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Statistical Analysis Plan

Approvals

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Role	Signatures
CMO Integrative Research Laboratories	Print Name:
	Sign Name:

Document History

Version	Date	Description of changes
Final 1.0	15-Jul-2024	Initial version
Final 2.0	13-Jan-2025	Terminology, abbreviations, renaming some outputs for clarity, suggested changes by Medical Writer implemented CGI-I, CGI-S tabulation added Relative fall rate definition added Description added about statistical test (Chi square and Fisher's exact on categorical response) Time periods reworked Bootstrap method added for treatment effect and CI calculation for primary analysis Data imputation details added in Missing data imputation section for ranked relative fall rate outcome
Final 3.0	06-Feb-2025	1. Revision of the Ranked relative fall rate derivation in the SAP Section 6.1.7. Derived Variables, and introduction of the robust estimate of the relative fall rate to be used for the ranked outcome. 2. Revision of the previous time restriction applied for the Prior Medications used by the patient, defined in the SAP Section 7.5 as the medications taken by the patient within the 4 weeks prior to first IMP administration. As per the current text in the SAP, all the medications prior to the first IMP administration will be considered prior medications. 3. Adding an imputation algorithm to handle the Partial dates for the Concomitant Medications and Prior Medications in the SAP Section 6.1.8. Data Adjustments/Handling/Conventions. 4. From the Primary and Secondary Analysis (Section 8.1 and 8.2 respectively) removed the Patient inclusion into the model as a Random Effect, and for the Primary



		Analysis set the Covariance Matrix to be estimated in the compound symmetry scheme.
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Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
ASA	American Statistical Association
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification system
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CBL	Change from Baseline
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI _s	Confidence Intervals
CSR	Clinical Study Report
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOT	End of Treatment
EMA	European Medicines Agency
FAS	Full analysis SET
FDA	Food and Drug Administration
FSH	Follicle Stimulation Hormone
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
IRLAB	Integrative Research Laboratories Sweden AB
IRS	Interactive Response System
LS	Least Squares
M-EDL	Motor Experiences of Daily Living
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale

Abbreviation	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MoCA	Montreal Cognitive Assessment
n	Number of patients with Non-missing Values
NPI	Neuropsychiatric Inventory
PPS	Per Protocol Set
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
QTcF	Fridericia's correct QT interval
RSS	Royal Statistical Society
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, Figures
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Integrative Research Laboratories Sweden AB (IRLAB) protocol number IRL752C003 (A Randomized, Placebo-controlled, Multi-center Phase IIB Study Evaluating the Efficacy of Pirepemat on Falls Frequency in patients with Parkinson's Disease), protocol version #5 dated 23-Jan-2024, specific protocol Germany version #5 dated 23-Jan-2024 and specific protocol Netherlands version #3 dated 26-Jan-2024. Reference materials for this SAP include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonisations (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials ([ICH, 1998](#)). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association ([ASA, 2018](#)) and the Royal Statistical Society ([RSS, 2014](#)), for statistical practice.

The planned analyses identified in this SAP may be included in the clinical study report (CSR), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved and signed prior to database lock.

In addition to the analyses described herein, the Sponsor plans to undertake several statistical analyses such as Bayesian analysis of the efficacy data. These analyses will be specified in a separate document, prepared by the Sponsor prior to database lock, and will be considered exploratory.

2. Study Objectives and Endpoints

2.1. Study Objectives

Study objectives and endpoints are summarized in [Table 1](#), along with corresponding analyses and related tables, listings, figures (TLFs).

Table 1: Study Objectives and Endpoints

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
Primary objective				
To evaluate the effects of pirepemat on falls frequency as compared to placebo	Change in falls rate from baseline period (approximately 1 month prior to randomisation) to the end of treatment as assessed by fall diary (28 days prior to dose de-escalation).	Reporting the Change in Fall Rate from Baseline (diary)	Main: Bootstrap sampling – medians - relative treatment improvement Section 8.1 Linear model based on ranked relative fall rates Section 8.1 Secondary: Negative binomial regression Section 8.1 Secondary: MMRM on Weekly Fall Rates and on Ranked Relative Fall Rates Section 8.1	Table 14.2.1.1 Relative Fall Rates – Median Improvement Full Analysis Set Table 14.2.1.2 Relative Fall Rates – Median Improvement Per-protocol Set Table 14.2.1.3 Ranked Relative Fall Rates – Linear Mixed Model Full Analysis Set Table 14.2.1.4 Ranked Relative Fall Rates – Linear Mixed Model Per-protocol Set Table 14.2.1.5 Relative Fall Rate Ratios – Negative Binomial Regression Analysis Full Analysis Set Table 14.2.1.6 Relative Fall Rate Ratios – Negative Binomial Regression Analysis Per-protocol Set Table 14.2.1.7 Weekly Fall Rates – MMRM analysis Full Analysis Set Table 14.2.1.8 Weekly Fall Rates – MMRM analysis Per-protocol Set Table 14.2.1.9 Ranked Relative Fall Rates – MMRM analysis Full Analysis Set Table 14.2.1.10 Ranked Relative Fall Rates – MMRM analysis Per-protocol Set Table 14.2.1.11 Fall rate and categorical response – descriptive statistics and analysis Full Analysis Set Table 14.2.1.12 Fall rate and categorical response – descriptive statistics and analysis Per-protocol Set Figure 14.4.1.1 Treatment difference in Relative Fall Rate Plot (based on relative fall rates primary model) Full Analysis Set Figure 14.4.1.2 Treatment difference in Fall Rate Plot (based on MMRM model) Full Analysis Set

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
				Listing 16.2.6.1a Fall Rates Full Analysis Set
Secondary objectives:				
To evaluate the effects of pirepemat on Parkinson's disease motor symptoms as compared to placebo.	Change in the total score of MDS-UPDRS part II (M-EDL) from baseline to Week 11.	MDS-UPDR Part II	MMRM model, Section 8.2	Table 14.2.2.1 Change from baseline in total score of MDS-UPDRS part II (M-EDL) – analysis Full Analysis Set Table 14.2.2.2 Change from Baseline in Total Score of MDS-UPDRS Part II (M-EDL) - Analysis Per-protocol Set
To evaluate the effects of pirepemat on apathy as compared to placebo.	Change in total score (Frequency*Severity) and Caregiver distress of NPI Item G (Apathy/Indifference) from baseline to Week 11.	NPI: Apathy/ Indifference	MMRM model, Section 8.2	Table 14.2.3.1 Change from baseline in total score (Frequency*Severity) and Caregiver distress of NPI Item G (Apathy/Indifference) – analysis Full Analysis Set Table 14.2.3.2 Change from Baseline in Total Score (Frequency*Severity) and Caregiver Distress of NPI Item G (Apathy/Indifference) - Analysis Per-protocol Set
Other objectives				
To evaluate the effects of pirepemat on Parkinson's disease symptoms and severity as compared to placebo.	Change in MDS-UPDRS part I from baseline to Week 11.	MDS-UPDRS Part I	MMRM model, Section 8.3	Table 14.2.6.1 Change from baseline in MDS-UPDRS part I – analysis Full Analysis Set
	Change in MDS-UPDRS part III from baseline to Week 11.	MDS-UPDRS Part III	MMRM model, Section 8.3	Table 14.2.6.4 Change from baseline in MDS-UPDRS part III - analysis

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
				Full Analysis Set
	Change in MDS-UPDRS part IV from baseline to Week 11.	MDS-UPDRS Part IV	MMRM model, Section 8.3	Table 14.2.6.6 Change from baseline in MDS-UPDRS part IV - analysis Full Analysis Set
	Change in MDS-UPDRS part IV item 4.3 (Time spent in the off state) from baseline to Week 11.	MDS-UPDRS Part IV	MMRM model, Section 8.3	Table 14.2.6.7 Change from baseline in MDS-UPDRS part IV Time spent in the off state - analysis Full Analysis Set
	Change in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of gait) from baseline to Week 11.	MDS-UPDRS Part II and III	MMRM model, Section 8.3	Table 14.2.6.9 Change from baseline in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of gait) – analysis Full Analysis Set
	Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part I items: 1.2 (Hallucinations and psychosis), 1.3 (Depressed mood), 1.5 (Apathy), 1.6 (Features of dopamine dysregulation syndrome), 1.8 (Daytime sleepiness), 1.9 (Pain and other sensations), 1.13 (Fatigue).	MDS-UPDRS Part I	MMRM model, Section 8.3	Table 14.2.6.1 Change from baseline in MDS-UPDRS part I – analysis Full Analysis Set
	Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part II items: 2.1 (Speech), 2.12 (Walking and balance).	MDS-UPDRS Part II	MMRM model, Section 8.3	Table 14.2.6.10 Change from Baseline in MDS-UPDRS part II items 2.1 (Speech), 2.12 (Walking and balance) – Analysis – Analysis Full Analysis Set

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
	Change in modified Hoehn & Yahr score from baseline to Week 11.	Modified Hoehn and Yahr Staging Score evaluation	MMRM model, Section 8.3	Table 14.2.7.1 Change from baseline in modified Hoehn & Yahr score -analysis Full Analysis Set
	Clinician Global Impression (CGI), Severity and Improvement at Week 6 and Week 11.	CGI-S/CGI-I Scores	Chi square test, Section 8.3	Table 14.2.7.5 CGI-S and CGI-I scores – descriptive statistics and analysis Full Analysis Set
To evaluate the effects of pirepemat on postural dysfunction as compared to placebo.	Change in scores from baseline to Week 11 for the following tests: Single leg stance test Tandem walking test	Tandem Walking, Single Stance Test	MMRM model, Section 8.3	Table 14.2.7.3 Change from baseline in Tandem Walking and Single Stance Test – analysis Full Analysis Set
	Change in MDS-UPDRS item 3.12 (postural stability) from baseline to Week 11.	MDS-UPDR Part III	MMRM model, Section 8.3	Table 14.2.5.1: Change from baseline in MDS-UPDRS item 3.12 (postural stability) Full Analysis Set
To evaluate the effects of pirepemat on cognitive function as compared to placebo.	Change in total MoCA score from baseline to Week 11.	MoCA	MMRM model, Section 8.3	Table 14.2.4.1 Change from baseline in total MoCA score – analysis Full Analysis Set

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
To evaluate the safety and tolerability of pirepemat	Patient incidence of treatment-emergent adverse events	Adverse event reporting and questioning	Descriptive statistics, incidence rates, Section 9.1	Table 14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Table 14.3.1.3 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity Table 14.3.1.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to IMP Table 14.3.1.5 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Table 14.3.1.6 Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to IMP Table 14.3.1.7 Adverse Events of Special Interest Related to Fall by System Organ Class and Preferred Term
	Clinically significant changes in vital signs	Blood pressure and pulse	Descriptive statistics, Section 9.5	Table 14.3.7.1 Descriptive Statistics of Results and Change from Baseline for Vital Signs Table 14.3.7.2 Orthostatic Changes in Vital Signs, Descriptive Statistics
	Clinically significant changes in physical examination	Physical examinations	Descriptive statistics, Section 9.4	Table 14.3.6.1 Physical Examination
	Clinically significant changes in clinical laboratory safety tests	Blood sampling for haematology, clinical chemistry and coagulation	Descriptive statistics, Section 9.2 and 9.3	Table 14.3.2.1 Descriptive Statistics of Results and Change from Baseline for Chemistry Table 14.3.2.2 Shift table for Chemistry Table 14.3.3.1 Descriptive Statistics of Results and Change from Baseline for Hematology Table 14.3.3.2 Shift table for Hematology Table 14.3.4.1 Shift table for Urinalysis Table 14.3.5.1 Events of Special Interest (Increase of liver enzymes values ALT or AST > 2xULN)

Objectives	Endpoints	Assessments	Analyses	Related TLF shells
	Clinically significant changes in ECGs	12-lead safety ECG (Electrocardiogram)	Descriptive statistics, Section 9.6	Table 14.3.8.1 Descriptive Statistics of Results and Change from Baseline for ECG S Table 14.3.8.2 Categorical ECG Results
To examine the relationship between dose and plasma concentration of pirepemat and pharmacodynamic effects.	Relation between dose and plasma concentration and pharmacodynamic effect	Blood sampling for plasma concentration of pirepemat and metabolites	Descriptive statistics for pharmacokinetic/ pharmacodynamic Section 9.7	Table 14.3.9.1 Summary of Plasma Concentration (unit) of Pirepemat Following Administration of Oral Dose Table 14.3.9.2 Summary of Plasma Concentration (unit) of M12 Metabolite Following Administration of Oral Dose Table 14.3.9.3 Summary of Plasma Concentration (unit) of M11b Metabolite Following Administration of Oral Dose Table 14.3.10.1 Summary of Change from Baseline of Fall Rate by Plasma Concentration of Pirepemat Figure 14.5.1.1 Box Plot of Plasma Concentration of Pirepemat by Timepoint and Treatment Arm Figure 14.5.2.1 Change from Baseline of Fall Rate at Week 11 versus Plasma Concentration of Pirepemat Figure 14.5.2.2 Change from Baseline of Total MoCA Score at Week 11 versus Plasma Concentration of Pirepemat Figure 14.5.2.3 Change from Baseline of MDS-UPDRS item 3.12 (postural stability) at Week 11 versus Plasma Concentration of Pirepemat

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; M-EDL = motor experiences of daily living; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMRM = Mixed Model for Repeated Measures; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; TLF = tables, listings, figures; ULN = upper limit of normal

3. Overall Study Design and Plan

3.1. Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled study with the primary objective to evaluate the efficacy of 84 days' treatment with pirepemat in patients with Parkinson's Disease exhibiting axial motor and cognitive impairment.

3.2. Sample Size and Power

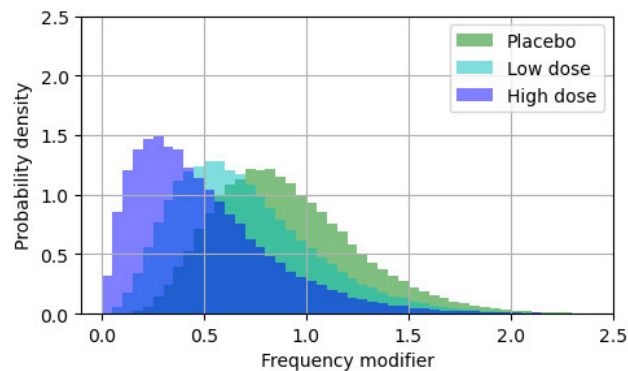
The initial sample size calculation (165 randomized patients) was made assuming a 45% relative decrease in fall rate in the active group vs. placebo and a baseline fall rate of 2.4 falls/4 weeks. The sample size has been re-estimated based on blinded review of falls data for the first 49 patients who have completed Visit 9. The data shows a considerably larger baseline fall rate (median 7.0 falls/4 weeks) than anticipated, and a large overall decrease in fall rate (median ca 50% decrease). The overall drop-out rate is approximately 15%, as initially assumed.

For the updated sample size calculation, trial outcomes are simulated with a data generating procedure that is consistent with the available blinded data yet affords us the freedom to specify a treatment effect size that is clinically relevant. The simulation proceeds in 2 steps, described briefly below and fully specified in the source code provided in the [Appendix](#).

First, a Bayesian model is used to fit a distribution to the fall rate during the baseline period, applying a hierarchical model where each patient has an underlying fall rate drawn from an inverse gamma distribution. The number of falls for each patient is then assumed to follow a Poisson distribution, truncated from below at $num_falls = 2$, to match the inclusion criterion. After fitting the model, baseline fall rates are sampled from the posterior predictive distribution. To exclude outliers that result from the long-tailed inverse gamma distribution, fall rates above 10 falls/day are discarded.

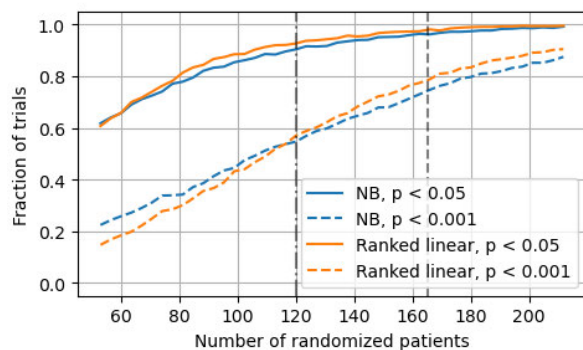
Second, fall rate changes from the baseline period to the end of study period (1 month) are modelled. Let $study_fall\ rate = baseline\ fall\ rate * rate_modifier$, where $rate_modifier$ is a random number for each patient, drawn from a distribution that we specify. It is assumed that the distribution is a gamma distribution with standard deviation 0.35, and a mean that depends on the treatment group assigned to the patient. Further, it is assumed that the mean is 0.9, 0.7 and 0.5 for the placebo group, low-dose group and high-dose group, respectively, i.e., a placebo effect of 10% ($1 - 0.9$) and a mean treatment effect for the high-dose group of 44% ($1 - 0.5/0.9$) relative to placebo. These distributions are plotted in [Figure 1](#).

Figure 1: Distribution of Underlying Relative Fall Rates Assumed for Each Treatment Group



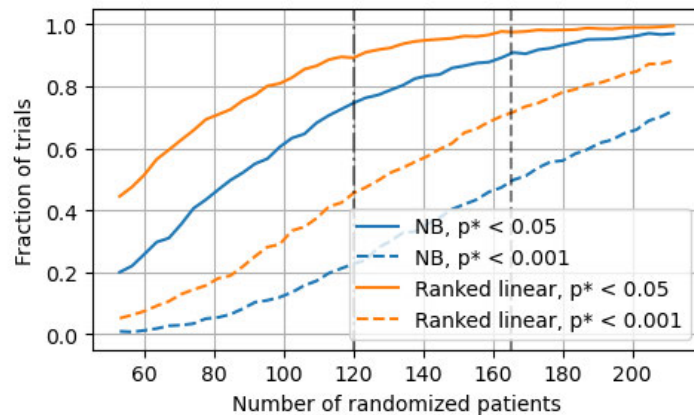
It is ensured that these distributions are plausible by measuring the mean and standard deviation for the empirical relative fall rate $(num_falls_study / num_days_study) / (num_falls_baseline / num_days_baseline)$. It is observed that the values measured for the blinded data are consistent with the data generation procedure (not shown).

Figure 2: Fraction of Trials Attaining <0.05 and <0.001 for the Comparison High-Dose vs. Placebo, Plotted Against the Number of Randomized patients



Using the above model, 1000 possible outcomes were simulated and the fraction of trials attaining a PP-value of 0.05 or below for the comparison of high-dose vs. placebo were measured. [Figure 2](#) shows how this power depends on the number of randomized patients in the study (assuming a non-completion rate of 15% which is consistent with the data collected so far). Similar results are obtained for 2 different analysis models, 1 negative binomial model, which is commonly used for modeling event data such as falls, and 1 linear model for which the dependent variable is the rank of the empirical relative fall rate. Both analyses achieve a similar power, reaching 90% at around 120 randomized patients. However, the ranked linear model is far less sensitive to outliers in the fall rate distribution. This is illustrated in [Figure 3](#), where the fall distribution of a single patient in the high-dose group was modified to match that of 1 heavy faller present in the blinded data. It is observed that the negative binomial model is very sensitive to this single outlier, whereas the power of the ranked linear model changes very little. For this reason, the ranked linear model is preferred for the primary analysis.

Figure 3: Power vs. Sample Sizes for the Negative Binomial and the Ranked Linear Model in the Presence of One Strong Outlier



Based on these results the sample size has been estimated to 120 randomized patients.

The blinded data review further showed that intercurrent events precluding adequate evaluation of falls do not occur with a high frequency, hence no adjustments to the sample size or analysis model are considered to be warranted related to intercurrent events.

3.3. Study Population

The study population consists of patients 55-85 years of age (inclusive) of both sexes with diagnosis of idiopathic Parkinson's disease, according to the United Kingdom Parkinson's disease Society Brain Bank criteria. More details for the study population can be found in the corresponding section of the protocol: inclusion and exclusion criteria are listed Sections 11.4 and 11.5, respectively.

3.4. Treatments Administered

Starting on Day 1 the IMP will be self-administered at home for twelve consecutive weeks; three oral daily doses (at approximately 8 am, 2 pm and 8 pm) as adjunct treatment to the patients' regular and stable antiparkinsonian medication.

Dosing will start with half the dose for the first week of treatment (i.e. 1 tablet t.i.d.), and then continue with full dose (2 tablets t.i.d.) until Week 11.

Dosing will be de-escalated according to pre-specified schedule during the last week of study treatment, ending with the last dose on Day 84 (Visit 8). During the treatment period Visits 3-8 will be performed after Week 2, 3, 4, 6, 8, 10, and 11. Patients and/or caregiver will also receive a phone call after the first week of treatment as a reminder to increase the dose and a phone call on the last day of treatment as a reminder to stop treatment. Method of Assigning patients to Treatment Groups

The study patients will be randomized to treatment with either pirepemat 100 mg t.i.d., pirepemat 200 mg t.i.d., or placebo (1:1:1) and treatment allocation will be performed via a web-based Interactive Response System (IRS).

The randomization will be stratified to ensure equal distribution of patients using cholinesterase

inhibitors across the 3 treatment arms.

3.5. Blinding and Unblinding

This is a double-blind study, thus, study patients, investigators, study staff and the sponsors will be blinded to the study treatments of pirepemat and placebo (tablets of pirepemat and placebo will be of identical appearance). All involved will remain blinded to the randomization scheme until the blind is formally broken for all patients. For this to occur all patients must have completed the study and the study database must be locked.

Prior to database lock, a treatment assignment may be unblinded only when knowledge of the treatment received is necessary for interpreting a serious adverse event (SAE), or essential for the medical management of the patient, or to provide critical safety information about a drug that could have implications for the ongoing conduct of the trial. Blinding codes must only be broken in emergency situations for reasons of patient safety or for regulatory submissions of Suspected Unexpected Serious Adverse Reaction (SUSAR) reports.

Investigators will receive a confidential code to access the IRS system that will enable them to selectively break the code for an individual patient. When the blinding code is broken, the reason must be fully documented and entered on the eCRF (electronic case report form).

If a patient's treatment assignment is unblinded, the medical monitor will be notified of the unblinding incident and the following information will be provided by the investigator: date, time, patient's trial identification, and the reason for unblinding. The patient will be withdrawn.

The identity and responsibility of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who are involved in the unblinding, and who have access to the unblinded treatment assignment, maintain the confidentiality of the information and do not divulge the treatment assignment.

3.6. Schedule of Events

A detailed schedule of assessment for the study is provided in Table 2.

Table 2: Schedule of Study and Study Procedures

Visit	V1 Screening	V2	Phone call ⁶	V3	V3b	V4	V5	V6	V7	V8	Phone call ⁸ EOT	V9	V12 ¹²	V13
	Screening period	Treatment period										Safety follow-up period		
Day	Up to 6 weeks before V2	0	7	14	21	28	42	56	70	77	84	1 day after EOT	12-14 days after EOT	33-37 days after EOT
Week	-6 to -4 weeks	0	1	2	3	4	6	8	10	11	12			
Visit window		-	±1 day	±1 day	±1 day	±2 days	±2 days	±2 days	±2 days	±2 days	-2 days			
Informed Consent	X													
Demographics	X													
Medical/surgical history	X													
Inclusion/Exclusion Criteria	X	X												
Prior and concomitant medications	X	X		X		X	X	X	X	X		X	X	X
Height	X													
Weight	X											X		
Physical Examination	X						X					X	X	
Vital Signs (incl. supine/standing BP)	X	X		X		X	X	X	X	X		X	X	
12-lead ECG	X						X			X		X	X	
Safety laboratory assessments ^{5,7,9}	X	X ¹		X ¹	X ^{1, 11}	X ¹	X ¹	X ¹	X ¹	X		X	X	X
Urine analysis ⁵	X									X		X	X	X
Dispense IMP (Investigational Medicinal Product)		X ¹⁰				X ⁴		X						
IMP administration at							X			X				

AD-ST-33.06 Effective date: 12-Nov-2020

Visit	V1 Screening	V2	Phone call ⁶	V3	V3b	V4	V5	V6	V7	V8	Phone call ⁸ EOT	V9	V12 ¹²	V13
	Screening period	Treatment period										Safety follow-up period		
Day	Up to 6 weeks before V2	0	7	14	21	28	42	56	70	77	84	1 day after EOT	12-14 days after EOT	33-37 days after EOT
Week	-6 to -4 weeks	0	1	2	3	4	6	8	10	11	12			
Visit window		-	±1 day	±1 day	±1 day	±2 days	±2 days	±2 days	±2 days	±2 days	-2 days			
clinical site														
IMP compliance assessment				X		X	X	X	X	X		X		
PK blood sampling, incl metabolite screening							X ²			X ²				
MDS-UPDRS	X	X					X			X				
Modified Hoehn & Yahr	X	X		X		X	X	X	X	X				
MoCA	X	X					X			X				
NPI		X					X			X				
Single leg stance test		X					X			X				
Tandem walking		X					X			X				
CGI-S		X					X			X				
CGI-I							X			X				
Randomization		X												
Confirm eligibility		X												
Distribute fall diary	X	X		X		X	X	X	X	X				
Fall diary review and collection		X		X		X	X	X	X	X		X		
Adverse Events, including assessment of suicide ideation and behavior ³	X	X		X		X	X	X	X	X		X	X	X

¹ Only liver chemistry (Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin)

² Taken within 15 min pre-dose and approx. 2 hours (± 15 min) after morning dose of IMP

³ Baseline symptoms from signature of Informed Consent Form up to first IMP administration, and Treatment Emergent Adverse Events (TEAEs) from first IMP administration

⁴ Patient will continue to use tablets in the bottle dispensed at V2, but a second bottle will also be dispensed at V4 to cover for the full period until V6.

⁵ Any safety lab result outside reference range and considered clinically significant should be followed with new samples until resolution, frequency of extra samples as judged by the Investigator

⁶ Phone call to remind the patient to increase (Day 7) the dose and to remind about fall diary completion and collection of the completed diary at study visit.

⁷ Hepatitis B Surface Antigen and Hepatitis C antibody testing are only performed at V1 Screening.

⁸ Phone call to remind the patient to stop treatment.

⁹ In exceptional circumstances, safety laboratory assessments can be performed at local laboratory.

¹⁰ Note that first IMP dispensation is performed at baseline visit (Day 0) but first administration is on Day 1, the day after the visit.

¹¹ Visit 3b does not have to be a visit to the clinical site, safety laboratory assessments can be performed at local laboratory instead.

¹² Visit 10 and Visit 11 existed in previous versions of the protocol and were removed. Naming of visits is kept for V12 and V13 despite absence of V10/V11.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values (unless otherwise specified), mean, standard deviation (SD), median, minimum, maximum, lower quartile and upper quartile as well as number of observations for both Actual values and change from baseline data (for pharmacokinetic [PK] variables the coefficient of variation [CV%] and geometric mean will also be presented).

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the patients had a response in a particular category. In general, the denominator for the percentage calculation will be based upon the total number of patients in the analysis set of interest (e.g., the Safety Set [SS], the Full Analysis Set [FAS] and the Per Protocol Set [PPS]).

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-sided tests implementing throughout without statistical adjustment for ‘multiplicity’ of analysis testing performed, and *P* values will be reported. Corresponding 2-sided 95% confidence intervals (CIs) will be presented for statistical tests. For calculating CIs for the median, SAS non-distribution method will be used.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

A medical monitor will continuously monitor safety assessments and if there are any trends or specific assessment results of concern, an independent Data Safety Monitoring Board (DSMB) will convene to review and discuss the case(s) to determine the next step.

The DSMB will also convene:

- When the 25th and 75th patients have completed the Follow-Up visit
- As soon as there has been a SUSAR

Recruitment will continue throughout the DSMB assessments.

The DSMB has the right to break the blind for the involved patients, request extra assessments, and recommend to the sponsors that the study be suspended, amended, terminated or lower doses be given, if considered appropriate.

5. Analysis Sets

The following analysis sets are planned for this study:

- **Safety Set (SS):** The Safety Set includes all patients who receive at least 1 dose of IMP.
- **Full Analysis Set (FAS):** The FAS includes all patients who are randomized and treated, who receive at least 1 dose of IMP and who provide at least 1 post baseline efficacy assessment on primary or secondary efficacy endpoints.
- **Per-protocol Set (PPS):** The PPS includes all patients in the FAS who have at least 80% compliance of study IMP (recorded compliance between 80-120%) and completed Week 11 (Visit 8) and have no major protocol deviations that would lead to exclusion from PPS set as per decision at blinded data review meeting.

Assignment of patients to sets will be confirmed at a blinded data review meeting to be held before the study database is locked.

Patients who receive the wrong treatment according to the randomization schedule throughout treatment period will be analyzed according to the treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For the fall rate endpoint: All collected data before first treatment (consecutive data recorded for approximately 1 month before start of Investigational Medicinal Product (IMP) administration) are considered for fall rate baseline.

For other endpoints: The last observation recorded before the first dose of treatment (if on same day, then it is considered baseline) will be used as the baseline observation for all calculations of change from baseline unless specified otherwise.

6.1.2. Adjustments for Covariates

For the primary endpoint analysis, strata for cholinesterase inhibitor use will be used as covariates in both models.

For the negative binomial regression model, log(fall rate at baseline), treatment group as a factor and log(time) as the offset parameter.

For analyzing other continuous variables, cholinesterase inhibitor use, treatment, country, and treatment by country (if significant) covariates will be used in the mixed model for repeated measures (MMRM) model.

6.1.3. Multiple Comparisons

This study is intended to evaluate the effect of pirepemat on falls, with the aim to inform decision making for the program to proceed to phase 3. The analyses will be performed with the high dose vs. placebo as the first analysis. Followed by Low dose vs. Placebo and the combination of high dose and low dose vs. Placebo.

6.1.4. Handling of Dropouts or Missing Data

The patients that screen fail, may be re-screened once if, in the opinion of the investigator, the reason for the screen fail could be mitigated. If a patient withdraws prematurely from the study treatment for any other reason than due to an adverse event (AE) or other safety concern, a new patient can be randomized to replace the withdrawn patient. The replacement will be managed through a centrally administered study wide randomization list. The reason for the patient's withdrawal from the study must be recorded.

Missing endpoint values in this study may result from patients discontinuing from the study prematurely or missing intermediate assessments while remaining on study.

Since the primary endpoint is a model for the rank of the relative fall rate, for patients with missing data we need to impute the rank. The imputation will only be done for evaluation period ranks. The method for imputation will be:

1. For each patient who has successfully completed the study (i.e. patients who are not prematurely discontinued), compute the rank of the relative fall rate for the evaluation period. Rescale it to the interval (0, 1) by $(\text{rank} - 1) / (\text{Maximum rank} - 1)$.
2. For every other patient (i.e. prematurely discontinued), identify the last 28 days prior to discontinuing treatment. Identify all other patients that remain in the study for these 28 days. Calculate the rank of the patient in question by comparing the relative fall rate for these 28 days. Rescale it to the interval (0, 1) by: $(\text{rank} - 1) / (\text{Maximum rank} - 1)$. Repeat for each discontinued patient.

Impute the ranks for the prematurely discontinued patients with the ranks in point 1 above.

To handle missing data for the secondary endpoints MMRM method will be used.

6.1.5. Analysis Visit Windows

Analyses of all variables for this study, unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available, and the unscheduled/repeated measurement falls within the analysis visit windows as described in [Table 3](#). Otherwise, visits will be analyzed as scheduled, and unscheduled/repeated measurements falling outside of the visit windows will be excluded from analysis and only listed. In case 2 unscheduled visits fall in the same time window, the visit closest to the target day will be considered (taking the first unscheduled in case of equal difference with the target day).

Table 3: Analysis Visit Windows

Analysis Day*	Analysis Visit	Week	Study Day	Lower Limit (Study Day)	Upper Limit (Study Day)
Screening	Screening Visit 1	– -6 -4 Weeks	to 0	-42	-24
Baseline	Visit 2	Week 0	1	1	1
Day 14	Visit 3	Week 2	15	14	16
Day 21	Visit 3b	Week 3	22	21	23
Day 28	Visit 4	Week 4	29	27	31
Day 42	Visit 5	Week 6	43	41	45
Day 56	Visit 6	Week 8	57	55	59
Day 70	Visit 7	Week 10	71	69	73
Day 77	Visit 8	Week 11	78	76	78
Day 84	EOT	Week 12	85	85	85

*Analysis day is calculated from Day 1 being the date of first dose.

6.1.6. Pooling of Sites

There will be no pooling of sites.

6.1.7. Derived Variables

Analysis days from [Table 3](#) are used for the following derivations.

- Baseline for safety measurements: last measurement before or on first dose date.
- Change from baseline = value at current time point – value at baseline.
- Treatment emergent adverse event (TEAE) = Any AE not present prior to the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.
- **Baseline period for primary efficacy endpoint:** the period with complete fall diary data (for at least 4 weeks, i.e. 28 days) prior to first dose day. Baseline period for primary efficacy endpoint: the period with complete fall diary data (at least 4 weeks) prior to first dose day
- Calculate the number of days between date of first dose until the date of the last day prior to de-escalation. If date of de-escalation is missing, the date of visit 8 should be used
 - Evaluation period: Use the last 28 days for the evaluation period

- Period 2: Use the preceding 25 days
- Period 1: Use the remaining days following baseline
- De-escalation period: period that starts with the dose de-escalation and ends with EOT
- Fall frequency for periods of interest:
 - Baseline: count the number of falls for whole baseline period prior to the first dose
 - Period 1: count the number of falls in period 1
 - Period 2: count the number of falls in period 2
 - Evaluation period: count the number of falls in evaluation period
- Number of days falls data assessed and diary completed for periods of interest:
 - Baseline: count the number of days falls data assessed for whole baseline period prior to the first dose
 - Period 1: count the number of days on which falls were assessed in period 1
 - Period 2: count the number of days on which falls were assessed in period 2
 - Evaluation period: count the number of days on which falls were assessed in the evaluation period
 - De-escalation period: count the number of days on which falls were assessed starting from de-escalation date until EOT
- Weekly fall rate = total number of falls by patient by week having Day 1 (dated of first dose) as reference point.
 - Baseline: count the number of falls for whole baseline period prior to the first dose divide by the number of days when falls were assessed in this period as per eCRF and multiply by 7
 - Period 1: count the number of falls in period 1, divide by the number of days when falls were assessed in this period as per eCRF and multiply by 7
 - Period 2: count the number of falls in period 2, divide by the number of days when falls were assessed in this period as per eCRF and multiply by 7
 - Evaluation Period: count the number of falls in the evaluation period, divide by the days when falls were assessed in this period as per eCRF and multiply by 7
 - De-escalation period: count the number of falls between de-escalation date and last dose date divide by the number of days when falls were assessed in this period as per eCRF and multiply by 7
- **Relative fall rate** (weekly fall rate in each period/weekly fall rate in baseline period × 100%)
- **Ranked relative fall rate:**
 - For the number of patients having a relative fall rate of zero, if one of these patients had a large number of falls at baseline, there is a high confidence that this low relative fall rate is due to an actual improvement rather than random fluctuations. When ranking the data, it should be assured that such patients are ranked lower than patients with relative fall rate zero but a low number of falls at baseline. Therefore, a **robust** estimate of the relative fall rate is calculated to be used for the ranked outcome, using the following formulation:

Robust relative fall rate (RRFR) = ((Number of falls in period + 1) / (Number of days in period)) / ((Number of falls at baseline + 1) / (Number of days in baseline)).

- After the calculation of the RRFR, the rank of the **robust** relative fall rate can be computed for all periods, as follows: Set 1st rank as lowest relevant fall rate. Same rates are ranked as the same rank, using lowest rank. Rescale ranks to the interval (0, 1) by (rank - 1) / (Maximum rank - 1). For patients not meeting *evaluation period criterion* for fall diary collection, please impute based on section 6.1.4 imputation description. For other periods, no imputation is planned.
- **Responder categories:** Relative fall rate in evaluation period × establish categories responder: ≤ 75%, ≤ 50% and ≤ 25%.
- Fridericia's correct QT interval (QTcF) categories at baseline or at any time point: >450 and ≤480, >480 and ≤500, >500
- QTcF categories – based on post baseline increase: >30 and ≤60, >60
- Number of doses administered: Number of doses administered are calculated from dispensed and remaining number of tablets in the dispensed bottles. Used amount is calculated by bottle, and all used added up.
- NPI Total Score: Frequency*Severity.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not patient to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in 4 decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) version 24.1 thesaurus.

A treatment-related AE is any AE with a relationship to the IMP of "Related": probable or possible. In case relationship for AE could not be assessed, AE will be considered as related, as per worst case scenario.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date before the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

If partial times occur, the convention is as follows: if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose (use 08:00 in case of first dose is morning dose, 14:00 if afternoon dose and 20:00 if evening dose.), otherwise if both the hour and minute are missing and the date is not the date of first dose

the time assigned is 12:00; if the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and if the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later. Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 if the date is not the same as the date of first dose.

These conventions will be applied only to TEAE onset dates and times, and with the following precaution: if the missing date and time reflect the date and time of onset of an TEAE, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the eCRF.

Meanwhile, partial dates for Concomitant and Prior Medications will be imputed as follows: If both the month and day are missing, the date will be imputed as June 30 of the given year. If the year and month are present but the day is missing, the 15th of the specified month will be imputed.

7. Study patients and Demographics

7.1. Disposition of patients and Withdrawals

The numbers of patients enrolled, randomized, completing, and discontinued early from the trial and discontinued from treatment, along with reasons for withdrawal and number of patients in each analysis set will be tabulated overall and by treatment group when possible.

For all categories of patients, percentages will be calculated using the number of randomized patients as denominator. The total number of screening failures and the reasons for screen failure will be presented overall.

Prematurely discontinued patients' frequencies will be tabulated.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, ethnicity, height, weight, and body mass index (BMI) will be summarized by treatment group and overall, for the FAS.

For the continuous variables, the number of non-missing values and the mean, SD, minimum, median, maximum, lower quartile and upper quartile will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

The number and percent of patients reporting medical/surgical history will be tabulated by treatment group and overall, grouped by MedDRA system organ class (SOC) and preferred term (PT) (coded using MedDRA v.24.1). This analysis will be conducted for the FAS. Data for all patients will be listed.

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7.4. Exposure and Compliance

The number and percentage of patients administered study treatment, total patients with dose escalated to full dose after first week, total patients with dose de-escalation performed according to protocol, total patients with dose reduction to half dose during the study, IMP compliance since start of IMP treatment and number of doses administered will be presented in tabular form.

7.5. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that are used by the patient prior to first IMP administration will be considered prior medications. Any medication used from first administration of IMP until the last follow-up assessment will be considered as concomitant. If a medication starts prior to first IMP administration and continues after the first IMP administration, it will be considered both prior and concomitant. Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) Global B3 (v. Sep 2021), and Anatomic Therapeutic Chemical (ATC) Level 4 and preferred name will be tabulated.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is to evaluate the effects of pirepemat on fall rate as compared to placebo through the change in fall rate from baseline period (all falls rate data from approx. 1 month before Day 1) to the evaluation period (i.e. the last 4 weeks before the de-escalation period (or EOT in case of discontinuation without de-escalation) as assessed by fall diary.

The analysis of the primary endpoint, fall rate, will be performed by means of a linear model, using the ranks of the relative fall rates as dependent variable, strata for cholinesterase inhibitor use as covariate, and treatment group as a factor (SAS Proc Mixed).

The relative treatment improvement will be also computed using bootstrap sampling. Results will be presented as median relative event rate ratio with 95% CI. The primary treatment effect is the ratio between the median fall rate in the high dose group and the Placebo group. Compute a confidence interval through the following bootstrap procedure:

1. Compute 10000 bootstrap estimates of the median relative fall rate for the high dose group and 10000 bootstrap estimates for the median relative fall rate for the control group.
2. Pair them up to compute 10000 estimates of the relative event rate ratio (median relative fall rate of high dose group) / (median relative fall rate of placebo group)
3. Order these estimates and compute the 2.5 and 97.5% percentile. This is the confidence interval.
4. Compute the relative improvement as $(1 - \text{relative event rate ratio}) * 100\%$

As a sensitivity analysis of primary endpoint relative fall rate, fall rate will be analyzed using

negative binomial regression in SAS Proc Genmod, with log(fall rate at baseline), days during baseline period and strata for cholinesterase inhibitor use as covariates, treatment group as a factor, and log(time) during the evaluation as the offset parameter. The result will be presented with the 95% CI for the event rate ratio.

For the sensitivity analysis no data imputation will be performed. If fall diary data is collected for at least 21 days out of 28 days for the target evaluation period, i.e., the last 4 weeks before the de-escalation period (or EOT in case of discontinuation without de-escalation), data will be included for the analysis having the offset as the (log of) actual recorded duration in the negative binomial model.

As an additional sensitivity analysis, treatment groups will be compared for weekly fall rate outcome using MMRM. The weekly fall rate at each period (Period 1, Period 2, Evaluation period) is the dependent variable. The model will include the baseline weekly fall rate as a fixed effect covariate, with fixed effect categorical factors for cholinesterase inhibitor use, treatment group (pirepemat and placebo), time period, an interaction term of treatment by time period and country). Denominator degrees of freedom will be calculated according to Kenward-Roger method, a compound symmetry covariance structure will be used to model the within-patient errors. The result will be presented using least squares (LS) means for each treatment along with estimated treatment difference and a 95% CI for this difference.

An MMRM will also be performed on ranked relative fall rates. The ranked relative fall rate at each period (Period 1, Period 2, Evaluation period) is the dependent variable. The model will include fixed effect categorical factors for cholinesterase inhibitor use, treatment group (pirepemat and placebo), time period, an interaction term of treatment by time period, and country). Denominator degrees of freedom will be calculated according to Kenward-Roger method, a compound symmetry covariance structure will be used to model the within-patient errors. The result will be presented using least squares (LS) means for each treatment along with estimated treatment difference and a 95% CI for this difference.

For graphical presentation both the median and mean relative fall rate will be presented per period with a 95% CI.

The primary analysis will be the treatment difference of patients randomized to 600 mg pirepemat (higher dose) against placebo. Additionally, pairwise treatment differences of pirepemat 300 mg (lower dose) and placebo as well as all patients randomized to pirepemat (overall) and placebo will be analyzed.

Primary analyses will be performed on FAS.

8.1.1. Sensitivity Analyses of the Primary Efficacy Endpoint

The sensitivity analysis of the primary efficacy endpoint is to evaluate the change in fall rate from baseline period (all falls data before Day 1, data from approximately 1 month) to the 4-week evaluation period as assessed by fall diary performed on the PPS as described in section 8.1.

8.1.2. Analysis of Categorical Response Variables

Categorical responses: Relative fall rate (fall rate in evaluation period/fall rate in baseline period)

× 100): $\leq 75\%$ / $>75\%$, $\leq 50\%$ / $>50\%$, $\leq 25\%$ / $>25\%$ will be analyzed Chi-Square test without continuity correction and with Fisher's exact test. P values from both tests will be output to summary table. Comparison will be performed for Pirepemat Higher Dose vs Placebo, Pirepemat Lower Dose vs Placebo and Pirepemat Overall vs Placebo groups.

8.2. Secondary Efficacy Analysis

Secondary analyses will evaluate the effects of pirepemat at 11 weeks (Visit 8) on Parkinson's' disease motor symptoms (score of Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] part II [Motor Experiences of Daily Living, M-EDL]) and apathy (total score (Frequency*Severity) and caregiver distress of Neuropsychiatric Inventory (NPI) Item G (Apathy/Indifference) as compared to placebo. Treatment groups will be compared for the change from baseline to Week 11 (Visit 8) using MMRM. The observed change from baseline score at each scheduled post-baseline visit is the dependent variable. The model will include the baseline score as a fixed effect covariate, with fixed effect categorical factors for cholinesterase inhibitor use, treatment group (pirepemat and placebo), visit, country, treatment by visit interaction term. Denominator degrees of freedom will be calculated according to Kenward-Roger method, and an unstructured covariance structure will be used to model the within-patient errors. The result will be presented using LS means for each treatment along with estimated treatment difference and a 95% CI for this difference.

The unstructured variance/covariance matrix will be used to model the variances and covariances for time points included in the model. The unstructured variance/covariance does not impose any restrictions on the pattern of the matrix elements. If there is a convergence issue with the unstructured covariance model, the following variance/covariance matrix structures will be used in the following order: 1) heterogeneous Toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry. The first variance/covariance structure which does not have a convergence problem will be the one used for the analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Analyses will be performed on the FAS and repeated for evaluation of the sensitivity and robustness on the PPS.

8.3. Exploratory Efficacy Analysis

The exploratory efficacy endpoints of this study include the following:

- Change in MDS-UPDRS part I from baseline to Week 11
- Change in MDS-UPDRS part II from baseline to Week 11
- Change in MDS-UPDRS part III from baseline to Week 11
- Change in MDS-UPDRS part IV from baseline to Week 11
- Change in MDS-UPDRS part IV item 4.3 (Time spent in the off state) from baseline to Week 11
- Change in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of gait) from baseline to Week 11

- Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part I items: 1.2 (Hallucinations and psychosis), 1.3 (Depressed mood), 1.5 (Apathy), 1.6 (Features of dopamine dysregulation syndrome), 1.8 (Daytime sleepiness), 1.9 (Pain and other sensations), 1.13 (Fatigue)
- Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part II items: 2.1 (Speech), 2.12 (Walking and balance)
- Change in modified Hoehn & Yahr score from baseline to Week 11
- Change in scores from baseline to Week 11 for the following tests:
 - Single leg stance test (elapsed time for both legs in seconds)
 - Tandem walking test
- Change in MDS-UPDRS item 3.12 (postural stability) from baseline to Week 11
- Change in total Montreal Cognitive Assessment (MoCA) score from baseline to Week 11
- CGI-S and CGI-I scores by Time Point (Baseline, Week 6, Week 11)

Description of MDS-UPDRS scores:

0: Normal

1: Slight

2: Mild

3: Moderate

4: Severe

Description of Hoehn and Yahr scale scores:

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

Description of MOCA scores:

Executive/visuospatial function, max 5 points

Naming, max 3 points

Attention, max 6 points

Language, max 3 points

Abstraction, max 2 points

Recall, max 5 points

Orientation, max 6 points

TOTAL, max 30 points

MOCA Interpretation:

26-30 points: Normal cognition

18-25 points: Mild cognitive impairment

10-17 points: Moderate cognitive impairment

Under 10 points: Severe cognitive impairment

Tandem walking score interpretation:

0 - Normal for 10 steps

1 - 1 to 3 deviations

2 - >3 deviations

3 – Cannot complete

4 - Cannot attempt

CGI-S score descriptions:

1 = Normal, not at all ill

2 = Borderline ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill of subjects

0 = Not Assessed

CGI-I score descriptions:

1=Very much improved

2=Much improved

3=Minimally improved

4=No change

5=Minimally worse

6=Much worse

7=Very much worse

NPI score descriptions:

SEVERITY of the symptom (how it affects the patient): 1 = Mild (noticeable, but not a significant change) 2 = Moderate (significant, but not a dramatic change) 3 = Severe (very marked or prominent, a dramatic change)

DISTRESS caregiver experiences due to that symptom (how it affects caregiver): 0 = Not distressing at all 1 = Minimal (slightly distressing, not a problem to cope with) 2 = Mild (not very distressing, generally easy to cope with) 3 = Moderate (fairly distressing, not always easy to cope with) 4 = Severe (very distressing, difficult to cope with) 5 = Extreme or Very Severe (extremely distressing, unable to cope with)

FREQUENCY of the symptom: 1. Occasionally- less than once per week, 2. Often - about once per week, 3. Frequently -several times per week but less than every day.

The statistical analysis will be similar to the analysis described in Section 8.2 for continuous variables. The statistical analysis will consist of an MMRM model, including results at previous time points and including cholinesterase inhibitor use, treatment (also treatment and timepoint interaction), and country as covariates, will be used to compare the treatment group to placebo across all exploratory efficacy endpoints with continuous variables. The result will be presented using LS means for each treatment along with estimated treatment difference and a 95% CI for this difference.

The analysis of categorical variables will be analyzed using Chi-Square test without continuity correction.

The individual treatment proportion will be presented by n and % together with a 95% CI. Exploratory analyses will be performed on FAS and won't be repeated for PPS.

All data will be displayed in by-patient listings.

8.4. Subgroup Analyses of Efficacy Variables

No specific subgroup analyses have been identified.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and electrocardiogram (ECG) results.

All safety analyses will be performed on the Safety Set.

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9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA v. 24.1

An AE summary table will be created presenting the following occurrences:

- Adverse event
- Adverse event categorized as severe
- Adverse event related to IMP
- Serious adverse event
- Serious adverse event related to IMP
- Adverse events of special interest (AESIs) related to fall
- Adverse event leading to death

Frequencies of the above will be presented for both dose levels vs placebo.

The number and percent of patients reporting TEAEs, grouped by MedDRA SOC and PT (coded using MedDRA v. 24.1), will be tabulated by severity and treatment group. In the case of multiple occurrences of the same TEAE within the same patient, each patient will only be counted once for each PT.

Adverse event summaries will be repeated for treatment-related (probable or possible) and not related AEs.

In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported; AEs with a missing relationship will be considered as related, AEs with a missing severity will be considered as severe.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged.

9.1.1. Adverse Events of Special Interest Related to Fall

A summary of incidence rates (frequencies and percentages) of AESIs related to falls (and are treatment emergent) will be prepared for the Safety Set by treatment group, SOC, and PT. No inferential statistical tests will be performed.

A data listing of AEs related to fall will also be provided, displaying details of the event(s) captured on the eCRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and tabulated by SOC and PT and presented by treatment group.

9.2. Clinical Laboratory Parameters

Laboratory test results of clinical chemistry, hematology, coagulation parameters and urine samples will be summarized descriptively by treatment and time point as both observed values and change from baseline values. Events of Special Interest (increase of liver enzyme values alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $> 2 \times$ upper limit of normal [ULN]) will be summarized.

Only central laboratory data will be used for summaries, local laboratory data will be listed.

The number of patients with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

Abnormal values will be flagged in data listings and clinical significance will be indicated; a separate listing of clinically significant abnormal values will be presented.

All laboratory data for all patients will be listed.

9.3. Liver Events

Liver event data (as collected in eCRF) will be listed. Increase of Liver Enzymes Values (ALT or AST $> 2 \times$ ULN) will be presented in a summary table.

9.4. Physical examination

Head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities will be tabulated by treatment. The number and proportion of patients with abnormal and normal results and those with assessments not done will be presented for the safety set by assessment, visit and treatment group.

Data for all patients will be listed.

9.5. Vital Signs

Descriptive summaries of actual values and changes from baseline for each variable for each patient, by time point and treatment will be calculated for pulse, supine systolic blood pressure and supine diastolic blood pressure.

For blood pressure and pulse rate, the orthostatic changes will be calculated as standing minus supine readings. Patients meeting the following criteria will be identified:

- patients with > 20 mmHg reduction (standing minus supine) in systolic blood pressure at 1 minute or 3 minutes of standing.
- patients with > 10 mmHg reduction (standing minus supine) in diastolic blood pressure at 1 minute or 3 minutes of standing.

Data of measurements meeting the above criteria will be listed. In data listing, investigator's observation on any orthostatic changes will be presented.

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Data for all patients will be listed. Abnormal, clinically significant results will be listed separately.

9.6. Electrocardiogram Results

Descriptive summaries of actual values and changes from baseline, for each variable for each patient, by time point and treatment will be calculated for PQ, QRS, QT and QTcF. patients with QTcF > 500 ms and change from Baseline of QTcF of > 30 ms and 60 ms will be tabulated.

Data for all patients will be listed.

9.7. Pharmacokinetic Analysis

Pharmacokinetic (PK) analyses will be based on the FAS.

Blood samples for PK analysis of pirepemat and metabolites will be collected within 15 min pre-dose and approximately 2 hours ($\pm$ 15 min) post dose on Week 6 (Day 42) and Week 11 (Day 77).

Plasma concentration data will be summarized by dose group and timepoint using summary statistics. Data will be presented in terms of number (n), arithmetic mean, (SD), minimum and maximum value, the geometric mean and CV%, and number of values that are below the limit of quantification (BLQ). Dose normalized data will be presented.

For plasma concentration data, all BLQ values will be set to 0 for summary statistics and graphs. Any missing concentrations will not be imputed and will be left missing. Individual patients' plasma concentration data will be presented in a data listing.

If results from both sample A and B are available, then results from A sample are used for the analysis, if B is only available, then results from B sample are used.

Plasma concentration data together with pharmacodynamic data will be used to explore the relation between dose and plasma concentration and pharmacodynamic effect and/or efficacy endpoint graphically. For Week 11 figure, evaluation period percentage change from baseline fall rates will be displayed.

These data may also be analyzed by nonlinear mixed effects modeling (PK/PD modeling) in conjunction with additional PK/PD data from other PK/PD studies. The modeling analysis plan will be described in separate PK analysis plan.

Available metabolite concentrations (M12 [IRL991] and M11b [IRL1010]) will be analyzed similarly.

The plasma concentrations of additional metabolites (IRL1053 and IRL1168) will be measured as an exploratory analysis. This data will be collected in a separate database and will be described in a separate bioanalytical report.

10. Differences from protocol

The following differences are planned in the analysis compared to the clinical study protocol:

- Two additional MMRM models added for the primary outcome measure.

- Instead of site, country will be used as effect in MMRM models.
- By gender tabulation of AEs, exposure and compliance and demographics is not planned.
- Evaluation phase is defined in SAP for early discontinued patients as well: last 4 weeks before dose de-escalation date or maximum 4 weeks before EOT in case of early discontinued patients without de-escalation.
- Periods are defined in SAP, Period 1 from Day 1 to Day 25 and Period 2 from Day 26-Day 49.
- Protocol does not define endpoint Relation between dose and plasma concentration and pharmacodynamic effect in detail. Outputs/descriptions were added consulting PK analyst.
- Statistical test for categorical response categories is added in SAP.
- CGI-I and CGI-S endpoints and tabulation descriptions added in SAP. These were not described under endpoint section in the Protocol, only under Objectives, however data presentation is planned.
- Liver laboratory values analysis is planned in SAP presenting ALT/AST >2xULN. Liver events are collected on a separate CRF page and will be listed. Liver value tabulation is not connected to liver event CRF data, it is based purely on laboratory data.
- Protocol does not include the endpoint related to CGI-S and CGI-I assessments. The corresponding endpoint is added in SAP.

11. References

ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. <http://www.amstat.org/about/ethicalguidelines.cfm>

ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. <https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/>.

12. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (eCRF page or listing number).

The following are planned summary tables for protocol number IRL752C003. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

12.1. Planned Tables and Figures

Number and title	Population
Table 14.1.1 Patient Disposition	All patients
Table 14.1.2 Demographics and Baseline Characteristics	Full Analysis Set
Table 14.1.3 Medical/Surgical History by System Organ Class and Preferred Term	Full Analysis Set
Table 14.1.4 Prior Medications by ATC Level 4 and Preferred Name	Full Analysis Set
Table 14.1.5 Concomitant Medications by ATC Level 4 and Preferred Name	Full Analysis Set
Table 14.1.6 Exposure and Compliance	Full Analysis Set
Table 14.2.1.1 Relative Fall Rates – Median Improvement	Full Analysis Set
Table 14.2.1.2 Relative Fall Rates – Median Improvement	Per-protocol Set
Table 14.2.1.3 Ranked Relative Fall Rates – Linear Mixed Model	Full Analysis Set
Table 14.2.1.4 Ranked Relative Fall Rates – Linear Mixed Model	Per-protocol Set
Table 14.2.1.5 Relative Fall Rate Ratios – Negative Binomial Regression Analysis	Full Analysis Set
Table 14.2.1.6 Relative Fall Rate Ratios – Negative Binomial Regression Analysis	Per-protocol Set
Table 14.2.1.7 Weekly Fall Rates – MMRM analysis	Full Analysis Set
Table 14.2.1.8 Weekly Fall Rates – MMRM analysis	Per-protocol Set
Table 14.2.1.9 Ranked Relative Fall Rates – MMRM analysis	Full Analysis Set
Table 14.2.1.10 Ranked Relative Fall Rates – MMRM analysis	Per-protocol Set
Table 14.2.1.11 Fall rate and categorical response – descriptive statistics and analysis	Full Analysis Set
Table 14.2.1.12 Fall rate and categorical response – descriptive statistics and analysis	Per-protocol Set
Table 14.2.2.1 Change from baseline in total score of MDS-UPDRS part II (M-EDL) – analysis	Full Analysis Set
Table 14.2.2.2 Change from baseline in total score of MDS-UPDRS part II (M-EDL) – analysis	Per-protocol Set
Table 14.2.3.1 Change from baseline in total score (Frequency*Severity) and Caregiver distress of NPI Item G (Apathy/Indifference) – analysis	Full Analysis Set
Table 14.2.3.2 Change from baseline in total score (Frequency*Severity) and Caregiver distress of NPI Item G (Apathy/Indifference) – analysis	Per-protocol Set
Table 14.2.3.3 Neuropsychiatric Inventory – descriptive statistics	Full Analysis Set
Table 14.2.4.1 Change from baseline in total MoCA score – analysis	Full Analysis Set
Table 14.2.4.2 Montreal Cognitive Assessment – descriptive statistics	Full Analysis Set
Table 14.2.5.1 Change from baseline in MDS-UPDRS item 3.12 (postural stability)	Full Analysis Set
Table 14.2.6.1 Change from baseline in MDS-UPDRS part I- analysis	Full Analysis Set
Table 14.2.6.2 MDS-UPDRS part I- descriptive statistics	Full Analysis Set

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Number and title	Population
Table 14.2.6.3 MDS-UPDRS part II- descriptive statistics	Full Analysis Set
Table 14.2.6.4 Change from baseline in MDS-UPDRS part III – analysis	Full Analysis Set
Table 14.2.6.5 MDS-UPDRS part IV- descriptive statistics	Full Analysis Set
Table 14.2.6.6 Change from baseline in MDS-UPDRS part IV – analysis	Full Analysis Set
Table 14.2.6.7 Change from baseline in MDS-UPDRS part IV Time spent in the off state – analysis	Full Analysis Set
Table 14.2.6.8 MDS-UPDRS part IV- descriptive statistics	Full Analysis Set
Table 14.2.6.9 Change from baseline in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of gait) – analysis	Full Analysis Set
Table 14.2.6.10 Change from Baseline in MDS-UPDRS part II items 2.1 (Speech), 2.12 (Walking and balance) - Analysis	Full Analysis Set
Table 14.2.7.1 Change from baseline in modified Hoehn & Yahr score - analysis	Full Analysis Set
Table 14.2.7.2 Modified Hoehn & Yahr score -descriptive statistics	Full Analysis Set
Table 14.2.7.3 Change from baseline in Tandem Walking and Single Stance Test – analysis	Full Analysis Set
Table 14.2.7.4 Tandem Walking and Single Stance Test – descriptive statistics	Full Analysis Set
Table 14.2.7.5 CGI-S and CGI-I scores – descriptive statistics and analysis	Full Analysis Set
Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events	Safety Set
Table 14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.1.3 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Set
Table 14.3.1.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to IMP	Safety Set
Table 14.3.1.5 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.1.6 Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to IMP	Safety Set
Table 14.3.1.7 Adverse Events of Special Interest Related to Fall by System Organ Class and Preferred Term	Safety Set
Table 14.3.2.1 Descriptive Statistics of Results and Change from Baseline for Chemistry	Safety Set
Table 14.3.2.2 Shift table for Chemistry	Safety Set
Table 14.3.3.1 Descriptive Statistics of Results and Change from Baseline for Hematology	Safety Set
Table 14.3.3.2 Shift table for Hematology	Safety Set
Table 14.3.4.1 Shift table for Urinalysis	Safety Set
Table 14.3.5.1 Events of Special Interest (Increase of liver enzymes values ALT or AST > 2xULN)	Safety Set

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Number and title	Population
Table 14.3.6.1 Physical Examination	Safety Set
Table 14.3.7.1 Descriptive Statistics of Results and Change from Baseline for Vital Signs	Safety Set
Table 14.3.7.2 Orthostatic Changes in Vital Signs, Descriptive Statistics	Safety Set
Table 14.3.8.1 Descriptive Statistics of Results and Change from Baseline for ECG	Safety Set
Table 14.3.8.2 Categorical ECG Results	Safety Set
Table 14.3.9.1 Summary of Plasma Concentration (unit) of Pirepemat Following Administration of Oral Dose	Full Analysis Set
Table 14.3.9.2 Summary of Plasma Concentration (unit) of M12 Metabolite Following Administration of Oral Dose	Full Analysis Set
Table 14.3.9.3 Summary of Plasma Concentration (unit) of M11b Metabolite Following Administration of Oral Dose	Full Analysis Set
Table 14.3.10.1 Summary of Change from Baseline of Fall Rate by Plasma Concentration of Pirepemat	Full Analysis Set
Figures	
Figure 14.4.1.1 Treatment difference in Relative Fall Rate Plot (based on relative fall rates primary model)	Full Analysis Set
Figure 14.4.1.2 Treatment difference in Weekly Fall Rate Plot (based on MMRM model)	Full Analysis Set
Figure 14.5.1.1 Box Plot of Plasma Concentration of Pirepemat by Timepoint and Treatment Arm	Full Analysis Set
Figure 14.5.2.1 Change from Baseline of Fall Rate at Week 11 versus Plasma Concentration of Pirepemat	Full Analysis Set
Figure 14.5.2.2 Change from Baseline of Total MoCA Score at Week 11 versus Plasma Concentration of Pirepemat	Full Analysis Set
Figure 14.5.2.3 Change from Baseline of MDS-UPDRS item 3.12 (postural stability) at Week 11 versus Plasma Concentration of Pirepemat	Full Analysis Set

12.2. Planned Listings

Number and title	Population
Listing 16.2.1.1 Patient Disposition	All patients
Listing 16.2.1.2 Study Populations	All patients
Listing 16.2.1.3 Randomization	All patients
Listing 16.2.2.1 Protocol Deviations	All patients
Listing 16.2.4.1 Demographics and Baseline Characteristics	Full Analysis Set
Listing 16.2.4.2 Medical History	Full Analysis Set
Listing 16.2.4.3 Prior and Concomitant Medications	Full Analysis Set
Listing 16.2.5.1 Exposure	Full Analysis Set

Number and title	Population
Listing 16.2.5.2 Compliance	Full Analysis Set
Listing 16.2.5.3 Individual Plasma Concentration (unit) of Pirepemat and Metabolites	Full Analysis Set
Listing 16.2.6.1a Fall Rates	Full Analysis Set
Listing 16.2.6.1b Fall Diary Data	Full Analysis Set
Listing 16.2.6.2 Montreal Cognitive Assessment	Full Analysis Set
Listing 16.2.6.3 Tandem Walking and Single Stance Test	Full Analysis Set
Listing 16.2.6.4 Neuropsychiatric Inventory: Apathy/Indifference	Full Analysis Set
Listing 16.2.6.5 Clinical Global Impression – Severity (CGI-S) and Improvement (CGI-I) Scale	Full Analysis Set
Listing 16.2.6.6. Modified Hoehn and Yahr Staging Score	Full Analysis Set
Listing 16.2.6.7.1 Unified Parkinson’s Disease Rating Scale Part I	Full Analysis Set
Listing 16.2.6.7.2 Unified Parkinson’s Disease Rating Scale Part II	Full Analysis Set
Listing 16.2.6.7.3 Unified Parkinson’s Disease Rating Scale Part III	Full Analysis Set
Listing 16.2.6.7.4 Unified Parkinson’s Disease Rating Scale Part IV	Full Analysis Set
Listing 16.2.7.1 Adverse Events	Safety Set
Listing 16.2.7.2 Serious Adverse Events	Safety Set
Listing 16.2.7.3 Liver Events	Safety Set
Listing 16.2.8.1 Serum Chemistry Results	Safety Set
Listing 16.2.8.2 Hematology Results	Safety Set
Listing 16.2.8.3 Coagulation Results	Safety Set
Listing 16.2.8.4 Serology Results	Safety Set
Listing 16.2.8.5 Urinalysis Results	Safety Set
Listing 16.2.8.6 FSH and Estradiol Results	Safety Set
Listing 16.2.8.7 Liver Chemistry Results	Safety Set
Listing 16.2.8.8 Cystatin-C Results	Safety Set
Listing 16.2.8.9 Abnormal and Clinically Significant Laboratory Results	Safety Set
Listing 16.2.9.1 Vital Signs Data	Safety Set
Listing 16.2.9.2 Vital Signs – Orthostatic Hypotension	Safety Set
Listing 16.2.9.3 Physical Examination Results	Safety Set
Listing 16.2.9.4 ECG Results	Safety Set

Appendix

Figure 4: Source Code for Sample Size Estimation

```
from functools import partial
import pymc as pm
import numpy as np
import pandas as pd
from diskcache import Cache
from read_data import get_visit_falls_table

cache = Cache(".diskcache")

@cache.memoize() # Fit the model once and cache the results
def get_baseline_samples(draws=4000, tune=2000, distribution=pm.InverseGamma):
    df = (
        get_visit_falls_table()
    ) # Returns a pandas dataframe with the number of falls per patient per visit
    baseline_df = df[df["Visit"] == "V2 - Baseline"]

    # Exclude patients with less than 11 days of observation
    filtered_baseline_df = baseline_df[baseline_df["Number of days"] > 10]

    coords = {"obs_idx": filtered_baseline_df["Patient ID"].values}
    with pm.Model(coords=coords) as baseline_fall_model:
        # Hyperparameters
        alpha = pm.HalfNormal("alpha", 10)
        beta = pm.HalfNormal("beta", 10)
        # Parameters
        daily_rate = distribution(
            "daily_rate", alpha, beta, shape=len(filtered_baseline_df)
        )

        # Likelihood
        y_raw = pm.Poisson.dist(mu=daily_rate * filtered_baseline_df["Number of days"])
        # Truncate at 2 falls to match the inclusion criterion
        y = pm.Truncated(
            "y",
            y_raw,
            lower=2,
            observed=filtered_baseline_df["Number of falls"],
            dims="obs_idx",
        )

        # Inference
        trace = pm.sample(draws=draws, tune=tune)
        posterior_predictive = pm.sample_posterior_predictive(
            trace, baseline_fall_model, ["daily_rate"]
        )
        rate_samples = (
            posterior_predictive["posterior_predictive"]["daily_rate"]
            .to_numpy()
            .ravel()
        )
        outliers = rate_samples > 10
        print(rate_samples.max())
```