Efficacy, Safety, and Tolerability of Fosmetpantotenate (RE-024), a Phosphopantothenate Replacement Therapy, in Patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN): A Randomized, Double-Blind, Placebo-Controlled Study With an Open-Label Extension

Unique Protocol ID:	024PKAN15004
NCT Number:	NCT03041116
EudraCT Number:	2016-001955-29
Date of Protocol:	23 May 2019

CLINICAL STUDY PROTOCOL

EFFICACY, SAFETY, AND TOLERABILITY OF FOSMETPANTOTENATE (RE-024), A PHOSPHOPANTOTHENATE REPLACEMENT THERAPY, IN PATIENTS WITH PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION (PKAN): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH AN OPEN-LABEL EXTENSION

PROTOCOL NUMBER: 024PKAN15004

IND #: 121943
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Version 1	**13 September 2016**
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Version 3	**06 February 2019 (United States Amendment Only)**
Version 4	**23 May 2019 (includes United States v3 and United States Administrative Letter 4)**

Sponsor: Retrophin, Inc.
3721 Valley Centre Drive, Suite 200
San Diego, CA 92130
USA

Investigator Signature	Date
Investigator Name (please print or type)	

Study Contact Information

Medical Monitor(s):	North America: PPD Email: PPD Europe: PPD Email: PPD
Serious Adverse Event Reporting:	ProPharma Group Email: PPD Fax: See study manual
Product Handling/Complaints	Tel: PPD Email: PPD
Medical Director	PPD PPD Retrophin, Inc. Tel: PPD Email: PPD
Clinical Project Manager:	PPD PPD Retrophin, Inc. Tel: PPD Email: PPD
Global Safety Officer:	PPD PPD Retrophin, Inc. Tel: PPD Email: PPD

Signature Page for Sponsor's Representative

I have reviewed and approved the protocol entitled, "Efficacy, Safety, and Tolerability of Fosmetpantotenate (RE-024), a Phosphopantothenate Replacement Therapy, in Patients with Pantothenate Kinase-associated Neurodegeneration (PKAN): A Randomized, Double-blind, Placebo-controlled Study with an Open-label Extension"

PPD

May 23rd, 2019
Date

Retrophin, Inc.

1. SYNOPSIS

NAME OF COMPANY
Retrophin, Inc.
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NAME OF FINISHED PRODUCT
fosmetpantotenate (RE-024)

NAME OF ACTIVE INGREDIENT
Methyl 3-((2*R*)-2-hydroxy-4-(((((*S*)-l-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)oxy)-3,3-dimethylbutanamido) propanoate

TITLE:

Efficacy, Safety, and Tolerability of Fosmetpantotenate (RE-024), a Phosphopantothenate Replacement Therapy, in Patients with Pantothenate Kinase-associated Neurodegeneration (PKAN): A Randomized, Double-blind, Placebo-controlled Study with an Open-label Extension

PROTOCOL NO.: 024PKAN15004

INVESTIGATOR STUDY SITES:

Approximately 20 sites in the North America, Europe, and other regions will participate in this study.

OBJECTIVES:

Efficacy Objective: To evaluate the efficacy of fosmetpantotenate over 24 weeks in patients with pantothenate kinase-associated neurodegeneration (PKAN)

Safety Objective: To assess the safety and tolerability of fosmetpantotenate in patients with PKAN

Other Objectives:

- To determine the pharmacokinetics (PK) following multiple doses of fosmetpantotenate in patients with PKAN
- To explore potential biomarkers of disease, along with their potential response to treatment in patients with PKAN

Endpoints associated with these objectives are listed in the ENDPOINTS section.

METHODOLOGY:

This is a pivotal, randomized, double-blind, placebo-controlled, multi-center, 2-arm study evaluating 24 weeks of treatment with fosmetpantotenate or placebo in patients with PKAN aged 6 to 65 years, with a 278-week open label extension period. If the product becomes commercially available during the extension period, patients may transition to commercial product before the end of the open-label extension period.

Following screening, patients meeting all eligibility criteria will be enrolled in the study. Patients will be randomized in a 1:1 ratio to receive either fosmetpantotenate or placebo for a 24-week double-blind period. Treatment in the double-blind period will begin with dose escalation for Days 1 through 3, followed by the full dose 3 times daily (TID) starting on Day 4. Matching placebo will be given according to the same dose escalation sequence as active investigational product.

After completing the 24-week double-blind period, patients will be eligible to receive open-label fosmetpantotenate in the study for up to 278 weeks followed by a phone safety review 4 weeks later. The total study duration will be approximately 310 weeks.

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Data Monitoring Committee

After 8 patients aged 18 to 65 years complete 3 weeks of study treatment in the double-blind period, the independent Data Monitoring Committee (DMC) will review safety data to determine whether the study can continue as planned, including initiating enrollment of patients aged 6 to <18 years. Enrollment of patients 18 to 65 years of age (only) will continue while this review is occurring. If the DMC determines it is safe to continue the study, enrollment of patients 6 to <18 years of age will begin, and enrollment of patients 18 to 65 years of age will continue.

Similarly, after the first 8 patients aged 6 to <18 years complete 3 weeks of study treatment in the double-blind period, the DMC will review the safety data from all patients to date and determine whether the study can continue as planned. Enrollment of patients 18 to 65 years of age and up to 8 additional patients aged 6 to <18 years of age may continue while this review occurs. If the DMC determines it is safe to continue the study, enrollment of patients 6 to 65 years of age will continue.

The DMC will also review safety data periodically throughout the study as described in the DMC charter.

NUMBER OF PATIENTS:

Approximately 82 patients aged 6 to 65 years will be enrolled in the study to achieve a target sample size of at least 74 patients completing the double-blind period of the study. Patients will be randomized in a 1:1 ratio to receive either fosmetpantotenate or placebo in the double-blind period, followed by open-label treatment with fosmetpantotenate. Randomization will be stratified by weight (≥40 kg, ≥20 kg but <40 kg, or <20 kg) and by age group (pediatric [ages 6 to <18 years] or adult [ages 18 to 65 years, inclusive]).

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A patient will meet all of the following criteria to be eligible for this study.

1. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent, and where required, the patient is willing to provide assent.
2. The patient has a diagnosis of PKAN as indicated by confirmed mutations in the pantothenate kinase 2 (*PANK2)* gene (if available, the specific mutation will be recorded).
3. The patient has a score of ≥6 on the Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living (PKAN-ADL) scale.
4. The patient is male or female aged 6 to 65 years, inclusive.
5. If sexually active with male partners, the female patient of childbearing potential agrees to use a medically acceptable method of contraception for the duration of the study and for at least 30 days after the last dose of investigational product. Females are considered of childbearing potential if they are post-menarchal, have not been surgically sterile for at least 6 weeks (ie, total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) and are pre-menopausal (menopause is defined as cessation of menstruation for at least 1 year). Acceptable methods of contraception include:

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A. the simultaneous use of stable combined (estrogen and progestogen containing) or progestogen-only hormonal contraception (eg, oral, transdermal or intravaginal) associated with inhibition of ovulation in conjunction with a double-barrier method (eg, condom with spermicide or diaphragm with spermicide), or;

B. the use of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) in place for at least 3 months or;

C. vasectomized partner, (vasectomy at least 3 months prior to screening), or;

D. sexual abstinence

6. If sexually active with female partners, the sexually mature, nonsterile male patient agrees to use a medically acceptable method of contraception for the duration of the study and for at least 90 days after the last dose of investigational product. Males are considered surgically sterile if they have undergone bilateral orchiectomy or vasectomy at least 3 months prior to screening. Acceptable methods of contraception include:

   A. the simultaneous use of stable combined (estrogen and progestogen containing) or progestogen-only hormonal contraception (eg, oral, transdermal or intravaginal) associated with inhibition of ovulation by the female partner in conjunction with a double barrier method (eg, condom with spermicide or diaphragm with spermicide), or;

   B. the female partner's use of an IUD or IUS in place for at least 3 months, or;

   C. the female partner is surgically sterile for at least 6 weeks or is at least 1 year postmenopausal.

7. The male patient agrees to not donate sperm for at least 90 days after the last dose of investigational product.

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has required regular or intermittent invasive ventilatory support to maintain vital signs within 24 weeks prior to randomization.
2. The patient has been (or is currently) enrolled in a clinical trial involving an investigational product or non-indicated use of a drug or device within 30 days prior to randomization.
3. The patient has a positive serologic test for Hepatitis B virus surface antigen (HBsAg), Hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) at screening.
4. The patient has a history of metastasized or ongoing malignancy, regardless of whether or not it has been or is being treated.
5. The patient has a serious, unstable medical or psychiatric condition not related to PKAN that, in the opinion of the Investigator, could interfere with the patient's ability to participate in the study safely or to complete the scheduled study assessments, or that would confound the assessment of safety or efficacy.
6. The patient has a history of drug or alcohol use disorder within the past 1 year.

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7. The patient has a history of suicide attempts within the past 1 year or is considered by the Investigator to be at imminent risk of suicide.
8. The patient has had a major surgical procedure within 30 days prior to screening.
9. The patient has had a deep brain stimulation (DBS) device implanted within 6 months prior to screening.
10. The patient has abnormal laboratory values at screening that, in the opinion of the Investigator, are clinically significant, and would compromise the safety of the patient during study participation.
11. The patient is a female who is pregnant or lactating, or who presents with a positive serum pregnancy test at screening, or a positive urine pregnancy test at Baseline.
12. The patient is unwilling or, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including study procedures and the visit schedule.
13. The patient is unable or unwilling to remain on their pre-study dose(s) of allowed concomitant PKAN maintenance medications and therapies (including DBS settings) for the double-blind period of the study. (See Section 8.3 of the protocol for discussion of concomitant medication/treatment use during the study, and Section 15.2.1 for a list of allowed concomitant medications and therapies.)
14. The patient has taken deferiprone within 30 days prior to screening.

Patients who do not meet eligibility criteria may be re-screened twice.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Fosmetpantotenate will be supplied in dried powder form for reconstitution and oral administration, packaged in a dose strength of 75 mg capsules, and, after receipt of regulatory approval, 75 mg and 300 mg sachets. In all patients, the 24-week double-blind period will begin with dose escalation on Days 1 through 3 (described below), followed by the full dose starting on Day 4. The full dose for patients aged 18 to 65 years will be 300 mg TID for a total daily dose of 900 mg. The full dose for patients aged 6 to <18 years will be determined by weight at screening: patients weighing ≥40 kg will receive 300 mg TID for a total daily dose of 900 mg (ie, the same as patients aged 18 to 65 years); patients weighing ≥20 kg but <40 kg will receive 150 mg TID for a total daily dose of 450 mg; and patients weighing <20 kg will receive 75 mg TID, for a total daily dose of 225 mg. All doses of investigational product will be taken with food.

Dose escalation on Days 1 through 3 will proceed as follows, based on age and weight at screening:

Patients aged 18 to 65 years and patients aged 6 to <18 years weighing ≥40 kg: On Day 1, patients will receive one 300 mg dose (in the morning); on Days 2 and 3, they will receive 300 mg twice daily (BID, at least 8 hours apart) for a total daily dose of 600 mg; and on Day 4, they will receive the full dosage of 300 mg TID (given at approximately 8 hour intervals) for a total daily dose of 900 mg.

Patients aged 6 to <18 years weighing ≥20 kg but <40 kg: On Day 1, patients will receive one 150 mg dose (in the morning); on Days 2 and 3, they will receive 150 mg BID (at least 8 hours apart) for a total daily dose of 300 mg; and on Day 4, they will receive the full dosage of 150 mg TID (given at approximately 8 hour intervals) for a total daily dose of 450 mg.

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Patients aged 6 to <18 years weighing <20 kg: On Day 1, patients will receive one 75 mg dose (in the morning); on Days 2 and 3, they will receive 75 mg BID (at least 8 hours apart) for a total daily dose of 150 mg; and on Day 4, they will receive the full dosage of 75 mg TID (given at approximately 8 hour intervals) for a total daily dose of 225 mg.

Elective dose reductions for safety or tolerability reasons only are allowed throughout the first 6 weeks of the double-blind period of the study. Dose reductions may only occur one time, according to the schedule in Section 6.5.3. Patients who are unable to tolerate the reduced dose will be discontinued from the study. The Investigator should attempt to increase the dose back to the patient's assigned fixed dose as safety and tolerability allow.

Once patients have been treated in the open-label period for at least 24 weeks, and after the second DMC review has occurred, dose increases of 1 level will be allowed for perceived lack of efficacy. Dose increases will only be allowed following consultation between the Investigator, the Medical Monitor, and the Sponsor, and only to the maximum dosage of 300 mg TID.

REFERENCE TREATMENT:

The matching placebo treatment will be administered orally.

ENDPOINTS:

Primary Efficacy Endpoint

The primary efficacy endpoint will be the change in the score from the PKAN-ADL, from Baseline to the end of the 24-week double-blind period.

Secondary Efficacy Endpoint

The secondary efficacy endpoint will be the change in the score from Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) from Baseline to the end of the 24-week double-blind period.

Safety Endpoints

The safety and tolerability of fosmetpantotenate will be assessed throughout the study by monitoring:

- Occurrence of adverse events (AEs). AEs will be classified according to their intensity (ie, mild, moderate, severe) and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification dictionary.
- Serial vital signs, weight, and physical examinations
- Serial clinical laboratory testing (chemistry, hematology, coagulation, and urinalysis)
- Columbia Suicide Severity Rating Scale (C-SSRS) Assessments
- Serial 12-lead electrocardiogram (ECG)

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will include change from Baseline to the end of the 24-week double-blind period in the following:

- Clinical Global Impression of Improvement (CGI-I)
- Barry Albright Dystonia (BAD) scale

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- Quality of Life (QoL):
  - Neuro-QoL, upper and lower extremity modules (adult and pediatric versions)
  - EuroQol 5-dimension, 3-level QoL instrument (EQ-5D-3L)/EuroQol-5D Youth Version (EQ-5D-Y)
- Functional independence: Functional Independence Measure (FIM)/Functional Independence Measure for Children (WeeFIM)
- Function measures:
  - Ambulation: 25-foot walk test (in appropriate patients)
  - Speech: Diadochokinetic (DDK) assessments (ie, alternating motion rate [AMR] and sequential motion rate [SMR])

Pharmacokinetics

Multiple dose PK of fosmetpantotenate in whole blood will be evaluated using a sparse sampling design. Blood samples may also be used for metabolite quantitation and/or identification.

Biomarkers

Exploratory biomarkers will be assessed in plasma.

Pharmacogenomics

Pharmacogenomic assessment may be performed on for drug metabolizing enzymes, transporters, or indicators of therapeutic response or safety. These assessments will only be performed where local regulations permit and where approved by the site's Institutional Review Board/Independent Ethics Committee (IRB/IEC), and will be subject to separate consent/assent by the patient/parent/legal guardian as appropriate.

STATISTICAL METHODS:

Power and Sample Size:

A total of 74 patients will provide approximately 80% power to detect a 3-point difference between treatment groups in the average change from Baseline scores from the PKAN-ADL, based on Student's t-test with alpha=0.05 (2-sided); this calculation assumes a standard deviation of 4.5 points for the change from Baseline scores. Additional patients will be randomized to ensure that at least 74 patients complete the double-blind period with evaluable data (ie, having assessments at Baseline and Week 24 for the PKAN-ADL).

Analysis Sets:

Safety Population:

Double-blind: The safety population will consist of all randomized patients who receive at least 1 dose of blinded investigational product. This population will be used for all summaries of patient accountability, demographic and Baseline data, and safety information, including AE incidence, for the double-blind period of the study.

Open-label: The safety population will consist of all patients who receive at least 1 dose of investigational product after entering the open-label period of the study. This population will be used for all summaries of patient accountability, demographic and Baseline data, and safety information, including AE incidence, for the open-label period of the study.

Full Analysis Set (FAS):

Double-blind: The FAS will consist of all randomized patients with at least 1 post-Baseline efficacy assessment. This population will serve as the basis for efficacy analyses from the double-blind period.

Open-label: The FAS will consist of all patients with at least 1 post-Baseline efficacy assessment in the open-label period of the study. This population will serve as the basis for efficacy analyses from the open-label period of the study.

Demographics and Baseline Characteristics:

Demographic data (including age, race, ethnicity, gender, height, and weight), PKAN-specific and other medical history, prior treatments, and pre-treatment clinical characteristics will be summarized by treatment group for the safety population.

Safety:

Safety analyses will be performed using data from the safety population. Safety will be evaluated on the basis of treatment-emergent AEs (TEAEs), vital signs, physical examinations, clinical laboratory assessments, C-SSRS assessments (in assessable patients), and ECG findings. Changes from Baseline in vital signs, weight, clinical laboratory values, and ECGs will be summarized by treatment group using descriptive statistics. All AEs will be coded by Preferred Term using the MedDRA classification dictionary. The incidence of TEAEs will be summarized by treatment group, and by severity and relationship to investigational product. Serious AEs (SAEs) and AEs leading to withdrawal from the study will be tabulated.

Pharmacokinetics:

Multiple-dose blood concentrations of fosmetpantotenate will be tabulated and summarized by dose cohort and sample time. Concentration measures may also be analyzed by nonlinear mixed-effects modeling, either alone or in conjunction with data from other studies. Available metabolite concentrations will be analyzed similarly. Summarizations will include appropriate descriptive statistics (eg, n, geometric mean, coefficient of variation, minimum, median, maximum).

Efficacy:

The primary efficacy analysis will be based on the FAS population defined for the double-blind period. For each patient, the change from Baseline in the PKAN-ADL score at Weeks 3, 6, 12, 18, and 24 of the double-blind period will be used for analysis. The treatment effect will be evaluated on the basis of mixed model repeated measures (MMRM) analysis using the restricted maximum likelihood method (REML). The model will be implemented using PROC MIXED in SAS, and will include fixed effects for treatment, age (pediatric/adult), visit and treatment-by-visit interaction, a random effect for patient, and Baseline PKAN-ADL score as a covariate. The PKAN-ADL measurement obtained prior to the first dose of investigational product will serve as each patient's Baseline value. Least-squares adjusted means and the adjusted mean difference between treatment groups will be reported at each study visit, along with 2 sided 95% confidence intervals (CIs) and the p-value for the treatment comparison. Additional sensitivity analyses will be performed to support the primary efficacy analysis.

Secondary and exploratory efficacy endpoints that are continuous measures will be evaluated using a similar mixed model for repeated measures or fixed-effect analysis of covariance, as appropriate. Summary statistics for efficacy measures will include graphical plots of means and mean change from Baseline values at each study visit, by treatment group. Treatment effects on categorical outcomes will be examined using frequency tables and tested via chi-square methods.

Biomarkers:

Biomarker assessments will be listed and summarized by time point using descriptive statistics (mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum) and graphical displays.

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Mean or mean change from Baseline (whichever is considered more relevant) plasma concentration-time profiles will be plotted on either or both linear and semi logarithmic scales. Inclusion/exclusion of the data in the calculations will be determined using an outliers test.

Interim Analysis:

The efficacy and safety analyses of the double-blind period of the study will be performed after all patients have completed the double-blind period and reported in an interim clinical study report. In addition, the interim report will include all available data from patients in the open-label period as of the data cutoff date.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations used throughout the protocol should not be used by the site when documenting AEs, medical history, etc. on source documents.

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALT	Alanine aminotransferase
AMR	Alternating motion rate
ANCOVA	Analysis of covariance
BAD	Barry Albright Dystonia scale
BID	Twice daily
CDISC	Clinical Data Interchange Standards Consortium
CGI-I	Clinician's Global Impression of Improvement
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CoA	Coenzyme A
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DBS	Deep brain stimulation
DDK	Diadochokinetic(s)
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D-3L	EuroQol, 5-dimension, 3-level QoL instrument
EQ-5D-Y	EuroQol-5D Youth Version
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FIM	Functional Independence Measure
GCP	Good Clinical Practice
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

Abbreviation	Definition
IWRS	Integrated web response system
LOCF	Last observation carried forward
MDS	Movement Disorder Society
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
NINDS	National Institute of Neurological Disorders and Stroke
NBIA	Neurodegeneration of the Brain with Iron Accumulation
OC	Observed case
PA	Pantothenate (vitamin B5)
PanK	Pantothenate kinase enzyme
PanK1	Pantothenate kinase 1 enzyme
PanK2	Pantothenate kinase 2 enzyme
PANK2	Pantothenate kinase 2 gene
PBMCs	Peripheral blood mononuclear cells
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PKAN	Pantothenate kinase-associated neurodegeneration
PKAN-ADL	Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living (scale)
PPA	Phosphopantothenic acid
QoL	Quality of life
REML	Restricted maximum likelihood (statistical method)
RTSM	Randomization and trial supply management
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SMR	Sequential motion rate
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TID	Three times daily
UPDRS	Unified Parkinson’s Disease Rating Scale
US	United States
WeeFIM	Functional Independence Measure for Children

4. INTRODUCTION

Pantothenate kinase associated neurodegeneration (PKAN), the most common form of Neurodegeneration with Brain Iron Accumulation (NBIA), is a progressive, often fatal, neurodegenerative disease estimated to affect 1 to 3 individuals per million people (Freeman, 2007). PKAN is an autosomal recessive genetic disorder caused by mutations in the pantothenate kinase2 gene (*PANK2*), resulting in defective pantothenate (PA, vitamin B5) metabolism. *PANK2* encodes pantothenate kinase 2 (PanK2), a regulatory enzyme that phosphorylates pantothenate as a key step in coenzyme A (CoA) biosynthesis. Defective PanK2 enzymes, which are localized primarily in mitochondria (Alfonso-Peccio, 2012; Balibar, 2011; Hörtnagel, 2003; McGuigan, 1996) in humans, are postulated to result in decreased concentrations of CoA in selectively vulnerable human tissues including brain. The majority of PKAN patients are diagnosed in the first 10 years of life, and affected children usually lose the ability to walk within 10 to 15 years after disease onset (Gregory, 2009). Early mortality is typically caused by disease-associated sequelae such as malnutrition or aspiration/pneumonia (Gregory, 2009). Clinical manifestations of PKAN include developmental delay in children, parkinsonism with Parkinson's-like freezing and bradykinesia, dystonia sometimes causing intractable pain, choreoathetosis, status dystonicus, dysarthria, spasticity, rigidity, and dysphagia often leading to feeding tube placement (Gregory, 2009; Gregory, 2004; Klopstock, 2005; Kruer, 2015). Age of onset does not seem to correlate with rate of progression; some patients progress rapidly to death within a few years, and others may live into their 30s to 50s with more slowly progressive symptoms of neurodegeneration (Gregory, 2009). All patients with PKAN experience significant morbidity and, eventually, severe functional impairment. The initial diagnosis of PKAN is often suggested by magnetic resonance imaging of the brain showing the near pathognomonic "eye-of-the-tiger" sign produced by disease-associated iron accumulation (Gregory, 2013), and confirmed by genetic testing (Gregory, 2009; Kruer, 2015). The diagnosis must be confirmed through genetic testing and identification of a *PANK2* mutation.

There are currently no approved disease-modifying treatments for patients with PKAN. A range of treatments are used to manage the dystonia and parkinsonism, as well as neuropsychiatric symptoms of PKAN, which are described in the literature as transiently effective (Kruer, 2015). These treatments include oral medications, injectables, and surgical interventions. Exploratory trials have been conducted with mixed results to date with Deep Brain Stimulation (DBS), baclofen (given orally or intrathecally), and deferiprone, an iron chelating agent. Deferiprone is currently being studied in a Phase 3 clinical trial.

Fosmetpantotenate (RE-024) is a phosphopantothenic acid (PPA) precursor designed to deliver PPA, the product of pantothenate kinase (PanK), to cells. Systemic administration of the product of PanK, 4' phosphopantothenic acid, is not effective since it does not cross cell membranes (Balibar, 2011). Fosmetpantotenate is designed to be metabolized intracellularly to PPA, becoming a substrate to downstream enzymes in the same manner as endogenously produced PPA, thus restoring CoA levels.

Retrophin (the Sponsor) is developing fosmetpantotenate as a potential phosphopantothenate replacement therapy for the treatment of PKAN. Primary pharmacodynamic studies indicate that fosmetpantotenate effectively delivers PPA to enzymes downstream of PanK2, the defective enzyme in PKAN. In vitro, CoA concentrations were increased in pantothenate kinase 1

knockout (Pank1-/-) mouse embryonic fibroblasts incubated with fosmetpantotenate at 200 µM. In vivo, single intraperitoneal or oral doses of fosmetpantotenate at 1.2 µmole/g increased CoA concentrations in the liver of Pank1-/- mice to levels comparable to or higher than that in wild-type mice. In contrast, neither PA nor PPA increased CoA in these in vitro and in vivo models. This result was expected due to the lack of pantothenate kinase 1 (PanK1) enzyme in Pank1-/- mice to convert PA to PPA intracellularly and the fact that PPA is not expected to cross the cell membrane. These data support evaluation of fosmetpantotenate for treatment of PKAN.

This clinical study will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of fosmetpantotenate in patients with PKAN.

4.1. Summary of Potential Risks

This section discusses data available at the time of this protocol revision. For further information and details concerning warnings, precautions, and contraindications, the Investigator should refer to the appropriate section of the fosmetpantotenate Investigator's Brochure (IB).

4.1.1. Fosmetpantotenate (RE-024) Non-Clinical Studies

A pivotal 28-day repeat-dose toxicity study was conducted in rats given twice daily oral doses of neat fosmetpantotenate at 125, 375, 1000 mg/kg/dose (250, 750, or 2000 mg/kg/day). Fosmetpantotenate-related adverse effects consisted of decreased body weight gain and increased alanine aminotransferase (ALT) in males and hepatocellular necrosis in both sexes at 2000 mg/kg/day, and squamous epithelium hyperplasia with occasional associated erosion/ulceration, hyperkeratosis, and/or inflammation in the stomach at 750 and 2000 mg/kg/day. All other fosmetpantotenate-related changes, including infiltrates of macrophages (often vacuolated) in various tissues, were not considered adverse or secondary to adverse gastric lesions.

A 90-day repeat-dose toxicity study was conducted in rats given twice daily oral doses of fosmetpantotenate at 125, 300, 625 mg/kg/dose (250, 600, or 1250 mg/kg/day). Fosmetpantotenate-related adverse effects consisted of panlobular hepatocellular hypertrophy, individual hepatocellular necrosis, hepatocellular vacuolation, bile duct hypertrophy, and/or vacuolated macrophages coupled with increased ALT in both sexes at ≥1250 mg/kg/day.

Two pivotal 7-day repeat dose oral toxicity studies were conducted in monkeys. Gastrointestinal disturbances evidenced by emesis, inappetence, soft/watery feces, and body weight loss were observed in both control and fosmetpantotenate-treated animals in both studies. In the second study, generalized lymphoid depletion in thymus was observed in both sexes, and thymus weights were decreased in males. Infiltrates of macrophages, frequently vacuolated, and occasionally accompanied by minimal to mild subacute/chronic inflammation, were observed in various tissues in monkeys at 700 mg/kg/day.

A pivotal 28-day repeat dose toxicity study was conducted in monkeys given twice daily oral doses of neat fosmetpantotenate at 100, 200, 350 or 1000 mg/kg/dose (200, 400, 700, or 2000 mg/kg/day). Two females at the 2000 mg/kg/day dose became moribund after the first dose on Day 2 and were euthanized. Adverse changes in albumin (18% decrease), sodium (2.6% decrease), and globulin (15% increase) at 1250 mg/kg were considered secondary to inflammatory or gastrointestinal effects. Fosmetpantotenate-related adverse pathologic changes

were limited to stomach ulceration at 1250 mg/kg/day, and red focus/foci and stomach ulceration at 2000 mg/kg/day in the animals that were moribund and euthanized.

For further details, refer to the fosmetpantotenate IB, which contains comprehensive information on non-clinical studies.

4.1.2. Fosmetpantotenate (RE-024) Clinical Studies and Other Use

In 2 Phase 1 studies of fosmetpantotenate (Study 024HVOL14004 and Study 024HVOL15008), single oral doses up to 3600 mg were safe and well tolerated in healthy adult volunteers, and no serious adverse events (SAEs) were reported. In the first study, which included fosmetpantotenate doses from 75 mg to 1800 mg (024HVOL14004), all AEs were mild in severity. Of the subjects who received fosmetpantotenate, 11/30 (36.7%) experienced 15 AEs, 10 of which were considered to be possibly related to the investigational product. Of these 10 AEs, 7 were related to taste (product taste abnormal); the remaining 3 AEs considered possibly related to investigational product included 1 event each of hiccups, throat irritation, and diarrhea. One AE of increased creatinine level uncertain etiology possibly dehydration (preferred term 'dehydration'), was initially considered possibly related. The safety review committee concluded that this AE was likely explained by dehydration due to reduced fluid intake. The sponsor assessed this AE as unlikely related to study drug.

In the second study (Study 024HVOL15008), which included fosmetpantotenate doses of 1800 mg and 3600 mg, 6 of 14 subjects (43%) receiving fosmetpantotenate experienced 14 AEs. One subject who received 1800 mg fosmetpantotenate reported 1 AE (abdominal discomfort) that was mild in severity and considered possibly related/related to investigational product. The remaining 13 AEs were reported in 4/8 (50%) subjects who received 3600 mg fosmetpantotenate. Of these 13 AEs, 11 were considered possibly related/related to the investigational product. These AEs included nausea (3 events); vomiting, dizziness, and headache (2 events each); and tremor and chills (1 event each). One event of vomiting was considered moderate in severity, and the remaining AEs were considered mild in severity. Thus, 3600 mg, which resulted in 1 moderate AE of vomiting and additional mild AEs in 3 other subjects, is considered the maximum tolerated dose.

In a Phase 1 food effect study (024HVOL15007) of the proposed clinical dose of 300 mg fosmetpantotenate in 29 adult subjects, the dose was safe and well-tolerated when given under either fasted or fed conditions; there were no SAEs, all AEs were mild in severity, and all AEs resolved by the end of the study. The 3 AEs considered possibly or probably related to drug included 1 AE (nausea) in the fed state, and 2 AEs (dizziness and headache) in the fasted state.

Across these 3 studies, no clinically meaningful findings were seen in the safety parameters evaluated.

In an uncontrolled, compassionate-use setting, transient, reversible transaminase elevations were reported by the treating physician in one patient receiving 240 mg/day but have not recurred to date in this patient upon gradual re challenge up to 210 mg/day. In the current study, patients undergo a medical evaluation (including an abdominal examination) at each visit. Signs or symptoms of gastrointestinal-related adverse effects will be evaluated medically as appropriate, which may, for example, include gastroscopy to evaluate for evidence of gastric erosion.

Other potential risks include lack of improvement while taking investigational product and/or worsening of PKAN signs and symptoms throughout the study.

4.2. Summary of Potential Benefits

It is hypothesized that treatment with fosmetpantotenate may improve signs and symptoms of PKAN and stabilize disease progression; however, it is unknown whether patients will see improvements in signs and symptoms of PKAN as a result of participating in this study.

5. STUDY OBJECTIVES

5.1. Efficacy Objective

The efficacy objective of this study is to evaluate the efficacy of fosmetpantotenate over 24 weeks in patients with PKAN.

5.2. Safety Objective

The safety objective of the study is to assess the safety and tolerability of fosmetpantotenate in patients with PKAN.

5.3. Other Objectives

Other objectives are:

- To determine the PK following multiple doses of fosmetpantotenate in patients with PKAN
- To explore potential biomarkers of disease, along with their potential response to treatment in patients with PKAN

6. INVESTIGATIONAL PLAN

6.1. Endpoints

6.1.1. Primary Efficacy Endpoint

The Unified Parkinson's Disease Rating Scale (UPDRS) is a comprehensive assessment of the burden and severity of signs and symptoms of parkinsonism captured via systematic interview and neurological examination. It has established clinimetric properties, with high internal consistency, very high correlation between the original UPDRS and the modified version (ie, the Movement Disorder Society- [MDS] UPDRS) (0.96), and a reliable factor structure (Goetz, 2008; Martinez-Martin, 2013). The UPDRS also correlates with other widely accepted measures of disability (Goetz, 2012). The UPDRS consists of 4 parts that can be used as individual scales or summed for a total score (Goetz, 2008).

Part II of the UPDRS is an in-depth health outcomes assessment of motor activities of daily living that are impaired by a wide range of neurological diseases, including PKAN. For this study, Part II of the UPDRS has been adapted to be optimally relevant to PKAN through a systematic revision involving experts, patient advocacy leaders, and regulatory interaction; it will serve as the primary efficacy endpoint and will be referred to in this protocol as the "Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living" scale, abbreviated as PKAN-ADL.

Thus, the primary efficacy endpoint for this study will be the change in the score from the PKAN-ADL, from Baseline to the end of the 24-week double-blind period.

6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoint will be the change in the score from Part III of the UPDRS from Baseline to the end of the 24-week double-blind period.

6.1.3. Safety Endpoints

The safety and tolerability of fosmetpantotenate will be assessed throughout the study by monitoring the occurrence of AEs and by serial vital signs, physical examinations, clinical laboratory parameters (chemistry, hematology, coagulation, and urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS) assessments (in assessable patients), and 12-lead electrocardiograms (ECG).

AEs will be classified as mild, moderate, or severe. The definitions of mild, moderate, and severe were developed from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard terminology v3.1.1. See Section 10.4.2 for definitions.

6.1.4. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will include change from Baseline to the end of the 24-week double-blind period in the following:

- Clinician Global Impression of Improvement (CGI-I)
- Barry Albright Dystonia (BAD) scale

- Quality of life (QoL):
  - Neuro-QoL, upper and lower extremity modules (adult and pediatric versions)
  - EuroQol 5-dimension, 3 level QoL instrument (EQ-5D-3L)/EuroQol-5D Youth Version (EQ-5D-Y)
- Functional independence: Functional Independence Measure (FIM)/Functional Independence Measure for Children (WeeFIM)
- Function measures:
  - Ambulation: 25-foot walk test (in appropriate patients)
  - Speech: Diadochokinetic (DDK) assessments (ie, alternating motion rate [AMR] and sequential motion rate [SMR])

6.1.5. Pharmacokinetic Endpoint

Multiple dose PK of fosmetpantotenate in whole blood will be evaluated using a sparse sampling design. Blood samples may also be used for metabolite quantification and/or identification.

6.1.6. Biomarkers

Exploratory biomarkers will be assessed in plasma. Potential biomarkers assessed may include succinate, lactate, maleate, pyruvate, alanine, acetone, acetoacetic acid, 3-hydroxybutyric acid, 2-hydroxybutyric acid, and acetylCoA. Although other biomarkers may be assessed, the samples will not be used for genetic testing.

6.1.7. Pharmacogenomics

Pharmacogenomic assessment may be performed on for drug metabolizing enzymes, transporters, or indicators of therapeutic response or safety. These assessments will only be performed where local regulations permit and where approved by the site's Institutional Review Board/Independent Ethics Committee (IRB/IEC), and will be subject to separate consent/assent by the patient/parent/legal guardian as appropriate.

Samples intended for pharmacogenomic (PGx) analyses will be collected at study sites. PGx sample analyses will be limited to variations that affect drug absorption, distribution, metabolism, and excretion (ADME), therapeutic response, or drug safety. Upon completion of the clinical phase of the study, pharmacokinetic (PK) data will be assessed. Pursuant to that assessment, PGx analyses will be performed, guided by, and as indicated by the PK analyses, and as informed by pre-clinical data. If PK analyses do not indicate the need for PGx, samples will be destroyed without analyses.

6.2. Study Design

This is a pivotal, randomized, double-blind, placebo-controlled, multi-center, 2-arm study evaluating 24 weeks of treatment with fosmetpantotenate or placebo in patients with PKAN aged 6 to 65 years, with a 278-week open-label extension.

Following screening, patients meeting all eligibility criteria will be enrolled in the study. Patients will be randomized in a 1:1 ratio to receive either fosmetpantotenate or placebo for a 24-week double-blind period. Treatment in the double-blind period will begin with dose

escalation for Days 1 through 3, followed by the full dose 3 times daily (TID) starting on Day 4. Matching placebo will be given according to the same dose escalation sequence as active investigational product (see Section 6.5.2). For patients 6 to <18 years, the daily dose patients receive will be based on their weight at the Screening visit and will not be changed due to changes in patient weight during the double-blind period.

After completing the double-blind period, patients will be eligible to receive open-label fosmetpantotenate in the study for up to 278 weeks followed by a phone safety review 4 weeks later. The total study duration will be approximately 310 weeks. If the product becomes commercially available during the extension period, patients may transition to commercial product before the end of the extension period.

After 8 patients aged 18 to 65 years complete 3 weeks of study treatment in the double-blind period, the independent Data Monitoring Committee (DMC) will review safety data to determine whether the study can continue as planned, including initiating enrollment of patients aged 6 to <18 years. Enrollment of patients 18 to 65 years of age (only) will continue while this review is occurring. If the DMC determines it is safe to continue the study, enrollment of patients 6 to <18 years of age will begin, and enrollment of patients 18 to 65 years of age will continue. Similarly, after the first 8 patients aged 6 to <18 years complete 3 weeks of study treatment in the double-blind period, the DMC will review the safety data from all patients to date and determine whether the study can continue as planned. Enrollment of patients 18 to 65 years of age and up to 8 additional patients aged 6 to <18 years of age may continue while this review is occurring. If the DMC determines it is safe to continue the study, enrollment of patients 6 to 65 years of age will continue.

Screening will take place within 29 days prior to the start of the double-blind period. Patients who fail screening for any reason may be re-screened up to 2 times. The protocol allows PKAN patients to be considered for participation three times (1 screening + 2 re-screening). If a given patient fails to qualify based on eligibility criteria, but the Investigator believes that this reason for non-qualification is a temporary situation, the patient can be screened a second time and a third time to determine whether he or she qualifies. Examples of such a situation include but are not limited to:

1. Abnormal labs suggestive of treatable, temporary abnormalities such as infection, anemia, dehydration, etc.
2. The patient had a major surgery within 30 days of screening, or DBS implantation within 6 months.
3. The patient has taken deferiprone within 30 days of screening.
4. The patient's symptoms are too mild to qualify with a PKAN-ADL Score < 6, but unfortunately it is possible that the disease will progress during the course of the trial enrollment such that the patient might qualify at a later date.

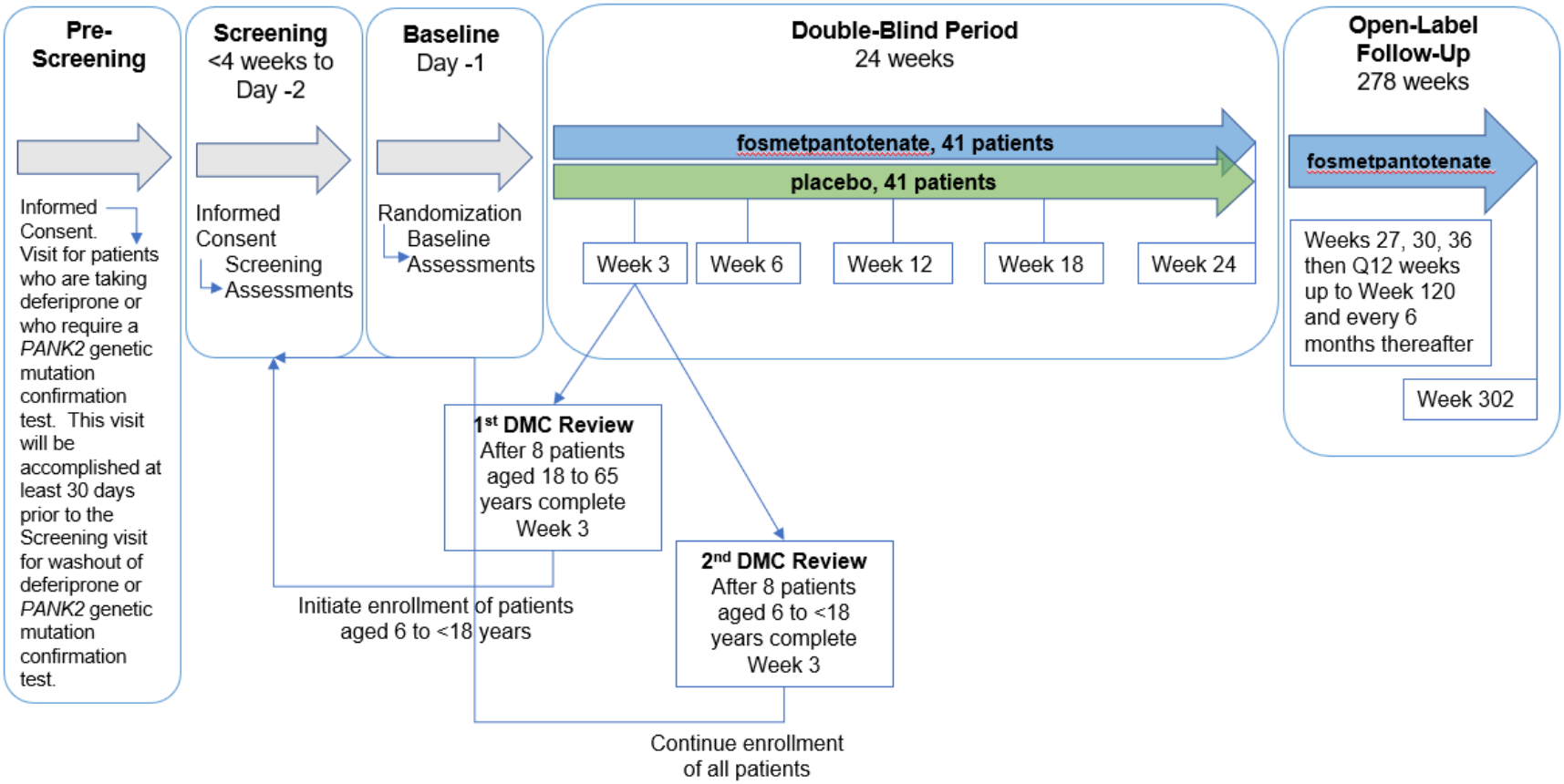
Assessment visits will occur at Baseline (Day -1), Days 1 through 4, and Weeks 3, 6, 12, 18, and 24. Patients may be admitted to an inpatient facility for safety monitoring from Baseline through completion of the Day 4 assessments for the double-blind period, or may be followed closely in a nearby outpatient setting. In order to provide training in proper administration, investigational product will be prepared and administered by site personnel, together with the patient and/or

family/caregiver, during in-clinic patient visits. Following adequate training, doses may be self-administered by the patient or caregiver at the site's discretion.

After the 24-week double-blind period, patients will receive fosmetpantotenate open-label for an additional 278 weeks. During the open-label period, assessment visits will occur at Weeks 27, 30, 36, 48, 60, 72, 84, 96, 108, and 120 and every 26 weeks thereafter (W146, W172, W198, W224, W250, W276, and W302). If the investigator determines that more frequent visits should occur after W120, additional unscheduled visits can be performed. Three-month (every 13 weeks) safety phone calls will be made in between each 6-month onsite visit following Week 120.

Flow charts depicting the study are presented in Figure 1 and Figure 2.

Figure 1: Study 024PKAN15004 Overview Flow Chart



AE = adverse event; PKAN-ADL = Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living (scale)

Note: Three-month (every 13 weeks) safety phone calls will be to assess PKAN-ADL, AEs, and Concomitant Medications in between each 6-month onsite visit following W120.

Figure 2: Study 024PKAN15004 Study Visits in Double-Blind and Open-Label Periods

A. Double-Blind Period

	Pre-Screening[1]	Screening	Baseline	Inpatient Blinded Treatment[2]				Blinded Treatment				
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Day/ Week		Days -29 to -2	Day -1 (Randomization)	D1	D2	D3	D4	W3 ± 3D	W6 ± 3D	W12 ± 3D	W18 ± 3D	W24 ± 3D

[1] For patients who are taking deferiprone or who require a *PANK2* genetic mutation confirmation test. This visit will be accomplished at least 30 days prior to the Screening visit for washout of deferiprone or *PANK2* genetic mutation confirmation test.
[2] Alternatively, patients may be followed closely in a nearby outpatient setting.

B. Open-Label Period

Visit	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22-V28[1]
Study Week	W27 ± 7D	W30 ± 7D	W36 ± 7D	W48 ± 7D	W60 ± 7D	W72 ± 7D	W84 ± 7D	W96 ± 7D	W108 ± 7D	W120 ± 7D	W146, W172, W198, W224, W250, W276, W302 ± 7D

AE = adverse event; PKAN-ADL = Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living (scale)

[1] Three-month (every 13 weeks) safety phone calls will be to assess PKAN-ADL, AEs, and Concomitant Medications in between each 6-month onsite visit following W120.

6.3. Completion of a Patient's Participation in the Study and Overall Study Completion

6.3.1. Completion of a Patient's Participation in the Study

Each patient will participate in the study for approximately 4 weeks during the screening phase, followed by 24 weeks of double-blind treatment and 278 weeks of open-label treatment. At the end of the open-label treatment period, study medication will be discontinued, and patients will be contacted by phone for a safety review 4 weeks later. Thus, patients will participate for a total of approximately 310 weeks.

A patient will be considered as having completed the study, regardless of whether the patient is on or off study medication, if the patient is followed until Week 302 or if rolled off early onto commercial product, whichever happens first. Patients who successfully complete the study will complete the Week 302 assessments listed in the schedule of events (Section 15.1). The visit

data, including final disposition of the patient, will be recorded on the End of Treatment /Early Termination electronic case report form (eCRF).

6.3.2. Overall Study Completion

The study will be considered complete when the last patient completes his/her final visit.

6.3.3. Premature Discontinuation from the Study

In general, patients should be encouraged to both stay on study medication and remain in the study until study termination/completion. However, patients or their parents/guardians are free to withdraw consent/assent and/or discontinue the patient's participation in the study at any time, without prejudice to subsequent standard of care treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or the Sponsor.

Reasons for premature discontinuation from the study may include:

- Death
- Voluntary withdrawal of patient/guardian assent/consent (complete withdrawal of consent requires a patient's/parent's/guardian's refusal of ALL methods of follow-up noted in the informed consent form: procedures, participation in reduced procedures/study visits, telephone/alternative contact only, source document or designated alternative contact, or access to medical records from alternative sources)
- Termination of the study by the Sponsor, or any regulatory authorities (see Section 13.4.5)
- Lost to follow-up
    - The Investigator must make every effort to contact patients who fail to return for scheduled visits so that they will not be declared "lost to follow-up."
    - Patients will be considered "lost to follow-up" only after reasonable, documented attempts to reach the patient prove unsuccessful. "Reasonable" is defined as at least 3 phone calls and a certified letter. This information and dates of attempted contact must be recorded in the patient's source documents.

A patient who chooses to not continue regularly scheduled study visits (ie, withdraws consent) will complete the Early Termination assessments listed in the schedule of events (Section 15.1) as close as possible to the patient's last dose of study medication. The visit data, including the primary reason for premature discontinuation from the study, will be recorded on the Early Termination eCRF. Post-study SAEs will be reported according to Section 10.5.2.

Decisions to prematurely discontinue patients from the study will be reviewed by the Investigator, the Medical Monitor, and the Sponsor.

6.4. Discussion of Study Design, Including Choice of Control Group

The heterogeneity of signs, symptoms, and key phenotypic features (eg, age at onset, rate of progression, and survival duration) in patients with PKAN is a critical consideration in designing a clinical study for this disease. Placebo-control is necessary to control for variability in disease

severity and rate of progression. A randomized, placebo-controlled, parallel design study allows for a balanced distribution of uncontrolled variables across randomized groups, and a rigorous assessment of true drug effects on the outcome variables, controlling for nonspecific effects.

Demonstration of a clinically meaningful treatment effect over a 24-week period is sufficient to establish fosmetpantotenate as safe and efficacious for the treatment of PKAN, as there are no effective treatments available to date for this debilitating disease. The double-blind period of the trial will evaluate the efficacy of fosmetpantotenate in improving signs, symptoms, and functioning in patients with PKAN, and the safety extension will evaluate whether these improvements are generally maintained during an open-label treatment period that aims to simulate more real-world therapeutic conditions (eg, concomitant medications, which are fixed during the 24-week double-blind period, may be adjusted during the open-label extension based on medical judgment).

6.5. Dosing Considerations

Investigational product will be prepared and administered by site personnel, together with the patient and/or family, during in-clinic patient visits in order to provide training in proper administration. Following adequate training, doses may be self-administered by the patient or caregiver at the site's discretion.

All investigational product should be taken with food. If necessary, investigational product may be given through a feeding tube.

Details regarding dosing can be found in the study manuals.

6.5.1. Dose Selection Rationale

A dose of 900 mg fosmetpantotenate daily, administered as 300 mg TID with food, will be used in this study for adult patients (18 and older) and pediatric patients weighing 40 kg or more.

Two lower dose strengths will be used for pediatric patients weighing less than 40 kg. For pediatric patients weighing at least 20 kg but less than 40 kg, a dose of 450 mg daily, administered in 3 equally divided doses of 150 mg (TID) with food, will be used. For pediatric patients weighing less than 20 kg, a dose of 225 mg daily, administered in 3 equally divided doses of 75 mg (TID) with food, will be used.

In the Phase 1 healthy adult volunteer studies (Studies 024HVOL14004, 024HVOL15007, and 024HVOL15008), fosmetpantotenate was safe and well tolerated at single oral doses up to 1800 mg, with no identifiable dose-related safety findings (see also Section 4.1). A dose of 3600 mg was associated with mostly mild gastrointestinal AEs. Administration of 300 mg fosmetpantotenate with a high-fat meal resulted in greater exposure and longer overall exposure time, without an increase in maximum fosmetpantotenate concentration (C_{max}).

PKAN is characterized by a large number of genotypic mutations of the *PANK2* gene that have an unclear relationship with phenotypic manifestations. Earlier-onset, rapidly progressive PKAN may be associated with decreased functionality of the PanK2 enzyme (Hartig, 2006); thus, higher doses than those used to date in patients with PKAN may be required in some patients to produce a treatment effect. A dose of 300 mg TID with food (900 mg daily), is therefore being used in

this study. The 300 mg dose was safe and well tolerated in both fed and fasted states in a Phase 1 food effect study.

Single-dose data from the Phase 1 studies also showed the absence of a relationship between blood exposure and any safety related signal until a dose of 3600 mg was used; additionally, no SAEs were reported in the studies. Therefore, of primary practical importance for this pivotal study was the selection of a dose that will be safe in pediatric patients, while showing efficacy for as many of these patients as possible.

The overall safety profile of fosmetpantotenate to date suggests that a weight-based pediatric dosing strategy, which facilitates ease of use for patients and their caregivers, is medically reasonable.

The mean weight for a normal 11 ½- to 12-year-old in the United States (US) is approximately 40 kg (Kuczmarski, 2002). However, patients under the age of 12 years, as well as adolescent patients who are underweight due to developmental delay or other nutritional and metabolic effects of PKAN, are likely to weigh less than 40 kg. In addition, patients ages 6 or older will be enrolled in this trial, who will likely also weigh less than 40 kg. Thus, for pediatric patients weighing less than 40 kg but at least 20 kg, the 900 mg daily dose (300 mg TID) will be reduced by 50% to 450 mg daily (150 mg TID). For the few pediatric patients weighing <20 kg, the dose will be reduced by an additional by 50% to 225 mg daily (75 mg TID). The conservative dosing approach outlined here reduces the daily fosmetpantotenate dose by approximately 2-fold relative to adults in children weighing less than 40 kg, and an additional 2-fold in children weighing less than 20 kg.

6.5.2. Dose Initiation

6.5.2.1. Double-Blind Period

The double-blind period will begin with dose escalation for Days 1 through 3, followed by the full dose (TID) starting on Day 4. Dose escalation on Days 1 through 3 will proceed as follows, based on the patient's age and weight at screening:

Patients aged 18 to 65 years and patients aged 6 to <18 years weighing ≥40 kg: On Day 1, patients will receive one 300 mg dose (in the morning); on Days 2 and 3, they will receive 300 mg twice daily (BID, at least 8 hours apart) for a total daily dose of 600 mg; and on Day 4, they will receive the full dosage of 300 mg TID (given at approximately 8 hour intervals) for a total daily dose of 900 mg.

Patients aged 6 to <18 years weighing ≥20 kg but <40 kg: On Day 1, patients will receive one 150 mg dose (in the morning); on Days 2 and 3, they will receive 150 mg BID (at least 8 hours apart) for a total daily dose of 300 mg; and on Day 4, they will receive the full dosage of 150 mg TID (given at approximately 8 hour intervals) for a total daily dose of 450 mg.

Patients aged 6 to <18 years weighing <20 kg: On Day 1, patients will receive one 75 mg dose (in the morning); on Days 2 and 3, they will receive 75 mg BID (at least 8 hours apart) for a total daily dose of 150 mg; and on Day 4, they will receive the full dosage of 75 mg TID (given at approximately 8 hour intervals) for a total daily dose of 225 mg.

6.5.2.2. Open-Label Period

Patients will receive open-label fosmetpantotenate after they complete the double-blind period of the study. No dose escalation is required for the open-label period. All patients (regardless of randomization assignment for the double-blind period) will initiate treatment with fosmetpantotenate in the open-label period according to the dose of study medication they were receiving at the end of the double-blind period; for patients 6 to <18 years of age, the initial dose may be adjusted, if needed, based on the patient's weight at the end of the double-blind period.

For patients 6 to <18 years of age, the dose will be adjusted as needed during the open-label period based on their weight taken at study visits every 24 weeks.

6.5.3. Dose Modification

Elective dose reductions for safety or tolerability reasons only are allowed, and only 1 time, throughout the first 6 weeks of the double-blind period of the study, according to the following schedule:

- Patients 18 to 65 years of age or 6 to <18 years of age and weighing ≥40 kg: the 300 mg TID dose may be reduced to 150 mg TID
- Patients 6 to <18 years of age and weighing ≥20 kg but <40 kg: the 150 mg TID dose may be reduced to 75 mg TID
- Patients 6 to <18 years of age and weighing <20 kg: the 75 mg TID dose may be reduced to 75 mg once daily

Patients who are unable to tolerate the reduced dose will be discontinued from treatment. The Investigator should attempt to increase the dose back to the patient's assigned fixed dose as safety and tolerability allow.

Once patients have been treated in the open-label period for at least 24 weeks, and after the second DMC review has occurred, dose increases of 1 level will be allowed for perceived lack of efficacy. Dose increases will only be allowed following consultation between the Investigator, the Medical Monitor, and the Sponsor, and only to the maximum dosage of 300 mg TID. Elective dose reductions for safety or tolerability reasons only are allowed, and only 1 time, throughout the first 6 weeks of the open-label period of the study.

Fosmetpantotenate will not in any case be used as a rescue medication.

6.5.4. Interruption and Discontinuation of Study Medication

6.5.4.1. Temporary Interruption of Study Medication

Patients who temporarily interrupt prior to completion of the study, will continue with study visits and assessments according to the schedule of study events (Section 15.1). Unless contraindicated, treatment should be resumed whenever possible (including between visits), and treatment resumption should be considered at every visit following study medication interruption. If the patient's dose was reduced prior to the temporary interruption, the study medication should be resumed at the reduced dose and the Investigator should attempt to increase the dose back to the patient's assigned fixed dose as safety and tolerability allow.

6.5.4.2. Permanent Discontinuation of Study Medication

A patient's investigational product may be discontinued at any time at the patient's/parent's/legal guardian's request or at the discretion of the Investigator, the Medical Monitor, or the Sponsor. Justifiable reasons for the Investigator or the Sponsor to discontinue a patient from treatment may include, but are not limited to:

- The patient experiences any AE, clinically significant laboratory abnormality, or intercurrent illness, or other medical condition that indicates to the Investigator that continuation on study medication is not in the best interest of the patient (adverse event).
- A significant protocol violation (ie, patient failed to meet entry criteria or did not comply with protocol requirements resulting in an unacceptable risk to the patient's health) (protocol deviation).
- Noncompliance with study medication (non-compliance with study drug).
- Patient or parent/legal guardian decision to stop study medication (withdrawal by parent/guardian).
- Investigator discretion (physician decision).
- The patient participates in another investigational study without the prior written authorization of the Sponsor or its designee (protocol deviation).
- The patient becomes pregnant (pregnancy); study medication must be discontinued immediately once the patient becomes aware of the pregnancy and the investigator must be notified of the pregnancy (pregnancy) (see also Section 10.6, Pregnancy Reporting).
- The patient's concomitant PKAN maintenance medications/therapies are adjusted during the double-blind period (protocol deviation).
- Patient is lost to follow-up (lost to follow-up).

Decisions to prematurely discontinue patients from study medication should be reviewed by the Investigator, the Medical Monitor, and the Sponsor.

Patients who permanently discontinue study medication early should be encouraged to continue study visits through Week 120 for continued collection of safety and efficacy data despite stopping study medication, but may withdraw consent at any time (see Section 6.3.3). Patients who agree to continue regularly scheduled study visits will complete the End of Treatment assessments listed in the schedule of events (Section 15.1) as close as possible to the patient's last dose of study medication. The visit data, including the primary reason for discontinuation of study medication, will be recorded on the End of Treatment eCRF. Subsequent study visit data will be recorded on the visit-specific eCRF, and the patient's final study visit will be recorded on the End of Treatment/Early Termination eCRF.

For patients who permanently discontinue study medication, the Investigator should resume standard of care treatment, including treatment with appropriate medications, as deemed necessary.

7. PATIENT POPULATION AND SELECTION

7.1. Inclusion Criteria

A patient will meet all of the following criteria to be eligible for this study.

1. The patient or parent/legal guardian (as appropriate) is willing and able to provide signed informed consent, and where required, the patient is willing to provide assent.
2. The patient has a diagnosis of PKAN as indicated by a confirmed mutation in the *PANK2* gene (if available, the specific mutation will be recorded).
3. The patient has a score of ≥6 on the PKAN-ADL scale.
4. The patient is male or female aged 6 to 65 years, inclusive.
5. If sexually active with male partners, the female patient of childbearing potential agrees to use a medically acceptable method of contraception for the duration of the study and for at least 30 days after the last dose of investigational product. Females are considered of childbearing potential if they are post-menarchal, have not been surgically sterile for at least 6 weeks (ie, total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) and are pre-menopausal (menopause is defined as cessation of menstruation for at least 1 year). Acceptable methods of contraception include:
   A. the simultaneous use of stable combined (estrogen and progestogen containing) or progestogen-only hormonal contraception (eg, oral, transdermal or intravaginal) associated with inhibition of ovulation in conjunction with a double-barrier method (eg, condom with spermicide or diaphragm with spermicide), or;
   B. the use of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) in place for at least 3 months or;
   C. vasectomised partner (vasectomy at least 3 months prior to screening), or;
   D. sexual abstinence
6. If sexually active with female partners, the sexually mature, nonsterile male patient agrees to use a medically acceptable method of contraception for the duration of the study and for at least 90 days after the last dose of investigational product. Males are considered surgically sterile if they have undergone bilateral orchiectomy or vasectomy at least 3 months prior to screening. Acceptable methods of contraception include:
   A. the simultaneous use of stable combined (estrogen and progestogen containing) or progestogen-only hormonal contraception (eg, oral, transdermal or intravaginal) associated with inhibition of ovulation by the female partner in conjunction with a double-barrier method (eg, condom with spermicide or diaphragm with spermicide), or;
   B. the female partner's use of an IUD or IUS in place for at least 3 months, or;
   C. the female partner is surgically sterile for at least 6 weeks or is at least 1 year postmenopausal.

7. The male patient agrees to not donate sperm for at least 90 days after the last dose of investigational product.

7.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has required regular or intermittent invasive ventilatory support to maintain vital signs within 24 weeks prior to randomization.
2. The patient has been (or is currently) enrolled in a clinical trial involving an investigational product or non-indicated use of a drug or device within 30 days prior to randomization.
3. The patient has a positive serologic test for Hepatitis B virus surface antigen (HBsAg), Hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) at screening.
4. The patient has a history of metastasized or ongoing malignancy regardless of whether or not it has been or is being treated.
5. The patient has a serious, unstable medical or psychiatric condition not related to PKAN that, in the opinion of the Investigator, could interfere with the patient's ability to participate in the study safely or to complete the scheduled study assessments, or that would confound the assessment of safety or efficacy.
6. The patient has a history of drug or alcohol use disorder within the past 1 year.
7. The patient has a history of suicide attempts within the past 1 year or is considered by the Investigator to be at imminent risk of suicide.
8. The patient has had a major surgical procedure within 30 days prior to screening.
9. The patient has had a deep brain stimulation (DBS) device implanted within 6 months prior to screening.
10. The patient has abnormal laboratory values at screening that, in the opinion of the Investigator, are clinically significant, and would compromise the safety of the patient during study participation.
11. The patient is a female who is pregnant or lactating, or who presents with a positive serum pregnancy test at screening, or a positive urine pregnancy test at Baseline.
12. The patient is unwilling or, in the opinion of the Investigator, is unable to adhere to the requirements of the study, including study procedures and the visit schedule.
13. The patient is unable or unwilling to remain on their pre-study dose(s) of allowed concomitant PKAN maintenance medications and therapies (including DBS settings) for the double-blind period of the study. (See Section 8.3 of the protocol for discussion of concomitant medication/treatment use during the study, and Section 15.2.1 for a list of allowed concomitant medications and therapies.)
14. The patient has taken deferiprone within 30 days prior to screening.

Patients who do not meet eligibility criteria may be re-screened twice.

8. TREATMENTS

8.1. Treatments Administered

The investigational product administered in this study is fosmetpantotenate, a phosphopantothenate replacement therapy.

8.2. Investigational Product(s)

Fosmetpantotenate active pharmaceutical ingredient is a yellowish oil.

The chemical name of fosmetpantotenate is methyl 3-((2R)-2-hydroxy-4-(((((S)-1-methoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)oxy)-3,3-dimethylbutanamido)propanoate.

Fosmetpantotenate contains 2 chiral carbon atoms with known absolute stereochemistry. The amino acid portion of the molecule is prepared from naturally occurring L-alanine. The secondary alcohol (OH) functionality is part of naturally occurring vitamin B5, and has R-stereochemistry. The phosphorus atom is also a chiral center, and is racemic; thus, fosmetpantotenate exists as a mixture of diastereomers.

Fosmetpantotenate will be supplied in dried powder form for reconstitution and oral administration, packaged in a dose strength of 75 mg capsules, and after receipt of regulatory approval, 75 mg and 300 mg sachets.

The placebo for the study will be representative of, and physically identical to, active fosmetpantotenate.

Details regarding blinding for fosmetpantotenate and placebo can be found in the study manuals.

8.2.1. Packaging and Labeling, Storage, and Preparation and Administration of Investigational Product

8.2.1.1. Study Drug Administration

Patients will be instructed to take the study drug 3 times daily (approximately 8-hour intervals) with food. The Investigator/designee will provide instructions on study drug preparation when patients have to take their dose of the study drug at home. If vomiting occurs, patients will be instructed not to take another dose of study drug and continue the study drug with their usual dosing schedule and inform the Investigator. In case the patients miss any dose of the study drug, they will be instructed not to take the missed dose immediately but follow their next scheduled dosing.

Study drug administration is outlined in Table 1.

Table 1: Study Drug Administration by Dose (Capsule)

Total Daily Dose	Each Dose	Number of Capsules		Total Number of Bottles (84 capsules/bottle) Double-Blind Period (24 weeks)	Total Number of Bottles (84 capsules/bottle) Open-Label Period (278 weeks)
		Per Day	Per Dose		
225 mg	75 mg	3	1	9	70
450 mg	150 mg	6	2	17	139
900 mg	300 mg	12	4	30	278

Table 2: Study Drug Administration by Dose (Sachet – Open Label Only)

Total Daily Dose	Each Dose	Number of Sachets				Total Number of Boxes (30 sachets/box) Open-Label Period (278 weeks)
		75 mg Sachet Per Day	75 mg Sachet Per Dose	300 mg Sachet Per Day	300 mg Sachet Per Dose	
225 mg	75 mg	3	1	NA	NA	128
450 mg	150 mg	6	2	NA	NA	255
900 mg	300 mg	NA	NA	3	1	128

8.2.1.2. Packaging, Labeling, and Storage

Study drug will be packaged by the Sponsor according to all local legal requirements. The study drug will be labeled in accordance with applicable regulatory requirements.

8.2.1.3. Study Drug Storage at Study Centers

The fosmetpantotenate powder for oral suspension in a dose strength of 75 mg and 300 mg and placebo to match fosmetpantotenate powder for oral suspension in a dose strength of 75 mg must be stored frozen (-20 ± 5°C), in a secure location with limited access. The fosmetpantotenate and placebo suspensions are to be kept at room temperature and should be used within 8 hours of preparation.

8.2.1.4. Study Drug Storage Instructions for Patients

Investigator/designee will provide the following instructions to the patients on the study drug storage.

- Keep the study drug in the freezer (- 20°C ± 5°C) OR (5°F to -13°F). Alternatively, patients can store the study drug in the refrigerator at 2°C – 8°C (36°F - 46°F) for up to 14 days. Patients/caregivers should be instructed to write the date it went into the refrigerator on the bottle to ensure they do not go past 14 days.
- Patients will be instructed to keep the prepared mixture of study drug and water at room temperature (15°C – 25°C) or (59°F - 77°F) and should be administered within 8 hours of preparation.

- While travelling, patients are instructed to use the freezer bags provided to them and make sure the study drug is stored per instructions once they reach destination.
- Patients are instructed to save and bring all empty study drug bottles and unused study drug to their next visit.

Patient and/or caregiver must take care to prevent the accidental ingestion of or exposure to this medication by anyone other than the intended recipient (patient).

Details on the packaging, labeling, preparation and administration of the fosmetpantotenate active pharmaceutical ingredient and placebo can be found in the study manuals.

8.3. Prior and Concomitant Medications and Therapeutic Procedures

Deferiprone is prohibited within 30 days prior to screening for the study and throughout the patient's participation in the study.

Double-blind Period: The PKAN maintenance treatments listed in Section 15.2.1 are allowed during the study. However, no changes or modifications to any of these treatments are allowed for 30 days prior to randomization until the completion of the double-blind period of the study, unless medically necessary and after consultation between the Investigator, the Medical Monitor, and the Sponsor (except in cases of medical emergency).

Open-Label Period: Dose adjustments of allowed concomitant treatments are permitted for optimal effect in the open-label period of the study.

Both Periods: Based on the Investigator's judgment, medical management of patients from screening through study completion may also include administering or modifying treatments (excluding deferiprone) for AEs, symptoms, or disease states unrelated to managing the symptoms of PKAN.

8.4. Method of Assigning Patients to Treatment

Patients will be assigned to a treatment group at Baseline by an integrated web response system (IWRS).

8.5. Randomization

Following screening, patients meeting all eligibility criteria will be enrolled in the study. Patients will be randomized via IWRS in a 1:1 ratio to receive either fosmetpantotenate or placebo during the 24-week double-blind period, followed by open-label treatment with fosmetpantotenate. Randomization will be stratified by weight (≥40 kg, ≥20 kg but <40 kg, or <20 kg) and age group (pediatric: ages 6 to <18 years, or adult: ages 18 to 65 years, inclusive) as measured at the Screening visit.

For the open-label period, all patients will receive fosmetpantotenate open-label.

The IWRS will also randomize patients to one of the sampling schemes for PK sampling as described in Section 9.4.

8.5.1. Blinding and Breaking the Blind

The first 24 weeks of treatment will be administered in a double-blind manner. The identity of the treatments will be concealed by the use of study drugs that are identical in packaging, labeling, and schedule of administration, appearance, taste, and odor. During the open-label extension, patients (including parents or legal guardians of patients <18 years of age) and site personnel will remain blinded to the patient's randomized treatment assignment.

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death). The patient's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

8.5.1.1. Breaking the Blind in Medical Emergency

Before breaking the blind of an individual patient's treatment, the Investigator should determine that the unblinded information is necessary, i.e., it will alter the patient's immediate management. In many cases, particularly when the emergency is clearly not related to the study drug, the problem may be properly managed by assuming that the patient is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor/Sponsor. Emergency code breaks will be performed using the IWRS. Only the Investigator and Medical Monitor will have access to unblinding through IWRS in case of emergency. Emergency unblinding should be performed only after the decision to discontinue the patient from treatment has been made. The unblinding procedure is described in the Randomization and Trial Supply Management (RTSM) User Guide. In cases of accidental unblinding, within 24 hours, the Investigator should immediately contact the Medical Monitor and ensure that every attempt is made to preserve the blind.

If the blind is broken, the date and time must be recorded in the IWRS and the reason must be recorded in the patient's source documentation.

8.5.1.2. Breaking the Blind for Regulatory Requirement

For Suspected, Unexpected, Serious Adverse Reactions (SUSARs), the Sponsor's Pharmacovigilance designee responsible for managing SAEs, will access the IWRS to obtain the patient's treatment assignment for the purpose of regulatory reporting.

Details of randomization and unblinding will be documented in the RTSM User Guide.

8.6. Treatment Compliance

Records of investigational product used, dosages administered, and intervals between visits will be kept during the study. Drug compliance will be performed by a count of investigational product units returned at each visit. Drug compliance is calculated as the number of actual investigational product units taken (based on product units returned at each visit) divided by the number of investigational product units that should have been taken during the dosing period multiplied by 100%. Patients will be asked to return all used and unused investigational product and packaging at each visit.

Compliance with treatment will be defined as having taken between 80% and 120% (inclusive) of the doses that should have been taken during the study.

9. STUDY ASSESSMENTS

9.1. Study Schedule of Events

The schedule of study assessments is in Section 15.1. Table 15.1-1 shows assessments for the double-blind period, and Table 15.1-2 shows assessments for the open-label period. Additional guidance on the completion of the assessments can be found in the study manuals.

9.2. Demographic and Screening Assessments

Approximately 82 patients will be enrolled in the study. The nature of this study and the potential risks associated with participation in the study will be explained to all potential study patients and their parent/legal guardian as appropriate. Written informed consent/assent will be obtained before any screening procedures are performed.

Demographic data will include age, race, ethnicity, and gender. Complete medical history, including a detailed history of PKAN on the PKAN-specific Medical History form, will be obtained, along with concomitant medications/therapies at enrollment.

Patients who are re-screened due to initial screening failure will undergo confirmation of inclusion and exclusion criteria, assessment of PKAN-ADL, UPDRS Part III, and any other necessary assessments (see Section 6.2).

9.3. Safety Assessments

The safety and tolerability of fosmetpantotenate will be evaluated by AEs and by serial vital signs, weight, physical examinations, clinical laboratory parameters, C-SSRS assessments (in assessable patients), and ECGs. See Section 10 for AE reporting requirements.

9.3.1. Physical Examination

Physical examinations will be performed according to the schedule of study assessments in Section 15.1. Complete physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Abbreviated physical examinations will evaluate the following body systems/organs: general appearance; dermatological; pulmonary; cardiovascular; abdominal; and neurological. Height will be recorded at Baseline for all patients; for patients who are <18 years of age at enrollment, height will also be measured at additional visits according to the schedule of study assessments. Weight will be collected according to the schedule of study assessment in Section 15.1 and recorded in kilograms.

9.3.2. Vital Signs

Vital sign measurements will be performed according to the schedule of study assessments in Section 15.1, and will include blood pressure, heart rate, respiration rate, and temperature.

9.3.3. Clinical Laboratory Tests

The clinical laboratory tests listed in Section 15.2.2 will be performed according to the schedule of study assessments in Section 15.1.

Investigators will evaluate the clinical significance of all abnormal laboratory values. All abnormal laboratory values considered clinically significant by the Investigator will be recorded as AEs in the eCRF and will be followed up until resolution or, if unresolved, until the final visit.

9.3.4. Electrocardiograms

Standard 12-lead ECGs will be performed at the time points specified in the schedule of assessments in Section 15.1.

Patients who have a DBS may experience interference with the ECG machine resulting in an inaccurate readout. In the best interest of the patient, the DBS device should not be turned off in an effort to collect the ECG, rather, using clinical judgement and following consultation with the Sponsor Medical Monitor, ECG assessments may be waived for these patients.

Complete details for performing ECG assessments are contained in the study manuals.

9.3.5. Columbia Suicide Severity Rating Scale

The C-SSRS will be administered at the time points specified in the schedule of assessments in Section 15.1. Patients will be administered the Screening/Baseline version of the C-SSRS at Screening. This assessment will serve as the baseline measurement of suicidality for each patient. At subsequent visits, patients will be administered the Since Last Visit version of the C-SSRS to assess changes in suicidality since Screening.

The C-SSRS will be administered to patients who are determined by the Investigator to be assessable. Assessable patients are defined as:

a) adults who are verbal and cognitively intact, such that questions can be understood and responded to in an understandable manner, or;

b) children who are verbal (ie, can respond to questions and be understood) and not cognitively impaired.

The pediatric version of the C-SSRS will be used for patients 6 to <12 years of age, and the adult version will be used for patients ≥12 years of age. Patients who are administered the pediatric version of the C-SSRS at Baseline will continue assessment with this scale throughout the study.

Patients who at any point in the evaluation or study process report the presence or emergence of serious suicidal ideation (ie, with some intent to act or a plan to act) will be evaluated immediately and then managed as medically appropriate (eg, referred immediately for treatment and/or hospitalized). The same will apply for any evaluation that reveals a potential medical emergency detected at any point through the course of the study.

Poland Only: Using clinical judgment, the Investigator may decide not to administer the C-SSRS for reasons other than lack of ability to assess the patient. Such a decision is to be documented in the CRF.

9.4. Pharmacokinetic Assessments

Whole blood samples for PK analyses will be obtained at visits specified in the schedule of assessments in Section 15.1. All patients will have a pre-dose blood draw at Baseline. For subsequent visits at which PK samples are obtained following the first dose of the day, patients will undergo 2 blood draws according to randomization to one of the sampling schemes in Table 2. Within each treatment group (ie, fosmetpantotenate and placebo), the number of patients assigned to each sampling scheme will be approximately equal, and the assignment will remain the same for all visits at which PK samples are obtained. The actual time of in-clinic administration of investigational product, and the exact time of each blood draw for PK analysis will be recorded to the nearest minute on the eCRF.

Table 2: Pharmacokinetic Sampling Schemes

Scheme Number	Blood Draw 1 (Minutes Post Dose)	Blood Draw 2 (Minutes Post Dose)
1	10 ± 5	60 ± 10
2	10 ± 5	210 ± 15
3	10 ± 5	420 ± 15
4	20 ± 5	60 ± 10
5	20 ± 5	210 ± 15
6	20 ± 5	420 ± 15
7	45 ± 5	60 ± 10
8	45 ± 5	210 ± 15
9	45 ± 5	420 ± 15

9.5. Efficacy Assessments

9.5.1. Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living and Unified Parkinson's Disease Rating Scale Part III

The PKAN-ADL and Part III of the UPDRS will be administered to the patient at the time points specified in the schedule of assessments in Section 15.1. See Section 6.1.1 for further description of both scales.

9.5.2. Clinician's Global Impression of Improvement

The CGI-I will be administered to the patient at the time points specified in the schedule of assessments in Section 15.1.

The CGI-I is a global, 7-point scale used to assess the amount of improvement or worsening in a patient's illness relative to their condition prior to starting therapy. The score ranges from 1 (very much improved) to 7 (very much worse).

9.5.3. Barry Albright Dystonia (BAD) Scale

The BAD scale will be administered to the patient at the time points specified in the schedule of assessments in Section 15.1.

The BAD scale assesses dystonia in 8 domains on a 5-point ordinal scale, allowing systematic evaluation of secondary generalized dystonia. It generates a total score and ratings of individual body regions (Barry, 1999; Montbaliu, 2010).

9.5.4. Quality of Life

The Neuro-QoL (upper and lower extremity modules; adult version for patients ≥18 years of age and pediatric version for patients <18 years of age) and EQ-5D-3L/EQ-5D-Y quality of life instruments will be administered to the patient at the time points specified in the schedule of assessments in Section 15.1.

The Neuro-QoL is a domain-specific instrument that was developed by the National Institute of Neurologic Disorders and Stroke (NINDS) for adults and children with neurologic disorders (Cella, 2012). The upper (fine motor and activities of daily living) and lower (mobility) extremity modules assess a range of practical tasks and activities that are relevant to patients with neurodegenerative motor disease and are designed to be sensitive to clinically meaningful improvement in a neurology patient with relatively severe motor impairment. The upper extremity function module includes 20 items that assess the ability to carry out various activities involving digital, manual, and reach-related functions, ranging from fine motor to self-care activities. The lower extremity function module includes 19 items that assess the ability to carry out various activities involving the trunk region and increasing degrees of bodily movement, ambulation, balance, or endurance.

The EQ-5D-3L (administered to patients ≥18 years of age) is a widely used self-report scale that assesses 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) across 3 levels (from "no problems" to "extreme problems") (EuroQol Group, 1990). The scale also records the patient's self-rated health on a vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. The EQ-5D-Y (administered to patients <18 years of age) is a youth friendly version of the EQ-5D-3L. The EQ-5D-Y contains the same 5 dimensions and 3 levels as the EQ-5D-3L, but using child friendly wording; it also uses the same visual analogue scale for the patient to self-rate health (van Reenen, 2014). Patients who are administered the EQ-5D-Y at Baseline will continue assessment with this scale throughout the study.

9.5.5. Functional Independence Measure (FIM)

The FIM (patients ≥18 years of age) or WeeFIM (patients <18 years of age) will be administered to the patient at the time points specified in the schedule of assessments in Section 15.1.

The FIM is a measure of patient functioning that is widely used in rehabilitation medicine to assess the basic quality of daily living activities in persons with physical impairments. It has established reliability, validity, and responsiveness to change, and captures clinically meaningful gradations of functional independence (Ottenbacher, 1996). The FIM contains 18 items that assess motor and cognitive tasks on a 7-point ordinal scale. The score ranges from 18 (total

assistance) to 126 (complete independence). The WeeFIM is a direct derivative of the FIM, assessing self-care, mobility, and cognition in children, as well as in patients with motor, communicative, and neurodevelopmental disabilities up to 21 years of age. Patients who are administered the WeeFIM at Baseline will continue assessment with this scale throughout the study.

9.5.6. Function Measures

The 25-foot walk test will be administered to patients who can safely walk independently, with assistive devices, or with the support of another person at the time points specified in the schedule of assessments in Section 15.1. Evaluation at the Screening Visit will determine whether the patient can be evaluated safely during the study.

The timed 25-foot walk test is a widely used quantitative measure of lower extremity function and ambulation. The patient is timed while walking 25 feet as quickly and safely as possible; the task is then immediately repeated with the patient walking back to the starting point. Patients may use assistive devices or the support of another person. The same assistive device or method of support should be used for each assessment throughout the double-blind period. A maximum time limit of 3 minutes per trial is allowed for completion of the task (Cutter, 1999; Fischer, 2001). If the patient's gait improves during the study such that the walk test can be completed with less assistance than at Baseline (eg, changes from needing a cane to walking independently or from needing a walker to needing only a cane), the assessment should be repeated (ie, a second set of walking from and to the starting point).

DDK assessments (AMR and SMR) will be administered at the time points specified in the schedule of assessments in Section 15.1. These assessments will test oral motor function (lip, jaw, and tongue). Sites will video record the assessments, which will be rated by a central rater.

DDK is a common component of the cranial nerve examination used by neurologists and speech language pathologist to assess oral motor function. Both the AMR and SMR assessments require the participant to produce a target syllable (eg, puh-puh-puh) or syllable sequence (eg, puh-tuh-kuh) as fast and accurately as possible within one breath. Because the syllables are produced at a rapid rate, the task is intended to be physiologically demanding, thus testing the physiologic capacity of the oral motor system. Performance is quantified using 2 scores: repetition rate in seconds (also called DDK rate), and repetition count (ie, the number of repetitions produced in one breath). Normative data for DDK is widely published (Kent, 1987), and DDK has been shown to be a strong indicator of oromotor impairments due to amyotrophic lateral sclerosis (Dworkin, 1980; Rong, 2016) and other neurologic conditions including ataxia (Sidtis, 2010), Parkinson's disease (Tjaden, 2003), multiple sclerosis (Tjaden, 2003) and traumatic brain injury (Wang, 2004).

9.6. Exploratory Measures

9.6.1. Biomarkers

Blood samples for assessment of the potential biomarkers listed in Section 6.1.6 will be obtained at the time points specified in the schedule of assessments in Section 15.1. The actual time of

in-clinic administration of investigational product, and the exact time of blood sampling for biomarker analysis will be recorded to the nearest minute on the eCRF.

9.6.2. Pharmacogenomics

Blood samples for potential pharmacogenomic assessment will be drawn in patients who sign separate consent/assent. Blood samples for pharmacogenomic assessment should be drawn at the Screening visit, if possible; however, samples may be drawn at any visit through Visit 6, if needed. Potential assessments may include drug metabolizing enzymes, transporters, or indicators of therapeutic response or safety.

9.6.3. Additional Exploratory Assessment for Research

A blood sample will be collected at 2-3 different sites from up to a total of 8 eligible patients (half adult, half pediatric) with different confirmed mutations in PANK2 to generate peripheral blood mononuclear cells (PBMCs).

To be eligible to participate, patients must have negative serologic tests for all tests outlined in Section 15.2.2. Patients will be required to sign a separate consent to participate in this exploratory substudy. If a patient discontinues participation in the substudy, their participation in the main study will not be affected.

9.7. Unscheduled Visits

If a patient requires an unscheduled visit, the following assessments (at a minimum) should be performed:

- Assessments related to the purpose of the unscheduled visit
- AEs
- Concomitant medications

9.8. Home Care

Patients may be offered an opportunity to have some study visits performed in their home. If an Investigator agrees with the patient to utilize home care services, a licensed nurse will contact the patient to schedule the visits. In order to conduct the home visits, the home care nurse, the home care agency, and the home care services provider may have access to the patient's personal data including their individually identifiable protected health information, such as the patient's name, address, or phone number. This type of information will only be used as necessary to schedule and conduct the home visits and will not be provided to the Sponsor of this study.

9.9. Travel and Reimbursement

In order to support patient's participation in the study and improve adherence to study assessment schedules, travel and reimbursement vendors have been arranged for use at the patient's discretion. In order to provide travel and/or reimbursement services, the provider may have access to the patient's personal data including their individually identifiable protected health information, such as the patient's name, date of birth, address, phone number, and email.

This type of information, in accordance with local regulations, will only be used in relation to travel and/or reimbursement and will not be provided to the Sponsor of this study.

10. ADVERSE EVENT REPORTING

10.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of the investigational product (active or placebo) in a clinical investigation patient, which does not necessarily have a causal relationship with the investigational product. An AE can, therefore, be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Adverse events may include:

- Symptoms described by the patient
- Clinically significant changes in the patient's physical examination or other signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests, ECG, X-rays, etc.) that reflect a change from Baseline and/or that may result in changes in administration of investigational product or in an alteration in medical care (diagnostic or therapeutic)
- Conditions present at Baseline that have either worsened or recurred following resolution

The patient will be evaluated for new AEs and the status of existing AEs at each study visit, including the screening period, or at any time contact is made with the patient outside of a scheduled visit. The Investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications.

Of note, bitter taste of study medication will not be captured on the AE eCRF. Any symptoms caused by the taste of study medication (eg vomiting, gagging) must be reported as an AE.

10.2. Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following:

- Death: The patient died as the result of the event.
- Is life-threatening: An AE that places the patient, in the view of the Investigator or the Sponsor, at immediate risk of death from the AE as it occurred, ie, does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of an existing hospitalization: The patient may be hospitalized as part of the clinical use and monitoring of the investigational product as outlined in the protocol or by the judgment of the Investigator; in this case, the hospitalization would not meet serious criteria. However, if medically significant changes in the patient's condition develop during hospital monitoring that meet AE criteria and prolong the patient's hospitalization, these events should be recorded as serious AEs.

Note: Planned or elective hospital admissions for treatment/procedures for a condition/disease that existed prior to signing the informed consent should be recorded during the patient's screening visit and will not be captured as SAEs. If, however, the admission or procedure occurs other than planned due to a worsening of the condition, the event should be recorded as an SAE.

- Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product.
- Other medically important serious medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.3. Adverse Events of Interest (AEOI)

Abnormalities in ALT, AST and total bilirubin are considered AEOIs and must be reported to the Sponsor's Medical Monitor within 24 hours of awareness if one of the following conditions are met:

- The abnormality represents a new elevation in ALT or AST >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN; or
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to starting study medication.

In such instances, the following steps will be taken:

1. Temporarily discontinue study medication.
2. Repeat testing of ALT, AST, alkaline phosphatase and total bilirubin, to be completed within 48 to 72 hours (if possible) to confirm the abnormalities.
3. If the abnormality is confirmed by repeat results or after consulting with Sponsor Medical Monitor:
    a. Complete an AEOI Report Form that documents both the liver function test findings and any associated signs or symptoms, and report by email to the SAE contact on the Study Contact Information page of this protocol.
    b. Monitor liver enzymes and serum bilirubin 2 or 3 times weekly. The frequency of re-testing can decrease to once weekly or less if the abnormalities stabilize and the patient is asymptomatic.
    c. Perform additional testing to evaluate liver function, as appropriate (eg, international normalized ratio [INR], direct bilirubin).
4. Do not resume study medication until monitoring indicates abnormalities have resolved or stabilized.

Patients would not typically be allowed to resume study medication if they have:

- ALT or AST >8 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST >3 times ULN and total bilirubin >2 times ULN or INR >1.5
- ALT or AST >3 times ULN with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5% eosinophils)

Management of such patients should be closely coordinated with the Sponsor's Medical Monitor. In addition to monitoring liver function tests, the Investigator should perform other relevant clinical and laboratory measurements to identify potential causes of the abnormalities (eg, acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; biliary tract disease or exposure to hepatotoxic medications or environmental chemical agents).

Cases of increased liver function tests will always be considered serious (ie, medically important) if they meet both the following criteria:

- Study medication is suspected to have caused hepatocellular injury, generally shown by a confirmed elevation of 3-fold or greater above ULN in ALT or AST; and,
- The ALT or AST elevations are accompanied by a total bilirubin >2 times the ULN or INR >1.5, without initial findings of cholestasis (elevated serum alkaline phosphatase)

10.4. Evaluation of Adverse Events/Serious Adverse Events

10.4.1. Causality Assessment

Assessment of the relationship between the AE and exposure to the investigational product is important for regulatory reporting and assists in the overall analysis of the safety information. For each AE/SAE the Investigator will determine whether, based on available evidence, there is a reasonable possibility that the investigational product caused the event. Causal relationship will be classified according to the following criteria:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A causality assessment will be provided for each AE/SAE recorded, even if there is only limited information at the time. Upon receipt of follow-up information, the Investigator may change his/her assessment of causality and amend the AE/SAE report accordingly.

10.4.2. Severity Assessment

Severity indicates the intensity of the event and should not be confused with seriousness (see Section 10.2), which is an event outcome applied for the purpose of event classification and regulatory reporting.

Severity Grading

The Investigator will assess the severity of all AEs/SAEs as mild, moderate, or severe, based on the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.4.3. Outcome

Outcome describes the status of the AE.

The Investigator will provide information regarding the patient outcome of each AE.

Definitions for possible results of an AE outcome:

- Recovered/resolved: the event has improved or the patient recuperated
- Recovering/resolving: the event is improving
- Not recovered/not resolved: the event has not improved or the patient has not recuperated
- Recovered/resolved with sequelae: the patient recuperated but retained pathological conditions directly resulting from the disease or injury
- Fatal: termination of life as a result of an AE. There should be only one AE marked with this outcome
- Unknown: not known, not observed, not recorded, or refused

10.4.4. Action Taken Regarding the Investigational Product

The action taken with regard to the investigational product in response to the AE should be provided at the time the event is reported.

Options for action taken include the following:

- Drug Withdrawn: medication schedule was modified through termination of a prescribed regimen of medication

- Dose Reduced: medication schedule was modified by subtraction, either by changing the frequency, strength, or amount
- Dose Increased: medication schedule was modified by addition; either by changing the frequency, strength, or amount
- Dose Not Changed: medication schedule was maintained
- Drug Interrupted: medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Unknown: not known, not observed, not recorded, or refused
- Not Applicable: determination of a value is not relevant in the current context, for example, if the AE began and ended prior to treatment

10.4.5. Assessment of Expectedness

The expectedness of an AE/SAE will be determined by the Sponsor in accordance with the fosmetpantotenate IB.

10.5. Reporting Adverse and Serious Adverse Events

10.5.1. Reporting Adverse Events

AEs will be captured from the time the main study informed consent is signed to 30 days after the patient's last dose of investigational product or the patient's last scheduled visit, whichever occurs last.

- AEs should be recorded using appropriate medical terminology. When recording, it is preferable to provide a diagnosis. In the absence of a diagnosis, each sign and symptom should be captured as a unique AE. Sufficient information should be sought to assist the Investigator both in determining the diagnosis and in making a causality assessment.
- Reporting should not be delayed pending receipt of all required information. If information is unavailable at the time of the initial report, the Investigator is expected to follow-up until the required information has been obtained or until 30 days after the patient's last dose or last scheduled visit.

10.5.2. Reporting Serious Adverse Events

The necessity and time requirements for reporting of SAEs to the Sponsor or its designee are as follows:

- All SAEs will be reported by email to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the study manual within 24 hours of the Investigator's first knowledge of the event, regardless of causal relationship.
- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with available supporting documents (eg, discharge summary, autopsy report, diagnostic test results, etc.) should be provided by email to the SAE contact on the Study Contact Information page or by fax to the number in the study manual.

- Additional information that is not available at the time the initial SAE Report Form was completed will be promptly reviewed and provided by email to the SAE contact on the Study Contact Information page or by fax to the number in the study manual within 48 hours of receipt. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant patient/hospital records, discharge summaries, laboratory/test results or autopsy reports.
- If at any time after the patient has completed participation in the study (as defined in Section 6.3.1), the Investigator or study staff becomes aware of an SAE that they suspect is related to the investigational product (see Section 10.4.1), the event and any known details will be reported promptly by email to the SAE contact on the Study Contact Information page or by fax to the number in the study manual, following the reporting instructions above (Section 10.5.2).
- For medical emergencies, the IWRS can be used at any time by the Investigator to unblind the patient's treatment assignment, if deemed necessary to manage the event. For SUSARs, the Sponsor's Pharmacovigilance designee responsible for managing SAEs will access the IWRS to obtain the patient's treatment assignment for the purpose of regulatory reporting. Refer to the study manuals for unblinding procedures.

10.5.3. Follow-Up of Adverse Events/Serious Adverse Events

All AEs will be followed until resolution, until the condition stabilizes, or until completion of the patient's participation or study termination, whichever occurs first.

Serious AEs will be followed until resolution, until the condition stabilizes, or until the Investigator and the Sponsor agree that follow up is no longer necessary.

All AEs/SAEs documented at a previous visit/contact where event outcome is designated as not recovered/not resolved, recovering/resolving, or unknown should be reviewed by the Investigator at subsequent visits/contacts. SAEs that are ongoing after completion of the last scheduled visit will continue to be followed to determine the final outcome.

Rules for AE/SAE follow up apply to all patients, to the extent allowed by the patient's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate medical management to understand the nature and/or causality of the AE/SAE. The Sponsor or regulatory authorities may also request additional information regarding an SAE at any time.

All follow-up information will be promptly reviewed by the Investigator and provided by email to the contact on the Study Contact Information page of this protocol or by fax to the number in the study manual within the specified timelines. Additional AEs/SAEs may be identified during the review of follow-up information and should be processed in accordance with requirements defined throughout Section 10.

10.5.4. Reporting to Regulatory Authorities, Investigators and Institutional Review Boards/Independent Ethics Committees

The Sponsor will ensure that processes are in place for provision of SAEs and Expedited SAE reports (SUSARs) to regulatory authorities, Investigators and IRBs/IECs as required, within the specified timelines.

The Sponsor will submit SAE and/or SUSAR reports to regulatory authorities and the Investigator as required. In the US, Investigators will report SAEs and SUSARs to their local IRBs and the Contract Research Organization (CRO) will report SAEs and SUSARs to the central IRB in accordance with applicable standard operating procedures and/or local reporting requirements. In the European Union (EU) or Canada, the Sponsor or its designee will notify the IEC of any SUSARs.

Investigators will forward copies of the IRB/IEC notification to the Sponsor or its designee, when applicable.

10.6. Pregnancy Reporting

Although not an AE in itself, exposure to the investigational product during pregnancy must be reported, therefore all pregnancies will be recorded on the AE eCRF. If the Investigator suspects that a pregnancy was the result of an interaction between the investigational product and the contraceptive method, in addition to the pregnancy, the drug interaction should also be captured as a separate AE.

The Investigator will report any pregnancy associated with exposure to investigational product, including at least 30 days after final investigational product administration. When a site becomes aware that a patient or a male patient's partner is pregnant, they are to contact the Medical Monitor within 24 hours of the site staff becoming aware of the event, as well as complete an initial Pregnancy Notification Form and send by email it to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the study manual.

Female patients will be instructed to notify the Investigator and to stop taking study medication immediately if they discover they are pregnant. Male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant. In the latter instance, the partner must provide written consent before pregnancy information can be collected.

All pregnancies will be followed to outcome (ie, delivery, elective termination, spontaneous abortion). The Investigator will inform the patient that the Sponsor or its designee is required to gather information regarding the course and outcome of the pregnancy after exposure to the investigational product. All study related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known. The Investigator should further obtain follow-up information no later than 1 month after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

All information related to the pregnancy and its outcome will be assessed for the occurrence of an AE or SAE. Should an AE or SAE occur, it will be processed per study guidelines. Spontaneous abortions and stillbirths will always be reported as SAEs. If the pregnancy results in the birth of a child, and an AE/SAE occurs in the child, the data should be documented and, if

needed, an SAE report form should be completed and provided by email to the SAE contact on the Study Contact Information page of this protocol or by fax to the number in the study manual.

When investigational product is discontinued because of pregnancy, pregnancy will be documented as the reason for treatment discontinuation.

11. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

11.1. Recording of Data

The study will use eCRFs for data collection. The data will be entered by trained site personnel only. The Investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that the data can be verified against any source data.

Adverse events and medical history will be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at study initiation. Similarly, prior and concomitant medications and concomitant therapies will be coded using the latest version of World Health Organization Drug Dictionary available at study initiation. The versions employed at study start will be maintained throughout the project.

11.2. Data Quality Assurance

To ensure compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 11.4 for more details regarding this process.

11.3. Data Management

Data management will be performed by a qualified vendor under their standard operating procedures. The Sponsor will provide oversight.

11.4. Audits and Inspections

At any time prior to, during, or after completion of the clinical study, an audit or inspection may be performed by the Sponsor or designated representative, a regulatory authority, an IRB, or an IEC. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection. The Sponsor or a designated representative will be available to assist in the preparation of the study site for inspections. All pertinent study data will be made available for verification, audit, or inspection purposes.

12. STATISTICAL METHODS AND PLANNED ANALYSES

12.1. General Considerations

A Statistical Analysis Plan (SAP), specifying further details of the planned analyses, will be prepared and approved prior to lock of the database. This section presents a highlight of the approaches to be taken in performing the planned analyses.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Software (Version 9.2 or higher). Descriptive statistics include mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and frequency tables with counts and percentages for discrete variables.

Unless otherwise stated, "Baseline" will be defined as the last measurement obtained prior to the first dose of investigational product (pre-dose on Day 1). Hypothesis-testing will be performed at the 2-sided 5% significance level.

12.2. Determination of Sample Size

A total of 74 patients will provide approximately 80% power to detect a 3-point difference between treatment groups in the average change from Baseline scores from the PKAN-ADL, based on Student's t-test with alpha = 0.05 (2-sided); this calculation assumes a standard deviation of 4.5 points for the change from Baseline scores. Additional patients will be randomized to ensure that at least 74 patients complete the double-blind period with evaluable data (ie, having assessments at Baseline and Week 24 for the PKAN-ADL).

12.3. Analysis Sets

Double-Blind Period

Safety Population: The safety population will consist of all randomized patients who receive at least 1 dose of blinded investigational product. This population will be used for all summaries of patient accountability, demographic and Baseline data, and safety information, including AE incidence, for the double-blind period of the study.

Full Analysis Set (FAS): The FAS will consist of all randomized patients with at least 1 post Baseline efficacy assessment. This population will serve as the basis for all efficacy analyses for the double-blind period of the study.

Open-Label Period

Safety Population: The safety population will consist of all patients who receive at least 1 dose of investigational product after entering the open-label period of the study. This population will be used for all summaries of patient accountability, demographic and Baseline data, and safety information, including AE incidence, for the open-label period of the study.

Full Analysis Set (FAS): The FAS will consist of all patients with at least 1 post-Baseline efficacy assessment in the open-label period of the study. This population will serve as the basis for efficacy analyses from the open-label period of the study.

12.4. Demographics and Baseline Characteristics

Demographic data (including age, race, ethnicity, gender, height, and weight), medical history (including PKAN-specific medical history), prior treatments, and pre-treatment clinical characteristics will be summarized by treatment group for the safety population using descriptive statistics.

12.5. Patient Accountability

All patients who meet all inclusion criteria and no exclusion criteria for the study, sign the informed consent form, and are enrolled and exposed to the investigational product will be accounted for in the safety analyses. Screen failures will not be accounted for in the data presentation.

Accountability tables will summarize the following information by treatment group: the number of patients randomized, the number included in each analysis population, the number evaluated at each study visit, the number discontinued from treatment by reason for treatment discontinuation, and the number discontinued from the study by reason for study discontinuation. A by-patient data listing of study completion information, including the timing and reason(s) for premature treatment discontinuation or study withdrawal, if applicable, will be presented.

12.6. Study Treatment Usage and Compliance

Compliance information collected via dispensed/returned investigational product unit counts will be summarized descriptively for each treatment group, including frequency tables to indicate the number of patients at least 80% compliant with the dosing regimen during the double-blind and open-label periods of the study.

12.7. Safety Analyses

Safety analyses will be performed using data from the safety population. Safety will be evaluated on the basis of treatment-emergent AEs (TEAEs), vital signs, weight, physical examinations, clinical laboratory assessments, C-SSRS, and ECG findings.

12.7.1. Physical Examination and Vital Signs

Vital signs and body weight will be summarized by treatment group using descriptive statistics. Summary statistics will be calculated for both the actual value and the change from Baseline value at each scheduled visit.

Pre-study physical examination abnormalities and physical examination abnormalities reported at the end of study will be tabulated by body system.

12.7.2. Clinical Laboratory Tests and Electrocardiograms

Clinical laboratory and ECG data will be summarized by treatment group using descriptive statistics based on the observed values and change from Baseline values at each scheduled visit. In addition, the number and percentage of patients with laboratory values that shift categories (ie, below/within/above normal range) will be tabulated at each study visit. Patients with clinically

significant changes from Baseline in laboratory values will be summarized and flagged in data listings.

12.7.3. Adverse Events

All AEs will be coded by Preferred Term and System Organ Class using the most recent version of MedDRA available at study initiation. By-patient listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided. The by-patient AE data listings will include onset and resolution dates, verbatim term, System Organ Class**,** Preferred Term, treatment, severity, relationship to treatment, action taken for the event, and outcome.

TEAEs in the double-blind period are defined as AEs that are new or are a worsening of an existing condition that begins from the day of first dose of investigational product until the day after the last dose for the double-blind treatment period. The incidence of TEAEs will be summarized for each treatment group by Preferred Term within body system, overall and by severity and relationship to treatment. Incidence calculations will be based on the numbers and percentages of patients with AEs. Although a MedDRA term may be reported more than once for a patient, that patient will be counted only once for that MedDRA term.

12.7.4. Open-Label Period

Safety data collected for the safety population during the open-label period of the study will be summarized using descriptive statistics, including summary tables of AEs, summary tables and graphical plots of mean values over time for continuous measurements (eg, vital signs, weight, laboratory evaluations), and frequency tables for categorical data obtained at each study visit. The last measurement obtained prior to the first dose of open-label investigational product will serve as the Baseline value for assessing change from Baseline during the open-label period of the study.

12.8. Pharmacokinetic Analyses

Multiple-dose blood concentrations of fosmetpantotenate will be tabulated and summarized by dose cohort and sample time. Concentration measures may also be analyzed by nonlinear mixed-effects modeling, either alone or in conjunction with data from other studies. Available metabolite concentrations will be analyzed similarly. Summarizations will include appropriate descriptive statistics (eg, n, geometric mean, coefficient of variation, minimum, median, maximum).

12.9. Efficacy

12.9.1. Double-Blind Period

The primary efficacy analysis will be based on the FAS population defined for the double-blind period of the study (see Section 12.3). For each patient, the change from Baseline in PKAN-ADL scores at Weeks 3, 6, 12, 18, and 24 of the double-blind period will be used for analysis. The treatment effect will be evaluated on the basis of mixed model for repeated measures (MMRM) analysis to assess data from all visits simultaneously. The model will include fixed effects for treatment, age stratum (6 to <18 or 18 to 65 years), visit and treatment by-visit interaction, a random effect for patient within treatment group, and Baseline

PKAN-ADL score as a covariate. The PKAN-ADL measurement obtained prior to the first dose of investigational product will serve as each patient's Baseline value. Least-squares adjusted means and the adjusted mean difference between treatment groups will be reported at each study visit, along with 2-sided 95% confidence intervals (CIs) and the p-value for the treatment comparison.

The mixed-effect linear model will be implemented using PROC MIXED in SAS with the restricted maximum likelihood (REML) estimation method and Kenward-Roger degrees of freedom algorithm for the F-test. Significance tests will be based on least squares means using Type III sum of squares.

To support the primary efficacy analysis, analysis of covariance (ANCOVA) models will be applied to change from Baseline in PKAN-ADL scores assessed after 3, 6, 12, 18, and 24 weeks of treatment. For each week analyzed, the model will include treatment and age stratum (6 to <18 or 18 to 65 years) as fixed effects and Baseline PKAN-ADL score as a covariate. Estimates of the adjusted mean treatment differences and the 2-sided 95% CIs at each time point will be obtained from the model.

Secondary and exploratory efficacy endpoints that are continuous measures recorded at each study visit will be evaluated using the MMRM approach described above for the primary efficacy endpoint. Summary statistics for efficacy measures will include graphical plots of mean and mean change from Baseline values at each study visit, by treatment group.

Treatment effects on categorical outcomes will be examined using frequency tables and tested using Cochran-Mantel-Haenszel chi-square methods with stratification by age group (6 to <18 or 18 to 65 years).

12.9.2. Open-Label Period

Long-term treatment effects will be examined using data from the FAS defined for the open-label period (see Section 12.3). Efficacy measures will be summarized using descriptive statistics, including tabulations and graphical plots of mean values and mean change from Baseline values at each study visit. For this purpose, Baseline is defined as the last assessment prior to the first dose in the open-label period. Hypothesis testing will be applied in exploratory analyses to primary and secondary efficacy variables on data collected during the open-label period, as appropriate, to assess changes from Baseline, both overall and in the groups to which patients were initially randomized for the double-blind period (ie, fosmetpantotenate or placebo). Between-group t tests will be used to explore whether improvement is greater for patients who convert to fosmetpantotenate from placebo, compared to those maintained on active investigational product for the open-label period. Mixed-effect linear models may also be used to explore differences in the pattern of change over time between groups.

12.10. Biomarkers

Biomarker assessments will be listed and summarized by time point using descriptive statistics and, where appropriate, graphical displays.

Mean or mean change from Baseline (whichever is considered more relevant) plasma concentration time profiles will be plotted on either or both linear and semi-logarithmic scales. Inclusion/exclusion of the data in the calculations will be determined using an outliers test.

12.11. Missing or Invalid Data

The MMRM approach used for the primary efficacy analysis adjusts for missing data through a variance covariance structure. ANCOVA models will be used with both observed-case (OC) and last-observation-carried-forward (LOCF) procedures to account for drop-outs and ensure that the treatment effect is robust. No other data imputation procedures are planned.

12.12. Interim Analysis

The efficacy and safety analyses of the double-blind period of the study will be performed after all patients have completed the double-blind period and reported in an interim clinical study report. In addition, the interim report will include available data from patients in the open-label period as of a data cutoff date.

13. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice; ICH Guidelines for Safety Data Management, 1994; the Code of Federal Regulations (CFR 21 Parts 50, 56, and 312); and the European Union Clinical Trials Directive, 2001/20/EC.

13.1. Institutional and Ethics Review

This protocol and associated informed consent form, participant information sheet, any information provided to the patient, the IB, and any proposed advertising material will be submitted to an appropriate IRB/IEC, applicable regulatory authorities, and host institution(s) for written approval (where applicable). These documents will also be submitted to, and approved by, the above parties for all amendments to the original approved documents (where applicable). Documentation of any applicable approval(s) and the approved consent form will be received by the Sponsor or its designee prior to enrollment of patients and release of investigational product.

13.2. Data Monitoring Committee

During the conduct of the study, responsibilities of the DMC will be to periodically review safety study results, evaluate treatment groups for excess AEs, determine whether the basic study assumptions remain valid, evaluate whether the overall integrity, scientific merit and conduct of the study remain acceptable, and make recommendations to the Sponsor. Per the DMC charter, the DMC may request unblinded (unmasked) data for individual patients or in aggregate in the case of a safety concern that could potentially lead to a major study action.

DMC members are expected to have no substantive conflict of interest with the study. DMC members should not be directly involved with the conceptual design of the study, participate in any other study of this development program as Principal Investigator, Co-Investigator, or as physician caring for a study patient during the conduct of the study. In addition, DMC members are obligated to disclose concurrent participation in any DMCs of the same, related, or competing products. All DMC activities will be managed independently of the Sponsor by the Sponsor's CRO DMC Core Team, a two-member team that acts separately from the general project and trial management teams within the Sponsor and the CRO. The CRO's DMC Core Team is comprised of an Independent Statistician and a Medical Board Manager, who both serves as a central point of contact or firewall between the DMC members, the Sponsor and the CRO trial management teams.

The specific responsibilities of the DMC are described in the DMC charter, which is maintained as a separate document.

13.3. Changes to the Conduct of the Study or Protocol

Any changes to the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or its designee. All protocol changes will be documented in protocol amendment(s). Protocol amendment(s) will be signed by the Investigator and approved by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be

considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval will be returned to the Sponsor or its designee.

13.4. Investigator's Responsibilities

Refer to the study manuals for further details regarding the Investigator's responsibilities as outlined in the sections below.

The Investigator will provide progress reports and notifications of SAEs to the IRB/IEC according to local regulations and guidelines.

13.4.1. Patient Informed Consent

Investigators agree to adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient informed consent and assent (where applicable) forms and when obtaining consent and assent from the patient, parent, or legal guardian. Written informed consent is required prior to enrollment in the study. It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB/IEC-approved consent form.

The Investigator will ensure that each patient or parent or legal guardians (as appropriate) is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study as well as potential treatment alternatives. Investigators will ensure that consent/assent is obtained with the appropriate age range form. For developmentally delayed or cognitively impaired patients, Investigators will determine which age range assent will be appropriate based on the patient's physical and cognitive ability and will document the process of determination. Patients, or parents or legal guardians (as appropriate) will be notified that they are free to discontinue participation in the study at any time and will be given the opportunity to ask questions and allowed time to consider the information provided.

13.4.2. Case Report Form

Copies of pertinent records in connection with the study, including all source documents, will be made available to the Sponsor or its designee upon request with due precaution toward protecting the privacy of the patient.

Data will be entered by the site onto the eCRFs in the Electronic Data Capture system. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made on the eCRFs will be corrected by the site. Changes made to the data after initial entry onto the eCRF will be captured via an electronic audit trail and include the reason for change. Incomplete entries or entries needing additional explanation will be queried to the site for clarification.

13.4.3. Record Retention

The Investigator is responsible for oversight and maintenance of the study records and patient source documents. These records will be readily available for audit or inspection.

The Investigator will retain study records for at least 2 years after the last marketing approval has been granted, or until at least 2 years have elapsed since the formal discontinuation of the clinical program. However, these documents should be retained for a longer period, if required by other

applicable requirements (eg, applicable local regulatory requirement) or by an agreement with the Sponsor or its designee. The Investigator will contact the Sponsor or its designee prior to any record destruction.

Patient records or other source data will be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records will be retrieved and made available for review at the time of an audit or regulatory authority inspection.

13.4.4. Monitoring

A representative of the Sponsor or its designee will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. Non-compliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, if necessary. It is the responsibility of the Investigator to be present or available for consultation during monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation will be made available to the Monitor.

Study Monitors will perform source document verification according to the clinical monitoring plan to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP.

13.4.5. Study or Site Termination

If the Sponsor or its designee, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor or its designee and the Investigator. The Sponsor or its designee or regulatory authorities have the right to terminate the participation of either an individual site or the study at any time, for any reason, which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study.
- Knowingly false information from the study site is submitted to the Sponsor, its designee, or regulatory authorities.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to investigational sites regarding the end-of-study procedures.

13.4.6. Investigational Product Control

Control of investigational product is further detailed in the study manuals.

13.4.6.1. Receipt of Investigational Product

A proof of receipt, which details the quantity and description of the investigational product, will accompany the shipment from the Sponsor or its designee to the Investigator. The Investigator will provide the Sponsor or its designee with a signed and dated copy of this receipt (or an electronic equivalent) within 48 hours after receipt of investigational product, while retaining the original within the site pharmacy files. The Investigator is responsible for ensuring that the investigational product is maintained in a controlled location, with limited access, and under adequate storage conditions.

13.4.6.2. Disposition of Unused Investigational Product

All unused investigational products will be maintained under adequate storage conditions in a limited-access area. If any unused material is remaining upon completion of the study, the material will be returned to the Sponsor or its designee or destroyed only after the following has been completed:

- Accountability has been performed by a representative of the Sponsor or its designee.
- Appropriate investigational product return/destruction documentation has been completed by the pharmacist or his/her designee

Investigational product return/destruction documentation will be retained within the site pharmacy files.

13.4.6.3. Product Handling and Complaints Reporting

If any issues arise during the course of the study related to the quality of the investigational product, the clinical site pharmacist or pharmacy designee will contact the product handling/complaints group listed on the Study Contact Information page of this protocol.

13.4.7. Insurance

The Sponsor will maintain a liability insurance policy covering all clinical studies under its sponsorship, and that policy will comply with local laws and requirements. The Sponsor or its designee will provide a certificate of insurance to any IRB/IEC or regional Health Authority that may require such a document. Note that this Sponsor insurance coverage does not relieve the Investigator, the Institution, and their collaborators from each maintaining their own liability insurance policy for their clinical research activity.

13.4.8. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor. The anonymity of participating subjects must be maintained. Subjects will be identified in the eCRF system and other documents submitted to the CRO by their subject number and/or year of birth, not by name or initials. Documents not to be submitted to the CRO that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

All details related to the disclosure and publication of study data will be addressed in the Investigator's study contract.

13.4.9. Clinical Study Report

The Sponsor or its designee is responsible for preparing a clinical study report. Study results will be provided to the Investigator.

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15. APPENDICES

15.1. Appendix A: Schedules of Study Events

Written informed consent will be obtained prior to any protocol-required procedure.

Table 15.1-1. Double-Blind Period: Screening and Treatment

Visit	Pre-Screening[1]	Screening V1[2]	Baseline V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Unsched Visit[3]	End of Treatment/ Early Termination Visit/Final Contact[4]
Study Day/Week		Days -29 to -2	Day -1	D1	D2	D3	D4	W3 ± 3D	W6 ± 3D	W12 ± 3D	W18 ±3D	W24 ± 3D		
Patient registration / Obtain informed consent/assent	X	X												
Eligibility review	X	X	X											
Randomization			X											
Demographic characteristics		X												
Medical history[5]		X												
Weight		X	X						X	X	X	X		X
Height			X											
C-SSRS[6]		X[7]	X					X	X	X	X	X		X
Physical Examination/ Abbreviated Physical examination[8]		X	X					X	X	X	X	X		X
Vital signs[9]		X	X	X	X	X	X	X	X	X	X	X		X
12-Lead ECG[9]		X	X	X			X	X	X	X	X	X		X
Genetic testing for confirmation of PKAN	X[10]	X[10]												
Pharmacogenomic testing (as applicable)		X[11]												
Hematology[12]		X		X[13]			X[13]	X	X	X	X	X		X
Chemistry[12]		X		X[13]			X[13]	X	X	X	X	X		X
Serology[12]		X												

Visit	Pre-Screening[1]	Screening V1[2]	Baseline V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Unsched Visit[3]	End of Treatment/ Early Termination Visit/Final Contact[4]
Study Day/Week		**Days -29 to -2**	**Day -1**	**D1**	**D2**	**D3**	**D4**	**W3 ± 3D**	**W6 ± 3D**	**W12 ± 3D**	**W18 ±3D**	**W24 ± 3D**		
Coagulation[12]		X								X		X		X
Serum pregnancy[14]		X												
Urinalysis[12]		X		X[13]				X	X	X	X	X		X
Urine drug/alcohol screen[15]		X												
Urine pregnancy[14]			X*					*	*	X*	*	X*		X
PKAN-ADL		X	X					X	X	X	X	X		X
UPDRS Part III		X	X					X	X	X	X	X		X
BAD scale			X							X		X		X
CGI-I								X	X	X	X	X		X
25-foot walk test[16]		X	X						X	X	X	X		X
Neuro-QoL Adult/Pediatric (upper and lower extremity) [17]			X							X		X		X
EQ-5D-3L/EQ-5D-Y[17]			X							X		X		X
FIM/WeeFIM[17]			X									X		X
Diadochokinetic assessments[18]			X									X		X
PK sampling[19]			X				X		X		X			
Biomarkers			X[20]				X[21]		X[21]		X[21]	X[22]		X[22]
Blinded investigational product dispensing /accountability[23]				X	X	X	X	X	X	X	X	X[24]		X[24]
Open-label investigational product dispensing												X		
AE assessment	———						Continuous Monitoring					——→		
Conmeds/therapies	———						Continuous Monitoring					——→		

Abbreviations: BAD = Barry Albright Dystonia; CGI-I = Clinician Global Impression of Improvement; Con meds = concomitant medications; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; EQ-5D-3L/EQ-5D-Y = EuroQol 5-dimension, 3-level quality of life instrument/EuroQol-5D Youth Version; FIM/WeeFIM = Functional Independence Measure/Functional Independence Measure for Children; IRB/IEC = Institutional Review Board/Independent Ethics Committee; Neuro-QoL = quality of life measure for adults/children with neurological disorders; PK = pharmacokinetic; PKAN-ADL = Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living; Unsched = unscheduled; UPDRS = Unified Parkinson's Disease Rating Scale; V = Visit; W = Week

[1] For patients who are taking deferiprone or who require confirmation of mutation in the *PANK2* gene. This visit will be accomplished at least 30 days prior to the Screening visit for washout of deferiprone.

[2] Patients who fail screening for any reason may be re-screened up to 2 times. Re-screening will consist of confirmation of inclusion and exclusion criteria, for re-screening criteria, refer to the Section 6.2 and Section 9.2.

[3] If a patient requires an unscheduled visit, assessments related to the purpose of the visit should be performed (see Section 9.7).

[4] For patients who are prematurely withdrawn from treatment (End of Treatment) or from the study (Early Termination) during the double-blind period. Patients who agree to continue regularly scheduled study visits will complete the End of Treatment as close as possible to the patient's last dose of study medication. In addition to the Early Termination Visit, patients who prematurely discontinue from the study will be contacted (via telephone call) 30 days (±7 days) after the last dose of investigational product to ascertain patient safety. If a patient who has prematurely discontinued study medication, decides to withdraw consent/assent and discontinue from the study within 6 weeks of completing the End of Treatment, the End of Treatment Visit conducted at the time of study medication withdrawal may serve as the patient's final site visit.

[5] Includes the PKAN-specific Medical History Form.

[6] The C-SSRS will be completed in patients who are determined by the Investigator to be assessable. See Section 9.3.5 for definition of assessable patients and assessments.

[7] Patients will be administered the Screening/Baseline version of the C-SSRS at Screening.

[8] A complete physical examination will be performed at Screening (see Section 9.3.1 for assessments); an abbreviated physical examination will be performed at Baseline (Day -1); the Week 3, 6, 12, 18, and 24 visits, and the Early Termination visit, if applicable (see Section 9.3.1 for assessments).

[9] Vital signs and 12-lead electrocardiograms will be assessed 2 hours (± 30 minutes) after the first dose of the day at all visits**.** (Patients who have a DBS may experience interference with the ECG machine resulting in an inaccurate readout. In the best interest of the patient, the DBS device should not be turned off in an effort to collect the ECG, rather, using clinical judgement and following consultation with the Sponsor Medical Monitor, ECG assessments may be waived for these patients.)

[10] Genetic test (if required to determine eligibility) can be done at Screening if not performed during Pre-screening period. If available, the specific mutation will be recorded.

[11] Pharmacogenomic testing samples will be collected in patients who sign separate IRB/IEC-approved informed consent. Samples should ideally be collected at the Screening visit; however, if limitations present at this visit, the samples may be collected at any visit through Visit 6. See Section 9.6.2

[12] Clinical laboratory parameters to be measured are listed in Section 15.2.2.

[13] Samples will be taken within 2 hours (± 30 minutes) prior to the first dose of the day at these visits.

[14] To be assessed in women of childbearing potential only. Any positive urine pregnancy results will be confirmed by a serum pregnancy test. (*Norway and Poland specific procedure: Sexually active women of childbearing potential to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit. A positive urine pregnancy test will be confirmed by a serum test).

[15] To be conducted in patients 12 years of age and older. The Investigator should use clinical judgment to determine whether or not a patient with a positive test result should be admitted to the study (eg, if the Investigator believes that the result may be indicative of a drug or alcohol disorder, that the patient may not be able to comply with the protocol, or that participating in the study may put the patient at undue risk, the patient should be excluded per the exclusion criteria).

[16] To be administered to patients who can safely walk independently or with assistance. Screening evaluation will determine whether the patient can be evaluated during the study.

[17] See Section 9.5.4 and Section 9.5.5 for age-based administration guidelines.

[18] Diadochokinetic assessments will include alternating motion rate and sequential motion rate. Sites will video record the assessments, which will be rated by a central rater.

[19] All patients will have a pre-dose blood draw at Baseline. For subsequent visits, patients will be randomly assigned to a sampling scheme according to Table 2; assignment will remain the same for all visits. The actual time of administration of investigational product, and the exact time of blood sampling for PK analysis will be recorded to the nearest minute on the eCRF.

[20] At Baseline, 3 samples will be collected for biomarkers; the first will be collected prior to any assessments, and all 3 will be collected at least 3 hours apart.

[21] At the Week 1 Day 4, Week 6, and Week 18 visits, 2 samples will be collected for biomarkers, at the times of PK sample collection.
[22] At the Week 24 visit, 2 samples will be collected for biomarkers at least 3 hours apart. If the patient prematurely discontinues study medication, but does not withdraw from the study, 2 samples should be collected at least 3 hours apart at the End of Treatment visit.
[23] In order to provide training in proper administration, investigational product will be prepared and administered by site personnel, together with the patient and/or family/caregiver, during in-clinic patient visits. Following adequate training, doses may be self-administered by the patient or caregiver at the site's discretion.
[24] Blinded investigational product dispensation is not performed at the Week 24, End of Treatment Early Termination visits.

Table 15.1-2 Open-Label Period

Visit	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22-V28[13]	Unsched Visit[1]	End of Treatment/ Early Termination Visit/Final Contact[2]
Study Week	**W27 ± 7D**	**W30 ± 7D**	**W36 ± 7D**	**W48 ± 7D**	**W60 ± 7D**	**W72 ± 7D**	**W84 ± 7D**	**W96 ± 7D**	**W108 ± 7D**	**W120 ± 7D**	**W146, W172, W198, W224, W250, W276, W302 ± 7D**		
Weight		X	X	X		X		X		X	X		X
Height (if <18 years of age at enrollment)		X				X				X	X		X
C-SSRS[3]		X	X	X	X	X	X	X	X	X	X		X
Abbreviated physical examination[4]		X	X	X		X		X		X	X		X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X		X
12-Lead electrocardiogram[5]		X	X	X		X		X		X	X		X
Hematology[6]	X	X	X	X		X		X		X	X		X
Chemistry[6]	X	X	X	X		X		X		X	X		X
Coagulation[6]		X								X	X		X
Urinalysis[6]		X	X	X		X		X		X	X		X
Urine pregnancy[7]		X*	X*	X*	X*	X*	X*	X*	X*	X*	X*		X
PKAN-ADL		X	X	X	X	X	X	X	X	X	X		X
UPDRS Part III		X	X	X	X	X	X	X	X	X	X		X
BAD scale				X		X		X		X	X		X
CGI-I		X	X	X	X	X	X	X	X	X	X		X
25-foot walk test[8]			X	X		X		X		X	X		X
Neuro-QoL Adult/Pediatric (upper and lower extremity)[9]			X	X		X		X		X	X		X
EQ-5D-3L/EQ-5D-Y[9]				X		X		X		X	X		X
FIM/WeeFIM[9]				X		X		X		X	X		X

Visit	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22-V28[13]**	**Unsched Visit[1]**	**End of Treatment/ Early Termination Visit/Final Contact[2]**
Study Week	**W27 ± 7D**	**W30 ± 7D**	**W36 ± 7D**	**W48 ± 7D**	**W60 ± 7D**	**W72 ± 7D**	**W84 ± 7D**	**W96 ± 7D**	**W108 ± 7D**	**W120 ± 7D**	**W146, W172, W198, W224, W250, W276, W302 ± 7D**		
Diadochokinetic Assessments[10]				X		X		X		X	X		X
Pharmacokinetic sampling[11]		X											
Blood sample collection[14]	At Selected Sites Only: 1 Blood sample[15]												
Investigational product dispensing/accountability		X	X	X	X	X	X	X	X	X[12]	X[12]		X[12]
AE Assessment		Continuous Monitoring →											
Conmeds/therapies		Continuous Monitoring →											

Abbreviations: AE = adverse event; BAD = Barry Albright Dystonia; CGI-I = Clinician Global Impression of Improvement; Con meds = concomitant medications; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; EQ-5D-3L/ EQ-5D-Y = EuroQol 5-dimension, 3-level quality of life instrument/EuroQol-5D Youth Version; FIM/WeeFIM = Functional Independence Measure/Functional Independence Measure for Children; Neuro-QoL = quality of life measure for adults/children with neurological disorders; PK = pharmacokinetic; PKAN-ADL = Pantothenate Kinase-associated Neurodegeneration Activities of Daily Living; Unsched = unscheduled UPDRS = Unified Parkinson's Disease Rating Scale; V = Visit; W = Week

[1] If a patient requires an unscheduled visit, assessments related to the purpose of the visit should be performed (see Section 9.7).

[2] For patients who are prematurely withdrawn from treatment (End of Treatment) or from the study (Early Termination) during the open-label period. If a patient who has prematurely discontinued study medication, decides to withdraw consent/assent and discontinue from the study within 6 weeks of completing the End of Treatment Visit, the End of Treatment Visit conducted at the time of study medication withdrawal may serve as the patient's final site visit. If the study withdrawal occurs within 30 days of the patient's last dose of investigational product, the patient will be contacted (via telephone call) 30 days (±7 days) after the last dose of investigational product to ascertain patient safety. Patients who complete the study will be contacted (via telephone call) 30 days (±7 days) after the last dose of investigational product to ascertain patient safety.

[3] See Section 9.3.5.

[4] See Section 9.3.1 for abbreviated physical examination assessments.

[5] Vital signs and 12-lead electrocardiograms will be assessed 2 hours (± 30 minutes) after the first dose of the day at all visits. See Section 9.3.2 and Section 9.3.4. (Patients who have a DBS may experience interference with the ECG machine resulting in an inaccurate readout. In the best interest of the patient, the DBS device should not be turned off in an effort to collect the ECG, rather, using clinical judgement and following consultation with the Sponsor Medical Monitor, ECG assessments may be waived for these patients.)

[6] Clinical laboratory parameters to be measured are listed in Section 15.2.2. Laboratory assessments for coagulation factors to be collected once yearly during the open-label extension period.
[7] To be assessed in women of childbearing potential only. Any positive urine pregnancy results will be confirmed by a serum pregnancy test. (*Norway and Poland specific procedure: Sexually active women of childbearing potential to conduct pregnancy testing at home between study visits. Site will provide the patient enough tests to conduct pregnancy testing once per month until the next scheduled study visit. A positive urine pregnancy test will be confirmed by a serum test).
[8] See Section 9.5.6.
[9] See Sections 9.5.4 and Section 9.5.5 for age-based administration guidelines.
[10] See Section 9.5.6.
[11] See Section 9.4.
[12] Investigational product dispensation is not performed at the Week 302 or Early Termination visit.
[13] Three-month (every 13 weeks) safety phone calls will be performed to assess PKAN-ADL, AEs, and Concomitant Medications in between each 6-month onsite visit following W120.

At selected sites only:
[14] A blood sample will be collected at 2-3 different sites from up to a total of 8 eligible patients with different confirmed mutations in PANK2 to generate PBMCs.
[15] Blood sample collection for substudy can occur at any point after collection of substudy consent. To be eligible to participate, patients must have negative serologic tests at screening for all tests outlined in Section 15.2.2.

15.2. Appendix B: Supplemental Study Information:

15.2.1. Allowed PKAN Maintenance Treatments

The PKAN maintenance treatments listed below are allowed during the study; however, dosage changes or adjustments including DBS can only be made during the double-blind period of the study following consultation between the Investigator, the Medical Monitor, and the Sponsor (except in cases of medical emergency such as dystonic crisis). Based on the Investigator's judgment, concomitant medications (excluding deferiprone) may be administered or modified at any time during the course of the study to treat AEs, symptoms, or disease states unrelated to managing the symptoms of PKAN.

Trihexyfenidyl

Benzodiazepines

Anticholinergics

Pain medications

L-dopa

Other treatments for Parkinsonism

Antipsychotics

Antidepressants

Treatments for attention deficit/hyperactivity disorder

Baclofen (oral or intrathecal pump)

Deep brain stimulation (DBS; if implanted ≥ 6 months before screening, modifications to the settings are allowed; however, patients are not allowed to have a DBS implanted during the course of the study [double-blind and open-label])

Botulinum toxin; most recent injection must have occurred between 1 to 2 months prior to Baseline, and injections will continue on a regular schedule throughout the double-blind period.

15.2.2. Study Blood Assessments

Clinical Chemistry	**Hematology**	**Routine Urinalysis**
Sodium	Red blood cell count	Color
Potassium	Hemoglobin	Appearance
Chloride	Hematocrit	pH
Bicarbonate	MCV, MCH, MCHC	Specific gravity
Total protein	RBC distribution width	Protein
Albumin	Platelet count	Glucose
Calcium	White blood cell count	Ketones
Phosphate	WBC Differential (% and absolute)	Bilirubin
Glucose	• Neutrophils	Blood
Blood Urea Nitrogen	• Eosinophils	Urobilinogen
Creatinine	• Basophils	Nitrates
Total bilirubin	• Lymphocytes	Leukocyte esterase
Alanine aminotransferase	• Monocytes	Microscopic examination (performed if blood, protein, or leukocyte esterase is abnormal in urine)
Aspartate aminotransferase		
Gamma-glutamyl transferase		
Lactate dehydrogenase		
Alkaline phosphatase		
Creatine kinase		
Total cholesterol		
Triglycerides		**Potential Biomarkers[a]**
		Succinate
Serology/Screening Tests	**Coagulation**	Lactate
Hepatitis B surface antigen	Prothrombin Time, INR	Maleate
Hepatitis C antibody	aPTT	Pyruvate
HIV antibody		Alanine
Serum/Urine Pregnancy test		Acetone
Drug/Alcohol screen		Acetoacetic acid
		3-hydroxybutyric acid
		2-hydroxybutyric acid
		AcetylCoA

Abbreviations: aPTT= activated partial thromboplastin time; HIV=human immunodeficiency virus; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cells

[a] Additional potential biomarkers may be assessed**,** but the samples will not be used for genetic testing.

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