Numeric pain rating scale (NPRS) and daily sleep interference scale (DSIS) are collected daily using an e-diary form. The daily scores will be mapped to an analysis "Week" according to the following windows defined by Study Day in conjunction with study phases described above. Subjects are instructed to report the NPRS number that best indicates the average intensity of neuropathic pain over the last 24 hours throughout the study daily at bedtime. Subjects also complete the DSIS via their e-diary daily upon waking.

The weekly mean is defined as the sum of non-missing daily scores divided by the number of days with non-missing scores for that week. Subjects with fewer than 3 daily scores during an analysis week will be considered to have a missing weekly mean for that week.

The analysis window for efficacy endpoints will be defined based on the schematic as follows:

Table 2: Analysis Visit Window for weekly NPRS average pain intensity

Visit	Lower Bound in Study Day (inclusive)	Upper Bound in Study Day (inclusive)
Run-in period	First record during run-in period	-1
Randomized/treatment period		
Baseline	-7	-1
Week 1	1	7
Week 2	8	14
Week 3	15	21
Week 4	22	28
Week 5	29	35
Week 6	36	42
Week 7	43	49
Week 8	50	56

Week 9	57	63
Week 10	64	70
Week 11	71	77
Week 12 (EOT)	78	84
Follow-up period		
Week 13	85	91
Week 14	92	98
Week 15	99	105
Week 16 (EOS)	106	112

Note1: the NPRS number that best indicates the average intensity of neuropathic pain over the last 24 hours throughout the study daily at bedtime, recorded using e-dairy.

Note 2: Run-in visit is intended to describe run-in phase average pain score prior to first dosing in randomized phase.

Note 3: All available data will be used to calculate the weekly average mean up to Week 12 regardless of treatment discontinuation per ITT principle.

Note 4: If the last study dose for a patient is beyond the defined windowing for Week 12, only off study treatment days will be used to calculate off study treatment follow-up weekly mean.

Table 3: Analysis Visit Window for DSIS

Visit	**Lower Bound in Study Day (inclusive)**	**Upper Bound in Study Day (inclusive)**
Run-in period	First record during run-in period	-6
Randomized/Treatment period		
Baseline	-6	1
Week 1	2	8

Week 2	9	15
Week 3	16	22
Week 4	23	29
Week 5	30	36
Week 6	37	43
Week 7	44	50
Week 8	51	57
Week 9	58	64
Week 10	65	71
Week 11	72	78
Week 12 (EOT)	79	85
Follow-up period		
Week 13	86	92
Week 14	93	99
Week 15	100	106
Week 16 (EOS)	107	113

Note 1: Subjects complete the DSIS in the e-diary daily upon waking prior to daily dose.

Note 2: Run-in visit is intended to describe run-in phase average DSIS score prior to first dosing in randomized phase

Note 3: All available data will be used to calculate the weekly average mean up to Week 12 regardless of treatment discontinuation per ITT principle.

Note 4: If the last study dose for a patient is beyond the defined windowing for Week 12, only off study treatment days will be used to calculate off study treatment follow-up weekly mean.

Table 4: Analysis Visit Window for Safety, [redacted]

Visit	Lower Bound Study Day (inclusive)	Upper Bound Study Day (inclusive)	Target Day
Baseline[(a)]	Last record prior to dosing	Last record prior to dosing	1
Week 1*	2	12	8
Week 2	13	21	15
Week 4	22	35	29
Week 6	36	49	43
Week 8	50	63	57
Week 10	64	77	71
Week 12 (EOT)	78	91	85
Week 16 (EOS)	92	135	113
Note 1: Assessments are collected at scheduled in-clinic visit (target day) per protocol Note 2: [redacted] Note 3: Following Day 1, ECG is only collected at Week 1, Week 12 (EOT) and Week 16 (EOS)			

For unscheduled visits, if more than one observation is within the same window , the observation closest to the target day will be used.

However, if both the observations are equally distant from the target day, the latest one will be used if applicable or the average of both observations will be used; if repeated measurements are on the same day, then the last measurement will be used.

Mapping visits may be handled case by case as well, if appropriate.

If ≥2 assessments are available at a scheduled visit, then the mean of the assessments will be used for the analysis.

Early termination visits and unscheduled visits for safety data will be mapped in a similar way as above.

Some of the safety assessments are collected postdose in addition to the predose assessments (e.g. ECG, [redacted]). When windowing any predose assessments these should be the last available assessment prior to the dose. When windowing any postdose assessment they should correspond to the same dose as the predose assessment used for that visit. These summaries will present predose and postdose separately on by-visit summaries. If one of these assessments is collected at an unscheduled visit where there is no dosing, the assessment will be assigned as a predose assessment.

Descriptive statistics by visit for vital signs, ECG, lab [redacted] data will be summarized based on scheduled visits once unscheduled and early withdrawal visits are determined, as described above.

Unless being mapped to missing scheduled visits or specified, the assessments at unscheduled visits will not be used in the summary statistics but will be listed.

3.2. Study Treatment

Study drug, dosage, and mode of administration:

- RTA 901 capsules 10 mg orally once daily
- RTA 901 capsules 80 mg orally once daily
- Matching Placebo orally once daily

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.

3.3. Study Periods

3.3.1. 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 [± 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 last 7 days of Screening.

3.3.2. 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 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).

3.3.3. Treatment Period (Day 1 to Week 12/EOT)

The Treatment Period includes 8 clinic visits over 12 weeks. Within Part 1, 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.

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

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

The Follow-up Period includes 1 clinic visit on Day 113 ± 2, which must occur approximately 4 weeks following the EOT visit.

3.4. Key Derived Variables

3.4.1. Laboratory Evaluations Imputations

Any laboratory assessments less than the lower limit of detection (i.e., < LLD) are imputed as LLD/2. If no LLD is available, then the imputed value is the minimum numeric value listed divided by 2 (e.g., < 25 is 25/2=12.5). Laboratory assessments above the ULD are imputed as the ULD. If the lab result is qualitative but presented as > X and X is 10 times greater than the ULN or the ULN is not present, then the value X is used in the analysis.

3.4.2. Electrocardiogram Fridericia Corrected QT Interval

Electrocardiogram intervals are assessed locally at each site. The following formula is used to calculate the QTcF interval for analysis from QT and RR intervals:

- $QTcF = QT/\sqrt[3]{RR}$

where RR = 60 / (Heart Rate).

3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

The populations are stratified according to a standard of care (SOC) pain medication: duloxetine or pregabalin/gabapentin. Subjects entering the study must be taking duloxetine, pregabalin, or gabapentin.

3.5.2. Subgroup Variables

Subgroup analyses for NPRS average maybe performed to evaluate the consistency of the findings if appropriate on the ITT population. The baseline subgroup factors may include but not limited to:

- Age categories (<65 years, >=65 years)
- Sex (female, male)
- Ethnicity (Non-Hispanic/Latino; Hispanic/Latino)
- Race (White, Non-White)
- Standard of Care (duloxetine, pregabalin/gabapentin)
- Diabetes type (type 1, type 2)
- Baseline NPRS category (<7, >=7)
- Baseline DSIS category (<7, >=7)
- Duration of DPNP (by median)
- Baseline MNSI (by median)

If one of the subgroups has fewer than 10 subjects, then the corresponding subgroup analyses will not be performed.

3.6. Analysis Sets

Intent-to-Treat Analysis Set (ITT)

The ITT analysis set is defined as all randomized subjects who receive at least 1 dose of randomized study drug. The ITT analysis population will be used for the primary, secondary and exploratory efficacy endpoints. In analyses performed on the ITT analysis set, participants will be analyzed according to their planned treatment group.

Per-protocol set

The per-protocol population will include the ITT subjects who do not have any major protocol deviations deemed to meaningfully impact efficacy assessments. Subjects will be analyzed by randomized treatment.

Major protocol deviations that could impact efficacy include the following, although further efficacy-related deviations may be identified prior to treatment unblinding at database lock:

- Failing/meeting at least one relevant inclusion/exclusion criterion that could impact efficacy

- <80% or >120% treatment compliance during DB period based on time on treatment
- Prohibited medication use that could impact efficacy

Using of rescue medication over the prespecified daily limits during Run-in and treatment period:

- Acetaminophen/paracetamol not to exceed 3000 mg per day;
- Ibuprofen not to exceed 1200 mg per day (protocol version 3.0);
- Ibuprofen not to exceed 600 mg per day (protocol version 4.0).

A per-protocol analysis of the primary endpoint will be performed.

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. In analyses performed on the safety analysis set, participants will be analyzed according to their actual treatment received. Subjects who receive at least 1 dose of RTA 901 will be classified in the RTA 901 group.

[redacted]

4. List of Planned Study Analyses

4.1. Primary Analysis

After completion of Part 1 end of study visit (Week 16) for all randomized subjects, the formal planned analyses will be conducted to evaluate the safety, tolerability, efficacy, [redacted] of RTA 901 (10 mg or 80 mg) versus placebo.

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive summary statistics will be presented for all primary, secondary, and exploratory endpoints collected by visits and treatment group per schedule of assessment. Unless otherwise specified, for continuous endpoints, the summary statistics will generally include number of participants with data, mean, standard deviation, median, first and third quantiles and range. For categorical endpoints, the summary statistics will generally include number of participants with data, frequency counts and the percentage of those with data in each category. Analyses will be performed on the data from Part 1 alone.

The statistical software, SAS® Version 9.4 or above, will be used for all summaries and statistical analyses.

5.2. Participant Accountability

The summaries will be presented by treatment assignment (80 mg, 10 mg, or placebo).

The number (and percentage) of participants screened, Number of subjects who run-in; randomized, randomized and dosed; completed the treatment; discontinued treatment and the reasons for discontinuation; completed the study and the reasons for withdrawal will be summarized in a table.

A listing of participants who discontinued treatment/withdrew from Part 1 and the associated reasons for discontinuation/withdrawal will be presented.

The number (and percentage) of participants by analysis population will be summarized.

5.3. Demographic and Baseline Characteristics

Summaries of demographic and baseline characteristic data will be summarized by treatment group for the ITT population.

Demographic data, including age (years), age category (<65, >=65 years), sex, ethnicity, race, height, weight, and BMI will be summarized by treatment group and overall.

Baseline characteristics, including diabetic type (type 1, type 2), standard of care medication for DPNP (duloxetine, pregabalin/gabapentin), the duration since DPNP diagnosis , duration of diabetes diagnosis since first dosing (randomization phase), baseline HbA1C, baseline glucose, baseline NPRS score, baseline NPRS category (<7, >=7), baseline DSIS Score, baseline DSIS category (<7, >=7) will be summarized by treatment group and overall.

The duration from DPNP onset and duration of diabetes diagnosis since first randomized dose of study drug will be derived relative to date of DPNP diagnosis and date of diabetes diagnosis.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v24 or higher). A summary of medical history by system organ class and preferred term will also be provided for the safety population. A listing of medical history will be generated.

5.4. Protocol Deviations

Protocol deviations identified will be captured in a protocol deviation log. All protocol deviations are listed and a summary of major protocol deviation by treatment group will be also provided. Protocol deviations may include excluded medications, patients entering the study despite not satisfying all entry criteria, patients receiving wrong treatment or incorrect dose, or other major protocol deviations.

5.5. Study Treatment Exposure

The duration of study drug exposure will be based on the number of days on treatment from the first randomized dose of study drug until the last randomized dose of study drug (last dose – first dose + 1). The first dose should be administrated in clinic and recorded on the Day 1 dosing form. The last dose should be recorded on the end of treatment form.

The number and percentage of subjects in each of the following cumulative duration of exposure categories will be summarized weekly up to Week 12. In addition, days of exposure to the study drug will be summarized as a continuous variable with summary statistics by treatment group and overall.

5.6. Study Compliance

Treatment compliance during the treatment period will be assessed based on the capsules dispensed and returned as recorded in the eCRF.

Total number of doses dispensed, and total dose (mg) dispensed is calculated from total number of kit (bottle) recorded on the Study Drug Dispensation eCRF. One dose requires a capsule from 3 bottles. Total number of doses received is calculated from information on the eCRF of Study Drug Return and Study Drug Dispensation, as the (total number of doses dispensed – total number of doses returned). If a kit is not returned but the patient had a subsequent dispensation, then the non-returned kit is assumed to have been taken in full. However, if a kit is not returned and no kit is subsequently dispensed, then the non-returned kit is assumed to not have been taken. Study drug compliance (%) is calculated as 100 × total number of doses received / total number of exposure days of the randomized study drug.

5.7. Prior and Concomitant Treatments and procedure

5.7.1. 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.

5.7.2. 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.

5.7.3. 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.

Prior to implementation of protocol 4.0, 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) (protocol version 3.0).

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.

5.7.4. 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 5.7.2 of the protocol for NSAIDs prescribed for conditions other than DPNP);
- Muscle relaxers.

5.7.5. 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.).

Concomitant medications/procedure include those being taken at Screening or at any point throughout the study, up to and including the Week 16/EOS visit. Concomitant medication/procedure 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.

All concomitant medications will be coded using the World Health Organization drug dictionary (WHO Drug).

All concomitant non-drug treatments/procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA V24 or higher).

For the purposes of analysis concomitant medication (including medication or procedure) is defined as any therapy that was taken or administered on or after first randomized dose including follow-up period up to Week 16 (EOS). This includes therapies and procedures that were started prior to first randomized dose, if their use continued on or after the first randomized dose

Medications/therapies with missing start or stop dates, will also be considered as concomitant during double-blinded period as criteria below:

- If both the start and stop dates of a medication/treatment/procedure are missing.
- If the start date of a medication/treatment/procedure is missing and the stop date of the medication/therapy occurred on or after the date of first randomized dose of study drug.
- If the start date of a medication/treatment/procedure therapy occurred prior to the date of first randomized dose of study drug and the stop date of the medication/treatment/procedure is missing and the medication/treatment/procedure is listed as ongoing.
- If the start date of a medication/treatment/procedure occurred prior to the date of first randomized dose of study drug and the stop date of the medication/treatment/procedure is missing and the medication/therapy is not listed as ongoing, then the medication/treatment/procedure will be considered as concomitant.

The number and percentage of participants taking any concomitant medications will be summarized (including categories: prohibited medications, standard of care, allowed medications, and rescue medications) for the safety analysis population during double blinded period by treatment group and overall. The number and percentage of participants taking any concomitant non-drug treatments will also be summarized for the safety analysis population by treatment group and overall.

Prior medication (including medication or procedure) used during the run-in period is defined as any therapy that was taken or administered on or after the start of the run-in period to prior to the first randomized dose. This includes therapies and procedures that were started prior the start of the run-in period, if their use continued on or after the start of the run-in period.

The number and percentage of participants taking any prior medication during run-in period (before randomized treatment start date) will also be summarized for safety population by treatment and overall.

Concomitant medications will also be reviewed by a medical reviewer prior to the lock to determine allowed, prohibited medications and procedures according to the protocol. These will be summarized separately.

6. Efficacy endpoints

6.1. General considerations for efficacy endpoints

All efficacy analyses will be performed on the scheduled visits/study weeks for the ITT population. For NPRS and DSIS, the visit refers to study week.

The primary hypothesis is to test if there is 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.

Stratification factor (standard of care) will not be included for any modelling due to <10 patients of randomized patients taking duloxetine at randomization.

6.2. Multiplicity Control

A sequential stepwise testing will be performed on the primary endpoint for RTA 901 group (80mg, 10mg) compared to placebo in the following testing order to control the overall type I error at two-sided alpha level of 0.05:

- Step 1: Comparison of 80 mg group versus placebo group. If p-value <0.05, then proceed to Step 2. If not, testing for subsequent step is considered as exploratory.
- Step 2: Comparison of 10 mg group versus placebo group.

No formal testing will be performed for the secondary endpoints.

6.3. Primary endpoint of change from baseline in NPRS average pain intensity at week 12

The primary endpoint is the change from baseline in the average daily NPRS pain intensity score during Week 12.

The NPRS of pain intensity is a numeric scale, ranging from 0 (representing no pain at all) to 10 (representing the worst pain imaginable). The subject selects a whole number (0 to 10) that best indicates the intensity of their neuropathic pain in the past 24 hours. Subjects will report how they perceive their average neuropathic pain intensity during the past 24 hours at bedtime.

The weekly mean is defined as the sum of non-missing daily scores divided by the number of days with non-missing scores for that week. Subjects with fewer than 3 daily scores during an analysis week will be considered to have a missing weekly average for that week.

No imputation will be conducted at weekly mean level.

The MMRM model will include baseline NPRS score, visit, treatment, the interaction of treatment and visit, the interaction of baseline NPRS score and visit. The analysis visit will include all visits (study week) up to week 12 during double-blinded treatment period. An unstructured covariance (UN) matrix will be used to model the within-subject variability. Model convergence will be checked. If the unstructured covariance model fails to converge with the Newton-Raphson algorithm after increasing the default maximum iterations, the Fisher scoring algorithm will be used to provide initial values of the covariance parameters.

If the model does not converge with an unstructured covariance matrix, then the analysis visit will include weeks 1, 2, 4, 6, 8, 10 and 12 per protocol scheduled assessment visits.

In the event that none of the above methods yield convergence, the following covariance structures are substituted, in the order listed. Each subsequent covariance structure is used only if each previous covariance structure is used, and no previous model converged.

1. Heterogeneous Toeplitz covariance structure (assuming different variances at each time point and that measurements taken closer together in time are more highly correlated than those taken farther apart).
2. Toeplitz covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart).
3. First order auto-regressive [AR(1)] covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart, but the correlation is more constrained than the Toeplitz structure).
4. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time they were taken). A compound symmetry covariance structure was assumed in the sample size calculation.

The corresponding plots will also be generated. The primary inference will be based on the treatment comparison at Week 12. The LS means with standard errors of each dose level at each visit as well as of treatment differences between the RTA 901 group (10 mg, 80 mg) vs. placebo at each visit will be presented, along with 95% CI and p-value at each visit.

Descriptive statistics for observed data, including NPRS score and change from baseline in the NPRS weekly average scores, will be evaluated by treatment group and visit (including EOS visit) with descriptive statistics (mean, SD, median, 1st and 3rd quartiles, range) in the ITT population.

The change from baseline of weekly average NPRS score will also be analyzed for the per-protocol population using the same MMRM model as for the ITT population as a sensitivity analysis.

A sensitivity analysis will be performed excluding any data after a subject discontinued randomized study treatment.

An MMRM model including all post-randomization visits up to Week 16 will be performed as sensitivity analysis.

6.4. Secondary efficacy endpoints

6.4.1. ≥30% responder (yes/no) in NPRS average pain intensity at Week 12

The proportion of subjects who had ≥30% neuropathic pain reduction response, defined as a ≥30% reduction from baseline in the NPRS average pain intensity score at Week 12, will be analyzed with logistic regression using terms for treatment and baseline NPRS score. The odds ratio, its 95% CI and the p-value for RTA901 doses compared to placebo will be presented. Subject with missing weekly mean at Week 12 will be classified as non-responder.

The proportion of subjects who had ≥30% neuropathic pain reduction at each week will be summarized by visit and treatment group. For each visit, subjects with missing weekly mean will be classified as non-responder at the corresponding visit. A line plot of proportions for responders will also be presented by visit and treatment group.

6.4.2. ≥50% responder (yes/no) in NPRS average pain intensity at Week 12

The proportion of subjects who had ≥50% neuropathic pain reduction from baseline in the NPRS average pain intensity at Week 12 compared to baseline will be analyzed in a similar way as the 30% neuropathic pain reduction response in section 6.4.1.

The proportion of subjects who had ≥50% neuropathic pain reduction at each week will be summarized by visit and treatment group. For each visit, subjects with missing weekly mean will be classified as non-responder at the corresponding visit.

A line plot will also be presented by visit and treatment group.

Responder curve of the proportion of subjects achieving various level of percentage reduction thresholds from baseline in the weekly average neuropathic pain score at Week 12 will be generated in 1% increments from 0 to 100% by treatment group. Subjects will be considered to have reached the percentage threshold if they had a reduction (improvement) equal to or greater than a certain threshold in the weekly average neuropathic pain score at Week 12. Subjects with a missing weekly mean NPRS score at Week 12 will be classified as non-responder.

6.4.3. Proportion of rescue medication use

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), ibuprofen 200 to 400 mg every 4 to 6 hours as needed not to exceed 1200 mg daily (protocol version 3.0), or 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) (protocol version 4.0).

The rescue medications are recorded daily at bedtime in the e-diary. The number and percentage of subjects who used any rescue medication during the 12-week treatment period will be summarized by treatment group and study week.

A logistic regression model will be performed on proportion of rescue medication use at Week 12 including baseline NPRS score and treatment. The odds ratio, its 95% CI and the p-value for RTA901 doses compared to placebo will be presented.

6.4.4. Quantity and timing of rescue medication use

The amount of rescue medication used per day during the 12-week treatment period will be calculated as the total dosage recorded divided by total days of study drug exposure during the treatment period. The rescue medication used per day will be summarized using the mean, standard deviation, minimum, median and maximum by treatment group. Rank ANCOVA will be performed by category of rescues medication use (Acetaminophen, NSAIDs). The model will include rank of baseline NPRS and treatment group. P-value for the comparisons of RTA 901 group (10mg, 80mg) vs placebo will be presented.

Time to first occurrence of rescue medication use will be calculated for each patient during double-blinded treatment period. If subject had an event, the day of the event will be date of the first date of rescue medication use recorded in e-diary during the treatment period. If a subject withdraws from the study prior to Week 12 and the subject did not take any rescue medication, then the subject will be censored on the last day they were in the study. The start date for time to first occurrent of rescue medication use is defined as the date of the first randomized dose. The proportion of first occurrence of rescue medication use will be estimated using the Kaplan-Meier (KM) product limit method and be presented as KM curves over time. The KM estimates of median time to first occurrence of rescue medication use, percentiles (5^{th},10^{th},25^{th}, 50^{th} and 75^{th}) and associated 95% confidence limits will be presented. P-value from log-rank test will be presented.

6.4.5. Change from baseline in the DSIS

The DSIS is a numeric scale, ranging from 0 representing no interference with sleep to 10 representing complete inability to sleep. The subject selects a whole number (0 to 10) that best indicates his/her ability to sleep in the past 24 hours. The DSIS will be completed daily by subjects upon waking (3-minute self-administered questionnaire).

The weekly mean is defined as the sum of non-missing daily scores divided by the number of days with non-missing scores for that week. Subjects with fewer than 3 daily scores during an analysis week will be considered to have a missing weekly average for that week.

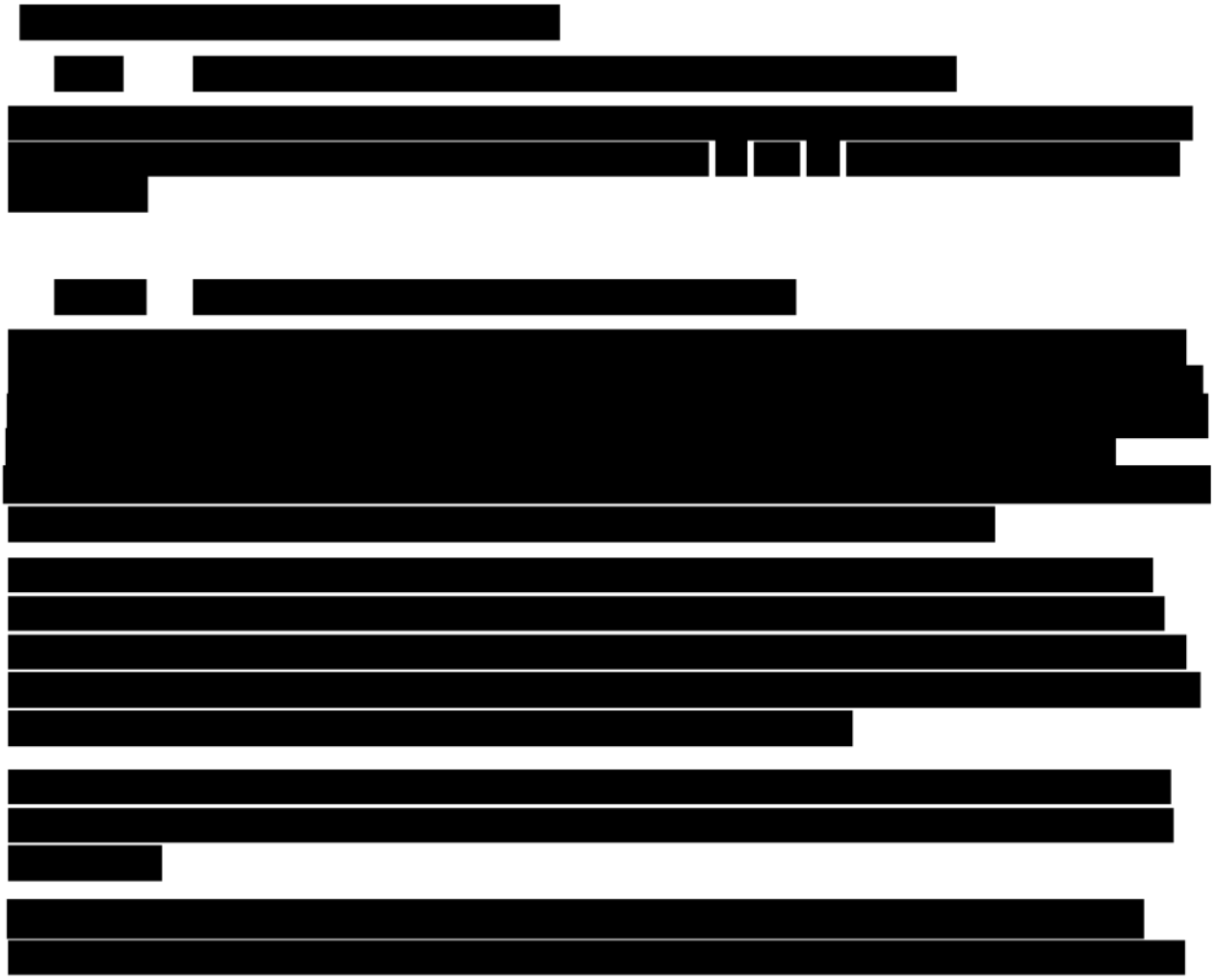
No imputation will be conducted at weekly average level.

Descriptive statistics for observed data, including actual value and change from baseline in weekly average DSIS score, will be evaluated by treatment group and visit (including EOS visit) with descriptive statistics (mean, SD, median, 1st and 3rd quartiles, range) in the ITT population.

Change from baseline in weekly DSIS average score will be analyzed through MMRM model. The MMRM model will include baseline DSIS score, visit, treatment, the interaction of treatment and visit, the interaction of baseline DSIS score and visit. Unstructured covariance will be used. All analysis visits up to Week 12 will be utilized. In the event that convergence issue occurs, similar subsequent steps will follow described in section 6.3

LS means and treatment differences will be presented with 95% confidence intervals, standard errors, p-values at each visit. A line plot of LS mean changes from baseline over time will also be provided.

A sensitivity analysis will be performed excluding any data after a subject discontinued randomized study treatment.



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7. Safety endpoints

All analyses of the safety data are performed using the safety analysis set. Descriptive statistics are presented by treatment group actually received in the safety analysis set. No statistical testing will be performed on the safety data.

7.1. Adverse Events

All AEs will be classified using MedDRA. In this study, only treatment emergent AEs (TEAEs) i.e. those that occurred or worsened after the first randomized dose will be analyzed. Such AEs will have an onset date on or after the date of first randomized dose or will have presented prior to the first randomized dose and subsequently worsened. Therefore, whenever an analysis of summary of AEs is mentioned, it is intended that this is in reference to treatment-emergent AEs.

Whenever possible, date/time will be used to determine whether an event is treatment emergent. If an event date (start or end) is incomplete, a TEAE will be determined assuming the most conservate way as follows:

- If onset day is missing and the month and year are the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset month and day are missing and the year is the same as or after the treatment start date, then that event is considered treatment emergent.
- If both onset date and end date are completely missing, an event will be considered as a TEAE.
- If onset date is completely missing and end date is not missing which is after the first randomized dose of study drug, an event will be considered as a TEAE.

The incidence of TEAEs will be summarized by dose level (or cohort) and overall RTA 901 as follows:

- Overall summary of TEAE
- TEAEs by primary SOC and MedDRA preferred term
- TEAEs by MedDRA preferred term
- TEAEs by MedDRA preferred term with incidence of >=2%
- SAEs by primary SOC and MedDRA preferred term
- SAEs by MedDRA preferred term
- Related SAEs by primary SOC and MedDRA preferred term
- TEAEs by maximum severity, primary SOC and MedDRA preferred term
- Related TEAEs by primary SOC and MedDRA preferred term
- TEAEs that led to discontinuation of study treatment by primary SOC and MedDRA preferred term
- TEAEs that led to study drug interruption by primary SOC and MedDRA preferred term
- TEAEs that led to withdrawal from study by primary SOC and MedDRA preferred term

- TEAEs that led to death by primary SOC and MedDRA preferred term

For the summary of TEAEs by severity, primary system organ class and/or preferred term, participants will be counted only once within each primary SOC/MedDRA preferred term and will only be counted under the maximum severity.

For the summary of TEAEs by relationship to study treatment, a subject will be counted only once and in the category of the strongest relationship to study treatment within each SOC/preferred term. The relationship to study treatment will be classified as related or not related.

Also, the AEs during the run-in period will be summarized by primary SOC and MedDRA preferred term.

Listings of all AEs, SAEs, AEs that led to study drug discontinuations, AEs that led to study withdrawals, and AEs that led to study drug interruption will be presented. Listing of death will be provided.

7.2. Laboratory data

Laboratory data will be evaluated to determine the incidence of abnormalities that emerge during the study. Changes in laboratory evaluations will be presented relative to baseline, which is defined as the closet visit prior to the subject start of randomized treatment. Baseline value is defined as data collected which are prior to and/or on the date of the first dose, usually also the same day as the Day 1 visit. If there is more than one value on or before Day 1, then the last non-missing value prior to (including on) the date of first randomized dose will be used as the baseline value.

Shift analyses

Each hematology, blood chemistry, coagulation parameter will be flagged as "low" or "high" relative to the parameter's normal range or as "unknown" if no results is available. All visits with available results, including unscheduled visits, will be included in shift analysis.

For each urinalysis laboratory parameter, the number and percentage of participants experiencing post-dosing shifts to abnormal will be summarized.

Each hematology and chemistry value will be flagged as "low", "normal", or "high" relative to the normal ranges of the laboratory that performed the assay, or as "unknown" if no result is available. Each urinalysis value will be flagged as "positive", "negative", or "unknown" if no value is available.

Shift from baseline to high/low status for hematology and chemistry parameters and shifts from baseline to high/positive for urinalysis will be presented. In each summary, the denominator for

the percentage is the number of patients at risk for the shift. The number at risk for a shift to low is the number of subjects whose baseline value was not low and who had at least one post-baseline value. The number at risk for a shift to high is the number of subjects whose baseline value was not high and who had at least one post-baseline value. Subjects will be counted only once for each parameter and each type of shift regardless of how many post-dosing assessments had that type of shift. A shift to high includes normal to high, low to high, and unknown to high; a shift to low includes normal to low, high to low, and unknown to low. A shift to positive includes 'negative' to 'positive' and 'unknown' to 'positive'.

Summary of change from baseline and other analyses

In addition to the shift analysis, descriptive statistics (N, mean, SD, median, 1st and 3rd quartiles, and minimum and maximum values) for observed laboratory values, change from baseline and percentage change from baseline in laboratory values of hematology, blood chemistry, and coagulation will be summarized by treatment group and visit. Hematology box and whisker plots will be presented. Only scheduled visits will be included in these summaries.

A listing of abnormal values will also be presented.

7.3. Vital signs

Summary statistical for actual values and change from baseline will be presented for each visit and vital sign parameters (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure). Weight will be summarized along with vital signs. For triplicate blood pressure measurements, the average of the 2nd and 3rd readings will be used for summarization. If fewer than three measurements are taken, the average of all blood pressure measurements will be used for any particular timepoint.

The incidence of potential clinically significant post baseline abnormalities will be summarized per the criteria below:

Table 5: Vital signs

Temperature	<36°C >38°C
Pulse	>100 beats per minute (bpm) <60 bpm
Systolic Blood Pressure	<90 mmHg >140 mmHg >160 mmHg
Diastolic Blood Pressure	<50 mmHg >90 mmHg >100 mmHg
Weight	7% or more increase from baseline 7% or more decrease from baseline
Respiratory Rate	<12 breaths/min >20 breaths/min

A listing of vital sign data will be provided.

7.4. ECG

For the ECG analysis, the baseline is the pre-dose assessment at the randomization visit. It is the last non-missing value before the first randomized dose if a single ECG was performed. If ECGs were performed in triplicate, the average will be used for the quantitative ECG parameters, while the worst status will be used for qualitative parameters.

The number and percentage of subjects with shifts from normal at baseline to abnormal in ECG results will be summarized. The worst post-baseline ECG status will be used for each patient. If there is no ECG result at baseline, the subject will be counted in the unknown category. A shift to abnormal will include a shift from "unknown" or "normal" at baseline to "abnormal" post-baseline.

The number and percentage of subjects with a QTcF increase from baseline of, > 30 to 60 msec, and > 60 msec will be summarized. In addition, the number and percentage of subjects with absolute QTcF values post-baseline of > 450 msec for males or > 460 msec for females and any post-baseline QTcF values of > 500 msec will be summarized. Subjects evaluated will be those who have a baseline assessment and at least one post-baseline QTcF assessment.

Table 6: Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	> 200 msec
QTcF	> 450 and ≤ 480 msec
	> 480 and ≤ 500 msec
	> 500
	Change from baseline: >30 and ≤ 60 msec
	Change from baseline: > 60 msec
Heart rate	< 40 beats/min
	> 100 beats/min

7.5. Physical examination

Abnormal findings which are noted after subjects received study treatment and are deemed by the investigator as clinically significant will be reported as AEs and included in AE analyses.

[redacted]

9. Changes from Protocol-Specified Analyses

The protocol definition of the intent-to-treat analysis set is all randomized subjects, however, for the definition in this SAP, ITT analysis set is defined as all randomized subjects who receive at least 1 dose of randomized study drug.

10. References

901-C-2102 Protocol V4.0 final 09May2024

901-C-2102 Protocol V3.0 08Feb2023

11. Appendices

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Appendix C. NPRS and DSIS in eDairy

- NPRS

- DSIS

Certificate Of Completion

Envelope Id: 445EA4303B3B432983D2E51840E95B99
Subject: Complete with Docusign: Cypress-SAP-v1.0_Final09Dec2024.docx
Vendor Name:
Source Envelope:
Document Pages: 51
Certificate Pages: 2
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Status: Completed

Signatures: 3
Initials: 0

Envelope Originator:
[redacted]
225 Binney St
Cambridge, MA 02142
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
09 December 2024 | 23:12

Holder: [redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 09 December 2024 | 23:14 Viewed: 09 December 2024 | 23:16 Signed: 09 December 2024 | 23:17
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
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Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 09 December 2024 | 23:14 Viewed: 09 December 2024 | 23:19 Signed: 09 December 2024 | 23:19
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	09 December 2024 | 23:14
Certified Delivered	Security Checked	09 December 2024 | 23:19
Signing Complete	Security Checked	09 December 2024 | 23:19
Completed	Security Checked	09 December 2024 | 23:19

Payment Events	Status	Timestamps