Sponsor: Annovis Bio Inc.

Protocol: ANVS-12003

Statistical Analysis Plan

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Effects of Posiphen® in Subjects with Early Alzheimer's Disease (AD) or Early Parkinson's Disease (PD)

Part 1-The evaluation of the safety, tolerability and pharmacokinetics of Placebo and 80 mg QD Posiphen in 14 Early AD and 14 Early PD patients

Part 2-The evaluation of the safety, tolerability and pharmacokinetics of Placebo and Posiphen 5 mg QD, 10 mg QD, 20 mg QD, 40 mg QD and 80 mg QD in 54 Early PD patients.

Current Protocol	ANVS-12003_AD-PD-CSFProtocol_v3_8-21-2020
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1	27/11/2020	Neil Parkinson	Original - Text
2	06/12/2020	Neil Parkinson	Updates to text following internal DML review
3	15/01/2021	David Fleet	Review and additional stats methods
4	05/02/2021	Neil Parkinson David Fleet	Part 1 PD and AD analyses to include both Within Group analyses (change from baseline for both AD and PD Placebo and 80mg QD groups) and Between treatment group comparisons (change from baseline differences for Placebo versus 80mg QD). Part 2 PD patient analyses to include Placebo and 80mg PD patients from Part 1, together with the 5mg, 10mg, 20mg and 40mg Part 2 PD patients. These analyses will include Within Group (change from baseline for PD Placebo, 5mg. 10mg, 20mg, 40mg and 80mg QD groups) and Between treatment group comparisons (change from baseline differences for Placebo versus the 5mg, 10mg, 20mg, 40mg and 80mg QD posiphen groups). Section 6.1 – 6.4.1 updated; Section 7 analysis table schedule added; Sections 7.2.1, 7.2.2, 7.2.3 and 7.4 updated throughout.
1 Final	26/02/2021	Neil Parkinson David Fleet	Text updated following Sponsor's comments dated 8 February 2021 and plot templates added (Appendix 2) and references to plot templates included within the SAP.

CONTENTS.

1. Introduction.

Progressive neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD) share many common characteristics, including the central role of neurotoxic aggregating proteins in their pathogenesis.

Posiphen has been shown to reduce the levels of several neurotoxic aggregating proteins that contribute to the progression of AD and PD. The aim of this study is to assess the potential effects of posiphen in patients with AD and PD in the assessment of target and pathway engagement in CSF and plasma. Collectively, these endpoints will help assess efficacy and add valuable information to the Posiphen clinical development programme.

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses and presentations of data collected from the three 'patient cohorts'. The findings will then be interpreted in four statistical reports which will include tables, figures and lists (TFLs) based on this SAP and to support the subsequent production of the Clinical Study Report (CSR).

This statistical analysis plan is based on protocol: ANVS-12003_AD-PD-CSFProtocol_v3_8-21-2020 and will be finalised before the first cohort complete Part 1 and are unblinded for analysis.

From a scheduling perspective, four separate analyses will be performed. The first once the first cohort of 14 PD patients have completed Part 1 and the second once the second cohort of 14 AD patients complete Part 1. The third analysis will be carried out when the third cohort (4 treatment groups) in Part 2 has completed all assessments but this will also include the Placebo and 80mg posiphen patients from the Part 1 PD cohort. The fourth analysis will include the pharmacokinetic data from both Part 1 (AD and PD patients) and Part 2 (PD patients), and, if required, a presentation of the results from the evaluation of infective particles in CSF and exosomes in plasma.

Given the study design (patient type and treatment dose) all safety evaluations will be reported separately in each of the first three analyses.

The following study documents were used for the preparation of this SAP:

- ANVS-12003_AD-PD-CSFProtocol_v3_8-21-2020 (protocol)
- ANVS 12003 (Annov 251151) SDTM 3.2 Annotated CRF v0.4 20200902

The example layouts of the data presentations are shown in Appendices 1-3 for tables, figures and listings, respectively.

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2. Objectives.

A broad range of objectives are specified in this early stage exploratory investigation. They include safety and tolerability in both patient groups (AD and PD). Pharmacodynamics and early Efficacy indicators with biomarker target engagement, pathway engagement and functional/cognitive measures respectively across both Part 1 and 2 of the study.

Drug pharmacokinetics in CSF and blood will also be characterised at the dose selected in AD and PD patients in Part 1 and across the range of doses selected in PD patients in Part 2.

Part 1 - Safety, tolerability, pharmacodynamics, efficacy and pharmacokinetics of posiphen (80mg QD after 25 days) in early AD and PD patients.

Part 2 - Safety, tolerability, pharmacodynamics, efficacy and pharmacokinetics of posiphen (5, 10, 20, 40mg QD after 25 days) in early PD patients.

The primary comparisons of interest performed in Part 1 and Part 2 are the changes from baseline (Within treatment group). The null hypothesis throughout is that there is no difference between the Day 25 end of treatment and Pre-treatment baseline (H0. $X_{end}=X_{base}$, H1. $X_{end}\hat{}=X_{base}$).

Between treatment group comparisons will also be done (but are of secondary interest due to the small sample size). Here, the null hypothesis is that there is no difference between any of the treatment groups at the end of treatment (H0. Placebo$=X_{5mg}=X_{10mg}=X_{20mg}=X_{40mg}=X_{80mg}$, H1. Placebo$\hat{}=X_{5mg}\hat{}=X_{10mg}\hat{}=X_{20mg}\hat{}=X_{40mg}\hat{}=X_{80mg}$).

2.1 Endpoints

2.1.1 Pharmacodynamics

Pharmacodynamic effects are based on target engagement outcome measures with the levels of neurotoxic proteins measured in plasma and CSF. Potential drug efficacy is assessed through pathway engagement measurements of the levels of proteins obtained in blood, plasma and CSF.

2.1.1.1 Target Engagement

Levels of neurotoxic proteins measured in plasma and CSF are:

- aSYN monomers
- Aβ monomers: Aβ40, Aβ42
- soluble Amyloid Precursor Proteins: sAPPα and sAPPβ
- T-tau and P-tau protein

2.1.1.2 Pathway Engagement

Levels of proteins involved in the toxic cascade and measured in plasma and CSF are:

- Axonal transport
- Inflammatory factors
- Synaptic factors
- Control proteins

Plus:

Infective particles (oligomers) in CSF
and
Exosomes from platelet-poor plasma

2.1.2 Efficacy (Functional/Cognitive)

Although clinical benefit is not expected within this early phase, exploratory investigation, the AD and PD specific tests performed will provide valuable information on likely estimates of

variability for use in future power calculations to support sample sizes for posiphen efficacy clinical trials.

For both AD and PD patients, the Mini-Mental State Examination (MMSE) will be used as a global measure of cognition and the Coding subtest from the Weschler Adult Intelligence Scales, 4th edition (WAIS-IV) will be used as a sensitive measure of CNS dysfunction.

AD patients will undertake the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-Cog 14) and functional impairment will be evaluated using the Clinical Dementia Rating (CDR) scale.

PD patients will undertake the MDS-Unified Parkinson's disease rating scale (MDS-UPDRS) to assess the non-motor and motor experiences of daily living.

2.1.3 Safety and Tolerability

Safety assessments for both parts of the study are based on physical examinations, clinical laboratory data, vital signs (blood pressure and heart rate), adverse events (AEs) and serious AEs [SAEs], ECGs (12 lead) and the Columbia suicide rating scale (C-SSRS). Adverse events are assessed throughout but all other assessments are to be made at entry (Baseline) and on the Day 25 final assessment day.

2.1.4 Pharmacokinetics

PK parameters of the parent drug, posiphen, will be determined for both AD and PD patients at 80mg QD dose group after 25 days of repeated dosing (Part 1) and for PD patients at 5, 10, 20, 40mg QD after 25 days of repeated dosing for PD patients (Part 2).

Specific parameters of interest are Area under the curve (AUC 0-t, 0-inf), maximum concentration (Cmax), time of maximum concentration (Tmax), half-life (t½), and clearance (CL).

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3. Study Design.

This study will be conducted in two parts: Part 1 will evaluate the safety, tolerability, and pharmacokinetics of Posiphen in 14 Early AD and 14 Early PD patients at 80 mg QD.

Each group will include 14 Early AD patients, randomly assigned, 10 to posiphen and 4 to placebo and 14 Early PD patients randomly assigned, 10 to Posiphen and 4 to placebo.

Part 1 will also include exploratory measures of pharmacodynamics and efficacy of Posiphen with target engagement, pathway engagement and functional/cognitive measures, including the degree of memory loss and cognitive function in AD patients as well as the degree of motor impairment and non-motor symptoms and quality of life in PD patients.

Part 2 will evaluate the safety, tolerability, and pharmacokinetics of posiphen in 40 patients with early PD, who will be randomly assigned to each of 4 dose levels; 5 mg QD, 10 mg QD, 20 mg QD and 40 mg QD.

Part 2 will also include exploratory measures of pharmacodynamics and efficacy of posiphen in Early PD patients with target engagement, pathway engagement and functional/cognitive measures, including the degree of motor impairment as well as other non-motor symptoms and quality of life in PD patients.

Full clinical details are given in the protocol.

3.1 Power and Sample Size Determination

This is an exploratory investigation of safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy focusing on target engagement, pathway engagement and functional/cognitive measures. Ten patients per dose group will provide sufficient data to demonstrate within group changes for sAPPα and sAPPβ to be of the order of 20-40% (see Table 1 below) and to characterise the PK of posiphen and support potential dose proportionality analyses.

Table 1: Sample Size Estimation

Biomarker	SD	Delta effect size	Within treatment group change	N/Group*
sAPPα	0.1695	0.3 to 2 SD	36%	9
sAPPβ	0.1695	0.3 to 2 SD	24%	9

*With 80% power and 0.05 two tailed significance level
NB. Alpha-synuclein (aSYN) and in neurotransmitters provide valuable supporting information but changes are anticipated to be smaller and would require larger group sizes.

3.2 Interim analysis

No interim analysis is planned.

However, on completion of Part 1, the biomarkers in the plasma and CSF samples will be analysed unblinded to determine what changes are needed to the biomarkers to be measured in Part 2. Since the conduct of the study in Part 2 will be identical to the conduct of the study in Part 1, recruitment will continue uninterrupted. The only potential change between Part 1 and Part 2 are the actual biomarkers to be measured. Due to COVID-19 causing recruitment challenges, at the time of intended analysis, Part 1 will now be analysed according to cohort. Therefore, the first analysis will occur after 14 PD patients have completed Part 1 and a second analysis will occur when 14 AD patients have completed Part 1.

3.3 Randomisation

For Part 1: For each cohort (AD, PD) up to 14 subjects will be randomised to posiphen or placebo in a ratio of 10 Active: 4 Placebo.

For Part 2: A sample size of up to 40 Early PD patients will be randomized to one of the 4 posiphen doses, 10 patients each dosed at 5 mg, 10 mg, 20 mg, or 40 mg.

The study is conducted in a blind manner and the randomization schedule for each cohort will be available once all patients in each cohort have completed the required schedule and the data have been locked for that cohort.

4. Population

Three analysis populations are defined for each of the three cohorts (Part 1 AD, Part 1 PD, Part 2 PD):

Intent to treat population

The Intention to treat population (ITT) includes all patients who received at least one dose of study medication and provide post baseline data. Analyses will be based on the treatment actually received and not necessarily that scheduled by the randomisation.

Safety population

The Safety population (Safety) includes all patients who received at least one dose of the study medication. Summaries of safety and tolerability will be based on the actual treatment received.

Pharmacokinetics population

The Pharmacokinetic population (PK) includes all patients who receive at least one dose of study medication and who provide sufficient data to enable parameter estimation.

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5. Study Methods

Assessments will be made during three visits (Screening, Baseline and Confinement); in addition there are two telephone calls to assess for adverse events. Specific clinic procedures and details of all assessments performed are given in Section 9 of the protocol.

5.1 Schedule.

Details of all assessments performed with timings are given in Table 2.

Table 2: Clinical Assessments Schedule

Visit Timing	Day -42 to 0		Day 14 (± 4)	1-3 days prior to confinement	Days 25 (± 2)		
Procedures	**Screening**	**Baseline**	**Phone**	**Pre-Confinement Phone Contact**	**Confinement**		
					Admission	**6-Hour Sampling**	**Discharge[e]**
Informed Consent	X						
Demographics	X						
Medical and Psychiatric History	X						
Height and BMI	X						
Inclusion and Exclusion Criteria	X	X					
Urine Dipstick Pregnancy Test	X						
Physical and Neurological Examination	X	X			X		X
AD & PD: MMSE	X	X			X		
AD: CDR	X	X			X		
AD: ADAS-Cog 14		X			X		
AD & PD: WAIS-IV		X			X		
PD: MDS-UPDRS	X[g]	X			X		
C-SSRS	X	X			X		
Vital Signs[b]	X	X			X	X	X
Clinical Lab Safety Tests	X	X[i]			X[i]		
12-Lead ECG	X	X			X		X
MRI of Brain[c]	X						
Adverse Events	X	X	X	X	X	X	X
Prior/Concomitant Medication	X	X	X	X	X	X	X
Randomization		X					
Dispense Study Drug		X					
Dosing Study Drug in Clinic		X				X	
Study Drug Compliance Check			X	X	X		
APOE Genotype and DNA Markers		X					
Blood Sampling for PK		X				X	
Lumbar Puncture for baseline Pharmacodynamics		X					
LP Catheter Placement[h]					X		
Collecting blood and CSF for Biomarkers in Plasma and CSF		X				X[f]	
24-Hour Phone Follow-Up[d]		X					X
Lumbar Xray[h] (Optional)	X						

[a] Refer to Section 9 for more details on visit timing and windows.
[b] Vital signs will include sitting blood pressure, pulse, temperature, respiration rate, and weight, except during the 6-hour Sampling Phase of the Confinement Visit when weight will not be included.
[c] An MRI of the brain will only be conducted if there is no brain MRI available from within the window specified in Inclusion Criteria.
[d] Phone Follow-up should occur approximately 24-hours after completion of the LP procedure at Baseline and after discharge from the Confinement Visit.
[e] The Early Discontinuation Visit will contain the same assessments as the Pre-confinement Visit.
[f] Sampling Times: 0,1,2,3,4,5,6 hrs (±10 mins for collection)
[g] Hoehn & Yahr Stage only for inclusion determination
[h] X-Ray is only required if LP insertion will not be performed with fluoroscopy

[i] Safety labs at baseline and confinement (for sample 0 hour) should be taken fasted

5.2 Treatment Measures.

Treatment measures are evaluated by pharmacodynamics and by efficacy endpoints.

5.2.1 Pharmacodynamic Endpoints

Pharmacodynamic endpoints are based on the assessments from protein levels in blood, plasma and CSF at the Baseline (0h Pre-dosing) and Day 25 (Confinement) visit (0h Pre-dosing, 1, 2, 3, 4, 5, 6h). Pre-dosing values at Baseline will be compared with Day 25 (Confinement) and derived as a percentage change from Baseline. The Percentage change from Day 25 0h pre-dose at 1, 2, 3, 4, 5 and 6h on Day 25 (Confinement) will also be derived and presented. The maximum percentage change determined over the 6h period may also be incorporated.

Table 3: Pharmacodynamic Endpoints

Pharmacodynamic measure	CSF	Plasma
Target Engagement		
aSYN monomers	X	
Aβ monomers:		
Aβ40	X	X
Aβ42	X	X
Soluble Amyloid Precursor Proteins:		
sAPPα	X	
sAPPβ	X	
Tau Proteins:		
T-tau	X	X
P-tau	X	X
Pathway Engagement		
Axonal Transport:		
Neurofilament light (NfL)	X	X
Inflammatory factors:		
Complement 3	X	

YKL40	X	
sTREM2	X	
GFAp	X	X
Synaptic factors:		
SNAP25	X	
Synaptotagmin	X	
Neurogranin	X	
Control proteins:		
Beta-trace protein	X	
Infective particles:		
aSYN oligomers	X	
Aβ oligomers	X	
Exosomes		X

5.2.2 Efficacy - Functional/Cognitive Measures

Patients will complete the appropriate questionnaires at Baseline and Day 25 (Confinement). For each, the Total score and, where appropriate the item/domain scores, will be calculated, and the Change from Baseline derived. Actual scores and Effect sizes ($(X_{Base}-X_{Day25})/SD$) will be presented.

MMSE is a 30 point test that is widely used for cognitive function that includes tests of orientation, attention, memory, language and visual-spatial skills.

WAIS-IV is a test to assess cognitive ability in adults which helps to examine the relationship between intellectual function and memory in seven subtests: Spatial Addition, Symbol Span, Design Memory, General Cognitive Screener, Logical Memory (I & II), Verbal Paired Associates (I & II), and Visual Reproduction (I & II). Performance is reported as five Index Scores: Auditory Memory, Visual Memory, Visual Working Memory, Immediate Memory, and Delayed Memory. Patients will be scored on the number of correct items from images and words shown in the space of two minutes.

MDS-UPDRS has four parts: Part 1 – non-motor experiences of daily living (13 items), Part 2 - motor experiences of daily living (13 items), and Part 3 – motor examination (20 scores based on 18 items plus Hoehn and Yahr Stage) and Part 4 – motor complications (6

questions). Each item is scored on a scale of 0 (normal) to 4 (severe). Scores from each part of the scale are combined to provide a total score.

ADAS-Cog14 is a test to evaluate cognition and differentiates between normal and impaired cognitive functioning by using a number of tests to assess memory, language and comprehension. Different Word lists were used in different countries to allow for language differences but validated versions were always used and always presented in the correct and standardised manner.

CDR is a global summary to identify the overall severity of dementia from domains; Memory, Orientation, Judgement and Problem solving, Community Affairs, Home and Hobbies and Personal care, each of which is rated on a 5 point score.

Table 4: Clinical Function and Cognitive Endpoint Scoring

Efficacy		Score Range (units)	Scale Direction
Cognitive Function Tests			
WAIS-IV	Total Score	Scaled Score 0 - 100	High score best
ADAS-cog14 (14 items)	Total Score (Count incorrect items)	0 - 90	Low score best (0=All correct)
ADAS-cog11 (11 items)	Total Score (Count incorrect items) Includes: Word Recall, Naming Objects and Fingers, Commands, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition, Language, Comprehension of Spoken Language, Word Finding Difficulty and Remembering Test Instructions	0 - 70	Low score best (0=All correct)
ADAS-cog 6 (6 items)	Total Score (Count incorrect items) Includes Word Recall, Naming Objects and Fingers, Commands, Constructional Praxis, Orientation, and Word Recognition Score	0 - 45	Low score best (0=All correct)
ADAS-cog 3 (Memory) (3 items)	Total Score (Count incorrect items) Includes Word Recall, Orientation, and Word Recognition	0 - 30	Low score best (0=All correct)
CDR	Individual item scores: Memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care	0 = Normal 0.5 = Very Mild Dementia 1 = Mild Dementia 2 = Moderate Dementia 3 = Severe Dementia	Global Summary Score range = 0 – 3 Low score best

	Sum of Boxes (Total Score)	0 - 18	Low score best
Non-Motor Experiences and Motor Function			
MDS-UPDRS	Individual scores	0 =Normal 1 = Slight 2 = Mild 3 = Moderate 4 = Severe	Low score best
	Total Score	0 - 208	Low score best
	Part 1 – non-motor experiences of daily living	0 -52	Low score best
	Part 2 - motor experiences of daily living	0 -52	Low score best
	Part 3 – motor examination	0 -72	Low score best
	Part 4 – motor complications	0 -24	Low score best
	Hoehn and Yahr	0 = Asymptomatic 1 = Unilateral involvement only 2 = Bilateral involvement without any impaired balance 3 = Severe disability 4 – Wheelchair bound or bedridden unless aided	Low score best
Disease Staging			
MMSE	Total Score (Count correct items)	0 - 30	High score best (0=Severe impairment / 30=No impairment)
	Categorical scores	24– 30 18 - 23 0 - 17	No cognitive impairment Mild cognitive impairment Severe cognitive impairment

5.3 Safety Measures.

Drug safety is assessed by monitoring adverse events, vital signs, physical examinations, 12-lead ECG, and concomitant medication data. These are supported by laboratory data assessments of blood and urine providing serum chemistry, haematology and urinalysis

evaluations. Patients will also use the Columbia suicide rating scale (C-SSRS) as an additional safety assessment on entry and at the confinement visit.

All reported adverse events will be coded into system organ class (SOC) and preferred term (PT) using the MedDRA dictionary version 23. The number of patients reporting adverse events during either the dosing or follow up periods is summarised according to the coded system organ class (SOC) and preferred term (PT). All adverse events are coded individually, even where combination events are reported simultaneously.

Adverse events starting or pre-existing events with an increase in severity on or after the first dose of study IMP are defined as treatment emergent adverse events (TEAE). An event starting before the first dose of study IMP will be identified as a pre-treatment sign or symptom (PTSS).

All laboratory data will be merged with the subject Case Report Form (CRF) database and summarised. Laboratory values will be defined as clinically significant according to the pre-specified abnormal limits, and will be summarised and listed by subject.

The Columbia suicide rating scale is a series of six questions in which the patient is asked to indicate whether they have experienced several thoughts or feelings relating to suicide over the past month. The responses to each question by patients in each cohort will be summarised by treatment group and visit.

5.4 Pharmacokinetic Assessments

Plasma samples are collected at Baseline (0h Pre-dosing) and Day 25 (Confinement) visit (0h Pre-dosing, 1, 2, 3, 4, 5, 6h). The actual values at 0h pre-dose and at 1, 2, 3, 4, 5 and 6h on Day 25 (Confinement) will also be derived and from these the parameters of the parent drug concentration vs time course profile will be determined for each individual patient.

Drug concentrations will be summarised using the designated sampling times (not the actual sampling times) using descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum, maximum, and number of observations) for each treatment group and cohort (Part 1 AD, Part 1 PD, Part 2 PD). However, all PK statistical analyses will be carried out on completion of Part 2. Therefore, the 80mg PD patient data from Part 1 will be included with the PK patient data from the four Part 2 PD patient groups for the PD PK analysis.

PK parameters will be derived using non-compartmental methods (Table 5) using SAS programming. All derivations will be performed using the actual times of blood sampling. All derived parameters (except t_{max}) will also be presented as descriptive summary statistics (mean, SD, minimum and maximum). The time to maximum concentration (t_{max}) will be displayed as median, minimum and maximum.

Table 5: Estimated Pharmacokinetic Parameters - Plasma

Parameter	Description	Calculation
C_{max}	Maximum drug concentration from individual concentration-time curve	Directly obtained from plot
t_{max}	Time to reach maximum concentration	Directly obtained from plot
C_{last}	Last measurable drug concentration	Directly obtained from plot*
T_{last}	Time of the last measurable concentration	Directly obtained from plot*
λ_z (K_{el})	Terminal-phase rate constant (λ_z) calculated- The value of λ_z from the slope of the regression line of lnC vs time Assuming - Data points should be randomly distributed around a single straight line; At least 3 data points used in the regression; Correlation coefficient of regression> 0.9000; Period of data points at least 2-fold greater than the calculated half-life	
$t_{1/2}$	Observed terminal elimination half-life	$T_{1/2} = \frac{\ln(2)}{\lambda_z}$
AUC_{0-t}	Area under the plasma concentration-time curve from time-zero to the time of the last measurable concentration.	Calculated using the linear trapezoidal rule ((t_2-t_1)*(C_1+C_2)/2)) during the ascending portion of the curve and the log-trapezoidal rule ((t_2-t_1)*(C_2-C_1)/ln(C_2/C_1)) during the descending portion of the curve.
$AUC_{0-\infty}$	Area under the concentration time curve from time-zero extrapolated to infinity	$AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
CL/F	Apparent systemic clearance	$CL/F = \frac{Dose}{AUC_{\inf}}$

*NB: Parameters used in derivations but not presented in data summaries.

For the purpose of calculating AUCs when two consecutive plasma concentrations are below the lower limit of quantification (LLOQ) after t_{max}, all subsequent values will be excluded from derivations. However, single 'embedded' missing values will be included in the derivations with extrapolation between the items.

5.5 Missing Data.

All possible efforts will be made to ensure complete data collection and no imputation of data will be performed.

5.6 Other Definitions

Baseline, Study Day and Event Duration are specifically defined as:

Baseline

Two baselines are defined:

1 Last assessment prior to first dose of study IMP on Day 0.

2 At 0 hours on Day 25 of the Confinement visit

Study Day

Study Day = (Date of event - first dose of study IMP) + 1.

Event Duration

Event Duration= (Date of resolution – Date of onset) + 1

6. Statistical Methods.

This statistical analysis plan specifies the requirements for the analysis and reporting of all data collected during the study.

All analyses and data reporting procedures will be undertaken using SAS® v9.4 in a Windows version 10 operating system environment.

The descriptive statistics produced will account for the nature and distribution of the data collected. For continuous variables (actual and percentage change from baseline), data will be presented as number (n), mean, median, standard deviation, and range. For discrete variables (Incidence, Response outcome) data will be presented as frequencies and proportions and the denominator will be the number of patients available.

Data collected from patients in each of the three cohorts (Part 1 AD, Part 1 PD, Part 2 PD) will be derived and summarised as described in section 5 and analysed according to the defined analysis population in section 4.

All comparisons of primary interest performed in Part 1 and Part 2 involve changes from baseline (Within treatment group). The null hypothesis throughout is that there is no difference between the Day 25 end of treatment and Pre-treatment baseline (H0. $X_{end}=X_{base}$, H1. $X_{end}\hat{}=X_{base}$).

Between treatment groups comparisons are also possible (but of secondary interest due to the small sample size). Here the null hypothesis is that there is no difference between any of the treatment groups at the end of treatment (H0. Placebo$=X_{5mg}=X_{10mg}=X_{20mg}=X_{40mg}=X_{80mg}$, H1. Placebo$\hat{}=X_{5mg}\hat{}=X_{10mg}\hat{}=X_{20mg}\hat{}=X_{40mg}\hat{}=X_{80mg}$).

6.1 Pharmacodynamic Endpoints

For the Part 1 AD and Part 1 PD cohorts, each variable measured in plasma and CSF will be analysed using an analysis of variance (ANOVA) model of the percentage changes from Baseline (between Baseline Day 0 Pre-dose 0h and Day 25 Pre-dose 0h). This will include Treatment group as a fixed effect and LSmeans (with 95% CI) for this effect will be presented (Within group).

Between group differences for 80mg vs Placebo will be assessed and presented (LSmeans +/- 95% CI) although results will be viewed cautiously given small control group samples size.

Then the percentage change from Baseline (Day 25 Pre-dose 0h) for each of the 6 hourly assessments will be analysed using a Repeated measured mixed model (RMMM) including Treatment group as a fixed effect, Time as the repeated effect and Subject as random term. Compound symmetry will be assumed for the covariance/correlation matrix. An overall average LSmean (with 95% CI) for the Treatment effect will be presented together with individual LSmean (with 95% CI) estimates for each hour. Treatment group differences will also be presented for the comparison between 80mg vs Placebo but the same caveat used given the control group subject sample size.

The maximum percentage change from Baseline (Day 25 Pre-dose 0h) over the 6 hours will also be analysed with an ANOVA model for both the Within treatment group and Between group (80mg vs Placebo) comparisons.

In the event of either model failing assumptions of normality or constant variance, a log transformed analysis of the actual values (*not percentage change*) will be substituted and the output estimates (means and 95% CIs) then back transformed by exponentiation to enable presentation of the ratio of values (%).

For the Part 2 PD cohort with 4 treatment dose groups (5, 10, 20, 40mg) the same analyses models will be employed. However, the data from the Part 1 PD patients will also be included (for those biomarker variables retained from Part 1 after evaluation at that stage) from both the Placebo and 80mg patient groups and combined with the Part 2 data. Within and Between group ANOVAs and RMMM model analyses will then be employed in a similar manner to Part 1. The Part 2 report of treatment group differences will include Placebo (from Part 1) versus each of the five active treatment groups, namely 5mg, 10mg, 20mg and 40mg from Part 2, and 80mg group from Part 1.

6.2 Functional Cognitive Endpoints

Prior to any formal statistical analyses of the cognitive and functional endpoints, each question, sub-domain and total score will be descriptively summarised and evaluated. Subsequently, formal statistical analysis of individual questions will only be performed and reported if any notable change from baseline is observed in the descriptive summaries. This process will be repeated at each analysis stage, i.e. Part 1 PD, Part 1 AD and Part 2 PD database locks.

For the Part 1 AD and Part 1 PD cohorts, the variables will be analysed using an ANOVA model of the Change from Baseline (Day 25 - Day 0). This will include Treatment group as a fixed effect, and LSmeans (with 95% CI) for this effect will be presented (Within group) together with Effect sizes ($(X_{Day\ 25}-X_{Base})/SD$). Between treatment group differences will also be presented for the comparison between Placebo and 80mg but interpreted cautiously.

For the Part 2 PD cohort with 4 treatment dose groups (5, 10, 20, 40mg) a similar ANOVA will be employed. However, the data from the Part 1 PD patients will also be included from both the Placebo and 80mg patient groups and combined with the Part 2 Parkinson patient data. Within and Between group ANOVA model analyses will then be employed in a similar manner to Part 1. However, in the Part 2 report, treatment group differences will include Placebo (from Part 1) versus each of the five active treatment groups, namely 5mg, 10mg, 20mg and 40mg from Part 2, and 80mg group from Part 1.

6.3 Safety Endpoints

All safety data will be summarised according to cohort and treatment dose group. Presentation formats of the data described in section 5 are given in section 7. For consistency with the pharmacodynamic and functional cognitive data analyses, the data from the Part 1 Parkinson patients will also be included from both the Placebo and 80mg patients and combined with the Part 2 Parkinson patient data for the third analysis.

6.4 Pharmacokinetic Endpoints

All PK analyses will be done on completion of Part 2, including the data from the Part 1 AD and PD patients.

6.4.1 Part 1 AD, Part 1 PD Cohort

All derived parameters for these patient groups will be presented descriptively as outlined in section 5.4. No formal analyses will be performed with the AD patient data. However, the 80mg PD patient data will be combined and included with the analysis of the four Part 2 Posiphen treatment groups.

For actual drug concentrations descriptive statistics (arithmetic mean, minimum, median, maximum, coefficient of variation (CV), standard deviation (SD) and number of observations) will be used and displayed graphically as arithmetic mean (±SD) plasma drug concentration value versus time (nominal) for each treatment/dose group using a log-linear format.

The derived pharmacokinetic parameters will also be displayed using descriptive summaries (arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum, maximum and number of observations) for each cohort and treatment/dose group. If appropriate, geometric means will be displayed in addition to the arithmetic mean.

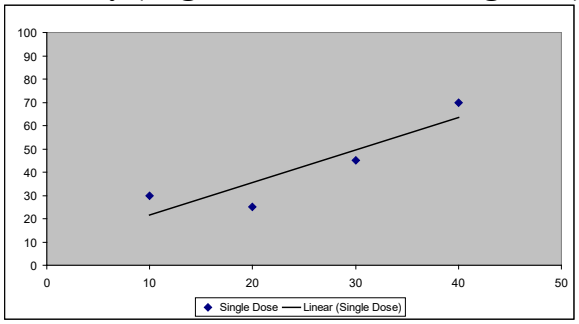
6.4.2 Part 2 PD Cohort

Although the PK parameters will be presented as for Part 1 (according to Treatment dose group) the C_{max} and AUCs will also be formally analysed to evaluate the relationship between the ascending dose groups (Dose-proportionality as in Figure 1). In addition to the patients from the four treatment groups in Part 2 (5mg, 10mg, 20mg and 40mg), the 80mg group of PD patients from Part 1 will be included.

This will involve an ANOVA power model using the log transformed individual patient derived parameters as an explanatory variable and with Treatment dose group as the dependent fixed effect. In the event of demonstrating an overall statistically significant difference, comparisons between all pairs of means will be performed using the Scheffe method. LSmeans point estimates with 95% CIs derived will be presented after back transformation (exponentiation) of all pairwise differences between doses as ratios (%). Significant differences ($p<0.05$) in the ratio of any two doses will be declared if the 95% confidence interval excludes 100%.

The regression slope (Figure 1) of the log transformed PK parameter against log Dose represents the power model (log(AUC)=a + b*(Dose)) where ‘a’ represents the intercept and ‘b’ the coefficient for linear slope). Therefore, a 90% confidence interval for the estimate of the slope excluding b=1 will indicate significant departure from linearity.

Figure 1: Dose Proportionality (Log PK Parameter vs Log Dose)



For the dose difference analysis, all dose group estimates will be presented as LS means with 95% CIs after back transformation of the log values and all pairwise comparisons with the lowest dose will be presented as ratios of LS means (%) with 95% confidence intervals. These will be presented graphically.

For both the Differences between doses and Dose proportionality analyses of the C_{max} and AUC parameters summaries of the model applied with Mean square error, Degrees of freedom, F statistic and resulting p-value for each model parameter will be displayed.

For Dose proportionality the coefficient of the linear slope (b) will be presented as a point estimate with 90% CI together with plots of log C_{max} vs Dose and log AUC vs Dose.

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7. Presentation.

As each cohort completes (Part 1 AD, Part 1 PD, and Part 2 PD) these data will be unblinded and the pharmacodynamics (Biomarkers in CSF and plasma), efficacy, and safety will be evaluated and presented accordingly.

Once all patients in Part 2 have completed, the PK data and infective particle and exosomes data from all three cohorts will be made available and analysed separately.

Summaries will be presented by cohort and treatment, visit and time recorded as appropriate.

The table below summarises the schedule for presentation of each cohort's statistical report output:

Analysis	Cohort	Deliverables
1	Part 1 – PD Patients (14)	Disposition Tables and Listings Biomarker* Tables, Figures and Listings Functional/cognitive Tables, Figures and Listings Safety Tables and Listings
2	Part 1 – AD Patients (14)	Disposition Tables and Listings Biomarker* Tables, Figures and Listings Functional/cognitive Tables, Figures and Listings Safety Tables and Listings
On completion of Part 2:		
3	PD Patients (54) – including 14 PD patients from Part 1 and 40 PD patients from Part 2	Disposition Tables and Listings Biomarker* Tables, Figures and Listings Functional/cognitive Tables, Figures and Listings Safety Tables and Listings
4	PD Patients (50) – including ten 80mg PD patients from Part 1 and forty PD patients (5mg, 10mg, 20mg and 40mg) from Part 2	PK analyses Tables, Figures and Listings
	AD Patients (10) – 80mg patients from Part 1	PK analyses Tables, Figures and Listings
	All patients (68) from Part1 and Part 2	Infective Particles in CSF: Tables, Figures and Listings Exosomes in plasma: Tables, Figures and Listings

*Biomarker results (excluding infective particles and exosomes) from assays conducted in Part 1 will be evaluated by the Sponsor and will inform the choice of assays and subsequent output from Part 2
NB: Infective particles and exosomes biomarker data will not be presented until after the completion of Part 2

Detailed 'table shells' for Part 1 and Part 2 will be produced to accompany this SAP. These not only describe table layout but table numbering formats and also the level of accuracy (number of decimal places) to be described in each table.

The following described tables and figures will be included in the statistical report.

7.1 Study Status.

7.1.1 Disposition

For each cohort enrolled into the study, patient disposition details will be presented by treatment group and overall. Disposition details include number Screened, number and percentage Randomised (ITT population), Treated (Safety population), Completed, Discontinued, and the Primary Reason for Discontinuation (Tables 14.1.1 and 14.1.2). For

each cohort, discontinuations from the study will be listed by treatment group and patient with the date of discontinuation, primary reason and the corresponding AE number if applicable (Listing 16.2.1.5).

7.1.2 Demographics.
For each cohort in the Safety population, patient demographic details (age, sex, race and ethnicity) will be summarised according to treatment group and overall (Table 14.1.3).

7.1.3 Protocol Deviations
For each cohort, protocol deviations will be listed by treatment and patient, showing the deviation details (Listing 16.2.1.4).

7.1.3 Concomitant Medication
For each cohort, prior and concomitant medications will be summarised by treatment group and overall according to the WHO drug dictionary ATC code levels 2 and 4 (Tables 14.1.4 and 14.1.5.

7.1.4 Medical History.
For each cohort, medical history details will be summarised according to the MedDRA system organ class and preferred term by treatment group and overall (Table 14.1.6). Height, weight and BMI will also be summarised (Table 14.1.7).

7.1.5 Drug Administration.
For each cohort, compliance with study drug administration will be summarised by treatment group as both percentage compliance and classified according to whether patients were less than or equal to/greater than 80% compliant (Table 14.1.8).

7.2 Pharmacodynamics

For each cohort, the levels of neurotoxic proteins in plasma and CSF collected at hourly intervals during the 6 hour post dose confinement, the actual values and change from baseline and percentage change from baseline will be summarized by treatment group.

7.2.1.1 Target Engagement - CSF

The target engagement CSF variables include: Aβ-40, Aβ-42, sAPPα, sAPP β, t-tau, p-tau-181 and a-SYN and are summarised in Tables 14.2.1.1.1 – 14.2.1.1.7.

Subsequently, the results from the Within group ANOVA model of the percentage changes from Baseline (between Baseline Day 0 Pre-dose 0h and Day 25 Pre-dose 0h) will be presented, together with Maximum Percentage Change over 6h (Day 25) from Baseline (Day 25 Pre dose 0h) (Model terms – Table 14.2.1.2; Model estimates – Table 14.2.1.3) and plotted as treatment estimates (Figures 14.2.1.1, Template 1).

Additionally, the percentage change from baseline (Day 25 Pre-dose 0h - Day 0 Pre-dose 0h) and the Maximum Percentage Change over 6h (Day 25) from Baseline (Day 25 Pre-dose 0h) will be analysed for Between group differences. This will initially involve analysing the change from baseline differences between the Placebo treatment groups in Part 1 and the 80mg patient groups from Part 1 in both the AD and PD cohorts, and subsequently the differences between the PD Placebo patients from Part 1 and the 5mg, 10mg, 20mg and 40mg Parkinson patient groups from Part 2; and repeating the PD Placebo versus PD 80mg

comparison (Model terms – Table 14.2.1.2; Model estimates – Table 14.2.1.3) and plotted as treatment estimate differences (Figures 14.2.1.2, Template 2).

Furthermore, the percentage change from Baseline (Day 25 Pre-dose 0h) for each of the 6 hourly assessments will be analysed using a Repeated measured mixed model (RMMM) and will be presented in Tables 14.2.1.4 and 14.2.1.5 for Within and Between treatment group model terms and estimates, respectively, together with corresponding plots (Figures 14.2.1.3, Templates 3 and 4, respectively).

On completion of the two Part 1 cohorts, the target engagement CSF biomarkers will be evaluated and this will inform a decision about which should be assayed and statistically analysed after Part 2 has been completed.

7.2.1.2 Pathway engagement – CSF

The pathway engagement CSF variables include: NfL, GFAp, Complement C3, YKL40, sTREM2, SNAP25, Synaptotagmin, Neurogranin and Beta-trace protein and are summarised in Tables 14.2.2.1.1 – 14.2.2.1.9.

Subsequently, the results from the Within group ANOVA model of the percentage changes from Baseline (between Baseline Day 0 Pre-dose 0h and Day 25 Pre-dose 0h) will be presented, together with Maximum Percentage Change over 6h (Day 25) from Baseline (Day 25 Pre dose 0h) (Model terms – Table 14.2.2.2; Model estimates – Table 14.2.2.3) and plotted as treatment estimates (Figures 14.2.2.1, Template 1).

Additionally, the percentage change from baseline (Day 25 Pre-dose 0h - Day 0 Pre-dose 0h) and the Maximum Percentage Change over 6h (Day 25) from Baseline (Day 25 Pre dose 0h) will be analysed using a Between group ANOVA model. This will initially involve analysing the change from baseline differences between the Placebo treatment group from Part 1 and the 80mg Parkinson patient group from Part 1, and subsequently the differences between the Placebo from Part 1 and the 5mg, 10mg, 20mg and 40mg Parkinson patient groups from Part 2 (Model terms – Table 14.2.2.2; Model estimates – Table 14.2.2.3) and plotted as treatment estimate differences (Figure 14.2.2.2, Template 2).

Furthermore, the percentage change from Baseline (Day 25 Pre-dose 0h) for each of the 6 hourly assessments will be analysed using a Repeated measured mixed model (RMMM) and will be presented in Tables 14.2.2.4 and 14.2.2.5 for Within and Between treatment group model terms and estimates, respectively, together with corresponding plots (Figures 14.2.2.3, Templates 3 and 4, respectively).

On completion of the two Part 1 cohorts, the pathway engagement CSF biomarkers will be evaluated and this will inform a decision about which should be assayed and statistically analysed after Part 2 has been completed.

7.2.2.1 Target Engagement - Plasma

The target engagement plasma variables include: Aβ-40, Aβ-42, t-tau and p-tau-181 and are summarised in Tables 14.2.3.1.1 – 14.2.3.1.4.

These variables are analysed as for the CSF variables:
Within group ANOVA model: Model terms – Table 14.2.3.2; Model estimates – Table 14.2.3.3) and plotted as treatment estimates (Figures 14.2.3.1, Template 1).

Between group ANOVA model: Model terms – Table 14.2.3.2; Model estimates – Table 14.2.3.3) and plotted as treatment estimate differences (Figure 14.2.3.2, Template 2).

Repeated measured mixed model (RMMM) – Within Group: Model terms – Table 14.2.3.4 and Model Estimates Table 14.2.3.5 and Between group also in Tables 14.2.3.4 and 14.2.3.5, respectively, together with corresponding plots (Figures 14.2.3.3, Templates 3 and 4, respectively).

On completion of the two Part 1 cohorts, the target engagement plasma biomarkers will be evaluated and this will inform a decision about which should be assayed and statistically analysed after Part 2 has been completed.

7.2.2.2 Pathway Engagement - Plasma
The pathway engagement plasma variables include: NfL and GFAp and are summarised in Tables 14.2.4.1.1 – 14.2.4.1.2.

These variables are analysed as for the CSF variables:
Within group ANOVA model: Model terms – Table 14.2.4.2; Model estimates – Table 14.2.4.3) and plotted as treatment estimates (Figures 14.2.4.1, Template 1).

Between group ANOVA model: Model terms – Table 14.2.4.2; Model estimates – Table 14.2.4.3) and plotted as treatment estimate differences (Figure 14.2.4.2, Template 2).

Repeated measured mixed model (RMMM) – Within Group: Model terms – Table 14.2.4.4 and Model Estimates Table 14.2.4.5 and Between group also in Tables 14.2.4.4 and 14.2.4.5, respectively, together with corresponding plots (Figures 14.2.4.3, Templates 3 and 4, respectively).

On completion of the two Part 1 cohorts, the pathway engagement plasma biomarkers will be evaluated and this will inform a decision about which should be assayed and statistically analysed after Part 2 has been completed.

7.2.3 Efficacy - Functional/Cognition
Prior to any formal statistical analyses of the cognitive and functional endpoints, each question, sub-domain and total score will be descriptively summarised and evaluated. Subsequently, formal statistical analysis will only be performed and reported if any notable change from baseline is observed in the descriptive summaries. This process will be repeated at each analysis stage, i.e. Part 1 PD, Part 1 AD and Part 2 PD database locks.

Depending on the outcome of these original evaluations:

All Cohorts: every patient is evaluated using the MMSE and WAIS-IV:
MMSE
The total score and absolute and standardised change from baseline for the MMSE functional cognitive measure or any sub-score (after initial evaluation) will be summarised by treatment group (Table 14.3.1.1). Scores from the individual questions will also be listed. The results from the Within treatment group ANOVA on the change from baseline will also be presented in Table 14.3.1.2 (model terms) and Table 14.3.1.3 (model estimates, LS means ±95% CIs) and plotted as treatment estimates (Figure 14.3.1.1, Template 1).

Additionally, the change from baseline differences between the Placebo treatment groups in Part 1 and the 80mg patient groups from Part 1 in both the AD and PD cohorts, and subsequently the differences between the PD Placebo patients from Part 1 and the 5mg, 10mg, 20mg and 40mg Parkinson patient groups from Part 2; repeating the PD Placebo versus PD 80mg comparison will be analysed. The results from these Between treatment group ANOVAs on the change from baseline will also be presented in Table 14.3.1.2 (model terms) and Table 14.3.1.3 (model estimates, LS means ±95% CIs differences) and plotted as treatment estimate differences (Figure 14.3.1.2, Template 2).

WAIS-IV

This will be summarised (Table 14.3.2.1) and analysed in a similar manner to the MMSE with results from the Within treatment group ANOVA on the change from baseline being presented in Table 14.3.2.2 (model terms) and Table 14.3.2.3 (model estimates, LS means ±95% CIs) and plotted as treatment estimates (Figure 14.3.2.1, Template 1).

Additionally, the change from baseline differences between the Placebo treatment groups in Part 1 and the 80mg patient groups from Part 1 in both the AD and PD cohorts, and subsequently the differences between the PD Placebo patients from Part 1 and the 5mg, 10mg, 20mg and 40mg Parkinson patient groups from Part 2; repeating the PD Placebo versus PD 80mg comparison will be analysed. The results from these Between treatment group ANOVAs on the change from baseline will also be presented in Table 14.3.2.2 (model terms) and Table 14.3.2.3 (model estimates, LS means ±95% CIs differences) and plotted as treatment estimate differences (Figure 14.3.2.2, Template 2).

Parkinson Patients – Parts 1 and 2

MDS-UPDRS

The MDS-UPDRS total score and four individual domain scores (Non Motor Aspects of Experiences of Daily Living; Motor Aspects of Experiences of Daily Living; Motor Examination; Motor Complications) or any sub-score (after initial evaluation) will be summarised (Tables 14.3.3.1) and analysed in a similar manner to the MMSE. The results from the Within treatment group ANOVA on the change from baseline and Between treatment group ANOVA differences (Part 1: Placebo vs 80mg; Part 2: Placebo vs 5mg, 10mg, 20mg, 40mg and 80mg) will be presented in Tables 14.3.3.2 (model terms) and Tables 14.3.3.3 (model estimates, LS means ±95% CIs) and plotted as treatment estimates (Figures 14.3.3.1 (Template 1) and 14.3.3.2 (Template 2), for Within and Between estimates, respectively).

Furthermore, the Hoehn and Yahr scores will be categorically summarised by treatment group and visit in both Parts 1 and 2 (Table 14.3.3.4).

Alzheimer Patients – Part 1 only

ADAS-cog

The ADAS-cog 14, 11, 6, 3 total score or any sub-score (after initial evaluation) will be summarised (Table 14.3.4.1) and analysed in a similar manner to the MMSE with results from the Within treatment group ANOVA on the change from baseline and change from baseline Between treatment group ANOVA difference between Placebo and 80mg AD patients being presented in Table 14.3.4.2 (model terms) and Table 14.3.4.3 (model estimates, LS means ±95% CIs) and plotted as treatment estimates (Figures 14.3.4.1 (Template 1) and 14.3.4.2 (Template 2), respectively).

CDR

The CDR scale will be categorically summarised by item (Memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care) and overall Global summary score by visit (Table 14.3.5). Additionally, the sum of boxes score will also be summarised and analysed following initial evaluation as described for the ADAS-cog (Tables 14.3.5.1, 14.3.5.2 and 14.3.5.3, for descriptive summaries, model and treatment estimates, respectively, together with corresponding Figures 14.3.5.1 (Template 1) and 14.3.5.2 (Template 2)).

7.3 Safety.

For consistency with the pharmacodynamic and cognitive/functional summaries and analyses and for comparative purposes, safety data from the Placebo and 80mg Part 1 PD patients will be combined with the data collected from the PD patients in Part 2. Consequently, all safety summaries will include: the Placebo and 80mg PD patients for the Part 1 PD cohort analysis report; Placebo and 80mg AD patients for the Part 1 AD cohort analysis report; and, for the Part 2 analysis report, Placebo and 80mg PD patients from Part 1 together with the 5mg, 10mg, 20mg and 40mg PD patients from Part 2.

7.3.1.1 Adverse Event Overview.

For each cohort, all adverse events and serious adverse events will be listed by treatment group and patient (Listing 16.2.1.1).

For each cohort and treatment group, an overview summary will display the frequency, number and percentage of patients, with any adverse event, pre-treatment sign and symptom (PTSS) and treatment emergent adverse events (TEAEs). Additionally, the table will include the number of TEAEs classed by CTCAE Grade (mild, moderate, severe, life threatening, death), relationship to drug (unrelated, possibly related, related), by severity evaluation (mild, moderate, severe), and overall numbers related to a study procedure, AEs leading to discontinuation of study IMP, SAEs, and death (Table 14.4.1.1).

7.3.1.2 Adverse Events (AEs) and Serious Adverse Events (SAEs).

For each cohort and treatment group, the number and percentage of patients with PTSS will be summarised by SOC and PT (Table 14.4.1.2). Similar tables will be presented for TEAEs (Table 14.4.1.3), Related TEAEs (14.4.1.4), TEAE and CTCAE grade (14.4.1.5.1 – 14.4.1.5.5), SAEs (14.4.1.6, TEAEs leading to discontinuation of study IMP(14.4.1.7) and TEAEs leading to death (14.4.1.8).

7.3.2 Laboratory Data.

For each cohort and treatment, laboratory data will be presented as normal summaries, actual values and change from baseline according to profile (Biochemistry: Tables 14.4.2.1.1 – 14.4.2.1.14; Haematology: Tables 14.4.2.2.1 – 14.4.2.2.10; Coagulation: Table 14.4.2.3; Urinalysis: Tables 14.4.2.4). The data will also be presented as Categorical ('Not Done', 'Abnormal NCS', 'Abnormal CS' and 'Normal') summaries by Treatment group according to profile (biochemistry, haematology and urinalysis) and visit as Tables 14.4.2.5. Urinalysis variables will also be presented as Categorical summaries (according to type) by Treatment group and visit as Tables 14.4.2.6.1 – 14.4.2.6.20. Scatter plots of pre-treatment vs. post-treatment values for all haematology and clinical chemistry variables will be displayed (Figures 14.4.2, Template 5).

7.3.3 Vital Signs

For each cohort, vital sign data and the change from baseline will be presented as numerical summaries by treatment group overall and visit, separated into individual test (Weight, BMI, Temperature, Systolic BP, Diastolic BP, Heart Rate (Pulse Rate), and Respiratory Rate Tables 14.4.3.1 – 14.4.3.7).

7.3.4 ECG

For each cohort, ECG data will be presented as numeric summaries (PR Interval, RR Interval, QRS Complex, QT Interval, and QTC Interval Measurement by Treatment group and overall according to visit (Tables 14.4.4.1 – 14.4.4.5). The ECG data will also be presented categorically overall ('Not Done', 'Abnormal NCS', 'Abnormal CS' and 'Normal') summary separately by cohort by Treatment group and overall according to visit (Tables 14.4.4.6).

7.3.5 Columbia suicide rating scale (C-SSRS)

For each cohort, the scores from each category of the C-SSRS will be summarised by treatment group and visit if any response is recorded as 'Yes' (Table 14.4.5).

7.3.6 Physical Examination and Neurological Examination.

For each cohort, the results of the physical and neurological examinations will be summarised by treatment group, overall and by visit (Table 14.4.6 and 14.4.7, respectively).

7.4 Pharmacokinetics

All PK statistical analysis will be carried out after the completion of Part 2.

For each cohort, the plasma concentration data and derived pharmacokinetic parameters of Posiphen will be listed by treatment group, patient and time point.

For each cohort, the actual values and derived pharmacokinetic parameters will be summarised using descriptive summaries (arithmetic mean, standard deviation, coefficient of variation, mean, median, minimum, maximum and number of observations) for each treatment dose group. If appropriate, geometric means will be displayed in addition to the arithmetic mean (Actual drug concentrations: Table 14.5.1; and, Parameter summaries: Table 14.5.2). Supporting plots will display drug concentration over the 6-hour confinement period by treatment group (Figures 14.5.1, Template 6), together with parameter summary Geometric LS Means +/- 90%CI (Figures 14.5.2, Template 7).

For Part 2, the statistical analysis of the Differences between doses for all Parkinson patients (including 5mg, 10mg, 20mg and 40mg from Part 2, and 80mg from Part 1) and Dose proportionality of both C_{max} and AUC parameters will include details of the model applied with Mean square error, Degrees of freedom, F statistic and resulting p-value for each factor or model parameter. For the dose difference analysis, all dose group estimates will be presented LS means with 95% confidence intervals after back transformation of the log values and all pairwise comparisons between doses will be presented as ratios of LS means (%) with 95% confidence intervals (Table 14.5.3). These will also be plotted as shown in Section 6.4.2 (Figure 14.5.3).

8. References.

ICHE9 “Statistical Principles For Clinical Trials” February 1998.
ICHE8 “General Considerations For Clinical Trials” July 1997.

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9. Finalisation of Statistical Analysis Plan.

The statistical analysis plan, and all relevant table shells will be finalised before the database lock of the Part 1, PD patient cohort.
