CLINICAL STUDY PROTOCOL REGY-DN-201

Study Title: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY OF RICOLINOSTAT IN PATIENTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Investigational Product: Ricolinostat (ACY-1215)

Protocol Number: REGY-DN-201

Study Phase: 2

IND Number: 130871

Sponsor: Regenacy Pharmaceuticals, INC
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VERSION HISTORY

Version Number	Version Date	Status
1.0	30 May 2017	Final
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4.0	16 June 2021	Final
5.0	24 September 2021	Final

SPONSOR APPROVAL

Sponsor's Signature	Date 24 Sept 2021

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1.0 INVESTIGATOR AGREEMENT

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol, except to eliminate an immediate patient risk, must be approved by the Sponsor and the Institutional Review Board prior to implementation. The Investigator will delegate study-related responsibilities only to individuals with proper experience, training, and credentials, and will fully review all aspects of the protocol with study personnel prior to their involvement. This study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH E6 GCP) guidelines, the Declaration of Helsinki, and all other applicable ethical and legal requirements.

The Investigator understands that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause. The Investigator may also choose to stop enrollment and study treatment if it becomes necessary to protect the best interests of the study patients. However, it is understood that study patients should be followed, as agreed with the Sponsor, for final evaluations of safety.

Investigator's Signature	Date

Investigator's Printed Name

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
%	percent
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration curve
BMI	body mass index
BPI-SF	brief pain inventory – short form
CBD	marijuana or cannabidiol
CFR	US Code of Federal Regulations
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DN4	Douleur Neuropathique 4
DPN	diabetic peripheral neuropathy
DSM	Diagnostic and Statistical Manual of Mental Disorders V
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EIU	Exposure In Utero
FDA	Food and Drug Administration
FOCBP	female of childbearing potential
FSH	follicle-stimulating hormone
g/dL	gram per deciliter
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin
HDAC	histone deacetylases
HDAC6	histone deacetylase 6
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
IENFD	intraepidermal nerve fiber density
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU/L	international units per liter
kg/m^2	kilogram per square meter
MAR	Medical Administration Record
MDT	Masquerading Disorders Tool
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
Mg	milligram
Mm	millimeter
mm^3	cubic millimeter
MMRM	mixed model repeated measures
mmHg	millimeters of mercury
Msms	milliseconds
ng*hr/mL	nanogram per milliliter per hour
NOAEL	no observed adverse effect level
NRS	numerical rating scale (or numerical pain rating scale)
NSAID	non-steroidal anti-inflammatory drugs
NTSS-6	Neuropathy Total Symptom Score – 6
PBMC	peripheral blood monocytes
PCR	polymerase chain reaction
pg/mL	picogram per milliliter
PGIC	Patient Global Impression of Change
PT	preferred term
QD	once daily
QOL-DN	Quality of Life-Diabetic Neuropathy
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SOC	System Organ Class
STZ	streptozotocin
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
UENS	Utah Early Neuropathy Scale
ULN	upper limit of normal

3.0 SYNOPSIS

Protocol Number:	REGY-DN-201
Title of Study:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Ricolinostat in Patients with Painful Diabetic Peripheral Neuropathy
Study Phase:	Phase 2
Number of Study Sites:	Approximately 50 investigative sites in the US
Study Objectives:	The primary objective of this study 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.
Methodology/ Study Design:	This is a randomized, double-blind, 2-arm, parallel group study of up to 274 evaluable patients designed to evaluate the safety and efficacy of the histone deacetylase 6 (HDAC6) inhibitor ricolinostat for painful DPN. The study includes an approximately 12-week randomized, double-blind, placebo-controlled Treatment period in which patients will receive either ricolinostat or placebo, followed by an approximately 12-week open label Safety Extension period during which all patients will receive ricolinostat 120 mg daily. Prior to randomization, patients will be enrolled in a baseline Pain Observation period from Day -14 to Day -1, during which the NRS (average and worst pain) will be recorded daily using an electronic daily diary that will be completed by patients to allow patients to familiarize themselves with the pain rating procedures, and to establish a baseline and confirm eligibility to participate. Patients will also initiate daily dosing with placebo (single-blind) during this time to evaluate compliance eligibility for participation. A daily diary will be used by the patient to record the pain assessments and rescue medication use. A follow-up phone contact will be conducted at Day -7 to Day -5 to review diary and dosing compliance. Following the baseline Pain Observation period, patients who meet entry criteria will be randomized in a 1:1 ratio to receive either ricolinostat or placebo. During the 12-week double-blind, placebo-controlled Treatment period, patients will return for assessments in accordance with the schedule of assessments described in Table 1. At the conclusion of the approximately 12-week open label Safety Extension period, patients will enter a Follow-up safety washout and assessment period, which will incorporate 2 visits at approximately 2 and 4 weeks following the final Safety Extension visit, with assessments performed as outlined in the schedule of assessments (Table 1).
Study Population:	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.
Sample Size:	The sample size for this study is planned to be approximately 274 evaluable patients, which provides a power of 0.8 for detecting 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, an effect size

	comparable to effect sizes observed in recent diabetic neuropathic pain studies using efficacious agents such as duloxetine and pregabalin (Smith et al, 2018). An effect size of this magnitude or greater, if observed in this study, would support the further investigation of ricolinostat as a potential treatment for painful DPN.
Study Eligibility:	Inclusion Criteria Eligible patients will meet the following 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 informed consent form (ICF). 3. Females of childbearing potential (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 at 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 follicle-stimulating hormone (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 a glycated hemoglobin (HbA1c) > 6.5% at the time of Screening. If the HbA1c at the time of Screening is less than 6.5%, 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 judgment sufficiently stable to allow participation 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 examination. 6. Douleur Neuropathique 4 (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. <u>Exclusion Criteria</u> Patients meeting any of the following criteria will be excluded from the study: 1. Females who are pregnant or lactating. 2. Extremely overweight, defined as body mass index (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 Masquerading Disorders Tool (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 Utah Early Neuropathy Scale (UENS) score > 24 at the time of Screening are also excluded from participation.
	7.	Have met Diagnostic and Statistical Manual of Mental Disorders V (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 Columbia Suicide Severity Rating Scale (C-SSRS; see Appendix II).
	10.	The use of marijuana or cannabidiol (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 (eg, 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 (eg, spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator) for the treatment of pain. 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/mm3, 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 (ie, patients with stage 3b or more severe 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values > 1.5 x the upper limit of normal (ULN). 21. Known human immunodeficiency virus (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 (ie, 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 coronavirus disease 2019 (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 (eg, 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 repeating the test, and if the repeat examination is within the acceptable range, the patient may participate.
Study Treatments:	Active Arm Ricolinostat 120 mg, taken once daily (QD) by mouth in the morning at least 30 minutes prior to eating and at least 2 hours after the last meal; each dose in 12 mL liquid formulation (10 mg ricolinostat per mL). Placebo Arm Placebo, 12 mL of liquid formulation with no active ingredient (i.e., ricolinostat), taken QD by mouth at least 30 minutes prior to eating and at least 2 hours after the last meal.
Duration of Study Treatment and Patient Participation:	Following the initial Screening and the 14 day placebo lead-in Pain Observation period, study treatment will be taken QD 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, and will be followed by an approximately 4-week washout and Safety Observation period.
Efficacy Evaluation:	Primary Endpoint The primary endpoint is the change from baseline in mean average pain intensity following 12 weeks of treatment as measured by the NRS. 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. Secondary Endpoints • Change in weekly mean worst pain from baseline to week12 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 brief pain inventory – short form (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 Neuropathy Total Symptom Score – 6 (NTSS-6). • Change from baseline to Week 12 in Norfolk Diabetic Quality of Life-Diabetic Neuropathy (QOL-DN). • Patient global impression of change (PGIC) at Week 4 and Week 12. • Rescue medication (acetaminophen) use. Exploratory Endpoints • Change in epidermal nerve fiber density in a subset of patients with painful DPN and reduced intraepidermal nerve fiber density (IENFD) at baseline after 24 weeks of treatment with ricolinostat. • Other exploratory endpoints may be identified at the time of analysis of the study data.
Safety Evaluations:	Safety evaluations will include assessment of adverse events (AEs), vital signs, physical examination, 12-lead electrocardiogram (ECG), and laboratory measures. An independent Data Monitoring Committee (DMC) will review safety after a vanguard cohort of at least 30 patients has had the opportunity to complete 4 weeks of treatment, and again after this cohort has had the opportunity to complete 12 weeks of treatment. The DMC will have another planned meeting to review safety when approximately 50% of the planned number of patients have been enrolled. The DMC may also meet for unplanned meetings should safety observations during the study warrant such meetings.
Statistical Methods:	Primary Analysis The primary analysis will be based on a mixed model repeated measures (MMRM) analysis to estimate the difference in change from baseline to Week 12 in mean average pain score in patients receiving ricolinostat versus those receiving placebo. The outcome will include the weekly mean change from baseline in the daily average pain scores computed each week during Week 1 through Week 12. The baseline average pain score will be computed as the mean of the average daily pain scores during the 7 days prior to randomization. The following covariates will be included in the model: baseline value of the pain score, visit, treatment group, use of concomitant medication for painful DPN (yes vs. no), a treatment group by visit interaction term, and a baseline pain score by visit interaction term. The model will first

	be fit with an unstructured covariance matrix. If this model does not converge, then additional structures will be considered as outlined in the protocol and Statistical Analysis Plan (SAP). <u>Key Secondary Analysis</u> The key secondary endpoint of the change from baseline in the average pain at Week 4 using the 11-point NRS will be assessed using a MMRM. The model will be fit with the average change from baseline in the NRS from Weeks 1 through 4 as the outcome and the baseline pain score, visit, treatment group, use of concomitant medication for painful DPN (yes vs. no), a treatment group by visit interaction term, and a baseline score by visit interaction term. The second key secondary endpoint of change in non-pain neuropathic signs after 12 weeks in patients as assessed by change in the UENS will be analyzed using an analysis of covariance (ANCOVA) model with the change from baseline as the outcome, and baseline UENS score, treatment group, and use of concomitant medication for painful DPN (yes vs. no) as covariates. The fixed-sequence method will be used to control the overall significance level at 0.05. The first key secondary endpoint of change from baseline in the average NRS score at Week 4 will only be tested if the primary endpoint of change from baseline in the average NRS score at Week 12 is statistically significant at 0.05. The UENS endpoint will only be tested if the key secondary endpoint of change from baseline in the average NRS score at Week 4 are statistically significant. <u>Secondary Analyses</u> The BPI-SF, NTSS-6, the Norfolk Diabetic QOL-DN will be analyzed using an ANCOVA model with the change from baseline at Week 4 or Week 12 for the given outcome and baseline value of the outcome, treatment group, and use of concomitant medication for painful DPN (yes vs. no) as covariates. The PGIC at Week 4 and Week 12 will be analyzed using a two-sample t-test. The proportion of patients achieving ≥ 30% and ≥ 50% improvement in mean NRS score from baseline to Week 4 and Week 12 will be summarized descriptively with chi-square tests used to test for differences between groups. Use of rescue medication (acetaminophen) will be analyzed using a chi-square test. <u>Exploratory Analyses</u> The change in IENFD at baseline and after 24 weeks of treatment with ricolinostat will be summarized descriptively. An ANCOVA model will be used to assess the change from baseline and differences between groups.
References:	American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes- 2020. *Diabetes Care.* 2020;43(Suppl 1):S14-S31. Smith SM, Jensen MP, He H, et al. A comparison of the assay sensitivity of average and worst pain intensity in pharmacologic trials: an ACTTION systematic review and meta-analysis. *J Pain*. 2018;19(9):953-960.

Table 1: Schedule of Assessments

	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	X														
Eligibility evaluation[1]	X				X										
Demographics	X														
Medical history	X		X		X										
C-SSRS[3]	X				X	X	X	X	X	X	X	X	X	X	X
Diabetes & painful DPN history	X														
Masquerading disorders tool	X														
Vital signs[4]	X				X	X	X	X	X	X	X	X	X	X	X
Height and weight	X														
Physical examination[5]	X				X	X	X	X	X	X	X	X	X	X	X
Skin integrity and wound healing[6]					X	X	X	X	X	X	X	X	X		X
12-lead ECG[7]	X				X	X				X			X		
Chemistry [8]	X				X	X		X		X			X		X
Hematology (CBC with differential)	X				X	X	X	X	X	X	X	X	X		X
HbA1c	X									X			X		X
Vitamin B12 and serum paraproteins	X														
Urine pregnancy test (if FOCBP)[9]	X		X		X	X	X	X	X	X	X	X	X	X	X
FSH and estradiol[10]	X														
SARS-CoV-2 (COVID-19) Qualitative PCR[11]	X														
Urine drug screen[12]	X		X[12]		X[12]	X[12]	X[12]	X[12]	X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]

	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
Urinalysis	X				X					X			X		
HIV, HBsAg, HCV screen	X														
DN4	X														
Intraepidermal nerve biopsy (eligible patients at selected sites only)					X								X[15]		
Numerical Pain Rating Scale			----------COLLECTED DAILY VIA DIARY----------												
Brief Pain Inventory Short Form (pain interference section only)					X			X		X			X	X	
Neuropathy Total Symptom Score – 6					X					X			X	X	
UENS	X				X					X			X	X	
Norfolk Diabetic QOL-DN					X					X			X	X	
Patient Global Impression of Change								X		X			X	X	
Patient training			X[13]	X[13]	X	X[13]	X[13]	X	X	X[13]	X[13]	X[13]	X[13]	X[13]	
Randomization[14]					X										
Dispense, collect and perform study drug accountability			X		X	X	X	X	X	X	X	X	X		
Record study drug			----------COLLECTED DAILY VIA DIARY----------												
Prior & concomitant medications	X		X		X	X	X	X	X	X	X	X	X	X	X
Adverse events					X	X	X	X	X	X	X	X	X	X	X
Schedule observation period			X												
Review prohibited			X												

	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
medications and rescue medication guidelines															
Phone contact and diary review				X[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.

COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Scale; DN4 = Douleur Neuropathique 4 Score; DPN = diabetic peripheral neuropathy; ECG = electrocardiogram; FOCBP = female of childbearing potential; HbA1c = glycated hemoglobin; HbsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; QOL-DN = Quality of Life-Diabetic Neuropathy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UENS = Utah Early Neuropathy Scale.

4.0 ETHICAL CONSIDERATIONS

4.1 Independent Review Board

In accordance with the US Code of Federal Regulations (CFR) 21 CFR 56, the protocol, ICF, any additional information for patients, and patient recruitment materials will be submitted to a properly constituted Institutional Review Board (IRB) prior to commencing the study. Verification of the IRB's review and approval of the protocol, ICF, and other materials will be required before investigational product is shipped to the study sites and study enrollment begins.

All subsequent protocol amendments or changes to the ICF, information for patients, and/or recruitment materials will be submitted to the IRB for review and approval prior to implementation. The IRB will be informed of any new information that becomes available during the study that could impact patient health and safety, including the occurrence of Suspected Unexpected Serious Adverse Reactions (SUSARs).

Periodic and final progress reports will be submitted to the IRB at appropriate intervals not to exceed 1 year.

4.2 Ethical Conduct of the Study

The study procedures outlined in this protocol will be conducted in accordance with the CFR governing Protection of Human Patients (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Application (21 CFR 312), and with the International Conference on Harmonisation Good Clinical Practice (ICH E6 GCP) guidelines, as appropriate. As such, this study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

4.3 Patient Information and Consent

Each study patient, upon deciding to participate, will sign the IRB-approved ICF before any study-related procedures are performed. The Investigator will ensure that each patient being considered for inclusion in this study is given a full explanation of the procedures and expectations for study participation. Study personnel will adhere to the requirements of 21 CFR 50 when obtaining consent from any potential study candidate, including explaining the rationale for and the details of the study, the risks and benefits of alternative treatments, and the extent of involvement. Once the essential information has been provided to the patient and fully explained by the Investigator (or a qualified designee) and it is felt the patient understands the implications and risks of participating in the study, the IRB-approved ICF will be signed and dated.

The patient will be given a copy of the signed consent, and the original will be maintained with the patient's records.

5.0 INTRODUCTION

5.1 Diabetic Neuropathic Pain

According to recent estimates, more than 400 million people worldwide and more than 30 million in the United States suffer from diabetes mellitus, while an additional 80 million people in the United States are prediabetic and at increased risk for progression to frank diabetes within 5 years (World Health Organization, 2016; Centers for Disease Control and Prevention, 2014). This constitutes a major health problem, as diabetes is associated with a number of complications that lead to significant morbidity and disability. Among the most common complications are diabetic neuropathies, which occur in up to 50% of patients and are characterized by loss of sensation, paresthesias, and, in approximately 10% to 20% of patients, pain (Pop-Busui R et al, 2017; Barrett, 2007; Veves, 2008). Patients with diabetic peripheral neuropathy (DPN) and diabetic neuropathic pain experience functional impairments as well as reduced quality of life, with negative effects on physical, emotional, social functioning, and sleep (Davies, 2006; Pop-Busui R et al, 2017).

5.2 Medical Need

Pharmacologic treatments for diabetic neuropathy have been shown to be efficacious for diabetic neuropathic pain, and not for other aspects of diabetic neuropathy. Multiple drugs including tricyclic antidepressants (eg, amitriptyline), selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) (eg, duloxetine), anticonvulsants (eg, gabapentin, pregabalin), and opiates (eg, oxycodone, tramadol) are used, but only pregabalin (Lyrica®), duloxetine (Cymbalta®), and the opioid tapentadol-ER (Nucynta) are approved by the US Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain. Unfortunately, many patients' symptoms fail to respond to these drugs, and among responders, few patients experience complete symptom control and remission of pain. Additionally, the available medications are associated with unwanted effects, and many patients tolerate them poorly. There thus remains a large, unmet medical need for new treatments that are efficacious and well-tolerated in patients with diabetic neuropathic pain, as well as more broadly for the treatment of diabetic neuropathy.

5.3 HDAC6 Inhibition and Ricolinostat

Histone deacetylases (HDACs) are a family of enzymes that remove acetyl groups from lysine residues on substrate proteins. The function of most HDACs is associated with gene transcription through modification of histone tail acetylation and regulation of chromatin dynamics. However, it has become apparent that some HDACs play a critical role in the regulation and function of lysine acetylation of non-histone proteins in most, if not all, major cellular functions (Choudhary, 2009). In particular, HDAC6 is localized predominantly in the cytoplasm of cells where it is crucial in regulating the stability and function of microtubules (Matsuyama, 2002; Zhang, 2003; Zilberman, 2009; Tapia, 2010; Badding, 2013). Microtubule transport is a crucial component of neuronal survival (Sudo, 2010; Tapia, 2010; Morfini, 2009). HDAC6 activity has been associated with a loss in fast axonal transport, which requires stable microtubules

(d'Ydewalle, 2011; Xu, 2014; Xiong, 2013; Govindarajan, 2013; Dompierre, 2007), and inhibition of HDAC6 with the selective inhibitor Tubastatin A reverses motor neuropathy in a mouse model of type 2 Charcot-Marie-Tooth disease (d'Ydewalle, 2011). These data suggest that inhibition of HDAC6 in peripheral neurons may preserve neuron function and reverse or ameliorate the axonal degeneration observed in peripheral neuropathies such as those common in patients with diabetes.

Ricolinostat is a potent inhibitor of HDAC6 activity (enzymatic IC_{50} value of 4.7 nM), is 10- to 12-fold less active against Class I HDAC enzymes (HDAC1, 2, 3, and 8), and has minimal activity against Class IIa HDAC enzymes (HDAC4, 5, 7, and 9). HDAC6 is the primary deacetylase enzyme for alpha tubulin (Matsuyama, 2002). Ricolinostat treatment increased the level of acetylated α-tubulin in primary rat dorsal root ganglion neurons. In a human neuroblastoma cell line, ricolinostat increased the level of acetylated α-tubulin in a dose-dependent manner.

Neurons are particularly sensitive to disruptions in intracellular transport via the microtubule network. Transport of mitochondria from the cell body to the nerve terminal through the axon (anteriograde transport), as well as transport back to the cell body (retrograde transport), are disrupted in many neurological conditions. Treatment of cultured dorsal root ganglion neurons with high glucose decreases transport in both directions. Pre-Treatment of the cells with ricolinostat prevents the disruption in mitochondrial transport.

Diabetic neuropathic pain is modelled in rats using the streptozotocin (STZ) rat model of tactile allodynia. Rats rendered diabetic by an injection of streptozotocin develop increased sensitivity to otherwise non-painful stimuli (tactile allodynia). Rats with established STZ induced tactile allodynia, as measured by von Frey filament paw withdrawal threshold, treated with ricolinostat showed an immediate restoration of normal paw sensitivity after the first dose. The effect persisted for several days following withdrawal of ricolinostat. The persistence of effect is in contrast with standard of care comparator gabapentin, which reversed tactile allodynia only in the hours following drug administration.

Current treatments for diabetic neuropathic pain are ineffective for the non-painful manifestations of DPN such as numbness and tingling. Mechanism of action studies with HDAC6 inhibitors in chemotherapy-induced neuropathy indicate that ricolinostat has the potential to treat these other symptoms in addition to neuropathic pain. In a mouse model of cisplatin-induced neuropathy, HDAC6 inhibition increased IENFD, reversed numbness, and restored mitochondrial function in peripheral nerves (Krukowski, 2016).

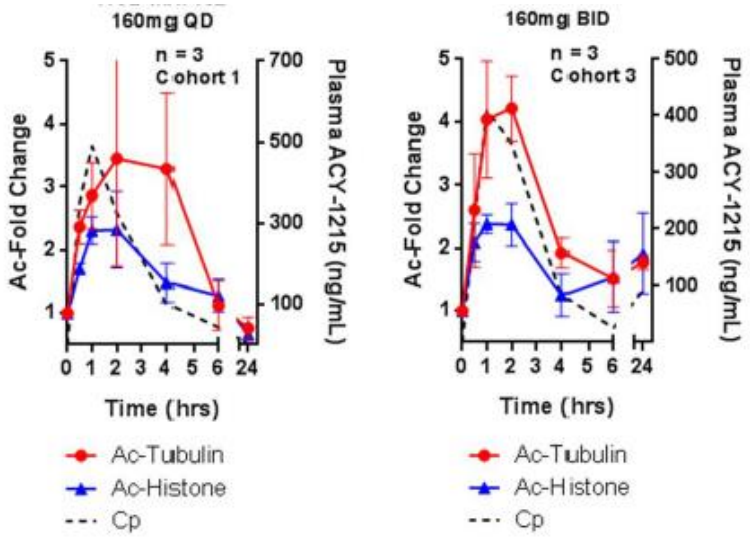
5.4 Dose Justification and Clinical Experience

As described below, a dose of 120 mg ricolinostat administered QD while fasted using a 10 mg/mL oral solution formulation is most likely to demonstrate a treatment benefit vs. placebo in this Phase 2 proof-of-concept study. This dose and dosing regimen selection is based on

pharmacokinetic, pharmacodynamic, and safety data from previous clinical studies, while maintaining appropriate safety margins to exposures achieved in long-term non-clinical toxicology studies.

The pharmacodynamic effects of ricolinostat treatment in humans have been assessed by measurement of concentrations of acetylated α-tubulin and acetylated histones in circulating peripheral blood monocytes (PBMCs) collected from clinical study patients. α-tubulin is a substrate for HDAC6 (Matsuyama, 2002) and ricolinostat increases concentrations of acetylated α-tubulin in PBMCs, multiple myeloma and neuroblastoma cell lines, and dorsal root ganglion neurons in a concentration-dependent manner in vitro. Accumulation of acetylated α-tubulin in PBMCs is therefore considered a proximal marker of intracellular HDAC6 target engagement by ricolinostat (Chang et al, 2007). Histone acetylation is catalyzed by Class 1 HDAC enzymes (eg, HDAC1, 2, 3, and 8) and hence accumulation of acetylated histone represents a marker of off-target pharmacological effects. Data from the 4 completed or ongoing studies in oncology patients demonstrate increases in levels of both acetylated α-tubulin and acetylated histone following ricolinostat dosing either alone or in combination with other oncology treatments. However, consistent with the selectivity of ricolinostat for HDAC6 over HDAC1, increases in acetylated α-tubulin are more robust and larger than changes in acetylated histone (Figure 1), suggesting that desired effects on α-tubulin can be achieved while limiting unwanted effects of histone acetylation. Additionally, the time-course profile of α-tubulin acetylation mirrors the ricolinostat plasma concentration vs. time profile (Figure 1), suggesting a direct relationship between ricolinostat exposure and its pharmacodynamic effect.

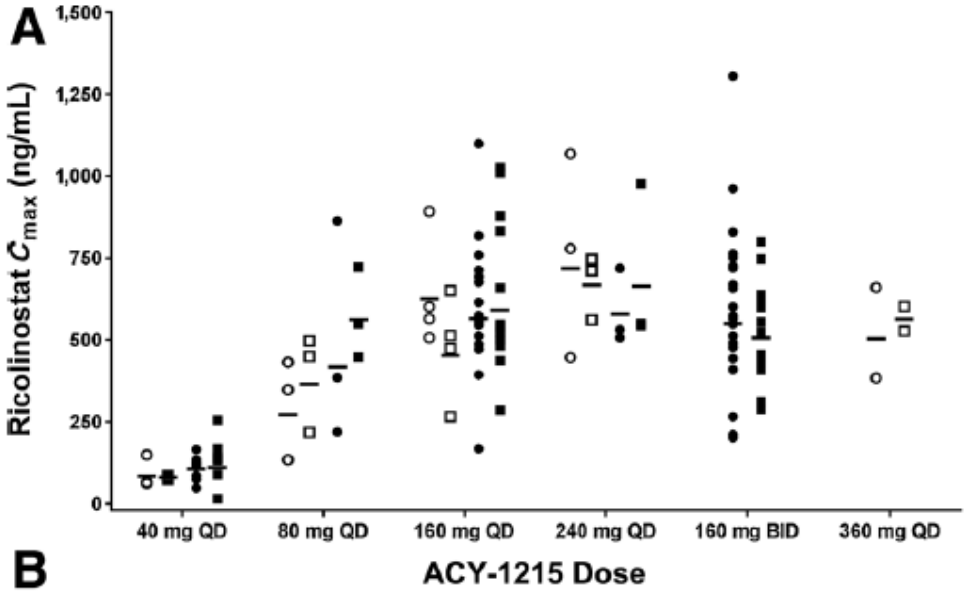
Figure 1: Ricolinostat Plasma Concentration and Pharmacodynamic Effect vs. Time Profiles Following Ricolinostat Treatment in Combination With Pomalidomide/Dexamethasone



Source: Study ACE-MM-102

Ricolinostat exposures from dosing with the previous 20 mg/mL oral solution formulation show dose-proportionality up to 160 mg, with an exposure plateau at dose levels ≥ 160 mg (Figure 2). Comparative bioavailability data demonstrate that a 120 mg dose of ricolinostat administered using the current 10 mg/mL oral solution formulation provides similar exposures to a 160 mg dose using the previous 12 or 20 mg/mL oral solution formulations (Study ACE-HV-100 and ACE-MM-104). Based on these data, a 120 mg ricolinostat dose has been selected for this study as most likely to provide the highest practically achievable ricolinostat exposure and the maximal achievable pharmacodynamic effect.

Figure 2: Maximum Observed Plasma Concentrations of Ricolinostat in Patients With Relapsed or Refractory Multiple Myeloma Dosed With Previous 20 mg/ml Oral Solution Formulation



Ricolinostat alone (open markers) or combination with bortezomib (closed markers). Circles denote first dose (Day 1) and squares repeat dosing (Day 11). Markers represent individual patients and the horizontal bars the geometric mean of the data for each group.
Source: Vogl et al, 2017 (Study ACY-100)

Selection of a once daily dosing regimen and the recommendation to dose while fasted are also based on pharmacodynamic considerations. Ricolinostat is a reversible inhibitor of HDAC6, and the proximal pharmacodynamic effect of acetylation of α-tubulin in peripheral neurons is expected to correlate with intracellular ricolinostat concentrations. By contrast, downstream pharmacological effects are anticipated to be more long-lived, as the overall acetylation status of α-tubulin reflects the sum of opposing tubulin acetyl transferase activities: HDAC6-mediated deacetylation is counterbalanced by the acetylation of assembled microtubules by α-tubulin

N-acetyltransferase 1 (Skultetyova et al, 2017). Even a short-lived decrease in HDAC6 activity is therefore expected to shift the acetylation equilibrium of stable microtubules over a longer time-scale. This is consistent with the results of in vivo pharmacology studies (eg, reversal of paclitaxel-induced neuropathy in rats) where the functional effects of the HDAC6 inhibitors were similar between once- and twice-daily dosing regimens and persisted beyond the end of dosing. On this basis, a QD dosing regimen has been chosen in preference to a twice-daily dosing regimen. With respect to food, although dosing with food appears to have no clinically relevant effect on ricolinostat bioavailability (Study ACE-HV-100), absorption is delayed and peak concentrations are lower. To the degree that pharmacodynamic effects are mediated by maximum plasma concentration (C_{max}) as well as area under the concentration curve (AUC), such effects might be smaller if dosed under fed conditions, and therefore ricolinostat will be dosed while fasted.

Clinical safety data from patients with multiple myeloma and healthy volunteers support selection of a 120 mg QD dosing regimen. Clinical data in patients are available from treatment studies of 229 patients assessing ricolinostat's efficacy in multiple myeloma. These data include 15 patients treated with ricolinostat monotherapy at doses up to 360 mg and 214 patients treated with ricolinostat at doses up to 360 mg in combination with several different anti-neoplastic agents. An additional 19 healthy volunteers received up to 3 doses of ricolinostat monotherapy using 2 different formulations in a relative bioavailability/food effect study. The median duration of ricolinostat monotherapy in oncology studies ranged from 1.7 weeks to 12.3 weeks across different dose cohorts, with a maximum duration of therapy of 29.5 weeks in a patient treated with up to 360 mg of ricolinostat daily. Treatment durations in studies of ricolinostat administered in combination with other chemotherapeutic agents have been longer, the longest being 174 weeks in combination with lenalidomide and dexamethasone.

Reviewing the safety data from the monotherapy studies, there did not appear to be a pattern of AEs or laboratory changes attributable to ricolinostat either acutely or during chronic treatment, as the observed AEs and changes in laboratory measures were generally those expected in a population of patients with hematologic malignancies and/or those seen with the oncolytic agents administered in combination with ricolinostat. Similarly, the safety findings in the combination studies did not demonstrate a pattern of AE or laboratory changes suggestive of a ricolinostat-specific serious safety concern. Specifically, there were few AEs among 19 healthy volunteers who received single doses of ricolinostat, while among the 15 patients who received ricolinostat monotherapy at doses up to 360 mg QD, many of the observed AEs were attributed to the underlying disease or intercurrent illness, and there was no clear relationship with dose (Vogl et al, 2017; Study ACY-100). Similarly, safety data from 214 patients who received ricolinostat in combination with other oncology treatments showed no clear dose-related trends in the pattern or incidence of AEs, except that twice daily ricolinostat dosing in combination with bortezomib and dexamethasone was associated with a higher incidence of nausea, vomiting, and diarrhea compared with a QD dosing regimen. The design and results of clinical trials of ricolinostat in combination with anti-neoplastic agents are detailed in the Investigator's

Brochure. Further safety information about ricolinostat is presented in the Investigator's Brochure. Overall the results of these studies do not suggest new concerns or a tolerability profile that would be specific or unsafe in patients with DPN.

The plasma pharmacokinetics of ricolinostat monotherapy are detailed in the Investigator's Brochure. Briefly, ricolinostat is rapidly absorbed (time to maximum plasma concentration ~1 hour) from the gastrointestinal tract, with an apparent plasma elimination half-life of approximately 3 hours. Ricolinostat has been studied in 2 oral formulations, 20 mg/mL and 10 mg/ml. For this study, the 10 mg/mL formulation has been selected for use. With this formulation, ricolinostat plasma exposures plateau at doses above 120 mg, a dose for which exposure (C_{max} and AUC) is similar to that observed with 160 mg in the previous 20 mg/mL formulation. Ricolinostat exposures at the proposed 120 mg clinical dosing regimen using the 10 mg/mL formulation are comparable to exposures associated with efficacy in non-clinical pharmacology studies. Peak plasma exposures from 120 mg QD dosing while fasted are expected to be approximately 600 ng/mL, corresponding to unbound exposures of approximately 150 nM. By comparison, ricolinostat inhibits HDAC6 in vitro with an IC_{50} of 5.7 nM and average peak exposures from 30 mg/kg dosing in rats were <500 ng/mL.

Table 2: Exposures in Humans Relative to Highest Exposures Observed in Rat and Dog Chronic Toxicology Studies

	C_{max} (mean [RSD] ng/mL)		**$AUC_{-infinity}$ (mean [RSD] hr*ng/mL)**	
Human exposure (120 mg)	609 (38%)		962 (30%)	
Rat (Day 180) (60 mg/kg)	Male	Female	Male	Female
	662 (+)	1069 (+)	2693 (+)	1736 (+)
Dog (Day 271) (30 mg/kg)	Male	Female	Male	Female
	7155 (40%)	4873 (33%)	18839 (34%)	13459 (33%)

+ RSD not calculated.

Source: Ricolinostat (ACY-1215) Investigator's Brochure, section 3.3.2.2 for chronic toxicology study details

Taken together, the available evidence suggests that a 120 mg dose will provide sufficient exposure to allow an informative test of the hypothesis that HDAC6 inhibition can ameliorate the symptoms of painful DPN while maintaining a favorable safety and tolerability profile based on acute and chronic non-clinical toxicology studies and previous human experience.

5.5 Study Design Rationale

The study described here is a Phase 2 proof-of-concept investigation of the efficacy of ricolinostat for the treatment of diabetic neuropathic pain. As noted above, ricolinostat is a potent inhibitor of HDAC6 enzyme activity and represents a promising novel approach to the treatment of diabetic neuropathic pain. As described above and in the Investigator's Brochure, preclinical data from animal models suggest that ricolinostat may offer advantages over currently available

therapies with respect to magnitude of effect, duration of effect, and/or tolerability. Because pain is measured subjectively, it can be subject to expectation bias or other non-specific effects, and in order to accurately assess the efficacy of interventions, it is important to control for this. For this reason, this study is designed as double-blind and placebo-controlled. The use of placebo rather than active comparator is required to provide a definitive understanding of whether observed improvement is or is not treatment-specific, and is justified on scientific and ethical grounds, as 1) there is no convincing evidence that the active treatments currently available to patients change the course of the disease, and thus patients are not put at risk for disease worsening or long-term harm by not administering currently available active treatments for limited periods; 2) rescue medication for acute episodes of pain is permitted in this protocol to ensure that patients are not at risk for excessive discomfort; and 3) per protocol, one medication that patients have been taking to treat their pain for at least 3 months at the time of Screening can be continued during the study provided the regimen has been stable and is expected to remain stable during the study.

6.0 STUDY OBJECTIVES

6.1 Primary and Key Secondary Objectives

- The primary objective of this study is to evaluate the safety and efficacy of ricolinostat compared with placebo for painful DPN as measured by an 11-point NRS after 12 weeks.
- Key secondary objectives include 1) evaluating the efficacy of ricolinostat at 4 weeks as assessed by NRS and 2) evaluating the efficacy of ricolinostat in improving non-pain neuropathic signs after 12 weeks as assessed by change in the UENS.

6.2 Secondary Objective

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

6.3 Exploratory Objectives

The exploratory objectives of this study are to assess the effects of ricolinostat on IENFD, a potential biomarker for efficacy, at 24 weeks in a subset of patients with painful DPN who have reduced IENFD at baseline.

7.0 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan Description

This is a randomized, double-blind, 2-arm, parallel group study of up to 274 evaluable patients designed to evaluate the safety and efficacy of ricolinostat for painful DPN.

After signing the ICF and agreeing to participate, initial eligibility assessments will be completed during a Screening visit scheduled between 45 and 14 days prior to planned randomization. Patients may continue one permitted medication for painful DPN if they have been taking it for at least 3 months prior to Screening, provided that the regimen and dose have been stable for at least 3 months prior to Screening and are expected to remain unchanged for the duration of the study. If any pain medication is stopped during the Screening period, then prior to proceeding to the Pain Observation Period:

1. The Investigator must document that there has not been a 'rebound flare,' or that if such a flare has occurred, it has resolved.

2. The Investigator must document that a steady state pain baseline is present.

3. A minimum period of time equal to at least 5 half-lives of the drug in question must pass.

Prior to randomization, patients will participate in a baseline Pain Observation period from Day -14 to Day -1, during which the NRS (average and worst pain) will be recorded daily using an electronic daily diary that will be completed by patients to allow patients to familiarize themselves with the pain rating procedures along with initiation of daily placebo dosing. During the Pain Observation period and thereafter during the study, patients will be allowed to use acetaminophen as rescue pain medication at a maximum dose of 500 mg at 6-hour intervals up to 4 times in any given 24-hour period. Patients will record the pain assessments and any rescue medication use. A follow-up phone contact will be conducted at Day -7 to Day -5 to review diary and dosing compliance.

At the end of the Pain Observation period, patients whose diary compliance, overall level of pain, and pain variability, along with placebo dosing meet entry criteria, will be randomized in a 1:1 ratio to receive either ricolinostat or placebo.

Pre-Treatment assessments will be completed as outlined in Table 1. The first dose of study drug will be given in the clinic and a 12-lead ECG will be performed 1-hour post-dose.

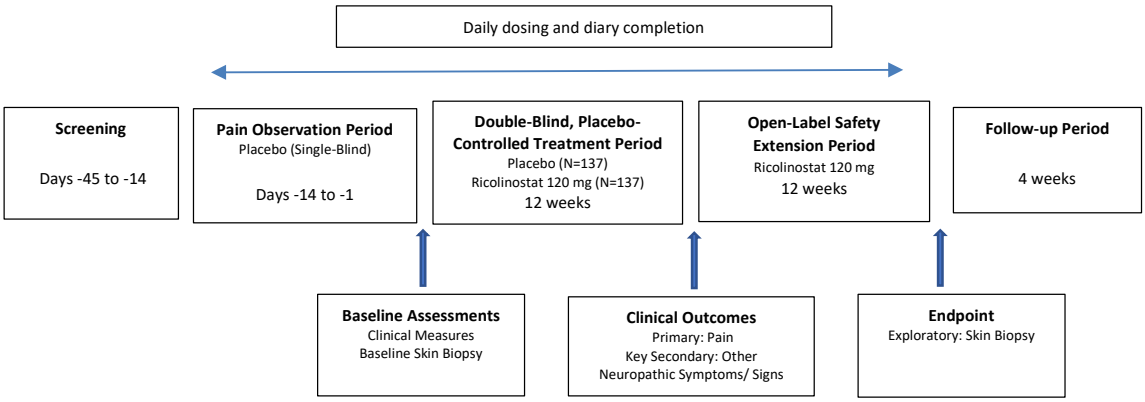
During the 12-week randomized, double-blind, placebo-controlled Treatment period, patients will return for assessments as per the schedule of assessments shown in Table 1. An electronic daily diary will be completed by patients to record study and rescue medication (acetaminophen) use, as well as NRS pain assessments. Rescue medication (as needed) and one permitted medication that has been used at a stable dose for at least 3 months prior to starting the Pain Observation period may be used during the study. Other pain medications are prohibited during the Treatment period. Diary data will be reviewed with the patient at each study visit to determine if further instruction is required and to document any discrepancies with study drug or rescue medication dosing.

At the conclusion of the approximately 12-week double-blind, placebo-controlled Treatment period, patients will enter an approximately 12-week open label Safety Extension period during which all patients will receive ricolinostat 120 mg daily and complete evaluations and clinic visits as per the schedule of events. At the conclusion of the Safety Extension, there will be an approximately 4-week washout and Safety Follow-up period, which will incorporate 2 visits at approximately 2 and 4 weeks following the final Safety Extension visit, with assessments performed as outlined in the schedule of assessments (Table 1).

IENFD will be studied in approximately 120 patients at a selected subgroup of investigational centers by skin biopsy during the baseline observation period and again at the end of the approximately 24 week treatment period. At each timepoint, two samples will be taken from each patient: one proximally on the lateral thigh 10 cm above the fibular head, and one distally towards the ankle 10 cm above the lateral malleolus. This sub-study will include at least 60 patients randomized to the ricolinostat group and a similar number of patients randomized to the placebo group. Based on 1:1 randomization to the study treatment arms, among 24 week completers, approximately half the sample of patients participating in the IENFD sub-study will have 24 weeks of exposure to ricolinostat and approximately half will have 12 weeks of exposure to ricolinostat, providing an opportunity to assess magnitude of change as well as time course of change in IENFD. This sub-study is exploratory and the null hypothesis of greatest interest is that the change from baseline in nerve fiber density is zero in the group receiving 6 months of ricolinostat. The power of this sample size to detect an effect is not known precisely. However, extrapolating from rates of nerve fiber regrowth in healthy subjects after capsaicin administration, assuming a moderate drug effect, and even assuming a slower rate of regeneration as compared with healthy subjects, the proposed sample is expected to provide approximately 80% power to detect an increase of 0.44 fiber/mm assuming a standard deviation of 1.2 fibers after 24 weeks of treatment. Because nerve fiber density may decrease with age, patients older than 75 years are not eligible to participate in the intraepidermal nerve fiber biopsy sub-study. To mitigate the risk that more than a simple ‘band-aid’ type dressing would be required after the biopsy, patients taking anticoagulants are not eligible for intraepidermal nerve fiber biopsy.

A study flow diagram is presented in Figure 3.

Figure 3: Study Design



7.2 Discussion of Study Design, Including the Choice of Control Groups

In order to accustom patients to the conditions they will encounter during the treatment portion of the study, during the pain observation period study medication will be administered under single-blind conditions (i.e site staff will be aware that placebo is being dispensed, but this will not be revealed to patients, who will not know whether they are receiving active drug or placebo during the pain observation period). The randomized treatment portion of the study is designed as a double-blind, placebo-controlled study for the initial ~12 weeks. As noted above, because expectancy and other non-specific improvements are commonly seen in studies of pain drug efficacy, the use of placebo rather than active comparator is required to provide a definitive understanding of whether observed improvement is or is not treatment-specific. Placebo is justified on the scientific grounds of ensuring that the results of the study are interpretable, and is acceptable ethically as 1) there is no convincing evidence that the available active treatments change the course of the disease, and thus patients are not put at additional risk for disease worsening or long-term harm by not administering currently available treatments for a limited periods; and 2) rescue medication for acute episodes of pain is permitted in this protocol to ensure that patients are not at risk for excessive discomfort.

While some effects in animal models appeared rapidly after dosing, in patients with diabetic neuropathic pain, ricolinostat's proposed mechanism of action (restoration of axonal transport with consequent improvement in synaptic function and reduction in aberrant pain signaling) could require a longer period of time to reach its full effect, particularly as most patients will have had chronic pain with longstanding changes in peripheral nerve function; such chronic changes may require more extended treatment to reverse. Therefore, this study incorporates an acute (~4-week) as well as longer (~12-week) assessment of efficacy. This will allow characterization of the course of response as well as the stability of response over time, will inform the design of future studies, and is consistent with regulatory requirements for registration endpoints in pain studies in which an efficacy assessment at 12 weeks is generally required. The

treatment durations planned for this study are supported by acute and chronic toxicology studies in animals that did not predict serious safety concerns in humans (details available in the Investigator's Brochure), and the available safety and tolerability data from studies of ricolinostat in patients with hematologic malignancies also did not suggest serious safety or tolerability concerns during either short or long-term treatment. The ~12-week open label Safety Extension will allow further assessment of safety and tolerability, which is important as drugs to treat diabetic neuropathic pain are generally used on a long-term basis.

In animal models, ricolinostat has been shown to reverse pathological reductions in IENFD. IENFD is also reduced in patients with diabetic neuropathy, and drug-induced increases in intraepidermal nerve density may represent a biomarker predictive of efficacy. Therefore, change from baseline to endpoint in IENFD will be measured in patients participating at a selected subgroup of sites.

7.3 Selection of Study Population

Patients with Type 1 or Type 2 diabetes suffering from painful distal symmetric sensorimotor polyneuropathy (painful DPN) present for at least 6 months (to ensure that symptoms are stably present) will be eligible to participate if they meet all inclusion and exclusion criteria. The diagnosis will be confirmed by the Investigator through medical history and physical examination as established by medical history and physical examination.

7.3.1 Inclusion Criteria

Eligible patients will meet the following 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 at 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 at the time of Screening is less than 6.5%, 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 judgment sufficiently stable to allow participation 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 examination.
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.

7.3.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

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 (see Appendix II).
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 (eg, 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 (eg, spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator) for the treatment of pain.

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 (ie, patients with stage 3b or more severe 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 x 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 (ie, 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 (eg, 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 repeating the test, and if the repeat examination is within the acceptable range, the patient may participate.

7.4 Randomization and Blinding

7.4.1 Patient Identification

After giving informed consent, study candidates will be registered in the Medpace Interactive Response Technology (IRT) and assigned a unique identification number (i.e., patient number). Patients will not be randomized until all Screening, Washout, Pain Observation, and Pre-Treatment/Day 1 procedures are completed. The assigned patient number will be used throughout the study on all records for identification purposes.

7.4.2 Randomization

Patients will be randomized 1:1 to receive either ricolinostat or placebo. The randomization schedule will be computer-generated and a blocked randomization by site with varying block sizes will be utilized. Specific block sizes will not be disclosed.

Once a patient is confirmed to be eligible on Day 1, and all Pre-Treatment procedures have been completed, treatment assignment (active or placebo) will be requested using the IRT. After entering the patient number and responding to the eligibility questions, a randomization number that corresponds to the treatment kit(s) will be assigned by the IRT.

7.4.3 Blinding

This is a double-blind study, meaning the patient, Investigator, and all site personnel will not know to which treatment arm a patient has been assigned. Furthermore, all Sponsor, contract research organization (CRO), and other clinical service provider personnel will remain blinded to treatment assignment throughout the study until database lock. In order to produce the randomization schedule and facilitate periodic data review by the DMC (see Section 10.3.8), an independent, unblinded statistician will be designated by the Sponsor.

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of patient safety. Unblinding the site for any other reason will be considered a protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind, if time permits. When the blind is broken, the reason must be fully documented. The Investigator will be informed of treatment assignment via Medpace IRT.

7.5 Study Duration

Patients will participate in the study for up to ~34 weeks, inclusive of the Screening, Pain Observation, double-blind, placebo-controlled Treatment, open label Safety Extension, and washout Follow-up periods.

During the Pain Observation period, patients will be dosed daily with placebo under single-blind conditions. During the approximately 12-week double-blind, placebo-controlled Treatment period, patients will be dosed daily with ricolinostat or placebo under double-blind conditions.

During the approximately 12-week open-label Safety Extension, all patients will receive ricolinostat.

7.6 Study Discontinuation

The Sponsor may choose to discontinue the study as a result of administrative, regulatory, or patient safety issues. The study may also be discontinued as a result of DMC review as described in Section 11.10.1.2. If the study is discontinued while patients are still on-study, the Sponsor will provide the Investigators with detailed instructions for stopping study drug and completing adequate safety follow-up. Similarly, if an Investigator decides to stop participating in the study, he/she will work with the Sponsor to identify a comprehensive plan for patient follow-up and study close-out.

7.7 Patient Discontinuation

A patient may choose to discontinue prior to the completion of all study visits and assessments for any of the following reasons:

- Patient withdraws consent or request discontinuation from the study for any reason.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
- Any serious AE (SAE), clinically significant AE, or severe laboratory abnormality.
- Pregnancy.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.
- The Investigator may discontinue study treatment if, in his/her clinical judgement, it is in the best interest of the patient.
- Termination of the study by the Sponsor or regulatory authority.

If a patient discontinues prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete a final set of evaluations in accordance with Section 9.8.

8.0 STUDY TREATMENTS

8.1 Study Drug Characteristics

8.1.1 Formulation

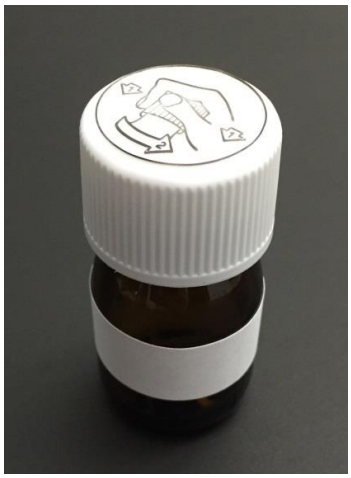
Both ricolinostat and placebo are liquid formulations to be administered orally in the morning. Each bottle of ricolinostat contains 12 mL of a 10 mg/mL solution. Placebo consists of the same

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.

8.1.2 Container, Closure, Packaging, and Labeling

Ricolinostat is supplied in 30 mL single use amber glass bottles with screw cap closures (see Figure 4 below). Placebo is supplied in identical containers. Bottles will be labeled in accordance with investigational product labeling requirements. Study kits will be labeled with the same information along with a code linked to the randomization schedule. When a patient is randomized through the IRT, a study kit code will be assigned.

Figure 4: Ricolinostat, 120 mg (10 mg/mL)



8.2 Study Drug Dose and Regimen

Study drug is to be administered once daily (QD) by mouth in the morning at least 30 minutes prior to eating and at least 2 hours after the last meal. Detailed dosing instructions will be provided in the Study Reference Manual, which will be reviewed with the Investigator and site personnel prior to the start of the study. Written instructions for patients (as reviewed/approved by the IRB) will also be provided.

8.2.1 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.

8.2.2 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.

8.3 Study Drug Handling and Management

8.3.1 Storage and Stability

Study kits containing ricolinostat and placebo bottles should be stored at room temperature (20 to 25°C [68 to 77°F]) away from direct sunlight. Patients will be instructed not to leave the study drug in the car for an extended period due to the potential for extreme temperature fluctuations.

At the clinic, study kits must be stored in an area of controlled access under the supervision of the Investigator's designated member of the study team. Patients will be instructed to keep the study drug in an area that cannot be accessed by children or other individuals who might tamper with it.

8.3.2 Study Drug Ordering, Shipment, Dispensing, and Accountability

All study kits will be maintained, inventoried, and shipped by the Sponsor's designated central distributor. The IRT will allow for ordering, monitoring of inventory, and automated shipment based on certain supply triggers.

The first shipment of study kits to sites will be initiated by the Sponsor after receipt of the required IRB approvals and administrative documentation. A site initiation visit will be scheduled with each Investigator to review the key elements of study conduct, including study drug management. Records must be maintained to document the receipt and disposition of all study drug.

Study drug will be dispensed as per the schedule of events. The first dose (Day 1) will be taken in the clinic so that an ECG can be performed ~one hour post-dose. Daily dosing will be recorded by the patient in the diary, which will be reviewed by site personnel at the next visit. Patients will be instructed to return all bottles (used and unused) to the clinic and any discrepancies between the diary and physical inventory will be discussed and documented. If necessary, site personnel will re-instruct the patient prior to dispensing the study drug for the following week.

All used kits and their contents will be retained for review by the Sponsor's designated study monitor. After the review is complete, empty bottles can be disposed in accordance with clinic policy for waste management. Any unused or partially used bottles should be retained. At the end of the study, or as directed by the Sponsor, the Investigator will be instructed to return or dispose of any unused product. All details of return or destruction must be documented and maintained with the study records.

8.4 Concomitant Medications

All prior and concomitant medications which are ongoing at the time of screening and those taken during the course of the study will be recorded in the patient's record and the study database. Any pain medication taken 30 days prior to Screening will also be recorded.

8.4.1 Concomitant Pain Medications and Therapies

Patients who have been on a stable regimen of an allowed pain medication (see Section 8.4.2 below) for at least 3 months prior to Screening and who have ongoing diabetic neuropathic pain that meets entry criteria may continue those medications during the study provided there is no plan to change the regimen during the study. Any pain medication that a patient has been previously taking on a regular basis but no longer takes must have been discontinued for at least one month prior to starting the Pain Observation period. Pain medications taken on an occasional or as needed basis (3 or less days in most weeks) must have been discontinued for at least 7 days prior to starting the Pain Observation period.

Patients who have continued to experience pain while using non-drug therapies for pain (eg, acupuncture, mindfulness therapy, etc) that have been ongoing for at least 3 months may continue these during the study, provided the type and intensity of such treatment remains stable during the course of the study. The following medications/devices are not permitted during the study:

- Non-steroidal anti-inflammatory drugs (NSAIDs including Advil and Motrin [ibuprofen], Aleve [naproxen, Bayer and Ecotrin [aspirin], etc).
- Opioid medications including, but not limited to, OxyContin (oxycodone), Percocet (oxycodone and acetaminophen), Vicodan (hydrocodone), Percodan (oxycodone and aspirin), Tylox (oxycodone and acetaminophen capsules), Demerol (meperidine), Ultram (tramadol), Nucynta (tapendatol), etc.
- Cannabinoids, including CBD.
- Topical preparations containing capsaicin, NSAIDs, or numbing agents (eg, lidocaine).
- Implanted medical devices (eg, spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator).

No patient may participate in the study if he/she has enrolled or previously (prior 30 days before initiation of the Screening period) participated in a study of an investigational drug, biologic, or medical device. Participation in a concomitant observational study where no treatment intervention is planned is allowed, provided the demands of such a study do not, in the opinion of the Investigator, overly burden the patient or put treatment study objectives at risk.

Patients will be queried about pain medications and therapies during each visit to determine if any of the prohibited items are being used.

8.4.2 Allowed Medications and Therapies

Patients will be permitted to continue using one medication for painful DPN from the list below, provided they have been taking the medication and the dose has been stable for at least 3 months prior to Screening and no changes in the regimen are planned or expected for the duration of the study. The requirements for pain eligibility must still be met regardless of whether a study candidate is taking one of the permitted medications during the Pre-Treatment Pain Observation period.

- Amitriptyline, ≤ 75 mg per day or other tricyclic antidepressants at equivalent doses
- Venlafaxine, ≤ 150 mg per day
- Duloxetine, ≤ 60 mg per day
- Gabapentin, ≤ 1200 mg per day
- Pregabalin, ≤ 300 mg per day
- Alpha lipoic acid ≤ 600 mg/day
- Carbamazepine ≤ 800 mg/day

Patients taking a higher dose of the one permitted medication for painful DPN in the above list can decrease their dose to the acceptable limit. A minimum of 7 days at the permitted dose should occur prior to starting the Pain Observation period.

Aspirin, if prescribed for cardiac prophylaxis and not for pain, is permitted. Throughout the study, patients will be allowed to take acetaminophen as rescue pain medication at a maximum dose of 500 mg at 6-hour intervals up to 4 times in any given 24-hour period. Use of rescue medication will be captured in the daily diary, which will be reviewed at each clinic visit by study personnel.

All other medications and therapies used to treat conditions other than pain are permitted at the discretion of the Investigator. All concomitant medication use will be recorded in the patient's record and the study database.

8.4.3 Prohibited Medications

Patients that requires treatment with drugs known to prolong the QT interval (including azithromycin, chloriquine/melfiloquine, clarithromycin, droperidol, erythromycin, moxifloxacin and sevoflurane) are not permitted.

9.0 STUDY VISITS AND PROCEDURES

9.1 Schedule of Study Procedures

The tabular schedule of assessments is provided in Table 1. The study is comprised of a Screening, Washout, Pain Observation, Treatment, Safety Extension, and Follow-up period as outlined in the sections below.

9.2 Screening and Washout Period (Day -45 to Day -14)

The timing of Screening evaluations will depend in part on whether the patient is using pain medications other than those permitted and described in Section 8.4.2. Patients on pain medication that is not permitted and taken on a regular basis should be scheduled so as to allow for a minimum of at least one month (30 days) washout prior to the start of the Pain Observation period. Patients on pain medication that is not permitted and taken on an occasional or as needed basis (3 or less days in most weeks) 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. All Screening and Washout procedures must be completed by Day -14 to allow for a 14-day Pain Observation period prior to randomization.

9.2.1 Screening Evaluation

Obtain informed consent before any study procedures are performed. After the patient signs the ICF, the following assessments will be performed:

- Assess eligibility based on inclusion/exclusion criteria;
- Obtain demographics (including gender, date of birth, race, and ethnicity);
- Record medical history (other than diabetes and painful DPN);
- Record diabetes history, including prior medication/treatment history;
- Record diabetic neuropathy history, including prior medication/treatment history;
- Administer C-SSRS (Screening version- 3 month and lifetime history) (see Appendix II);
- Perform MDT;
- Measure height and weight and calculate BMI;
- Obtain vital signs (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;
- Record prior medication history (other than diabetes and painful DPN);

- Perform physical examination (including general appearance; skin; head, eyes, ears, nose, and throat [HEENT]; chest [including heart/lungs], abdomen [including liver/kidneys], musculoskeletal, and sensory/neurological);
- Perform 12-lead ECG (after the patient has been resting in the supine position);
- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours), hematology, HbA1c, vitamin B12, and serum paraproteins;
  - FSH and estradiol (only for females less than 60 years of age with less than 2 years since last period);
  - HIV, hepatitis B virus surface antigen, and hepatitis C virus screen;
  - Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) Qualitative PCR (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);
- Collect urine samples for the following:
  - Urinalysis;
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen;
- Obtain DN4 score; and
- Perform UENS.

9.3 Pain Observation Period (Day -14 to Day -1/Pre-Treatment)

9.3.1 Day -14 Training Visit

On Day -14, the results of all Screening assessments will be reviewed in relation to the study eligibility criteria (see Section 7.3) to make a preliminary determination as to whether the patient is qualified for the study. Qualified patients will enter the Pain Observation period. As the pain observation period is conducted under single-blind conditions, site staff must take care not to reveal to patients that study medication during this time is placebo. The pain observation period will be initiated as follows:

- Review calendar and schedule Observation period (Day -14 to Day -1) with patient;
- Review prohibited medications that must not be used and rescue medication guidelines;
- Collect urine samples for the following:
  - Urine drug screen (performed at the discretion of the Investigator);
  - Urine pregnancy test (if FOCBP);

- Record medical history;
- Record prior medications;
- Dispense study drug assigned by IRT and instruct on dosing;
- Instruct patient to complete the following training modules in the WCG aLearn Leaning Management System platform: Accurate Pain Reporting, Placebo Response Reduction and Research Subject Responsibility; and
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use.

Patients will record the following information in the study diary on a daily basis:

- NRS (worst and average pain experienced each day);
- Daily dosing; and
- Rescue medication use, as applicable.

9.3.2 Follow-Up Phone Contact (Day -7 to Day -5)

A phone contact to the patient will be conducted for the following:

- Review diary entries and dosing compliance;
  - Review NRS entries (worst and average pain experienced each day) and rescue medication for past week and correct any misunderstandings if present;
- Schedule Day 1 clinic visit. A patient may be randomized after 10-14 days in the Pain Observation period if all eligibility requirements have been met.

9.4 Pre-Treatment/Baseline Visit (Day 1)

On Day 1, a final determination of study eligibility will be completed and placebo lead-in accountability will be performed. The diary will apply the pain eligibility algorithm to the stored data to determine if the patient is qualified. Additionally, placebo accountability will be performed for eligibility. Patients who meet the pain eligibility and placebo accountability requirement, and continue to meet all other eligibility criteria, will proceed to randomization and treatment.

The following Pre-Treatment assessments will be completed prior to randomization:

- Record medical history;
- Record prior medications;
- Administer C-SSRS (Since Last Visit version);

- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Perform 12-lead ECG (after the patient has been resting in the supine position);
- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours) and hematology;
- Collect urine samples for the following:
  - Urinalysis;
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Administer BPI-SF (pain interference section only);
- Administer NTSS-6;
- Perform UENS;
- Administer Norfolk Diabetic QOL-DN; and
- Perform intraepidermal nerve biopsy (eligible patients at selected sites).

Once all Pre-Treatment assessments have been completed, the patient will be randomized using the IRT. After randomization, the following will occur:

- Dispense study drug kit assigned by IRT. The patient will be shown how to take the first dose, which will be administered at the site.
- Perform 12-lead ECG (after the patient has been resting in the supine position) one hour (+/- 10 minutes) post-dose.
- Assess for post-dosing AEs.
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use.

9.5 Treatment Period (Week 1 to Week 12)

Following randomization on Day 1, patients will return to the clinic for visits as outlined in the schedule of events. During each visit, the procedures specified by the schedule of events for that visit will be performed.

9.5.1 Week 1

The following procedures will be performed at Week 1:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Perform 12-lead ECG (after the patient has been resting in the supine position);
- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours) and hematology;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator); and
- Dispense study drug assigned by IRT.

9.5.2 Week 2

The following procedures will be performed at Week 2:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood sample for the following:
  - Hematology;
- Collect urine samples for the following:

- Urine pregnancy test (if FOCBP);
- Urine drug screen (performed at the discretion of the Investigator);

- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator); and
- Dispense study drug assigned by IRT.

9.5.3 Week 4

The following procedures will be performed at Week 4:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours) and hematology;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Administer BPI-SF (pain interference section only);
- Administer PGIC;
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use; and
- Dispense study drug assigned by IRT.

9.5.4 Week 8

The following procedures will be performed at Week 8:

- Administer C-SSRS (Since Last Visit version);

- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood sample for the following:
  - Hematology;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen;
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator); and
- Dispense study drug assigned by IRT.

At the conclusion of the 12-week Treatment period, patients will enter the Safety Extension period.

9.6 Safety Extension (Week 12 to Week 24)

From Week 12 to Week 24, all patients will receive ricolinostat 120 mg daily. Patients will return to the clinic as outlined in the schedule of events and at each visit procedures specified in the schedule of events for that visit will be performed.

9.6.1 Week 12

The following procedures will be performed at Week 12:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Perform 12-lead ECG (after the patient has been resting in the supine position);
- Collect blood samples for the following:

  - Fasting chemistry (fasting of 8-10 hours), hematology, and HbA1c;
- Collect urine samples for the following:
  - Urinalysis;
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Administer BPI-SF (pain interference section only);
- Administer NTSS-6;
- Perform UENS;
- Administer Norfolk Diabetic QOL-DN;
- Administer PGIC;
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator); and
- Dispense study drug assigned by IRT.

9.6.2 Week 14

The following procedures will be performed at Week 14:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood sample for the following:
  - Hematology;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;

- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator); and
- Dispense study drug assigned by IRT.

9.6.3 Week 18

The following procedures will be performed at Week 18:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood sample for the following:
  - Hematology;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable; and
- Dispense study drug assigned by IRT.

9.6.4 Week 24

The following procedures will be performed at Week 24:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Perform 12-lead ECG (after the patient has been resting in the supine position);

- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours), hematology, and HbA1c;
- Collect urine samples for the following:
  - Urinalysis;
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Administer BPI-SF (pain interference section only);
- Administer NTSS-6;
- Perform UENS;
- Administer Norfolk Diabetic QOL-DN;
- Administer PGIC;
- Perform intraepidermal nerve biopsy (eligible patients at selected sites);
- Record concomitant medications and AEs;
- Collect returned study drug (used and unused bottles) and perform study drug accountability;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator).

9.7 Follow-Up Period (Week 26 and Week 28)

Approximately 2 and 4 weeks after the last dose of study drug, study patients will have follow-up visits during which the assessments specified for those visits will be performed.

9.7.1 Week 26

The following procedures will be performed at Week 26:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);

- Administer BPI-SF (pain interference section only);
- Administer NTSS-6;
- Perform UENS;
- Administer Norfolk Diabetic QOL-DN;
- Administer PGIC;
- Record concomitant medications and AEs;
- Instruct patient on daily completion of NRS (worst and average pain experienced each day) and rescue medication use, as applicable (at the discretion of the Investigator).

9.7.2 Week 28

The following procedures will be performed at Week 28:

- Administer C-SSRS (Since Last Visit version);
- Obtain vital signs (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;
- Perform directed physical exam to assess changes from the prior visit or new concerns;
- Assess skin integrity and wound healing, if applicable;
- Collect blood samples for the following:
  - Fasting chemistry (fasting of 8-10 hours), hematology, and HbA1c;
- Collect urine samples for the following:
  - Urine pregnancy test (if FOCBP);
  - Urine drug screen (performed at the discretion of the Investigator);
- Record concomitant medications and AEs.

At the conclusion of these evaluations, the patient will have completed the study.

9.8 Premature Discontinuation

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.

If the timing of the early termination 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.

10.0 EVALUATIONS AND STATISTICAL ANALYSES

10.1 Data Management and Quality Assurance

All study data resulting from protocol specified assessments will be entered into a 21 CFR Part 11 compliant database. At the clinical site, the data will be entered into an electronic data capture (EDC) system. Data entered in the study database will be reviewed against source documentation at clinical sites by the Sponsor's designated study monitor. Furthermore, ongoing review of the database will be performed in a blinded manner by data managers, statisticians, and clinical members of the CRO and Sponsor teams. All incomplete or incorrect entries will be queried for clarification. Any errors noted will be corrected by changing the incorrect entry. All corrections will be tracked in the system via an audit trail. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

The Sponsor's data management vendor will be responsible for:

- Database design and development (using a 21 CFR Part 11 compliant platform)
- Data capture form design and creation
- Study Investigator and research team instruction
- Database maintenance
- Study data review and quality assurance
- Database lock
- Raw dataset delivery for statistical analysis

All process aspects of data entry, access, review, validation, correction, coding, and finalization will be described in a separate Data Management Plan developed in conjunction with the data management vendor.

10.2 Efficacy and Safety Evaluations

10.2.1 Efficacy Assessments

10.2.1.1 Primary Efficacy Assessment

The primary efficacy assessment measure is the 11-point NRS where 0 represents no pain and 10 is the worst pain possible assessed after 12 weeks. Patients will record the average pain experienced each day. Patients will also record the worst pain experienced each day, which will be used as a secondary efficacy assessment. The NRS is a validated tool commonly used for pain assessment (Farrar, 2001). The NRS will be recorded daily by patients. To ensure that patients

understand and can properly complete the NRS, patients will receive training on how to rate and complete the NRS prior to the Pain Observation period and may also receive repeat training during the course of the study to aid in maintaining consistency of ratings throughout the study.

10.2.1.1.1 Numerical Pain Rating Scale

Data from the NRS, described previously in Section 10.2.1.1, will also form the basis of the following secondary endpoints:

- Mean pain intensity from Pre-Treatment [mean $NRS_{D-7\ to\ D1}$] to each weekly assessment through Week 4, comparing weekly means calculated using daily scores for 1) worst pain, and 2) average pain
- Percent change in mean pain intensity from Pre-Treatment [mean $NRS_{D-7\ to\ D1}$] to each weekly assessment through Week 4 and Week 12, comparing weekly means calculated using daily scores for 1) worst pain, and 2) average pain
- Proportion of patients achieving ≥ 30% and ≥ 50% improvement in mean NRS score from Pre-Treatment [mean $NRS_{D-7\ to\ D1}$] to the last week of treatment [mean $NRS_{D22\ to\ D28}$], using means for 1) worst pain, and 2) average pain

10.2.1.2 Secondary Endpoints

10.2.1.2.1 Brief Pain Inventory Questionnaire – Short Form

The BPI-SF is a validated tool commonly used in pain assessment (Zelman, 2005).

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.

A secondary study endpoint is the change from Pre-Treatment/Day 1 to Week 4 and to Week 12 in mean BPI-SF pain interference score.

10.2.1.2.2 Patient Global Impression of Change

The PGIC is a validated tool commonly used in pain assessment (Farrar, 2001).

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 1 = no change (or condition is worse), and 7 = a great deal better/considerable improvement. Examination of the PGIC scores at Weeks 4 and 12 will be a secondary study endpoint.

10.2.1.2.3 Neuropathy Total Symptom Score – 6

The NTSS-6 is a validated tool commonly used in neuropathic assessment (Bastyr III, 2005).

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.

A secondary study endpoint is the change from Pre-Treatment/Day 1 to Week 12 in the NTSS-6.

10.2.1.2.4 Utah Early Neuropathy Scale

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 (Singleton JR et al, 2008) and shown to have satisfactory operating characteristics including high interrater reliability and reproducibility, as well as favorable characteristics for measuring change over time (Robinson et al, 2019).

A secondary study endpoint is the change in non-pain neuropathic signs after 12 weeks in patients as assessed by change in the UENS.

10.2.1.2.5 Norfolk Diabetic Quality of Life-Diabetic Neuropathy

The Norfolk Diabetic QOL-DN is a validated tool commonly used in diabetic neuropathy (Vinik, 2005).

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.

A secondary study endpoint is the change from baseline to Week 12 in Norfolk Diabetic QOL-DN.

10.2.1.2.6 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.

10.2.1.3 Intraepidermal Nerve Fiber Density Determination

Intraepidermal nerve fibers are nociceptive C-fibers that are easily accessible from simple punch skin biopsies, and are quantifiable and reproducible. Small unmyelinated nerve fibers are easily and frequently damaged in diseases such as diabetes. A reduction in IENFD correlates with examination findings and symptoms of neuropathy. However, unlike large myelinated nerve fibers, small nerve fibers have a capacity for regeneration, even over short periods of time. There is a strong correlation between neuropathy severity and IENFD (Gibbons CH et al Neurology, 2009), and results are highly reproducible and reliable. Intra-epidermal nerve fiber biopsy is a powerful tool for defining pathological changes to nerve fiber density and has the potential to provide a means of assessing drug effects in a smaller number of patients as compared with patientive pain measures.

In preclinical studies, ricolinostat-associated functional improvements have consistently been associated with restoration of IENFD after experimentally induced nerve injury. Examination of IENFD in humans is intended to help understand whether any observed effects on pain and other neuropathic signs and symptoms are mediated by improvement in nerve function, and also to help assess whether ricolinostat has structural effects on peripheral nerves. The procedure is rapid (5-10 minutes), performed as an office procedure, and involves minimal discomfort or risk to patients. The biopsy site is ~ 3 mm, and heals with a 'band-aid.' Detailed procedural instructions will be provided in the Study Reference Manual.

10.2.1.4 Masquerading Disorders Tool

The MDT is a brief Investigator-administered Screening instrument that identifies disorders potentially confounding or masquerading as painful DPN (eg, plantar fasciitis, ischemic pain). The MDT is administered at Screening. Patients who are identified as having a positive finding on the MDT must be discussed with the Sponsor's Medical Monitor and approved before proceeding into the study.

10.2.2 Safety Assessments

The following safety assessments will be performed during the study as outlined in Table 1 and the data will be used for safety analyses as described in Section 10.3.7.

- Vital signs
- Physical examination (including skin integrity and wound healing, if applicable)
- 12-lead ECG
- Laboratory assessments (hematology, serum chemistry, and urinalysis)
- AEs

Skin integrity, the presence of wounds, and wound healing, if applicable, will be assessed Pre-Treatment (Day 1), weekly during the Treatment period and Safety Extension period, and at the final visit (Week 28). Examination of each wound, whether it was pre-existing on Day 1 or develops during the study, will include documentation of the wound's location, size, and depth along with assessment for signs of infection, such as erythema, edema, warmth, odor, or drainage. Signs of impaired healing or infection will be followed and evaluated to determine if they meet criteria for reporting as an AE.

10.3 Statistical Methods

10.3.1 Sample Size and Power

The sample size for this study is planned to be approximately 274 evaluable patients, which provides a power of 0.8 for detecting 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, an effect size comparable to effect sizes observed in recent diabetic neuropathic pain studies using efficacious agents such as duloxetine and pregabalin (Smith et al, Journal of Pain, 2018). An effect size of this magnitude or greater, if observed in this study, would support the further investigation of ricolinostat as a potential treatment for painful DPN. The estimates for power are conservative as the primary efficacy analysis will use an MMRM approach with 12 measures over time.

10.3.2 Analysis Approach

After all patients have completed their last visit of the 12-week double-blind, placebo-controlled period, a formal blinded review of the data will take place and the database will be locked after this review is finalized. At this point all data will be analyzed except for the measures whose analyses are based on the 24-week data. The SAP will detail the formal blinded data review process.

10.3.3 Primary Efficacy Outcome Measures

The null hypothesis is that there is no difference between the average change from baseline in the NRS score in the ricolinostat and placebo groups; the null hypothesis is stated as H_0: $\Delta_R = \Delta_P$, where Δ_R denotes the average change from baseline in the NRS score in the ricolinostat group and Δ_P denotes the average change from baseline in the NRS score in the placebo group. The alternative hypothesis is stated as H_A: $\Delta_R \neq \Delta_P$ with a two-sided significance level of 0.05.

The primary estimand for this study is defined by the following attributes:

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	Weekly mean of daily average pain based on the 11-point NRS.
Intercurrent events	All observations in patients who are on stable permitted concomitant pain medication for DPN and who started at least 3 months prior to Screening will be included. If there is a dose change, pain scores after the dose change will be considered missing and will be imputed using Medical Administration Record (MAR) assumption.
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 as measured by the NRS. Patients will record their average pain and worst pain on a daily basis in a diary starting seven days prior to randomization through the end of the study using the NRS, where 0 represents no pain and 10 represents worst possible pain. The baseline average pain score is the mean of the average daily pain scores recorded from day -7 to -1 of the study. (Note: For visits prior to randomization, study day=visit date-randomization date. For visits after randomization, study day=visit date-randomization date+1.) The weekly mean of the average pain will be calculated when four or more daily average pain scores exist for that week. If a patient has fewer than four daily average pain scores in a week, then the weekly mean pain will be set to missing for that week.

A MMRM approach will be used to analyze the change from baseline to Week 12 in the average NRS pain score, with the mean change from baseline in the average NRS pain score at each week as the outcome in the model. The model will include the following covariates: treatment, visit, treatment by visit interaction, baseline NRS pain score, baseline NRS pain score by visit interaction, and use of concomitant medication for painful DPNDNP (yes vs. no). The within-patient correlation will be modeled by using an unstructured covariance matrix. If the model does not converge, then a Toeplitz covariance structure will be used, which assumes that observations closer together are more correlated than those further apart in time. If convergence

is still not attained, then the auto-regressive of order one will be used, which has the same assumption as the Toeplitz model but is more restrictive. If the model still does not attain convergence, then compound symmetry variance-covariance models will be used, which assume equal correlation between measurements from a patient. Restricted maximum likelihood will be used as the method of estimation with the degrees of freedom approximated using the Kenward Rogers approach. The primary estimand will be obtained from this model.

It is assumed that short-term action of rescue medication does not affect the average daily pain score and scores that are collected during the use of rescue medication will be used in the analysis. Patients on a stable dose of permitted concomitant medication that has been started at least 3 months prior to starting the Pain Observation period will be included in the analysis. However, if there is a dose change, the pain scores after dose change will be set to missing and imputed under the assumption of MAR.

In order to assess the robustness of the primary analysis, the following additional sensitivity analyses will be performed:

1. A tipping point analysis with multiple imputation, in which the missing values in the ricolinostat arm will be assigned a shift parameter during imputation in order to determine the point where statistical significance changes.
2. An MMRM analysis with jump to reference, in which all missing values are imputed based on the placebo arm. This is a worst-case scenario where missing values among patients in the ricolinostat arm are imputed as if they came from the placebo arm.
3. An MMRM analysis using MAR and monotone missing assumptions.

The results of the sensitivity analyses will be presented in tables, figures, and a forest plot. Details will be provided in the SAP.

10.3.4 Key Secondary Outcome Measures

The key secondary outcome measures are the change from baseline in the mean NRS score at Week 4 and the change in non-pain neuropathic signs and symptoms after 12 weeks as assessed by change in the UENS.

For the first outcome of the change from baseline in the mean NRS score at Week 4, the analysis approach will be identical to that for the primary outcome, with the outcome consisting of the Week 1 through Week 4 average NRS measures. The result will be obtained from the MMRM model that is fit for the primary analysis. The estimated difference in the change from baseline between the treated and placebo groups at Week 4 will be computed as part of the primary analysis. This outcome will only be formally tested if the p-value associated with the primary

outcome is less than 0.05. If the p-value associated with the primary outcome is not statistically significant, a nominal p-value for the key secondary outcome will be presented.

The second endpoint of the change in the UENS from baseline to Week 12 will be formally tested only if the p-value associated with the key secondary outcome of change from baseline in mean NRS score at Week 4 is statistically significant. To assess this outcome, an ANCOVA model will be fit including the change from baseline in UENS at Week 12 as the outcome and baseline UENS score, treatment group, and use of concomitant medication for painful DPN (yes vs. no) as covariates.

10.3.5 Secondary Outcome Measures

The following secondary outcome measures will be analyzed as described for the primary efficacy analysis: change in mean BPI-SF pain interference score from Pre-Treatment/Day 1 to Week 4 and from Pre-Treatment/Day 1 to Week 12, change from baseline to Week 12 in the NTSS-6, and change from baseline to Week 12 in Norfolk Diabetic QOL-DN. ANCOVA models will be used for each of these analyses with the baseline value of the outcome, treatment group, and use of concomitant medication for painful DPN (yes vs. no) as covariates.

Proportion of patients achieving ≥ 30% and ≥ 50% improvement in mean NRS score from Pre-Treatment to the last week of treatment will be analyzed using a chi-square test. The PGIC at Week 4 and Week 12 will be analyzed using a two-sample t-test. Rescue medication (acetaminophen) use will be analyzed using a chi-square test.

10.3.6 Exploratory Efficacy Outcome Measures

The exploratory endpoint of change in IENFD from baseline to Week 24 will be analyzed in a subgroup of approximately 120 patients at selected sites. There are 3 comparisons of interest for this analysis:

1. Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 24 weeks.
2. Change from baseline in the IENFD in the group of approximately 60 patients that received ricolinostat for 12 weeks.
3. The difference in the change from baseline in the IENFD in the Intent-to-Treat population.

For the first two comparisons, an ANCOVA model with baseline density will be fit and the test of difference will be based on the significance level of the intercept term in the model. For the third comparison, an ANCOVA model with baseline density and treatment group as covariates will be used to calculate the nominal p-value.

10.3.7 Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and preferred term (PT). Only treatment-emergent AEs (TEAEs) will be

included in summary tables. A TEAE is defined as any AE that occurs after the start of study drug or was present at baseline and worsened after taking study drug.

The number and percent of patients with at least one 1) AE, 2) severe AE, 3) SAE, 4) AE leading to discontinuation, and 5) treatment-related AE will be presented by treatment arm for the Safety Population. The number and percent of patients with AEs will be presented by MedDRA SOC and PT for each treatment arm and overall. AEs will also be summarized by PT; by SOC, PT, and severity; and by SOC, PT, and relationship to study treatment. SAEs and AEs leading to discontinuation will also be presented.

The counts and percentages for AE summary tables will be based on the Safety Population. Patients with multiple unique events will be counted once per each unique PT and each unique SOC. If a patient has more than one AE that is coded to the same PT, the patient will be counted only once (using the maximum severity assigned) for that PT.

Observed values and change from baseline will be presented by visit and treatment group for hematology and chemistry laboratory tests. The number and percent of patients with hematology, chemistry, and urinalysis results outside the normal range will be presented by visit for each treatment arm. A second table will present shifts with respect to the lower limit of normal; the table will be repeated for shifts with respect to the ULN. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries, but will be listed. Another table will present findings of special interest, including selected hematology and serum chemistry abnormalities relevant to the assessment of safety.

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

10.3.8 Interim Analysis and Data Monitoring Committee

An independent DMC composed of 3 physicians and a statistician not employed by the Sponsor will periodically review data from the study in planned meetings as described below. Additionally, the DMC may, at its discretion, convene additional, unscheduled meetings at any time during the study.

Initial Safety Review: The DMC will review key safety data including the events of special interest specified in Section 11.10.2.2 after a vanguard cohort of at least 30 patients has had the opportunity to complete 4 weeks of treatment, and again after this cohort has had the opportunity to complete 12 weeks of treatment. Unless serious safety concerns have been observed, enrollment may continue while these reviews occur.

Subsequent DMC Meetings to Review Safety: The DMC will have another planned meeting to review safety when approximately 50% of the planned number of patients have been enrolled.

The DMC may also meet for unplanned meetings should safety observations during the study warrant such meetings.

Additional Planned Interim Analysis of Key Safety and Efficacy Data: an interim analysis of key safety and efficacy data may be conducted after approximately 50% of the planned number of patients enrolled and treated have had the opportunity to complete the 12-week double-blind, placebo-controlled treatment phase of the study to inform a decision regarding whether the study should stop for futility. To assess futility, the conditional power at the end of the study will be computed based on the data that are collected up to the interim analysis for the effect size of 0.34 that was used to calculate the power for the study. If the conditional power is less than 20%, the DMC may recommend stopping the study for futility. The conditional power will be calculated based on a two-sided t-test. The futility analysis may not occur if, for example, the study accrues quickly, as all or the large majority of patients may already be enrolled before approximately 50% of patients have finished the 12-week double-blind, placebo-controlled treatment phase.

The significance level associated with the primary and key secondary efficacy analyses will be adjusted based on the number of DMC meetings as described in the SAP.

11.0 SAFETY MONITORING AND RISK MANAGEMENT

11.1 Safety Events and Reporting

11.1.1 Definitions

Adverse Event (AE)	An AE is any unfavorable and/or unintended medical occurrence that presents during the course of the study (i.e., from the signature of informed consent through the Follow Up visit or earlier discontinuation, whichever comes first) regardless of its relationship to use of the investigational product. In studies of investigational products, no distinction is made between the investigational and control treatments with respect to AE reporting.
Serious AE (SAE) or Serious Suspected Adverse Reaction	Any AE or suspected adverse reaction that is deemed by the Sponsor or Investigator to have resulted in any of the following outcomes: death, a life-threatening AE (i.e., places the patient, in the opinion of the Sponsor or Investigator, at immediate risk of death from the reaction as it occurs), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

	Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Suspected Adverse Reaction	An AE for which there is a reasonable possibility that the investigational product caused the AE. A "reasonable possibility" means there is evidence to suggest the investigational product is causally related to the AE. Examples include: A single occurrence of an event that is uncommon and known to be strongly associated with an active ingredient or other component regardless of formulation; One or more occurrences of an event that is not commonly associated with an active ingredient or other component, but is atypical in the study population; The observation, when looking at data summaries, that a condition expected for the study population is occurring with increased frequency in comparison to concurrent or historical controls.
Treatment-Emergent AE (TEAE)	An AE that occurs after the patient has received the investigational product. AEs that occur during the Screening and Washout periods prior to treatment with the investigational product are not TEAEs.
Unexpected AE or Unexpected Suspected Adverse Reaction	Any AE or suspected adverse reaction not listed in the current Investigator's Brochure (IB) or for which the specificity or severity of the event is not consistent with the IB; or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB only referred to elevated hepatic enzymes or hepatitis.

11.1.2 Documenting and Reporting Adverse Events

The Investigator is responsible for routine assessments of AEs throughout the course of the study. All clinical complaints, symptoms, or signs that meet the AE definition will be documented in the patient's record and entered in the study database. Source documentation

should be maintained that allows for clear identification of each AE and the following parameters:

- Date of onset
- Date of resolution (or indication that the event continues as of the final visit)
- Intensity (mild, moderate, severe)
- Seriousness (per SAE definition)
- Relationship to study treatment
- Outcome

For study data collection purposes, the outcome of AEs captured in the database will be reviewed and made final at the time of the final study evaluation for each patient. If the AE is ongoing, this will be reflected in the record. However, the study Investigator is responsible for following all AEs until resolution or until no longer of clinical concern.

11.1.2.1 Assessment of Intensity (or Severity)

The intensity of each AE will be assessed using the following categories: mild, moderate, and severe.

- **Mild:** Easily tolerated by the patient, causes minimal discomfort and does not interfere with everyday activities.
- **Moderate:** Sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** Prevents normal everyday activities; treatment or other intervention usually needed.

There is an important distinction between a severe AE and a serious AE. The term “severe” designates the intensity of the event, while a “serious” AE meets specific criteria promulgated in 21 CFR 312.32 and described in Section 11.1.1.

11.1.2.2 Assessment of Relationship to Study Treatment

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

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal

relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent disease-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

11.1.3 Special Procedures for Reporting Serious Adverse Events

SAEs require additional detailed reports and follow-up. An SAE must be reported to the Sponsor immediately (within 24 hours) so as to facilitate discussion and implementation of necessary follow-up measures, and to enable the Sponsor to submit necessary reports to regulatory authorities, other Investigators, and IRBs. The Sponsor may request additional data and follow-up SAE reports to facilitate full disclosure to regulatory authorities, other Investigators, and IRBs in accordance with relevant regulation.

Initial Reports

All SAEs occurring from the time of first dose (start of Pain Observation period) of study drug until 30 days following the final dose of study drug must be reported to Medpace Clinical Safety

within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/e-mail the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety

Medpace SAE reporting line – USA:

Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3

Fax: +1-866-336-5320 or +1-513-579-0444

E-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

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

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

11.2 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety Follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax or e-mail it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety Follow-up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/e-mailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate

classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

11.3 Expedited Reporting

The Sponsor will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case, and the relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also inform all Investigators as required.

11.4 Clinical Laboratory Evaluations

Safety laboratory tests will include chemistry, hematology, and urinalysis. See Appendix I for a complete list of analytes. Chemistry laboratory tests will be collected after a minimum 8- to 10-hour fast.

Safety laboratory tests will be evaluated at the times indicated in the Schedule of Assessments table.

Abnormal Screening laboratory values that appear to be spurious (eg, 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 repeating the test.

If, in the opinion of the Investigator, any patient has a clinically significant abnormal laboratory finding in comparison to the value at the time of randomization or unresolved TEAEs, additional follow-up visits will be scheduled. Patients will be followed approximately once a week (or more frequently as deemed appropriate) until the Investigator determines that repeat laboratory findings are clinically unremarkable in comparison to baseline, or unresolved AEs return to prestudy levels or clinically acceptable levels.

If a patient experiences an SAE for which follow-up laboratories and review are required, the Investigator will schedule additional post dose visits as necessary.

If, in the opinion of the Investigator, any patient has a clinically significant AE at the follow-up call, the Investigator will provide additional follow-up until the AE returns to clinically acceptable levels.

The safety laboratory sample collection times may be refined based on emerging data to ensure study objectives are met.

11.5 Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and temperature, will be measured at the times indicated in the schedule of assessments (Table 1) using the following standardized procedures:

- Prior to measuring vital signs, the patient should be sitting for a minimum of 5 minutes with his/her back supported, feet flat on the floor, and his/her measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- Standing pulse and blood pressure will be obtained following sitting vital signs.
- An appropriately sized cuff should be used with the bladder centered over the brachial artery.
- The cuff size and arm used for the measurement should be recorded. Whenever possible, the same arm should be used for all vital sign assessments throughout the study.
- Blood pressure should be recorded to the nearest whole number on an automatic device.

11.6 Electrocardiograms

Twelve-lead ECGs will be performed at the times indicated in the Schedule of Assessments table.

Every effort will be made to eliminate any sources of physical (including any movement, eating, or drinking) or electrical interference. During these assessments, patients are not permitted to use cell phones, iPods, laptop computers, tablets, or any type of battery-operated or electrical device, and all of these devices must be turned off during the assessments.

All 12-lead ECGs will be performed with the patient resting in the supine position. Twelve-lead ECGs will be printed and all ECGs must be evaluated for the presence of abnormalities by a qualified physician. A digital recording of all ECGs for randomized patients will be submitted to a central reviewer. In the case of a disagreement between the local (site) reading and the central overread, the central overread interpretation of the ECG data will be utilized for all safety analyses.

Standard ECG parameters will be measured, and the following ECG parameters will be recorded:

- QRS interval
- Heart rate
- RR interval
- QT interval
- QTc (QTcF)

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline are noted on review.

11.7 Physical Examinations

A comprehensive physical examination will be performed at Screening. A comprehensive physical examination will consist of general appearance, skin, HEENT, chest (including heart/lungs), abdomen (including liver/kidneys), musculoskeletal, sensory/neurological.

Subsequent directed physical examinations will be performed at the times indicated in the Schedule of Assessments table. The directed physical examination 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 the Schedule of Assessments table. Skin breaches and wounds will be examined and

the following parameters recorded: location, size, depth, and evidence of erythema, edema, warmth, odor, or drainage.

All complete and limited physical examination findings must be recorded.

11.8 Height and Weight

Height and weight will be measured at the times indicated in the schedule of assessments (Table 1) and will be used to calculate BMI. Height will be measured with the patient's shoes off. Weight will be measured with the patient's shoes off and after the patient's bladder has been emptied.

11.9 Safety Data and Potential Risks

Toxicology studies have been conducted in rats (up to 6 months) and dogs (up to 9 months), and in both species the results support the use of ricolinostat during acute and chronic dosing. The study report from the rat 6-month study reported 'no ACY-1215-related macroscopic findings, organ weight changes, and microscopic findings at the Day 91 interim and Day 181/182 terminal sacrifice were noted. At the highest exposure observed in the chronic toxicology study in dogs, at study endpoint changes in some hematologic and clinical chemistry parameters were noted. Most of these changes remained within normal historical ranges, and all are monitorable in humans. Detailed descriptions of the design and results of these studies can be found in the Investigator's Brochure.

With respect to human data, clinical studies of ricolinostat have been conducted in 229 patients with multiple myeloma as described in Section 5.4 of this protocol and in the Investigator's Brochure. In these studies, ricolinostat was administered at doses from 40 mg to 360 mg as monotherapy or in combination with chemotherapy for extended periods, with a maximum treatment duration in the monotherapy study of 29.5 weeks and a maximum treatment duration of 174 weeks (~3.3 years) in combination studies. Details of the overall safety profile from these studies are provided in the Investigator's Brochure and above (see Section 5.4). Detailed safety results and descriptions of SAEs are also available in the Investigator's Brochure. Briefly, the observed SAEs were consistent with the serious underlying illness and poor health status of the study populations and did not suggest safety concerns attributable to ricolinostat. Similarly, the observed AEs or laboratory changes in the monotherapy as well as the combination studies, including episodes of neutropenia, anemia and changes in renal function in some patients, appeared to be consistent with the underlying malignancy and general health status of the patients and the known profiles of the chemotherapeutic agents being administered concurrently rather than attributable to ricolinostat.

No deaths occurred in healthy volunteers who received ricolinostat. Among the 229 individuals with refractory multiple myeloma treated with ricolinostat, 11 (5%) deaths occurred, of which 1 was in the monotherapy study and 10 were in the combination studies. No clear dose relationship to ricolinostat was observed, and all deaths occurred in patients who were ill with advanced

multiple myeloma. The causes of death were attributed to several different events: cardiac arrest/sudden death (N=2), pulmonary embolism (N=2), sepsis/septic shock (N=3), pneumonia (N=2), bacterial meningitis (N=1), and 'mental status changes,' with a number of terminal events described in the narrative (N=1). None of these deaths was judged by the assessing Investigator as likely due to treatment with ricolinostat, and all were consistent with the severe and progressive underlying neoplastic disease (refractory multiple myeloma) of the patients being studied. Further details are available in the Investigator's Brochure.

In the one healthy volunteer study conducted to date, the most common adverse effect reported in a study of healthy volunteers administered ricolinostat doses of 120 and 160 mg in crossover fashion was throat irritation (3 patients), and no SAEs were reported.

As described above, the overall body of safety data does not predict serious safety concerns specific to ricolinostat. However, as a result of their underlying disorder, patients with diabetes are at increased risk for a number of medical problems such as renal impairment and increased risk for infections. The available data do not suggest that ricolinostat is likely to increase these risks, but it is important to monitor these issues, and therefore the protocol will include specific monitoring for several potential AEs and laboratory changes designated as events of special interest and described in Section 11.10.2.2 below. Finally, with respect to skin biopsy, although patients with diabetes are at increased risk for poor wound healing related to vascular disease, the skin biopsy for IENFD is superficial, small, and commonly performed in patients with diabetic neuropathy, and poses minimal safety risk.

11.10 Risk Mitigation

11.10.1 Study Level Risk Mitigation

At the study level, risk will be mitigated through direct Investigator training, centralized safety data collection and monitoring, and periodic review of safety data by an independent DMC.

11.10.1.1 Training and Data Management

Measures specific to Investigator training and safety data management will be implemented as follows:

- Investigator and site personnel training will include a focused review of expectations for monitoring safety and implementing risk mitigation.
- Study data will be captured in real time using an EDC system, allowing for routine review of EDC data by the Sponsor's Medical Monitor and clinical team, independent of the timing of on-site monitoring review.
- Routine on-site review of study records and data by the Sponsor's monitoring affiliate will begin directly after the first patient is treated at each study center.

- A central clinical laboratory will be used for hematology, serum chemistry, and urinalysis to provide standardization across study centers, rapid on-line access to results, and customized alerts for results requiring exclusion/discontinuation, thereby allowing Investigators as well as the Sponsor's Medical Monitor to identify potential safety issues early; standardized reference ranges for each test will be provided on every report of results and will also be available in the laboratory manual.
- A core cardiovascular laboratory will be used to provide standardization in ECG collection and interpretation across study centers, with rapid on-line access to results and customized alerts for exclusion/discontinuation.
- SAE reports and associated data will be reviewed on an expedited basis by the Sponsor and its affiliates in order to meet reporting obligations and implement additional risk mitigation (if applicable).

11.10.1.2 Data Monitoring Committee

As described in Section 10.3.8, an independent DMC will meet periodically to perform a comprehensive review of accumulated safety data. In order to complete an informed review, the DMC will be provided with treatment assignment information for each patient (i.e., unblinded data). An independent, unblinded statistician will facilitate safety data review by the DMC.

The DMC will be provided with event and case report data on an ad hoc basis when a patient is discontinued for any of the AEs of special interest outlined in Section 11.10.2.2. As with the formal scheduled reviews, treatment assignment information will be included. The DMC will assess safety data for evolving trends, with particular attention to the events of special interest described below. As described above (Section 10.3.8) the DMC may also perform an interim analysis to assess efficacy or futility.

11.10.2 Patient Level Risk Mitigation

11.10.2.1 Patient Exclusion

Given the potential for undue risk, certain patients will be excluded from study participation as follows:

- Patients at risk for QT interval prolongation as a result of personal or family history, or with measured QTc prolongation on Screening ECG.
- Patients with any hematologic or select serum chemistry abnormalities suggesting serious, ongoing medical problems, including significant renal or hepatic impairment.
- Patients with significant comorbidities or other medical conditions, laboratory abnormalities, or psychiatric illnesses that would place the patient at increased risk.

- As the effect of ricolinostat on fetal development is not known, pregnant women or women wishing to become pregnant will be excluded from the study, as will FOCBP who do not agree to use contraception as outlined above. Breastfeeding mothers will also be excluded.

11.10.2.2 Adverse Events of Special Interest and Monitoring Procedure

The following AEs are designated as events of special interest, and, if observed as treatment-emergent during the study, should be addressed as described below: Anemia, leukopenia, neutropenia, thrombocytopenia, renal impairment, congestive heart failure, suicidality.

Observation	**Risk Management**
Clinical Laboratory Parameters for Adverse Events of Special Interest	
Cardiac Conduction: QTcF ≥ 500 ms or QTcF increase from baseline ≥ 60 ms and QTcF ≥ 480 ms	• For any observed case, the investigator should repeat the ECG assessment twice and compare the average of these 3 measurements of QTcF to the average of the 2 pre-treatment (i.e. screening and baseline) QTcF values • If confirmed, patient should be discontinued and appropriate follow-up instituted
Anemia: Hemoglobin decrease from baseline > 2 g/dL, or a decrease from baseline of at least 1.0 g/dL to a value below 11.5 g/dL (female) or 13 g/dL (male)	• For any observed case, repeat laboratory test within one week to confirm: o If the abnormality persists on repeat laboratory test, refer to section 11.10.2.2.1 for additional laboratory monitoring and initiate appropriate medical work-up to assess potential causes.
Leukopenia: White blood cell count < 2500/mm^3; or a decrease from baseline > 1500/mm^3	
Neutropenia: Neutrophil count < 1250/mm^3; or decrease from baseline > 500/mm^3	
Platelet count < 100,000/mm^3; or a decrease from baseline > 50,000/mm^3	
eGFR <30 ml/min/1.73 m^2	• Confirm with repeat test within one week; if confirmed, patient should be discontinued and appropriate follow-up instituted
C-SSRS: Response of "yes" to suicidal ideation questions 4 or 5; or response of "yes" to any suicidal behavior questions	• For C-SSRS response of yes to suicidal ideation items: evaluate and ensure patient's immediate safety; ensure patient has appropriate mental health follow up and any necessary intervention to assure patient's safety. If patient describes intent to act or formed plan (i.e., more than passive suicidal ideation), discontinue patient from study treatment, ensure appropriate mental health follow-up and schedule for safety follow-up.
Cardiac Function	

New onset symptomatic bradycardia observed during Treatment period; i.e., heart rate < 50 bpm with weakness, confusion, shortness of breath, chest pain or hypotension, or evidence of new onset (i.e., not previously diagnosed) congestive heart failure	• For bradycardia, repeat measurements at least 30 minutes later to confirm. For confirmed bradycardia or new onset congestive heart failure, stop study drug and initiate appropriate medical workup. • If no underlying, non-study drug-related cause can be ascertained, no further study drug should be administered, study discontinuation measures should be obtained, and the patient should be followed until resolution.

11.10.2.2.1 Hematological Adverse Events of Special Interest Confirmatory Monitoring

When an event is identified as meeting the pre-specified criteria for decrease from baseline in a laboratory sample at a post-randomization visit (sample 1) and confirmed in a second consecutively drawn sample (sample 2), the following additional monitoring will be put into place. Confirmation is defined as a repeat value that 1) meets the magnitude of decrease criterion from baseline relative to sample 1 and 2) that does not show a meaningful increase relative to sample 1. Baseline for this purpose is defined as the lowest of the available pre-randomization values.

If the decrease is confirmed, additional weekly samples for the ensuing 2 weeks (sample 3 and sample 4) will be collected (making a total of 4 samples over approximately 4 weeks) to ensure that parameters remain stable and do not go below pre-specified thresholds (see below) for discontinuation. During this monitoring, the patient may remain on study drug provided each of the following conditions are met:

- The observed values for all samples for the parameter in question remain above the following thresholds
  - 11.5/13.0 g/dL (Female/Male) for hemoglobin and at least 1 g/dL decrease from baseline
  - 2500/mm^3 for white blood cell count
  - 1250/mm^3 for neutrophils
  - 100,000 mm^3 for platelets
- There is not, in sample 2, 3, or 4 a further decrease relative to sample 1 in the measure being monitored
  - > 2 g/dL if the measure of interest is hemoglobin
  - > 500/mm^3 if the measure of interest is neutrophils,
  - > 1500 mm^3 if the measure of interest is white blood cell count,
  - > 50,000/mm^3 if the measure of interest is platelets.

- After samples 2, 3, and 4 have been obtained, and if no decrease relative to sample 1 meeting the criteria described in the above bullets has been observed, the patient may continue in the study on the usual visit schedule and the AESI is considered resolved.
- In the event samples 2, 3 and 4 show a further decrease from sample 1 that exceeds the above criteria for the relevant measure, drug administration is halted. A repeat laboratory sample should be obtained within one week. Provided this repeat sample shows an increase from the value among sample 2, 3 or 4 that triggered the halt, study drug may be reinstated, with weekly monitoring of the relevant parameter for at least 2 samples to ensure that values remain above 100,000/μL for platelets, 1250/mm3 for neutrophils and 2500/mm3 for WBCs.

Confirmed Events of Special Interest are recorded in the EDC system by completing the AE form electronically and indicating the event as an AE of Special Interest. Since these protocol defined AESIs are intended for safety monitoring, they may not be considered untoward medical events and their monitoring should not be used to infer relationship to drug.

When a patient is discontinued, best efforts should be made by the Investigator to complete final safety assessments and follow ongoing AEs until resolution or no longer of clinical concern.

12.0 ADMINISTRATIVE AND REGULATORY OBLIGATIONS

12.1 Confidentiality

12.1.1 Confidential and Proprietary Information

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate national or local authorities) must be kept in confidence by the Investigator. The Investigator may share the information with study personnel under his/her direct supervision only for the purposes of conducting the study.

12.1.2 Publication and Media Inquiries

All manuscripts or presentations based upon this study, including press statements and internal public notices and memoranda, must be submitted to the Sponsor for review and approval prior to release for publication or presentation. This review is necessary to ensure that proprietary, non-public information is protected in accordance with confidential disclosure agreement terms between the Sponsor and the Investigator.

During and after this study, the Investigator may receive inquiries from reporters or financial analysts. Investigators are to refer these inquiries to the Sponsor for disposition.

12.1.3 Patient Identity and Protected Health Information

In accordance with 45 CFR 160 and 164, Investigators must ensure that all information regarding the health of participating patients, including information generated during the course of this

study, is maintained in such a manner so as to prevent improper disclosure. Without prior authorization or waiver, information may not be released unless it has been edited to remove any and all identifiers (eg, names, addresses, contact information, dates of birth, social security numbers, medical record numbers, and all dates with the exception of year) that would allow for data to be linked to a specific individual. As a result, Investigators must provide a privacy notice to each study patient and obtain a release waiver as described below.

For data analysis and reporting purposes, the patient will be asked to sign an authorization for release and use of protected health information as part of the initial informed consent process. This authorization will allow the Investigator to make study results available to the Sponsor and its designated representatives, as well as applicable regulatory authorities, without first removing all unique identifiers (eg, dates of birth important to establishing the eligibility of patients). However, in any communications of data for this study, patients will be identified only by their initials and a unique study identification number.

12.2 Independent Review Board

The study protocol, ICF, and any other information that will be presented to study patients must be approved initially, and reviewed at least annually, by an IRB constituted in accordance with 21 CFR 56 and ICH E6 GCP guidelines. A copy of the initial IRB approval letter must be submitted to the Sponsor prior to study initiation. Investigational product will not be released to an Investigator without an assurance that final IRB approval has been granted. Subsequently, copies of all IRB correspondence should be submitted to the Sponsor on an ongoing basis.

12.3 Patient Recruitment and Informed Consent

12.3.1 Patient Referrals

Referrals are often an essential part of patient recruitment. Referrals to an Investigator can provide patients with access to investigational agents otherwise unavailable to the referring physician. It is important that the process of referring a patient to the Investigator conducting the study meets the requirements of ICH E6 GCP and 45 CFR 160 and 164 regarding the release of protected health information. Prior to referral, the patient should be asked if consent is given to share contact information and details of the medical condition with the Investigator. This consent should be documented by the referring physician.

12.3.2 Informed Consent and Other Written Information for Patients

The ICF and any other written information for patients should meet local requirements of language and interpretation. One copy of the signed ICF and any other written information will be given to the patient and the original will be retained by the Investigator in the study files. The ICF must include eight basic elements (purpose/scope/duration, risks/discomforts, benefits, available alternative procedures/treatment, confidentiality, compensation for research-related

injury, voluntary participation/withdrawal, and contact information) in accordance with 21 CFR 50.

12.4 Study Documentation

All data relevant to the assessments outlined in this protocol must be entered in the patient's record and the EDC system. Electronic data entered for each patient will be verified by comparison to source documents (medical records, study worksheets, diagnostic reports, ECG tracings, etc) at the study site by the designated study monitor. The Investigator must make patient data accessible to the designated study monitor, to other authorized representatives of the Sponsor, and to regulatory agency representatives. At the conclusion of the study, an electronic copy of each patient's case record in the EDC system will be provided to the Investigator for retention in the study file.

According to GCP, essential documents should be retained for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. In addition, records should be retained for at least two years after the formal discontinuation of clinical development of an investigational product. These documents should be retained for a longer period, however, if required by local regulatory requirements or through an agreement with the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, responsibility for the records should be formally transferred to an agreed-upon designee.

12.5 Protocol Compliance

Substantive changes in the protocol include alterations that affect the safety of patients or that alter the scope of the investigation, the scientific quality of the study, the experimental design, doses, assessment variable(s), the number of patients treated, or the patient selection criteria. These changes must be implemented via formal written protocol amendment only upon joint approval by the Sponsor and Investigator. Additionally, a protocol amendment must be reviewed and approved by the IRB prior to implementation. If a protocol amendment results in changes to the ICF, the revised form must also be approved by the Sponsor and the IRB prior to use.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient, and that are deemed crucial for the safety and wellbeing of that patient, may be instituted for that patient only. The Investigator or other attending physician will also contact the Sponsor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and the Sponsor must be notified in writing as soon as possible after the departure occurs. Furthermore, the Investigator will document in the patient's record and the electronic case report form (eCRF) the reasons for the departure from the protocol and the ensuing events.

12.6 Investigational Drug Accountability

It is the responsibility of the Investigator to ensure that proper procedures are implemented with regard to the receipt, storage, and dispensation of the investigational product(s). Shipping receipts, dispensing records, and inventory forms will be examined and reconciled periodically and at the end of the study by the designated study monitor. Both the study drug used during the course of the study and any remaining unused study drug must be accounted for on the Accountability Log provided to the Investigator by the Sponsor.

12.7 Study Monitoring

The designated study monitor will review the progress of the study as frequently as is necessary to ensure proper study conduct and accurate data collections through:

- Periodic on-site visits;
- Frequent telephone communications with the site; and
- Ongoing review of eCRF entries, clinical records, and administrative documents.

All records pertaining to the study will be made available to the study monitor during each site visit. To allow adequate time to assemble all of the records, visits will be confirmed well in advance whenever possible.

A separate Clinical Monitoring Plan will be prepared by the Sponsor and the designated clinical monitoring/site management CRO, which will include detailed guidance for site visit frequency, site-based data review and verification requirements, investigational product and essential document review, safety surveillance, remote eCRF data review, communications, and documentation (including reports of monitoring activity).

12.8 Reports

The Investigator shall make accurate and adequate written progress reports to the IRB at appropriate intervals, not exceeding one year.

The Investigator shall make an accurate and adequate final report to the IRB within 3 months after completion or termination of the study.

The Investigator shall immediately make an accurate and adequate special report to the Sponsor and the IRB (as applicable) for any serious adverse experience.

The Sponsor will prepare a final study report within a reasonable time frame after the data from the last completed patient has been tabulated. The final approved report will then be submitted to the appropriate regulatory authorities.

13.0 COVID-19 RISK MITIGATION

In March 2020, COVID-19, caused by infection with SARS-CoV-2, was characterized as a pandemic by the World Health Organization. The COVID-19 pandemic impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

13.1 Risk/Benefit Assessment in the Context of COVID-19

In general, the DPN population possesses moderate risk of serious complications from any infection or febrile illness because the underlying condition of diabetes and possible complications of cardiovascular disease may pose risk for worse outcomes and complication associated with COVID-19. The emergence of COVID-19 crises increases the overall infection risk in affected communities, including DPN patients who reside in those communities.

Participation in a clinical trial provides patients with increased access to healthcare resources and reinforcement of appropriate practices during a time of increased infection risk. Study patients will have access to healthcare professionals on a more intensive schedule than a normal clinical practice for the management of DPN.

To mitigate any risk of COVID-19 infection associated with study participation, this protocol provides flexibility for conducting remote visits (through telemedicine and/or home health visits) that will maintain patient access to healthcare resources while limiting any infection risk associated with study participation.

13.2 Remote Visits

In response to COVID-19 situations, remote visits consisting of telemedicine and/or home health visits may be conducted in lieu of certain in-clinic visits. The exceptions are the Screening visits and the baseline visit (Day 1), which must be conducted in the clinic. Table 3 specifies which activities can be conducted by a home health nurse or via telemedicine and which activities must be conducted in the clinic.

Table 3: Categorization of Study Activities

Remote Visits		In-Clinic Only Activities
Home Health Nurse Activities	**Telemedicine Activities**	
Obtain samples for the following labs: • Pregnancy test • Clinical safety labs	Review study diary/drug adherence Review new/ongoing AEs	Screening visit assessments Pain Observation Day -14 assessments

Vital signs 12-lead ECG Confirm patient completion of patient-reported outcome measures: • Brief Pain Inventory Short Form (pain interference section only) • Neuropathy Total Symptoms Score – 6 • Norfolk Diabetic QOL-DN • Patient Global Impression of Change	Review concomitant medications Limited physical exam including skin integrity and wound healing, if applicable[1] Dispense study treatment (direct-to-patient shipping of study treatment) Study treatment accountability Confirm patient completion of patient-reported outcome measures: • Brief Pain Inventory Short Form (pain interference section only) • Neuropathy Total Symptoms Score – 6 • Norfolk Diabetic QOL-DN • Patient Global Impression of Change • C-SSRS	Day 1 (Pre-Treatment baseline) assessments UENS Physical exam including skin integrity and wound healing, if applicable[1] Intraepidermal nerve biopsy

[1]If a physical exam cannot be performed in the clinic, a limited physical examination should be performed via telemedicine.

AE = adverse event; ECG = electrocardiogram; QOL-DN = Quality of Life-Diabetic Neuropathy; C-SSRS = Columbia Suicide Severity Rating Scale; UENS = Utah Early Neuropathy Scale.

If a site closes or a patient resides in a location where a shelter-in-place order is issued, the Investigator must consult with the Medical Monitor to determine the best course of action, particularly for those patients who have not yet completed the baseline visit. For patients that have completed the baseline visit, remote visit activities can proceed as outlined in Table 3. A combination of home health visit and telemedicine activities may be used. If in-clinic visits are no longer possible, activities categorized as in-clinic-only activities will not be conducted. If the shelter-in-place order is lifted after a missed clinic visit, attempts should be made to conduct the missed in-clinic-only activities via an unscheduled visit.

If a patient or a member of the patient's household is suspected or confirmed to have COVID-19, the Investigator must consult with the Medical Monitor to determine the best course of action. In this situation, only telemedicine activities can proceed. If the patient misses in-clinic visits during this time, an unscheduled visit will be conducted once the patient or member of his/her

household no longer has suspected or confirmed COVID-19. At a minimum, safety labs must be performed at the unscheduled visit. Patients cannot go more than 12 weeks or 2 consecutive visits without labs being drawn.

For scenarios not delineated here or for further clarification, the Investigator should consult the Medical Monitor to determine the best course of action.

13.3 Patient Disposition in the Context of COVID-19

If a patient develops active COVID-19 infection (whether confirmed or suspected) during the course of the study, the Investigator will work with the Medical Monitor to determine the best course of action, taking into consideration the AE and SAE guidelines in Section 11.0. If the study drug is discontinued or a patient is withdrawn from the study because of COVID-19, the reason for early termination will be captured in the EDC system as such.

13.4 Regulatory and Oversight Considerations in the Context of COVID-19

If planned onsite monitoring visits are not possible because of COVID-19, remote monitoring may occur, if allowed by local and federal legal and regulatory requirements. If source data are collected at a home health visit, those source documents will be maintained with the homecare staff until they can be transferred to the trial site. If a protocol deviation is the result of COVID-19-related circumstances, this information should be captured. The impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures will be discussed in the Clinical Study Report .

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15.0 APPENDICES

15.1 APPENDIX I – Clinical Laboratory Evaluations

Chemistry [Fasted]:

- Albumin
- Alkaline phosphatase
- ALT
- AST
- BUN
- Calcium
- Chloride
- Cholesterol
- Creatinine
- Calculated creatinine clearance
- GGT
- Glucose
- LDH
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Total CO_2 (measured as bicarbonate)
- Total protein
- Triglycerides
- Uric acid

Hematology:

- Hematocrit
- Hemoglobin
- MCH
- MCHC
- MCV
- Platelet count
- Red blood cell count (RBC)
- White blood cell count (WBC)
- White blood cell differential (% and Abs):
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

Other:

- Glycated hemoglobin (HbA1c)
- Urine pregnancy test (FOCBP only): point-of-care pregnancy test
- SARS-CoV-2 (COVID-19) Qualitative PCR
- Vitamin B12 and serum paraproteins

Complete Urinalysis:

- Color and appearance
- pH
- Specific gravity
- Bilirubin
- Glucose
- Ketones
- Leukocytes
- Nitrite
- Occult blood
- Protein
- Microscopic (including RBCs and WBCs)

Urine Drug Screen: point-of-care drug test

Serology

- Hepatitis B surface antigen
- Hepatitis C virus antibody
- Human immunodeficiency virus antibody

15.2 APPENDIX II – Suicidal Ideation/Behavior Screening

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a validated questionnaire that helps to identify suicidal ideation and behavior (Posner, 2011) in clinical and research settings. The C-SSRS is referred to in the General Recommendations section of the FDA Guidance for Industry on Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (Draft Rev 1; Aug 2012). The scale consists of two sections, one to assess suicidal intent or ideation and the other to assess suicidal behavior. Each section asks a small number of yes/no questions followed by scoring to quantify the intensity of ideation or behavior.

Two versions of the C-SSRS will be used in this study: Screening version (3 months and lifetime history) and the Since Last Visit version. The Screening version will be administered at the Screening visit. The Since Last Visit version of the C-SSRS will be administered at all subsequent assessment times. An investigator must review the C-SSRS data for each visit prior to the patient leaving the site and confirm that the patient did not express suicidal ideation or behavior that would require intervention.

Suicidal Ideation

There are 5 yes/no questions in the ideation section of the questionnaire that capture 1) a wish to be dead or not wake up, 2) non-specific thoughts of suicide, 3) specific thoughts of suicide method without intent to act, 4) some intent to act but without a specific plan, and 5) active ideation with specific plan and intent. When the patient responds yes to any of the ideation questions, the most severe (i.e., 1 – 5) ideation is further characterized on a scale of 0 – 5 with regard to frequency, duration and controllability of thoughts, as well as deterrents to and reasons for ideation.

Suicidal Behavior

The yes/no questions in the behavior section of the questionnaire ask about actual, interrupted, and aborted suicide attempts, as well as preparatory actions and non-suicidal injurious behaviors. The lethality of actual attempts is assessed on a scale of 0 – 4, and the potential lethality of non-lethal events (i.e., lethality = 0) is rated on a scale of 0 – 2.

Study Application

In this study, the C-SSRS will be used both to screen potential study candidates for suicidal ideation/behavior and to monitor enrolled patients for suicidality during the Treatment period.

At Screening, potential candidates who meet either of the following C-SSRS criteria will be excluded from study participation:

1. Yes response to Question 4 (some intent to act but without a specific plan) or 5 (active ideation with specific plan and intent) in the Suicidal Ideation section, or

2. Yes response to any of the Suicidal Behavior questions, including preparatory actions or injurious behaviors, for the 3 month period prior to Screening.

Furthermore, these same criteria *will result in patient discontinuation* if observed during the Treatment period (see Section 7.7).