Regenacy Pharmaceuticals, Inc.

Protocol REGY-DN-201
A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Ricolinostat in Patients with Painful Diabetic Peripheral Neuropathy

Statistical analysis plan

Prepared by:

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Protocol REGY-DN-201

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Abbreviations

AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BDR	blinded data review
BMI	body mass index
BPI-SF	Brief pain inventory questionnaire – short form
CBD	cannabidiol
COVID-19	coronavirus disease 2019
CS	cumulative sum
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DN4	Douleur Neuropathique 4 Questions
DPN	diabetic peripheral neuropathy
DSM V	Diagnostic and Statistical manual of Mental Disorders
ECG	Electrocardiogram
ESI	Event of special interest
FAS	full analysis set
FOCBP	female of child-bearing potential
FSH	follicle stimulating hormone
HbA1c	Glycated hemoglobin
HbsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HDAC6	histone deacetylase 6
HIV	Human immunodeficiency virus
IB	Investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IENFD	Intraepidermal nerve fiber density
ITT	intent to treat

Abbreviations, continued

MAR	missing at random
MDT	masquerading disorders tool
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-Mental State Examination
MMRM	mixed model repeated measure
NCS	normalized cumulative sum
NRS	numerical pain rating scale
NTSS-6	neuropathy total symptom score - 6
PCR	polymerase chain reaction
PGIC	patient global impression of change
PPP	per protocol population
pSAF	pre-randomized safety population
QOL-DN	Norfolk diabetic quality of life – diabetic neuropathy
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
TEAE	treatment emergent adverse event
UENS	Utah Early Neuropathy Score
ULN	upper limit of normal
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the planned analyses for Regenacy's Protocol REGY-DN-201, entitled "A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Ricolinostat in Patients with Painful Diabetic Peripheral Neuropathy". This SAP is based on version 5 of the protocol, dated September 24, 2021.

This SAP is to be interpreted in conjunction with the protocol. Should the SAP and protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. If the final clinical study report (CSR) contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guidelines E9 (Statistical Principles for Clinical Trials) [1].

2. Study objectives

2.1. Primary objective

The primary objective is to evaluate the safety and efficacy of ricolinostat compared with placebo for painful diabetic peripheral neuropathy (DPN) as measured by an 11-point numerical pain rating scale (NRS) after 12 weeks.

2.2. Key secondary objectives

The key secondary objectives are:

- Evaluating the efficacy of ricolinostat at 4 weeks as assessed by NRS, and
- Evaluating the efficacy of ricolinostat in improving non-pain neuropathic signs after 12 weeks as assessed by change in the UENS.

2.3. Secondary objective

The secondary objective of this study is to assess the efficacy of ricolinostat for non-pain diabetic peripheral neuropathic signs and to further assess efficacy in painful DPN.

2.4. Exploratory objective

The exploratory objective of this study is to assess the effects of ricolinostat on intraepidermal nerve fiber density (IENFD), a potential biomarker for efficacy, in a subset of patients with painful DPN treated with ricolinostat at 24 weeks.

3. Study design and conduct

3.1. Study design

This is a randomized, double-blind, 2-arm, parallel group study of approximately 274 evaluable patients designed to evaluate the safety and efficacy of histone deacetylase 6 (HDAC6) inhibitor ricolinostat for painful DPN. The study includes a 12-week randomized, double-blind, placebo-controlled treatment period in which patients will receive either ricolinostat or placebo, followed by a 12-week open-label safety extension period during which all patients will receive ricolinostat 120 mg daily.

3.2. Study population

This study will enroll patients at up to 50 sites in the United States. Patients with Type 1 or Type 2 diabetes suffering from painful distal symmetric sensorimotor polyneuropathy (painful DPN) present for ≥ 6 months who meet all inclusion and exclusion criteria are eligible to participate. Eligible patients will be randomized in a 1:1 ratio to receive either ricolinostat or placebo.

Exhibit 1 and Exhibit 2 display the study's inclusion and exclusion criteria, respectively.

Exhibit 1. Inclusion criteria

1. Able to understand the study's purpose and requirements, and able to voluntarily provide informed consent to participate.
2. Age ≥ 18 years and < 80 years at the time of signing the ICF.
3. FOCBP must agree to use reliable contraceptive methods for the duration of the study and for at least 3 months after completing treatment with study drug. For the purposes of this study, reliable methods of contraception include abstinence, oral contraceptives, hormonal contraceptive implants such as Nexplanon, hormonal vaginal ring such as NuvaRing, intrauterine devices in place for a least 3 months, or barrier methods used in conjunction with spermicide. To be considered post-menopausal and of non-child-bearing potential, women less than 60 years with less than 2 years since their last period must have FSH > 40 IU/L and estradiol < 20 pg/mL unless on hormone replacement.
   Male patients participating in the study must also agree to use these reliable contraceptive methods if sexually active with a FOCBP partner and also agree to abstain from sperm donation from Day 1 through 3 months after completing treatment with study drug.
4. Type 1 or Type 2 diabetes of at least 6 months duration that meets American Diabetes Association criteria (American Diabetes Association, 2020) with an HbA1c > 6.5% at the time of Screening. If the HbA1c < 6.5% at the time of Screening, evidence that the patient meets American Diabetes Association criteria for diabetes must be documented and reviewed with the sponsor prior to entering the patient in the study. Additionally, the diabetes should be adequately controlled, with an HbA1c < 11% and no evidence of severe hypoglycemia requiring hospitalization within the past 6 months, and in the investigator's judgement sufficiently stable to allow patients in the study.
5. Painful distal symmetric sensorimotor polyneuropathy due to diabetes as defined by having 1 or more relatively symmetric, distally accentuated (stocking or stocking-glove) neuropathic symptom(s) and 1 or more relatively symmetric, distally accentuated (stocking or stocking-glove) neuropathic sign(s), except that diminished reflexes are not, in the absence of at least 1 other neuropathic sign, sufficient to make the diagnosis. Neuropathic symptoms can include pain, numbness, tingling, or weakness in a distal to proximal (stocking and glove) distribution; signs can include impaired pinprick, light touch, vibration, or position sense. The neuropathy must have been present (by history) for at least 6 months and must be confirmed and documented by the investigator based on clinical history and physical examinations.
6. DN4 score ≥ 4.
7. Meets initial diary criteria during the 14 days in the pain observation period as determined by an algorithm that includes diary compliance, overall level of pain, and day-to-day variability in pain, including at least 5 of 7 daily entries completed the 7 days prior to Day 1, and a mean intensity and standard deviation within a pre-specified bound (the precise bounds are held as double-blind to avoid introducing bias into the ratings). Additionally, at least 5 of 7 doses of placebo must be taken the 7 days prior to Day 1 as prescribed during the pain observation period for patients to be eligible to continue in the study.
8. Able to adhere to the study visit schedule and other protocol requirements.

Exhibit 2. Exclusion criteria

1. Females who are pregnant or lactating.
2. Extremely overweight, defined as BMI > 40 kg/m^2
3. Difficulty understanding instructions for diary use as determined by the investigator or other issues that are likely to make compliance with study requirements difficult.
4. Presence of any neuropathy other than DPN and/or significant risk factors for neuropathy other than diabetes, including Charcot Marie Tooth disease; alcohol abuse; B12 deficiency not adequately treated; uncontrolled hypothyroidism; evidence of paraproteins by serum immunofixation; history of chemotherapy with neurotoxic agents such as platinum analogs, taxanes, vinca alkaloids, eribulin, bortezomib and other proteasome inhibitors; or immunomodulatory agents such as thalidomide, lenalidomide, pomalidomide, neurotoxic check-point inhibitors, or any other chemotherapy known to have neurotoxic effects.
5. Other pain conditions that could confound the results of this study, or other chronic pain condition(s) that could affect compliance with pain medication restrictions or confound pain assessments. In addition to a general history and clinical examination, this will be assessed using the MDT. Patients who screen positive on this tool for a potentially confounding disorder must be discussed with and approved by the sponsor's Medical Monitor prior to being randomized into the study.
6. Painful DPN patients who have undergone lower limb amputations, are non-ambulatory, or whose walking is so impaired as to require a walker or other assistance for ambulation. Individuals whose neuropathy is so severely advanced as to create a significant risk that the neuropathy will be poorly responsive to treatment as defined by a UENS score > 24 at the time of Screening are also excluded from participation.
7. Have met DSM V criteria for opioid use disorder or DSM V criteria for alcohol use disorder (moderate or severe) within the past 2 years.
8. Opioid use at a dose of ≥ 30 morphine milligram equivalents on 3 or more days a week during the month prior to Screening.
9. Active suicidal ideation or suicidal behavior as assessed by the investigator and/or by a rating of 3 or greater on the C-SSRS.
10. The use of marijuana or CBD during the 30 days prior to starting study drug.
11. A positive urine screen for illicit or non-prescribed controlled substances at baseline.
12. Have been using non-drug interventions for pain (e.g., acupuncture, mindfulness therapy, etc.) for at least 3 months prior to starting study drug may continue these interventions, however such treatments may not be initiated during the study, and any patients who plan to initiate such treatment during the study are excluded from participation.
13. Repeated use (greater than 3 occasions) of over-the-counter capsaicin on extremities within 3 months of Screening or prescription Qutenza use within 6 months of Screening.
14. Implanted medical device (e.g., spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator) for the treatment of pain.

Exhibit 2. Exclusion criteria, continued

15. Has a QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec (male) or > 460 msec (female) or > 480 msec with right bundle branch block on 12 lead ECG at Screening, or requires treatment with drugs known to prolong the QT interval (including azithromycin, chloriquine/melfiloquine, clarithromycin, droperidol, erythromycin, moxifloxacin and sevoflurane), or has a known history of torsade de pointes or congenital long QT syndrome.
16. Family or personal history of long QT syndrome or ventricular arrhythmias including ventricular bigeminy, previous history of QT prolongation not attributable to an identified and transient cause, or need for treatment with medications associated with QT prolongation.
17. Hemoglobin < 11.5 g/dL (female) or < 13 g/dL (male), total white blood cell count < 2500/mm^3, neutrophil count < 1250/mm^3, lymphocyte count < 1000/mm^3, or platelet count < 100,000/mm^3.
18. eGFR of < 45 mL/min/1.73 m^2 (i.e., patients with stage 3b or more several renal disease are excluded).
19. Serum bilirubin values > 2.0 mg/dL. Individuals with known hereditary benign hyperbilirubinemia (Gilberts' syndrome) and a bilirubin < 3.0 may participate in the study after discussion and agreement with the sponsor's medical monitor.
20. Serum ALT or AST values > 1.5 × the ULN.
21. Known HIV positive or active hepatitis virus (A, B, or C) infection.
22. Participation within 1 month of Screening in a clinical trial involving treatment with an investigational product. Concurrent participation in an observational study (i.e., no investigational treatment being used) is allowed provided it does not interfere with the procedures and conduct of this protocol.
23. Any serious medical condition or comorbidity, laboratory abnormality, or psychiatric illness not otherwise specified that could place the patient at undue risk during trial participation, that could confound the results of the study, or that could reasonably be expected to affect patient compliance with study requirements for treatment and evaluation, as judged by the investigator.
24. Any known recent exposure within the 14 days prior to initial Screening to COVID-19 or symptoms of COVID-19 infection or other reason to suspect COVID-19 infection as assessed by the investigator at the time of initial Screening.

Note: Abnormal Screening laboratory values that appear to be spurious (e.g., laboratory error), or that are the result of an identified transient event that if resolved is unlikely to recur, may be repeated once. Should this occur, the investigator should document the reason for the repeated test, and if the repeat examination is within the acceptable range, the patient may participate.

3.3. Study treatments

Both ricolinostat and placebo are liquid formulations to be administered orally in the morning. Each bottle of ricolinostat contains 12 mL of a 10 mg/mL solution. Placebo consists of the same liquid formulation, excluding the active ingredient (i.e., ricolinostat). Bitrex® is used in the placebo formulation to mimic the bitter taste of the active ingredient.

3.3.1. Active arm

One bottle of ricolinostat (120 mg in 12 mL) will be taken by mouth daily for approximately 24 weeks, which includes an approximately 12-week double-blind, placebo-controlled treatment period and an approximately 12-week open label safety extension period. Kits will be assembled and labeled so that active and placebo supplies are indistinguishable; a single randomization code will be used for each patient.

3.3.2. Placebo arm

One bottle of placebo (12 mL) will be taken by mouth each morning daily during the pain observation period and active treatment phase of the study.

3.4. Schedule of events

Exhibit 3 displays the schedule of events and assessments.

Exhibit 3. Schedule of events

	Screening		Pain Observation Period[2] Placebo (Single-Blind) Lead-In		Double-Blind, Placebo-Controlled Treatment Period					Open Label Safety Extension				Follow-up Period	
	Screening Evaluation[1]	Washout	Training Visit	Training Follow-up	Pre-Treatment Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 18	Week 24	Week 26	Week 28
Day	-45 to -14		-14 to -7	-7 to -5	1	5 to 9	12 to 16	26 to 30	54 to 58	82 to 86	96 to 100	124 to 128	166 to 170	180 to 184	194 to 198
Informed consent	×														
Eligibility evaluation[1]	×				×										
Demographics	×														
Medical history	×		×		×										
C-SSRS[3]	×				×	×	×	×	×	×	×	×	×	×	×
Diabetes & painful DPN history	×														
Masquerading disorders tool	×														
Vital signs[4]	×				×	×	×	×	×	×	×	×	×	×	×
Height and weight	×														
Physical examination[5]	×				×	×	×	×	×	×	×	×	×	×	×
Skin integrity and wound healing[6]					×	×	×	×	×	×	×	×	×		×
12-lead ECG[7]	×				×	×				×			×		
Chemistry[8]	×				×	×		×		×			×		×
Hematology (CBC with differential)	×				×	×	×	×	×	×	×	×	×		×

Exhibit 3. Schedule of events, continued

	Screening		Pain Observation Period[2] Placebo (Single-Blind) Lead-In		Double-Blind, Placebo-Controlled Treatment Period					Open Label Safety Extension				Follow-up Period	
	Screening Evaluation[1]	Washout	Training Visit	Training Follow-up	Pre-Treatment Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 18	Week 24	Week 26	Week 28
Day	-45 to -14		-14 to -7	-7 to -5	1	5 to 9	12 to 16	26 to 30	54 to 58	82 to 86	96 to 100	124 to 128	166 to 170	180 to 184	194 to 198
HbA1c	×									×			×		×
Vitamin B12 and serum paraproteins	×														
Urine pregnancy test (if FOCBP)[9]	×		×		×	×	×	×	×	×	×	×	×	×	×
FSH and estradiol[10]	×														
SARS-CoV-2 (COVID-19) Qualitative PCR[11]	×														
Urine drug screen[12]	×		×[12]		×[12]	×[12]	×[12]	×[12]	×	×[12]	×[12]	×[12]	×[12]	×[12]	×[12]
Urinalysis	×				×					×			×		
HIV, HBsAg, HCV screen	×														
DN4	×														
Intraepidermal nerve biopsy (eligible patients at selected sites only)					×								×[15]		
Numerical Pain Rating Scale			Collected daily via diary												
Brief Pain Inventory Short Form (pain interference section only)					×			×		×			×	×	
Neuropathy Total Symptom Score – 6					×					×			×	×	

Exhibit 3. Schedule of events, continued

	Screening		Pain Observation Period[2] Placebo (Single-Blind) Lead-In		Double-Blind, Placebo-Controlled Treatment Period					Open Label Safety Extension				Follow-up Period	
	Screening Evaluation[1]	Washout	Training Visit	Training Follow-up	Pre-Treatment Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 18	Week 24	Week 26	Week 28
Day	-45 to -14		-14 to -7	-7 to -5	1	5 to 9	12 to 16	26 to 30	54 to 58	82 to 86	96 to 100	124 to 128	166 to 170	180 to 184	194 to 198
UENS	×				×					×			×	×	
Norfolk Diabetic QOL-DN					×					×			×	×	
Patient Global Impression of Change								×		×			×	×	
Patient training			×[13]	×[13]	×	×[13]	×[13]	×	×	×[13]	×[13]	×[13]	×[13]	×[13]	
Randomization[14]					×										
Dispense, collect and perform study drug accountability			×		×	×	×	×	×	×	×	×	×		
Record study drug			Collected daily via diary												
Prior & concomitant medications	×		×		×	×	×	×	×	×	×	×	×	×	×
Adverse events					×	×	×	×	×	×	×	×	×	×	×
Schedule observation period			×												

Exhibit 3. Schedule of events, continued

	Screening		Pain Observation Period[2] Placebo (Single-Blind) Lead-In		Double-Blind, Placebo-Controlled Treatment Period					Open Label Safety Extension				Follow-up Period	
	Screening Evaluation[1]	Washout	Training Visit	Training Follow-up	Pre-Treatment Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 14	Week 18	Week 24	Week 26	Week 28
Day	-45 to -14		-14 to -7	-7 to -5	1	5 to 9	12 to 16	26 to 30	54 to 58	82 to 86	96 to 100	124 to 128	166 to 170	180 to 184	194 to 198
Review prohibited medications and rescue medication guidelines			×												
Phone contact and diary review				×[2]											

Note: If a patient is discontinued early from the study for any reason, the investigator should make every effort to ensure that the final assessments at Week 24 are completed as outlined in the schedule of events. The reason for discontinuation will be recorded in the patient's record and the study database.

1. Screening evaluations for patients on pain medication that is not permitted should be scheduled so as to allow for a minimum washout of 7 days prior to the start of the Pain Observation period. Patients who are not taking pain medication and do not require washout can be scheduled for Screening evaluations at any time during the period with the understanding that it may take several days before laboratory results are available.
2. All patients are required to complete the Pain Observation period from Day -14 to Day -1. During the Pain Observation Period, on Day -7 to -5, a phone contact to the patient will be conducted to review diary and dosing compliance and provide re-training as necessary. The Day 1 clinic visit will be scheduled during this call. A patient may be randomized after 10-14 days in the Pain Observation period if all eligibility requirements have been met. An algorithm comprised of several aspects of the diary data will determine final eligibility prior to randomization.
3. C-SSRS Screening version used for Screening. Subsequent visits will use the Since Last Visit version.
4. Vital signs include temperature, respiration rate, pulse, and blood pressure while patient is sitting after a minimum 5-minute rest. Standing pulse and blood pressure to be obtained following sitting vital signs.
5. A comprehensive physical examination will be performed at Screening; subsequent physical examinations will be directed exams to assess changes from the prior visit or new concerns.
6. Skin breaches and wounds will be examined and the following parameters recorded: location, size, depth, and evidence of erythema, edema, warmth, odor, or drainage.
7. 12-lead ECG after the patient has been resting in the supine position. On Day 1, an additional 12-lead ECG will be obtained 1 hour (+/- 10 minutes) post-dose.
8. Chemistry will be collected in a fasting state (8 to 10 hours fasting).
9. A urine pregnancy test is required at Screening and Day 1 (prior to randomization) for females of child-bearing potential, and must be negative for treatment to proceed.
10. Only for females less than 60 years of age with less than 2 years since last period.
11. Only required if any recent exposure within past 14 days prior to Screening to COVID-19 and/or symptoms of COVID-19 along with reason to suspect COVID-19.
12. Urine drug screen is required at Screening and Week 8, and may be performed at any other visit at the discretion of the Investigator.
13. Patient training is required at Day-14, Day 1, Week 4 and Week 8. Patient training may be repeated, as applicable, at other visits during the study at the discretion of the Investigator. Day-14 training is conducted in the WCG aLearn Learning Management System platform. The following training modules are to be completed: Accurate Pain Reporting, Placebo Response Reduction and Research Subject Responsibility.
14. On Day 1, all assessments are to be performed prior to randomization. Once randomized, patients will be given the first dose of study drug in the clinic and an ECG will be performed 1 hour post-dose.
15. If visit is being conducted as an early termination visit and the timing is during the Safety Extension (Week 12 to Week 24), collection of the intraepidermal nerve biopsy should occur if patient previously provided consent and intraepidermal nerve biopsy collection occurred at Day 1.

4. Outcome variable definitions

4.1. Screening and baseline characteristics

Screening characteristics: The following will be collected at the Screening visit; inclusion and exclusion criteria; gender, date of birth, race, ethnicity, medical history, prior medications, diabetic history, prior diabetic medication and treatment history, C-SSRS, Masquerading Disorders Tool (MDT), height, weight, BMI, temperature, respiration rate, pulse (sitting and orthostatic), blood pressure (sitting and orthostatic), 12-lead ECG, fasting blood chemistry, blood samples including virus screen (HIV, hep B, hep C, SARS-CoV-2), urinalysis, urine pregnancy test (if FOCBP), urine drug screen, DN4, and UENS.

The following will be collected during the pain observation period; urine drug screen (at Investigator's discretion), urine pregnancy test (if FOCBP), medical history, prior medications, daily NRS diary, rescue medication use (as appropriate), and medication compliance.

Baseline characteristics: The following will be collected at the baseline visit: medical history, prior medications, C-SSRS (update from Screening assessment), temperature, respiration rate, pulse (sitting and orthostatic), blood pressure (sitting and orthostatic), physical exam, skin integrity assessment, wound healing assessment (if applicable), ECG, fasting blood chemistry, hematology, urinalysis, urine pregnancy test (if FOCBP), urine drug screen (at Investigator's discretion), brief pain inventory questionnaire – short form (BPI-SF) (pain interference section only), neuropathy total symptom score – 6 (NTSS-6), Utah early neuropathy scale (UENS), Norfolk diabetic quality of life – diabetic neuropathy (QOL-DN) assessment, and intraepidermal nerve biopsy (for eligible patients at selected sites).

4.2. Efficacy assessments

The effect of study drug will be evaluated using several validated instruments as described below.

4.2.1. Numerical Pain Rating Scale (NRS)

NRS is an 11-point assessment measure where 0 represents no pain and 10 is the worst pain possible assessed after 12 weeks. The NRS is a validated tool commonly used for pain assessment. The NRS will be recorded daily by patients.

4.2.2. Brief Pain Inventory Questionnaire – Short Form (BPI-SF)

The BPI-SF questionnaire includes a location of pain diagram (question 2) and a number of questions designed to rate pain over a specified time period (questions 1 and 3 to 5), to rate actual pain (question 6), to capture pain treatment currently received (question 7), and to establish how much relief the patient experiences from pain treatments (question 8). Question 9 is designed to establish how pain interferes with the patient's life over a specified time period and includes several sections: general activity (section A), mood (section B), walking ability (section C), normal work (section D), relations with other people (section E), sleep (section F), and enjoyment of life (section G).

The BPI-SF produces two scores: pain intensity (questions 1-8) and pain interference (question 9, items A-G). For this study, the pain interference items only will be administered as detailed in the schedule of events and scored; pain intensity/severity is already captured in the NRS and therefore to avoid redundancy questions 1-8 will not be administered in this study.

4.2.3. Patient Global Impression of Change (PGIC)

The PGIC is comprised of a single question administered at the end of the treatment period (Day 28) to assess the overall quality of life since the beginning of study treatment. The answer is scored from 1 to 7 on a gradient where the endpoint anchors are 1 = very much improved, and 7 = very much worse.

4.2.4. Neuropathy Total Symptom Scores – 6 (NTSS-6)

The NTSS-6 tool is a 6-item symptom score questionnaire that was developed to selectively identify the existence of, and evaluate the frequency and intensity of, individual neuropathy sensory symptoms experienced frequently by patients with painful DPN. The six questions interrogate: 1) numbness or insensitivity; 2) prickling or tingling; 3) burning sensation; 4)

aching pain or tightness; 5) sharp, shooting, lancinating pain; and 6) allodynia or hyperalgesia. The investigator or another qualified member of his/her team will assess the patient and complete the NTSS-6 questionnaire weekly during the treatment period, or upon premature discontinuation if applicable.

4.2.5. Utah Early Neuropathy Scale (UENS)

The UENS is a physical examination-based scale designed to assess early sensory predominant polyneuropathy. Compared with other scales, the UENS emphasizes severity and spatial distribution of pin (sharp) sensation loss in the foot and leg and focuses less on motor weakness. The UENS has been validated and shown to have satisfactory operating characteristics including high interrater reliability and reproducibility, as well as favorable characteristics for measuring change over time.

4.2.6. Norfolk Diabetic Quality of Life-Diabetic Neuropathy (QOL-DN)

The Norfolk Diabetic QOL-DN is a 47-item, self-administered questionnaire designed to measure the relationship between symptomatic diabetic neuropathy and quality of life from the perspective of the patient. The questionnaire is composed of two parts: questions related to symptoms experienced by the patient and questions related to the impact of the patient's neuropathy on activities of daily life.

4.2.7. Use of rescue medication

Use of rescue medication will be recorded by the patient in the daily diary beginning at the start of the pain observation period on Day -14 and ending on Week 12, the last day of the treatment period, or upon premature discontinuation as applicable.

4.2.8. Intraepidermal Nerve Fiber Density Determination (IENFD)

There is a strong correlation between neuropathy severity and a reduction in intraepidermal nerve fiber density. Intraepidermal nerve fiber biopsy is an effective tool for defining pathological changes to nerve fiber density and may have the potential to assess drug effects in a smaller number of patients as compared with subjective, symptom-based pain assessments. Examination of IENFD is intended to help understand whether any observed

effects on pain and other neuropathic signs and symptoms are mediated by improvement in nerve function. It may also help assess whether ricolinostat has structural effects on peripheral nerves.

4.3. Efficacy endpoints

4.3.1. Primary endpoint

The primary efficacy endpoint for this study is change from baseline in mean average pain intensity following 12 weeks of treatment as measured by the NRS.

4.3.2. Key secondary endpoints

- Change in mean average pain intensity from baseline to Week 4 as measured by the NRS.
- Change in non-pain neuropathic signs after 12 weeks in patients as assessed by change in the UENS.

4.3.3. Secondary endpoints

- Change in weekly mean worst pain from baseline to Week 12 and Week 4 as measured by the NRS.
- Proportion of patients achieving ≥ 30% and ≥ 50% improvement in mean NRS score from baseline to Week 4 and to Week 12.
- Change in mean BPI-SF pain interference score from Pre-Treatment/Day 1 to Week 12.
- Change in mean BPI-SF pain interference score from Pre-Treatment/Day 1 to Week 4.
- Change from baseline to Week 12 in the NTSS-6.
- Change from baseline to Week 12 in Norfolk diabetic QOL-DN score.
- PGIC at Week 4 and Week 12.
- Rescue medication (acetaminophen) use.

4.3.4. Exploratory endpoints

The exploratory endpoints for this study are:

- Change in intraepidermal nerve fiber density (IENFD) from baseline to Week 24 will be analyzed in a subgroup of approximately 120 patients at selected sites. Note that placebo subjects will have received ricolinostat for 12 weeks, while treated subjects will have received ricolinostat for 24 weeks. There are 4 comparisons of interest for this analysis:
  - Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 24 weeks.
  - Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 12 weeks.
  - The difference in the change from baseline in the IENFD in the Intent-to-Treat population at Week 24.
- Other exploratory endpoints may be identified at the time of analysis of the study data.

4.4. Safety assessments

Safety will be assessed throughout the study by the monitoring for and recording of adverse events (AE), clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, pulse, respiratory rate, and temperature), ECG, physical examination, and height and weight findings as per the procedures detailed in the Schedule of Assessments (Exhibit 3).

4.4.1. Adverse events

An adverse event (AE) is defined as any unfavorable and/or unintended medical occurrence that presents at any time from when the informed consent is signed through the final follow-up visit or earlier discontinuation (whichever comes first), regardless of relationship to the investigational product.

A *treatment-emergent adverse event* (TEAE) is any event that occurs after the start of study drug or was present at baseline and worsened after taking study drug.

Serious adverse events (SAE) are the subset of adverse events that are deemed by Regenacy or the Investigator to have resulted in any of the following: death, placing the patient at immediate risk of death, an inpatient hospitalization, a prolongation of existing hospitalization, a persistent or significant incapacity or disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or an event that requires significant medical intervention to avoid those outcomes listed above.

Suspected adverse reactions are the subset of AEs for where this is a reasonable possibility that the investigational product caused the adverse event.

An *unexpected AE* is any suspected adverse reaction that is not listed in the current investigator's brochure (IB) or for which the severity is more extreme than what is listed in the IB; or is inconsistent with the general investigational plan or current application if the IB is not available.

Events of special interest (ESI): The following events are defined to be of special interest: anemia, leukopenia, thrombocytopenia, renal impairment, congestive heart failure, and suicidality.

4.4.2. Laboratory safety assessments

The laboratory tests that will be collected at the timepoints specified are presented in the schedule of events (Exhibit 3). Abnormal Screening laboratory values that appear to be spurious, or that are the result of a transient event, may be repeated once; in this circumstance the repeated value will be utilized as the value of record for analysis purposes.

4.4.3. Vital signs

Vital signs will be measured as per the schedule of events (Exhibit 3). At indicated timepoints, temperature, respiration rate, pulse, and blood pressure will be measured while patient is sitting after a minimum 5-minute rest. Standing pulse and blood pressure will be obtained following sitting vital signs.

Descriptive statistics for vital signs will be presented by treatment group.

4.4.4. Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening Evaluation, Pre-Treatment baseline, Week 1, Week 12, and Week 24 after the patient has been resting in the supine position. On Day 1 (Pre-Treatment Baseline), an additional 12-lead ECG will be obtained 1 hour (+/- 10 minutes) post-dose.

Descriptive statistics for ECG results will be presented by treatment group.

4.4.5. Physical examinations

A standard physical examination will occur in accordance with the schedule of events (Exhibit 3). Post-baseline physical examinations will assess changes from the prior visit or new concerns.

Assessment of skin integrity and wound healing, if applicable, will also be performed at the times indicated in Exhibit 3. Skin breaches and wounds will be examined, and the following parameters recorded: location, size, depth, and evidence of erythema, edema, warmth, odor, or drainage.

4.4.6. Height and weight

Height and weight will be measured at the times indicated in the schedule of events (Exhibit 3) and will be used to calculate BMI.

5. Database lock and unblinding

5.1. Blinded data review (BDR) review of selected data prior to database lock

The clinical database will undergo a "soft lock" when the last patient that is still in the randomized control period has completed their Week 12 visit or early study discontinuation. During the soft lock, all variables will be locked for changes except for those variables that will continue collection during the 12-week open label period (e.g., adverse events, laboratory assessments, IENFD, etc.); the data from these variables will be locked for all records collected

prior to and through the Week 12 visit. To avoid inadvertent unblinding, any data collected after Week 12 during the open label period will remain unlocked, excluded from analysis, and blinded with respect to treatment group assignment.

After the soft lock and prior to accessing the randomized treatment assignments, a review of locked blinded data will occur to accomplish the following objectives: 1) assess the impact of missing data on study analysis, 2) assess and correct the database for inconsistent data, 3) identify the per-protocol population and, 3) finalize the methods needed for analysis of the study objectives while still blinded to results. Outputs consisting of tables, listing, and figures without treatment groups or with randomly generated treatment group assignments will be produced, as needed, to accomplish the blinded data review.

A second (unblinded) data review may occur after the final patient has completed the Week 28 visit or early study discontinuation. The data collected after the initial soft lock will be analyzed during the second data review. The procedures and objectives for this data review are the same as those described above after study completion of the randomized control period.

5.2. Database lock

After completion of all BDR procedures, validation of the project databases and Regenacy's approval of the BDR, the clinical database will be locked. After the database lock and the authorization for unblinding, the treatment codes will be merged to the analysis datasets. After database lock, final endpoint analysis may commence. Note that there will be two separate database locks that follow soft locks and data reviews; one after the randomized control period has completed and one after the Week 28 follow-up period has completed.

5.3. Authorization for unblinding

The fire-walled unblinded analysis team at Medpace will have access to the treatment codes for analysis purposes. After database lock, top-line results will be available to Regenacy.

6. Statistical analyses

Statistical analyses will be performed using SAS® software version 9.4 or later.

6.1. Statistical methodology

6.1.1. Sample size determination

The sample size for this study is planned to be approximately 274 evaluable patients. This sample size provides 80% power to detect a treatment difference of 0.8 points on the NRS. Assuming a pooled standard deviation of 2.35, this corresponds to a standardized effect size of approximately 0.34.

6.1.2. Analysis populations

The following populations are planned:

- Pre-randomized safety population (pSAF): All patients who have at least one observation during the pain observation period (day -14 to day -1/pre-treatment) and who were not randomized.
- Safety population (SAF): All patients who been randomized and received at least one dose of study drug
- Intent to treat (ITT) population: All patients randomized regardless of study drug administration
- Full analysis set (FAS) population: All patients who receive at least one dose of study drug, have a baseline average NRS score and, have at least one post-baseline average NRS score.
- Per-protocol population (PPP): All patients in the FAS population who have no major protocol violations, a valid baseline value of the NRS, meet all inclusion/exclusion criteria, missing no more than 2 weeks of diary data, and have a mean compliance rate of at least 60% (i.e., on average provide ratings on 4 or more days of each week).

6.1.3. General considerations

When presented, listings will be presented by patient number, treatment group, and measurement time.

In all analyses, the same number of decimal places as in the raw data will be presented for point estimates and univariate analysis. One more decimal place than in the raw data will be presented when reporting mean and standard deviation.

Continuous variables will be summarized by treatment group using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. The denominator for all categorical variables is the number of randomized patients.

All statistical testing will be based on a two-sided significance level of 0.05 unless otherwise stated.

Baseline is defined as the last observation prior to initiation of study medication.

Baseline assessment for the NRS is expected to be the mean of the values collected during the 5-9 days that 1) follow the training visit follow-up assessment at the end of the first week of the pain observation phase and 2) immediately precede randomization (i.e., prior to the initial study drug dose administration). Should this value be unavailable (for example, if less than 5 days were present between the training visit follow-up visit and randomization) or should the timing of the evaluation in relation to the first administration of study drug not be determinable (e.g., missing time for baseline assessment or missing time value for study drug administration) then the mean of the 5 days of the NRS ratings closest to and before randomization will be selected as the baseline value. Instead of relying solely on visit labels in the clinical database for post-baseline values, results collected at a particular time will be attributed to a specific time point by calculating the time relative to randomization.

For all other assessments, the baseline assessment is the last value for that assessment collected prior to randomization and the first administration of study drug.

For visits (or events) that occur on or after randomization, study day is defined as:

Study day = date of event – randomization date + 1

For visits (or events) that occur before randomization, study day is defined as:

Study day = date of event – randomization date

6.1.4. Visit windows

Analysis visits and their windows are defined using derived study day (Section 6.1.3) instead of relying on visit labels in the clinical database because clinical visits may occur outside protocol-specified windows. Study day and days after last dose are calculated using the actual date of each scheduled and unscheduled assessment and compared to the target for each analysis visit as specified in Exhibit 4.

If a parameter is assessed or measured more than once within a visit window, the one that is closest to the protocol-scheduled time point (i.e., target) is used for the purposes of data analysis and summary. If two assessments are equidistant from a target, the earlier assessment is used. If the visit used for analysis includes two assessments on the same day, the average of the two measurements is used.

Records from visits not closest to the target study day, and therefore not used in analyses, are presented in by-subject data listings.

Exhibit 4. Example of study days and analysis timepoints

Analysis visit	Label	Study day[a]	Analysis window
0	Day 1[b]	1	1
1	Week 1	5	2 ≤ study day ≤ 9
2	Week 2	14	10 ≤ study day ≤ 18
4	Week 4	28	24 ≤ study day ≤ 32
8	Week 8[c]	56	52 ≤ study day ≤ 60
12	Week 12[d]	84	14 ≤ days after last dose ≤ 32
14	Week 14	98	94 ≤ study day ≤ 102
18	Week 18	126	122 ≤ study day ≤ 130
24	Week 24[e]	168	164 ≤ study day ≤ 172
26	Week 26[f]	182	14 ≤ days after last dose ≤ 32
28	Week 28	196	192 ≤ study day ≤ 200

a) Study Day is relative to the date of randomization (Section 6.1.3).

b) Day 1 is the last measurement prior to the first study drug administration.

c) Week 8 is the end of the double-blind, placebo-controlled treatment period.

d) Week 12 is the start of the open-label safety extension period.

e) Week 24 is the end of the open-label safety extension period.

f) Week 26 is the start of the follow-up period.

6.1.5. Procedures for handling missing data

6.1.5.1. Missing data on the primary efficacy endpoint

The primary efficacy endpoint (e.g., NRS) is captured in a daily log. Missing daily NRS entries will be handled by performing a simple weekly average of the daily scores so long as four or more entries occur during the week. If three or fewer entries occur during the week, then the scores' weekly average will be set to missing for that week. Missing values will be multiple imputed using missing at random multiple imputation for intermittent missing values and reference-based imputation for all other missing data. These data will be part of the blinded data review with the option to change the approach to the summary score during the blinded data review process.

6.1.5.2. Missing UENS

The key secondary endpoint will be analyzed using missing at random imputation for intermittent missing data and reference-based imputation for all other missing data.

6.1.5.3. Missing data for secondary endpoint

Missing values for secondary endpoints will not be imputed. All results will be analyzed under the complete case scenario.

6.1.5.4. Missing or partial stop- or start-dates for adverse events

Missing or partial stop- or start-dates for adverse events will be imputed using the most conservative (e.g., worst case scenario) assumption. In all cases of missing or partial information, the site will be instructed to attempt to obtain the missing details. The rules for imputation follow:

- If the starting day is missing, then the day will be imputed to the 1st of the month unless the starting month is the same as the randomization month.
- If the starting day is missing and the starting month is the same as the randomization month, then the starting day will be imputed to the randomization day and the event will be assumed to be treatment emergent.
- If the starting month or year is missing, then the starting date will be imputed to the randomization date and the event will be assumed to be treatment emergent.
- If the end day is missing, then the end day will be imputed to be the last day of the month.
- If the end month is missing and the end year is the same as the study termination year, then the event date will be set to missing and the event will be assumed to be "on going" at time of study termination.
- If the end month is missing and the end year is before the year of study termination, then the end date will be imputed to the last day of the year (31DECXX).

6.1.5.5. Missing or partial stop- or start-dates for concomitant medications

Missing or partial stop- or start-dates for concomitant medications will be imputed using the most conservative (e.g., worst case scenario) assumption. Study sites will be instructed to

attempt to obtain the missing details in all cases of missing or partial information. The rules for imputation follow:

- If the starting day is missing, then the day will be imputed to the 1st of the month unless the starting month is the same as the randomization month.
- If the starting day is missing and the starting month is the same as the randomization month, then the starting day will be imputed to the randomization day and the medication will be assumed to be treatment emergent.
- If the starting month or year is missing, then the starting date will be imputed to the randomization date and the medication will be assumed to be treatment emergent.
- If the end day is missing, then the end day will be imputed to be the last day of the month.
- If the end month is missing and the end year is the same as the study termination year, then the event date will be set to missing and the patient will be assumed to be on the medication at time of study termination.
- If the end month is missing and the end year is before the year of study termination, then the end date will be imputed to the last day of the year (31DECXX).

6.2. Demographics and baseline characteristics

The following demographics and baseline characteristics will be presented in summary tables by treatment for the ITT and SAF (excluding ITT) populations: demographic characteristics (age, sex, race, ethnicity), weight, height, BMI, pulse, medical history, prior medications, laboratory examinations, vital signs, and ECG.

6.3. Patient disposition

Patient disposition will include the number of patients who enroll in the study and the number and percentage of patients included in each analysis population. The frequency and percentage of patients who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment.

7. Primary efficacy analyses

The efficacy analysis will be conducted within the estimand framework. A summary of the attributes of the estimand is provided in Table 1.

Table 1. Estimand attributes for the primary efficacy analyses

Estimand attribute	Description
Population	Full analysis set population, which consists of all patients who receive at least one dose of study drug and have baseline average pain intensity score and at least one post-baseline average pain intensity score.
Endpoint	Change from baseline in weekly mean of daily average pain based on the 11-point NRS at 12 weeks.
Intercurrent events	All values collected after treatment discontinuation will be included in the analysis. All missing values due to treatment or study discontinuation will be imputed using reference-based imputation with missing values imputed based on the placebo data. All other intermittent missing values will be imputed under the assumption of missing at random with each missing value imputed based on the treatment group assignment. Any missing values related to software issues with the electronic diary will be treated as missing at random. This hypothetical scenario assumes that the treatment had no further benefit in patients that discontinued study medication while accounting for the disease trajectory and trial effect.
Summary measure	Difference between ricolinostat arm and placebo arm as measured by change from baseline in average pain at Week 12.

The primary estimand is the difference in the mean change from baseline through Week 12 in the average pain score as measured by the NRS. The null and alternative hypotheses to be tested for these estimands are H_{01}: $\Delta_{RIC} = \Delta_{PBO}$ and H_{A1}: $\Delta_{RIC} \neq \Delta_{PBO}$ where Δ_{RIC} denotes the average change from baseline in the average NRS score at Week 12 in the ricolinostat arm, and

Δ_{PBO} for the placebo arm. The hypothesis will be tested using a mixed model repeated measures (MMRM) model as described Section 7.2.

7.1. Primary analysis

The primary analysis will use a mixed model repeated measure (MMRM) approach with all missing values imputed using the method of reference-based multiple imputation. Using this approach, missing values resulting from treatment and/or study discontinuation are imputed using the information in the placebo group. Reference-based imputation assumes that any missing data are not missing at random. Intermittent missing values will be imputed assuming MAR with imputed values estimated based on the patient's treatment group assignment. The model and details of the imputation approach are discussed further in this section. The strategy for the analyses is as follows:

1. Fit the MMRM using an unstructured covariance matrix. If the model fails to converge, additional covariance structures will be tested until a covariance structure is identified. Once the covariance structure is identified, the structure will be used for all modeling. (See Section 7.2)
2. Using MAR multiple imputation, intermittent values will be imputed based on the treatment group to which the patient is randomized. (See Section 7.3)
3. Apply reference-based multiple imputation to the data sets obtained from the MAR multiple imputation and obtain the results for the primary efficacy analysis. (See Section 7.3)
4. Conduct the appropriate sensitivity analyses. (See Section 7.4)

7.2. Identification of the primary model

The primary endpoint is change from baseline in mean average pain intensity over the 12 weeks of treatment as measured by the weekly average NRS in the FAS population. The primary endpoint will be analyzed using a MMRM analysis. The MMRM will be fit with the weekly mean change from baseline in the NRS score at Weeks 1, 2, 4, 8 and 12 as the outcome. The following covariates will be included in the model: baseline NRS score, visit, treatment group, concomitant medication for painful DPN (yes vs. no), treatment group by visit interaction term, and baseline NRS score by visit interaction. A restricted maximum likelihood will be used as the method of estimation with the degrees of freedom approximated using the

Kenward Rogers approach (see Table 4 for an example of the MMRM code to be used for the primary model). The model will be fit with an unstructured covariance matrix. If the MMRM with an unstructured covariance matrix does not converge, the following covariance structures will be substituted in the order listed below. Each subsequent covariance structure will be used only if each previous covariance structure fails to converge. The covariance structure for the final model will be the first structure in the sequence that produces a stable model that converges.

1. Toeplitz covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart).
2. 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 more constrained than the Toeplitz structure).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

Once the primary model is established, this model will be used for all analyses.

7.3. Primary efficacy analysis

The primary model, as outlined in Section 7.2, will be used for this analysis. The analysis will consist of three steps: identify the primary model and covariance structure, impute all intermittent missing values under the assumption of MAR, and impute all remaining missing values under reference-based imputation. After the imputed datasets are created, Rubin's rule is used to obtain the final estimates and significance levels.

7.3.1. Imputation of intermittent missing values

The imputation of the intermittent missing values is executed using the code below. Note that the code presented here is not final and will be vetted on blinded data prior to use for the final analyses. The variables to be included in the analyses are as follows:

- DELT_NRS – change from baseline in NRS. Note that DELT_NRSX denotes the change from baseline in NRS at Week X.
- BASE_NRS – baseline value of NRS

- AVISITN – denotes visit number
- CONMED – a yes/no variable indicating use of concomitant pain medication
- TRT – denotes treatment group
- USUBJID – denotes patient ID

Table 2. SAS code to create datasets satisfying monotone missing condition

```
** Rearrange data for use in PROC MI;
proc sort data= DATA_IMP(observed data set);
      by USUBJID TRT BASE_NRS;
run;

proc transpose data= DATA_IMP out=DATA_IMP1;
      by USUBJID TRT BASE_NRS;
      ID AVISITN;
      VAR DELT_NRS;
run;

proc sort data= DATA_IMP1;
      by USUBJID;
run;

proc mi data=DATA_IMP1 nimpute=100 round=0.1 seed=
out=OUT_IMP_TRT_RIN;
      where TRT eq "RIN";
      var   BASE_NRS(baseline) CONMED
            DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7 DELT_NRS8
            DELT_NRS9 DELT_NRS10 DELT_NRS11 DELT_NRS12;
      mcmc  chain=multiple impute=monotone;
run;

proc mi data=DATA_IMP1 nimpute=100 round=0.1 seed=
out=OUT_IMP_TRT_PBO;
      where TRT eq "PBO";
      var   BASE_NRS(baseline) CONMED
            DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7 DELT_NRS8
            DELT_NRS9 DELT_NRS10 DELT_NRS11 DELT_NRS12;
      mcmc  chain=multiple impute=monotone;
run;

data OUT_IMP_CONT;
      set OUT_IMP_TRT_RIN OUT_IMP_TRT_PBO;
run;
```

7.3.2. Reference-based imputation

The datasets created through the code in Table 2 are then used for the reference-based imputation. The code for the reference-based imputation is as follows:

Table 3. SAS code for reference-based imputation

```
proc sort data= OUT_IMP_CONT;
   by _IMPUTATION_ USUBJID;
run;

proc mi data=OUT_IMP_CONT nimpute=1 round=0.1 seed=
out=CONT_BASED_CONTROL;
 by _IMPUTATION_;
      class CONMED;
      var   BASE_NRS CONMED
            DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7
            DELT_NRS8 DELT_NRS9 DELT NRS10
                  DELT_NRS11 DELT_NRS12;

      mnar modelDELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 NRS7
            DELT_NRS8 DELT_NRS8 DELT_NRS10
                  DELT_NRS11 DELT_NRS12;
 / modelobs=(TRT = "PBO"));
run;
```

After the reference-based imputation is completed, the primary results are obtained, by first computing the outcome in each of the 100 imputed datasets and then combining the results across these datasets. The code for these analyses can be found below.

Table 4. SAS code for MMRM analysis as part of the imputation process

```
proc mixed data=COMBINE method=reml alpha=0.025 covtest;
      by _IMPUTATION_;
      class  AVISITN(ref=LAST) TRT USUBJID CONMED;
      model DELT_NRS = BASE_NRS CONMED TRT AVISITN TRT*AVISITN
      BASE_NRS*AVISITN/ solution ddfm=kr;
      repeated VISITNUM / subject=USUBJID type=TBD r;
      estimate 'RIN - PBO AT WK 12' TRT 1 -1
      TRT*AVISITN 0 0 0 0 1 0 0 0 0 -1
            / CL;
      lsmeans TRT*AVISITN/diff;
      ods output estimates=SI_ESTIMATES;
run;
```

The analysis outlined in Table 4 will produce 100 estimates of the difference between the ricolinostat and placebo groups in change from baseline in NRS at Week 12. These values are contained in SI_ESTIMATES. Note that the "type =" option in the repeated statement will need to be modified to include the covariance structure that is selected for the primary model. The output from the estimate statement should be compared to that of the lsmeans statement to ensure that the correct comparison is selected. Table 5 provides the code for the implementation of Rubin's rules to obtain the combined estimates of treatment effect at the two dose levels.

Table 5. SAS code for Rubin's rule

```
proc mianalyze data=LSM alpha=0.05;
 by TRT VISITNUM;
      modeleffects estimate;
      stderr stderr;
      ods output ParameterEstimates=Week_12_MMRM_LSM;
run;
```

7.4. Sensitivity analyses

The following sensitivity analyses will be performed:

1. MMRM based on the data as observed, noting that incomplete diary data for a given week is defined as missing (see Section 6.1.5.1). A MMRM will be fit to the data using all non-missing values. This analysis will use a modification of the code presented in Table 4.
2. A MMRM model will be fit using missing at random imputation. Using this approach all missing values will be imputed based on the treatment group to which the patient was randomized.
3. A tipping point analysis will be conducted to assess the robustness of the result and the validity of the missing at random assumption.

The code for the use of missing at random multiple imputation is provided below. The input dataset to execute this code is OUT_IMP_CONT which is obtained from running the code provided in Table 2. After running the code in Table 6, the code provided in Table 4 and Table 5 is executed with the dataset names changed as needed.

Table 6. SAS code for missing at random imputation

```
proc sort data= DATA_IMP_CONT;
      by USUBJID;
run;

proc mi data=OUT_IMP_CONT (where= (TRT=”RIC”)) nimpute=1 round=0.1
      seed= out=IMPDAT_RIC;
  by _IMPUTATION_;
      class CONMED;
      var   BASE_NRS CONMED
            DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7 DELT_NRS8
            DELT_NRS9 DELT_NRS10 DELT_NRS11 DELT_NRS12;
      monotone reg (DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7 DELT_NRS8
            DELT_NRS9 DELT_NRS10 DELT_NRS11
                DELT_NRS12)/details);
run;

proc mi data=OUT_IMP_CONT (where= (TRT = “PBO”)) nimpute=1
round=0.1   seed= out=IMPDAT_PBO;
  by _IMPUTATION_;
      class CONMED;
      var   BASE_NRS CONMED
            DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                  DELT_NRS5 DELT_NRS6 DELT_NRS7
            DELT_NRS8 DELT_NRS9 DELT_NRS10
                  DELT_NRS11 DELT_NRS12;
      monotone reg (DELT_NRS1 DELT_NRS2 DELT_NRS3
                  DELT_NRS4 DELT_NRS5 DELT_NRS6
            DELT_NRS7 DELT_NRS8 DELT_NRS9 DELT_NRS10
                DELT_NRS11 DELT_NRS12/details);
run;

data RANDOM_IMP_MAR;
      set IMPDAT_RIC IMPDAT_PBO;
run;
```

A tipping point analysis will be used to assess the validity of the MAR assumption.

1. The datasets generated from the code in Table 2 will be used for this analysis.

2. The PROC MI procedure in SAS is applied to each of the 100 datasets subsetted to the placebo group and all missing values in the placebo group are imputed. These 100 datasets will then be used for the tipping point analysis. These datasets can be obtained from the code for the placebo patients in Table 6.

3. For the tipping point analysis with a shift parameter, patients in the ricolinostat group with a missing value will be multiply imputed separately from the placebo-treatment arm and are assigned a shift parameter in the imputation procedure for progressively worse (higher) scores to find the point at which statistical significance is lost. Specifically, if the outcome of the hypothesis test favors ricolinostat over the placebo group (p-value <0.05), then one point is added as a shift parameter in the imputation for the ricolinostat group, while keeping the data for the placebo group unchanged. This is implemented using the code in Table 7.
4. A mixed model repeated measures (MMRM) model is used to analyze each of the 100 completed data sets. PROC MIANALYZE is used to combine these results to obtain the final estimates for the given value of the shift parameter. (See Table 4 and Table 5).
5. This "NRS shifting", as outlined in steps 3 and 4, is repeated with one shift point at a time until the hypothesis test no longer rejects the null hypothesis in favor of the ricolinostat group over the placebo group (i.e., when the p-value becomes greater than 0.05). Additional increments may be used to locate the tipping point. If the result is not quite statistically significant, progressively higher scores are added to find the point at which statistical significance is attained. The code to generate the imputed datasets for this analysis is provided in Table 7.

All results will be summarized in tables and a forest plot.

Table 7. SAS code for tipping point analysis

```
proc mi data= OUT_IMP_CONT (where=(TRT="RIC")) nimpute=1 round=
      seed= out=IMPDAT_TRT;
      by _IMPUTATION_;
      var  BASE_NRS CONMED
           DELT_NRS1 DELT_NRS2 DELT_NRS3 DELT_NRS4
                DELT_NRS5 DELT_NRS6 DELT_NRS7 DELT_NRS8
           DELT_NRS9 DELT_NRS10 DELT_NRS11 DELT_NRS12;

      monotone reg (/details);

      mnar adjust (DELT_NRS /shift=&S.);
run;

data COMBINE;
      set IMPDAT_TRT IMPDAT_PBO;
run;
proc sort data=COMBINE;
      by _IMPUTATION_;
run;
```

8. Key secondary analyses

8.1. Estimands

There are two key secondary outcomes: the change from baseline in the NRS at Week 4 and the change from baseline in the UENS at Week 12. The estimands for the NRS at Week 4 and the UENS at Week 12 are described in Table 8 and Table 9, respectively.

Table 8. Estimand attributes for the key secondary outcome of change from baseline in NRS at Week 4

Estimand attribute	Description
Population	Full analysis set population, which consists of all patients who receive at least one dose of study drug and have baseline average pain intensity score and at least one post-baseline average pain intensity score.
Endpoint	Change from baseline in the weekly mean of daily average pain based on the 11-point NRS at Week 4.
Intercurrent events	All values collected after treatment discontinuation will be included in the analysis. All missing values due to treatment or study discontinuation will be imputed using reference-based imputation with missing values imputed based on the placebo data. All other intermittent missing values will be imputed under the assumption of missing at random with each missing value imputed based on the treatment group assignment. This hypothetical scenario assumes that the treatment had no further benefit in patients that discontinued study medication while accounting for the disease trajectory and trial effect.
Summary measure	Difference between ricolinostat arm and placebo arm as measured by change from baseline in average pain at Week 4.

Table 9. Estimand attribute for the key secondary endpoint of UENS at Week 12

Estimand attribute	Description
Population	Full analysis set population, which consists of all patients who receive at least one dose of study drug and have baseline average pain intensity score and at least one post-baseline average pain intensity score.
Endpoint	Change from baseline in weekly mean of daily average pain based on the UENS at Week 12.
Intercurrent events	All values collected after treatment discontinuation will be included in the analysis. All missing values due to treatment or study discontinuation will be imputed using reference-based imputation with missing values imputed based on the placebo data. All other intermittent missing values will be imputed under the assumption of missing at random with each missing value imputed based on the treatment group assignment. This hypothetical scenario assumes that the treatment had no further benefit in patients that discontinued study medication while accounting for the disease trajectory and trial effect.
Summary measure	Difference between ricolinostat arm and placebo arm as measured by change from baseline in average pain at Week 12.

The analyses will follow those used for the primary efficacy analyses with a MMRM and multiple imputation as described in Section 7.

8.2. Adjustment for multiplicity

If the significance level for the primary endpoint is statistically significant then each of the key secondary endpoints will be tested using a fixed sequence method with the following testing sequence:

- Change in mean average pain intensity from baseline to Week 4 as measured by the NRS.
- Change in non-pain neuropathic signs after 12 weeks in patients as assessed by change in the UENS.

Nominal p-values will be reported for all other analyses.

9. Secondary analyses

The secondary endpoints for this study and a description of the analysis approach for each endpoint are provided below:

- Change in weekly mean worst pain from baseline to Week 12 and Week 4 as measured by the NRS will be analyzed using MMRM as outlined in Section 7.2.
- Proportion of patients achieving ≥ 30% and ≥ 50% improvement in mean NRS score from baseline to Week 4 and to Week 12 – will be summarized descriptively. Comparisons between the ricolinostat and placebo groups will be made using a Fisher's exact test.
- Change in mean BPI-SF pain interference score from Pre-Treatment/Day 1 to Week 12 will be analyzed using MMRM as outlined in Section 7.2.
- Change in mean BPI-SF pain interference score from Pre-Treatment/Day 1 to Week 4 will be analyzed using MMRM as outlined in Section 7.2.
- Change from baseline to Week 12 in the NTSS-6 will be analyzed using MMRM as outlined in Section 7.2.
- Change from baseline to Week 12 in Norfolk diabetic QOL-DN score will be analyzed using MMRM as outlined in Section 7.2.
- PGIC at Week 4 and Week 12 will be analyzed using an ANCOVA model with treatment group as a covariate.
- Rescue medication (acetaminophen) use will be analyzed based on mean daily used from baseline to Week 12 and mean weekly used from baseline to Week 12. Mean weekly use from baseline to Week 12 will be analyzed using the MMRM approach outlined for the primary efficacy analysis.

10. Exploratory analyses

The exploratory endpoints for this study and a description of the analysis approach for each endpoint are provided below. Change in intraepidermal nerve fiber density (IENFD) from baseline to Week 12 and Week 24 will be analyzed in a subgroup of approximately 120 patients at selected sites. There are 4 comparisons of interest for this analysis:

- Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 24 weeks. The change from baseline in IENFD will be assessed at 24 weeks using a t-test to test the null hypothesis that the change from baseline in IENFD is zero.
- Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 12 weeks. The change from baseline in IENFD will be assessed at 12 weeks using a t-test to test the null hypothesis that the change from baseline in IENFD is zero. .
- The difference in the change from baseline in the IENFD in the Intent-to-Treat population at Week 24. An ANCOVA model with change from baseline as the outcome and baseline value and treatment group will be used to test for a difference in groups.
- Other exploratory endpoints may be identified at the time of analysis of the study data.

11. Safety analyses

All safety analyses will be performed using the safety population. Safety and tolerability will be assessed by clinical review of all safety parameters including AEs, laboratory values, and vital signs. The safety analyses will include all results collected from randomization through the end of the study. All safety presentations will be presented by treatment group (180µg, 120µg, and placebo).

11.1. Adverse events

AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 22.0 coding system. Frequency tables will be presented by treatment groups summarizing:

- All treatment-emergent AEs

- All treatment-emergent AEs by severity
- All treatment-emergent AEs ≥ 3 in severity
- All treatment-emergent treatment-related AEs
- All ESIs
- All treatment-emergent meeting the pre-specified criteria for serious AEs (SAEs)
- All AEs leading to discontinuation

11.2. Clinical laboratory evaluations

Each laboratory value and change from baseline (when appropriate) will be summarized in tables and figures for hematology, blood chemistry and urinalysis for each treatment at Screening, discharge, and end of study. Boxplots of laboratory values will be provided. Shift tables may also be provided.

11.3. Physical examination

A listing of physical examination findings will be provided by patient.

BMI will be summarized for each treatment group at Screening and is calculated from the patient's height and weight.

11.4. Vital signs

Each resting vital sign observed value and change from baseline (when appropriate) will be summarized for each treatment group at Screening, pre-dose, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours post–dose administration. Each orthostatic vital sign observed value and change from baseline (when appropriate) will be summarized for each treatment group at Screening, pre-dose, 2 hours, 4 hours, 8 hours, and 24 hours post–dose administration.

11.5. 12-lead electrocardiogram

Each 12-lead ECG observed value and change from baseline (when appropriate) will be summarized for each treatment group at Screening, pre-dose (not required if Screening ECG is conducted on the day of dosing), 2 hours, and 24 hours post–dose administration. In addition,

frequency tabulation of the overall ECG results (Normal, abnormal normalized cumulative sum [NCS], and abnormal cumulative sum [CS]) will be summarized (to include any emergent arrhythmias and determination of resolution). Conduction intervals including PR, QRS, QT (>450, >500ms) and QTc (>450, >500 ms) will be summarized and tabulated. Shift tables of clinically significant findings will be reported for corresponding QT and QTc interval changes.

11.6. Concomitant medications

Concomitant medications will be summarized (n and %) by anatomical therapeutic chemical (ATC) class and preferred term (coded by WHO Drug coding dictionary March 2019) for each treatment group. This table will also include an overall total column.

12. References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). ICH Harmonized Tripartite Guideline; 1998.